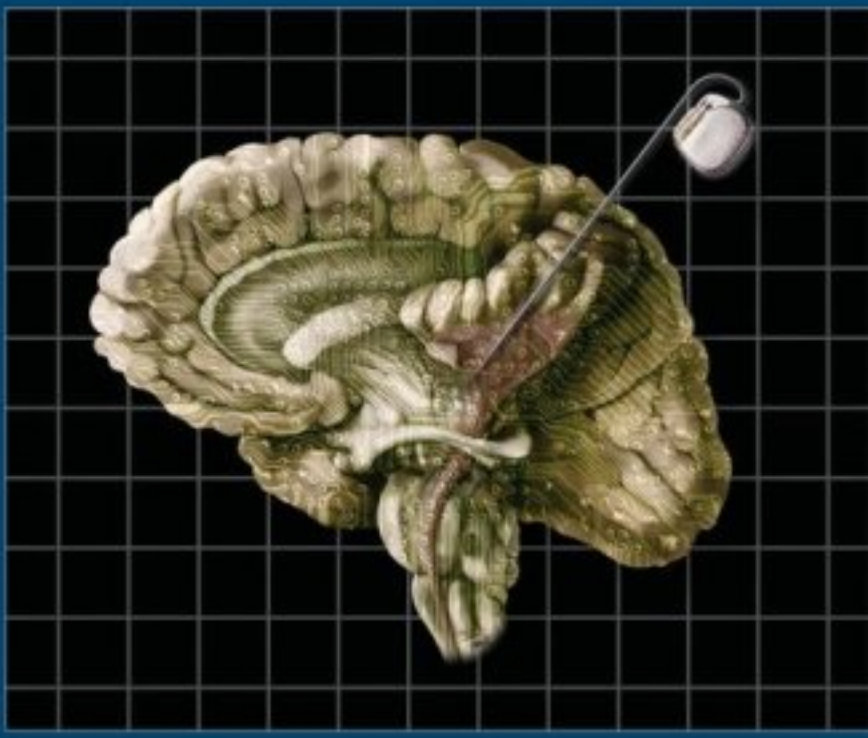
D. E. Sakas and B. A. Simpson (eds.)

Operative Neuromodulation

Volume 2: Neural Networks Surgery



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Operative Neuromodulation

Volume 2:
Neural Networks Surgery

Edited by
D.E. Sakas and B.A. Simpson

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Preface

Operative Neuromodulation is a rapidly evolving multidisciplinary biomedical and biotechnological field that opens new options and possibilities not only for helping patients but also for understanding the role of the nervous system in modulating all other bodily systems. Many specialties are involved and multidisciplinary collaboration is necessary for the further progress of the field. The International Neuromodulation Society (INS) exists to promote, disseminate, and to be an advocate for the science, education, best practice and accessibility of all aspects of neuromodulation. The INS is directly associated with the International Functional Electrical Stimulation Society (IFESS) which aims to promote the research, application, and understanding of electrical stimulation as it is utilized in the field of medicine. The World Federation of Neurosurgical Societies (WFNS) has realised the potential of the field and recently created a Neuromodulation Committee. Undoubtedly, many other neuromodulation committees will be founded in other specialties and all of them, in close collaboration with the INS, will advance neuromodulation. With this book, we aim to facilitate a world-wide dissemination of authoritative information regarding this scientific and clinical field, and to promote an expansion of current medical practice and research into this area. Furthermore, we wish to contribute towards a constructive integrative relationship between the biomedical and technological fields involved in neuromodulation. It is hoped that this book will have a positive impact in the continuously evolving research and practice of neuromodulation.

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Introduction

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An introduction to neural networks surgery, a field of neuromodulation which is based on advances in neural networks science and digitised brain imaging

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Summary

Operative Neuromodulation is the field of altering electrically or chemically the signal transmission in the nervous system by implanted devices in order to excite, inhibit or tune the activities of neurons or neural networks and produce therapeutic effects. The present article reviews relevant literature on procedures or devices applied either in contact with the cerebral cortex or cranial nerves or in deep sites inside the brain in order to treat various refractory neurological conditions such as: a) chronic pain (facial, somatic, deafferentation, phantom limb), b) movement disorders (Parkinson's disease, dystonia, Tourette syndrome), c) epilepsy, d) psychiatric disease, e) hearing deficits, and f) visual loss. These data indicate that in operative neuromodulation, a new field emerges that is based on neural networks research and on advances in digitised stereometric brain imaging which allow precise localisation of cerebral neural networks and their relay stations; this field can be described as *Neural networks surgery* because it aims to act extrinsically or intrinsically on neural networks and to alter therapeutically the neural signal transmission with the use of implantable electrical or electronic devices. The authors also review neurotechnology literature relevant to neuroengineering, nanotechnologies, brain computer interfaces, hybrid cultured probes, neuromimetics, neuroinformatics, neurocomputation, and computational neuromodulation; the latter field is dedicated to the study of the biophysical and mathematical characteristics of electrochemical neuromodulation. The article also brings forward particularly interesting lines of research such as the carbon nanofibers electrode arrays for simultaneous electrochemical recording and stimulation, closed-loop systems for responsive neuromodulation, and the intracortical electrodes for restoring hearing or vision. The present review of cerebral neuromodulatory procedures highlights the transition from the conventional neurosurgery of resective or ablative techniques to a highly selective "surgery of networks". The dynamics of the convergence of the above biomedical and technological fields with biological restorative approaches have important implications for patients with severe neurological disorders.

Keywords: Operative neuromodulation; neural networks surgery; digitised brain imaging; computational neuromodulation; neuroprostheses; chronic pain; movement disorders; epilepsy; psychiatric disorders; hearing loss; visual loss.

Definitions

In biology, neuromodulation can be defined as the process by which chemical substances, neurons or neural networks excite, inhibit or tune adjacent or remote neurons or neural networks in order the latter to deliver responses, which are better adapted to the demands of the environment of an organism and more suitable for ensuring its successful survival. In the clinical context, several definitions have been proposed and the most widely accepted are described below. *Neuromodulation* is a) the science of how electrical, chemical, and mechanical interventions can modulate or change central and peripheral nervous system functioning, b) the form of therapy in which neurophysiological signals are initiated or influenced with the intention of altering the function and performance of the nervous system and achieving therapeutic effects or c) the therapeutic alteration of activity in the central, peripheral or autonomic nervous systems, electrically or pharmacologically, by means of implanted devices. More recently, it has been proposed that neuromodulation is the reversible use of electrical stimulation or centrally-delivered pharmaceutical agents to manipulate nervous system activity in order to treat specific types of chronic pain, spasticity, epilepsy, ischemia, cardiac, bowel, bladder dysfunction, nervous system injury, and movement, visual, auditory or psychiatric disorders [15].

All the above imply the implantation of a device by the therapist in the body of the patient. Neuromodulation therapy has inevitably an interventional or operational character. Hence, in the clinical or therapeutic setting,

it is more accurate to name this therapy as *Operative Neuromodulation*. We propose that *Operative Neuromodulation* is defined as the field of altering electrically or chemically the signal transmission in the nervous system by implanted devices in order to excite, inhibit or tune the activities of neurons or neural networks and produce therapeutic effects. The definition is neither the best possible not the last one to be proposed. Undoubtedly, in the years to come, better definitions may be proposed. The difficulty in defining neuromodulation may, in part, reflect the fact that this is a subject with at least two key areas of complexity. First, it is a rapidly evolving multidisciplinary biomedical and technological field and secondly, the procedures are performed on the nervous system, but they can affect any organ or system of the human body. Currently, the specialists who are involved in neuromodulation belong primarily to neurosurgery, anesthesiology, neurophysiology, neurology, cardiology, and orthopedics, but because of the systemic effects and benefits, this relatively new discipline of medicine is likely, gradually, to encompass or influence most medical specialities.

It is worthwhile to define various relevant terms. The most common can be found below and are elaborated in the respective articles in this volume. *Functional neurosurgery* is a field of neurosurgery designed to restore the physiological activity of the nervous system by either highly selective ablative procedures or by implantable devices that influence the signalling, by chemical or electrical means, and excite, inhibit or tune conduction in the nervous system in order to produce therapeutic effects. *Neuroprosthetics* is the field of neuroprostheses, i.e. artifical devices that generate electrical stimuli and excite the nervous system, by initiating action potentials in nerve fibers, in order to replace the function of damaged parts of the nervous system. *Neural engineering* is a field that applies methods and principles of engineering, physical and mathematical sciences to investigate the nervous system and design and construct its interfaces with technological devices in order to develop novel therapeutic approaches to diagnose and treat neurological diseases. Alternatively, *Neural engineering* is the science that aims to interface electronics to brain, spinal cord, and nerves by combining the potentials of microsystems technology and microelectronics with the current understanding of the electrochemical, neuroanatomical and neurophysiological properties and constraints of the nervous system. *A brain computer interface* is a technological interface between a brain and a computer which intercepts neural signals from the brain and uses them to control an electronic device without requiring any motor output from the user. *Brain computer interfaces* can also be defined as electronic brain implants that translate the intention to communicate or move into either effective communication through a robotic device or computer cursor, or actual movement of paralyzed limbs. *Neuromimetics* is the scientific field of designing and constructing human-made compounds, devices, substances or processes that imitate the natural neurological materials, structures, forms or processes. *Neurotechnology* describes how chemical engineering, nanotechnology, electronics, neuroinformatics and neurophysiology intersect to investigate the development of devices which incorporate or are based on neural networks. *Computational neuromodulation* is the field that studies the mathematical and biophysical aspects of modulation in neurobiological systems. *Neuroinformatics* is the discipline which addresses the computational requirements for the integration of the existing diverse range of neuroscientific data sets in order to formulate a ''systems level'' understanding of nervous system processes. Alternatively, *neuroinformatics* may be defined as the study and understanding of computation, parallel processing and management of information in the brain in order to understand more general complex and highly parallel systems, either artificial or natural. Presently, neuroinformatics is concentrated in three specific fields aiming to the development of: a) neuroscience databases, b) brain imaging acquisition and analysis, and c) experimental and theoretical methods for the analysis of parallel processing in the brain. Neuroinformatics is strictly associated with *Computational Neuroscience* and *Neural Computation*. The latter also called *Neurocomputation* aims both to understand how neural systems process information and also, to construct information processing technological devices that could replace lost functions in the central or peripheral nervous system. This definition is based on the philosophical and scientific assumption that the brain is essentially an information processing and generating biological device.

Neuromodulation, neural networks science and advanced stereometric digitised brain imaging: the foundations of neural networks surgery

In this volume, the articles describe techniques that are performed either *in contact with the cerebral cortex or cranial nerves* or *in deeply located structures inside the brain*. The first category includes procedures such as motor cortex stimulation (MCS) for pain or vagus nerve

stimulation (VNS) for epilepsy. The second category includes procedures such as deep brain stimulation (DBS) for Parkinson's disease. All these procedures aim to modulate neural networks in the brain in order to produce therapeutic effects. Many of these techniques are possible only because they can be based on computerized brain imaging. Brain structural and functional imaging can nowadays be subjected to advanced digitised stereometric analysis; this makes it possible, for the first time, to ''visualise'' the location of relay nodes and operate on them virtually working inside the neural networks in the brain. The fact that it is feasible to operate essentially inside a neural network brings operative neuromodulation and functional neurosurgery to a higher level. The articles of this volume describe such advanced applications and their compilation signifies the emergence of *Neural Networks Surgery.* Hence, *Neural networks surgery* can be defined as the field of operative neuromodulation that utilizes current advances in neural networks research and methods of accurate digitised stereotactic brain imaging for localisation of neural networks and their relay stations in order to alter neural signal transmission and modulate their activity therapeutically by implantable electrical or electronic devices. This is not a matter of semantics or of simply introducing a new topology. This special field of neuromodulation highlights the transition from the conventional neurosurgery of resective or ablative procedures to a ''surgery of networks'' and to surgical treatments of high specificity for re-engineering of deranged neural function. Furthermore, this field points out that great developments should be expected in neuromodulation based on biophysics, neural transmission and neural networks research and computational neurobiology [19].

In this volume, the authors have been selected because of their long standing contribution or innovative works performed over the years and presented at major international meetings. In the included articles, an extended spectrum of neuromodulation is presented from cortical or deep brain stimulation to the forefront of current applications utilizing biohybrid materials. The articles examine the established neuromodulation systems and the new or emerging applications for pain, movement disorders, cardiovascular disease, epilepsy, psychiatric illness, impairment of hearing and vision. The key objectives are to describe the state of the art, put an emphasis on the better understanding of the neural networks involved and of the basic science underlying the effects of neuromodulation. The articles contain detailed technical descriptions of surgical techniques, practical clinical information such as criteria and guidelines for selecting suitable patients for neuromodulation, descriptions of how to organize the right multidisciplinary team, how to deal with borderline cases, and how to evaluate outcome. Special emphasis has been placed on the search for common parameters in the successful versus the failed neuromodulatory applications. The authors conclude with personal suggestions for further improvements and their views on the future prospects of the neuromodulatory applications. There is also a section on computational neuromodulation, a field where research in electrochemical phenomena such as the oscillation or synchronization of cells in combination with computer modelling, will create new neuromodulatory therapeutic possibilities.

Sections of current volume

Undeniably, the management of chronic pain has been one of the most succesful applications of neuromodulation. The first part of this volume is dedicated to the management of pain by intracranial procedures. The recognised goals of pain treatment are the reduction in the intensity of patient's pain while improving both physical and emotional functioning; to meet these goals, pain practitioners should be able to use all the ''tools of their trade'' [11]. In the articles that follow the most advanced neurosurgical ''tools'' and techniques for pain management are described. *Burchiel* and colleagues juxtapose the cerebral neuromodulatory and neuroablative procedures for chronic severe pain. Since 1981, when motor cortex stimulation (MCS) was introduced in clinical practice, it has evolved to an effective treatment for intractable neuropathic pain. In their respective articles, *Lazorthes*, *Canavero*, and *Saitoh* offer their critical review of published series on the topic. In the light of their extensive experience, these authors along with *Pirotte*, and *Cioni* provide detailed reports on patient selection, preoperative assessment, methods of cortical targeting, surgical technique, complications and outcome. This sequential presentation of experience, by experts (which can be found in other sections of the volume as well) provides the reader with an indepth knowledge and understanding of the subject. *Riegel et al.* describe in detail the technique for localisation of the precentral gyrus based on neuronavigation and intraoperative phase reversal of somatosensory evoked potentials. The role of anodal, cathodal or bipolar stimulation in correlation with the clinical response to MCS is analyzed in a combined contribution by two expert groups leaded by *Holsheimer*

and *Nguyen*, respectively. Evolving procedures for the management of refractory neuropathic pain are also presented. *De Ridder* describes the technique of primary somatosensory cortex stimulation and *Aziz* his experience on DBS of the periventricular and periaquaductal grey matter. *Steude* and *Merhkens* present the biggest series on electrostimulation of the trigeminal ganglion for trigeminopathic pain. Finally, *Goadsby* provides an overview of neuromodulatory treatments for trigeminal autonomic cephalalgias.

Over the last 15 years, it has been widely accepted that neuromodulation plays a pivotal role in the management of movement disorders with Parkinson's disease being the most established indication. *Schurman* and *Bosch* provide a concise review on DBS versus ablative procedures and transplantation. Similarly, *Voges*, *Koulousakis* and *Sturm* present an overview of DBS enriched with remarks reflecting their own experience of over 500 cases. *Fountas et al.* review research and clinical data and analyze the advantages and the disadvantages of recording local field potentials from the basal ganglia while the technical considerations of DBS are described in detail by *Sakas* and colleagues. *Velasco et al.* report on the prelemniscal radiation as an alternative target of DBS for Parkinson's disease. *Gill* presents intraparenchymal administration of glial cell line-derived neurotrophic factor (GDNF) for Parkinson's disease and *Lozano* the current literature and personal considerations on electrical versus chemical neuromodulation. *Vandewalle*, *Alterman*, and *Sun et al.* report on DBS for Tourette syndrome, torsion dystonia, and tardive dystonia, respectively. MCS was recently reported as an alternative treatment for Parkinson's disease; two leading Italian groups (*Canavero*, *Cioni*) present their results. Finally, *Galanda*, based on his patient series, proposes the anterior lobe of the cerebellum as an alternative DBS target for movement disorders secondary to cerebral palsy.

Over the last two decades, carefully selected cases of refractory epilepsy have been successfully managed by neuromodulatory procedures. *Theodore*, *Karceski*, and *Villemure* and *Pollo* provide three excellent reviews on the available research and clinical evidence supporting the application of electrical stimulation in intractable epilepsy; neuroanatomical and pathophysiological background, selection criteria, surgical procedures and outcomes of VNS, transcranial magnetic stimulation, and DBS of thalamus, subthalamic nucleus, cerebellum or hippocampus are presented extensively. Separate articles provide elaborate descriptions of VNS for medically-refractory epilepsy (*Boon*, *Moutaery*, *Sakas*). The efficacy of DBS of thalamus (*Krauss*, *Velasco*, *Baltuch*), hippocampus (*Velasco*, *Van Roost*, *Vonck*) and cerebellum (*Krauss*) in controlling intractable epileptic seizures is analyzed and the current limitations and future prospects are highlighted. *Fountas* and *Smith* describe the clinical results of a novel closed-loop system for brain electrical stimulation. Finally, *Boulis et al.* bring forward the gene therapies as alternative therapeutic modalities in the management of epilepsy.

The potential therapeutic role of neuromodulatory procedures in alleviating psychiatric disorders is increasingly recognized. *Sakas*, *Simpson* and colleagues review the history of psychiatric neurosurgery, underlining the transition from the ablation of brain tissue to the chronic electrical stimulation of neural networks. *Friehs*, *Carpenter* and colleagues provide an interesting report on rationale, pathophysiological background and efficacy of VNS for depression. Separate articles report the anatomicophysiological substrate, the surgical considerations and the outcome of chronic electrical stimulation of three distinct deep brain structures i.e. nucleus accumbens (*Nuttin*, *Sturm*, and *Rasmussen*), inferior thalamic peduncle (*Jimenez*), and posteriomedial hypothalamus (*Franzini*, *Broggi*), in order to improve the lives of patients with obsessive-compulsive disorder (OCD) or depression.

Currently, the field of restoring severely impaired hearing and vision by highly sophisticated neuroprostheses lies in the forefront of neuromodulatory and biotechnology research. The current state of auditory brainstem implants is widely reviewed by experienced specialists (*Di Girolamo*, *Manrique*) while particular emphasis has been given in the subtonsillar approach (*Seki*) and the stereotactic implantation of the device (*Kuhta*). Furthermore, *De Ridder*, *De Mulder* and colleagues propose auditory cortex stimulation for alleviating intractable tinnitus and highlight the prospects of the field. *Thanos et al.* review thoroughly the current evidence of implantable visual prostheses; concerns related to retinal and cortical implants, limitations in their technological implementation and biocompatibility, as well as essential modifications to improve the interfaces between technical devices and the biological environment are analyzed. *Patrinos* and *Viola* report on the U.S.A artificial retinal program which aims to produce a retinal prosthesis that will enable blind patients to read large print and ambulate with ease; the technical considerations are highlighted and the preliminary clinical data are reviewed. In addition, two leading German groups (*Walter*, *Hosticka*) provide interesting information on

design and manufacturing of epiretinal prosthesis and discuss the potential obstacles and further steps towards the improvement of this system.

This volume concludes with two separate sections dedicated, respectively, to computational neuromodulation and emerging applications. Computational modelling and its clinical dynamics are highlighted with respect to motor cortex stimulation (*Holsheimer* and *Manola*), electrophysiological activity of basal ganglia (*Nikita*) and neuromodulation of aging (*Sikstrom*). *Aziz* provides hints into the potential role of DBS in the management of intractable cardiovascular disorders. An introduction to the rapidly evolving field of brain computer interfaces is presented by *Sakas* and colleagues. *Warwick* provides an expert's review on the application of implants in order to link bi-directionally the technology with the human nervous system. Two innovative areas of technological research are the nanoelectrode arrays and the cultured neural probe; the use of carbon nanofibers arrays in increasing accuracy of DBS and the potential of a hybrid type of neural prosthetic information transducer, for stimulation and/or recording of neural activity are signalized in respective articles, by *Andrews* and *Rutten*. *McIntyre* provides two articles bringing forward sophisticated computerized methodologies in DBS procedures. These are expected to optimize the electrode placement prior to permanent implantation, individualize the stimulation parameters and maximize the clinical efficacy. Finally, *Sakas* and colleagues highlight the future treatment implications that exist in the neuroanatomical connections of the basal ganglia and the limbic system (metaphorically, the connection of *motion* with *emotion*); ''old'' targets for movement disorders may indicate ''new'' neuromodulation targets for anxiety and affective disorders.

Socioeconomic aspects of neuromodulation

A large number of patients with neurological disorders are considered untreatable with medications or have suffered loss of function. For such patients, neuromodulation may prove the only option. A gradually increasing number of cost-benefit studies have started to prove the efficacy and financial gains to health systems from neuromodulatory procedures on patients. In spite of this, in many insurance or scientific organizations there is a ''value for money'' debate i.e., whether it is worthwhile to perform neuromodulation. It is well known that many patients are denied the benefit of neuromodulatory procedures on the basis of mistaken medical or cost considerations. To address such problems, there is a need for formulation of principles and guidelines for doctors and patients on the correct application of neuromodulation. It is also important to continue to develop a framework for the ethically correct collaboration of health care professionals with the companies that produce neuromodulation devices. Undeniably, expert opinions on neuromodulation should spread across the world. In this process, we should be constantly aware that brain-based correction of brain malfunction involves intervening in a complex and poorly understood system, that the likelihood of unanticipated problems is high and that there are considerable ethical implications of such advanced neurotechnological applications for the individuals and the society [3]. The International Neuromodulation Society exists ''to promote, disseminate, and advocate for the science, education, best practice and accessibility of all aspects of neuromodulation''. This multidisciplinary society is established to be inclusive of all scientists, physicians, bioengineers, members of the industry, and other professionals who have a primary interest in the field of neuromodulation [11]. The INS is directly associated with the International Functional Electrical Stimulation Society (IFESS) which aims to promote the research, application, and understanding of electrical stimulation as it is utilized in the field of medicine. In 1999, the INS and IFESS became sister societies. The importance of this field has recently been recognized by the World Federation of Neurosurgical Societies (WFNS), which decided that a special Committee on Neuromodulation should be formed. This Committee, in collaboration with the International Neuromodulation Society (INS), has the aim of disseminating the right information and promoting the correct application of neuromodulation treatments around the world.

Computational neuromodulation

In nature, neuromodulation is expressed at a cellular, synaptic, or network level. Neurons and networks are multiply modulated and the convergence and divergence in modulation is very extensive. Computational neuromodulation is a special field of computational biology dedicated to the study of the biophysical and mathematical characteristics of the electrochemical modulation in the nervous system. Given the complexity of neuromodulation in nature, the computational approach may not only provide a deeper understanding but also provide the solid foundation for more refined clinical applications. The potential of this field is briefly discussed below. All

types of neurons (motor, sensory, and interneurons) and networks are subject to neuromodulation. Modulation may be induced by extrinsic neural projections to a circuit or intrinsically by the circuit neurons themselves [5]. Areas of neuromodulation may include the synaptic drive, synaptic efficacy, and sensory encoding [9]. Modulation can alter the intrinsic properties of neurons and the strength of synaptic connections, change their time-course, voltage-dependence and synaptic conductance. Neuromodulation, acting on a single membrane current, may or may not bring the neuron across the boundaries of different behaviors, depending on the conductance of the neuron membrane [9, 13]. It is well known that many neurons are silent when isolated, others fire single action potentials tonically, and others fire bursts of action potentials. Neuromodulation can transform a ''tonically-firing'' into a ''bursting'' neuron. In the thalamus, a transition between ''tonic'' and ''bursting'' firing is associated with the transition between awake and sleep. The encoding of sensory information in spike trains is subject to modulation, while in other conditions, modulation may offer a short synaptic input that can ''jump start'' a circuit [14].

All the signalling networks in the cell are interlinked, so that modulation of one current is likely to change the state of numerous pathways in the cell and possibly alter responses to other modulatory interventions [13]. Modulation can reconfigure an anatomically defined network into different functional circuits, by altering intrinsic properties of neurons within the network or the synaptic strength. Extrinsic modulation can tune and configure whole networks and organize ensembles of circuits in numerous regions of the nervous system [10]. In this process, networks or neurological systems can be biased into different functional outputs, in much the same way as changing parameters in a network model should bias or modify the output of the network [13]. Neuromodulation can also have a great impact on development because modulators can influence process outgrowth and synapse formation. If most synapses and the intrinsic properties of neurons within a circuit are subject to modulation, then synaptic strength and its plasticity are not fixed, but are ever changing. The neuromodulatory environment changes over development because of sequential acquisition of cotransmitters in modulatory projection neurons [13]. Theoretically, in operative neuromodulation, implanted devices could act by altering or exerting influence on membrane currents that can be activated, inhibited, or otherwise altered. However, operative neuromodulation is not likely to have the great range of effects that natural neuromodulation has. It is inherently more specific and restricted. Clinical efficacy may improve if we succeed in understanding better the computational aspects (amplification, convergence and divergence of effects) [13] and the electrochemical phenomena (oscillation or synchronization of cells) [5] and develop devices that could reproduce or influence such computational aspects of naturally occurring neuromodulation.

Much computational work will be needed to understand how it is possible for biological circuits to be so richly modulated while retaining stable function. A relevant concept is autoregulation. ''Autoregulation'' maintains the ''internal stability'' of a biological system despite ''external'' changes, provided these changes do not exceed certain limits, i.e. the ''limits of autoregulation''. The autoregulation is achieved by neurogenic and metabolic mechanisms and has numerous computational aspects. Most neurological systems including the pain systems, may operate by autoregulatory mechnanisms. From a theoretical perspective, each pain system through evolution is expected to be organised to interpret as painful the various stimuli that act outside its ''limits of autoregulation'' while other stimuli, inside the ''limits of autoregulation'' should be interpreted as non-painful. Electrical or chemical modulators or other influences can modify the ''range'' or ''limits'' of autoregulation of a system. When the ''autoregulation'' of a pain system is lost because of intrinsic changes or external injuries, the system starts interpreting as painful the stimuli, which previously were not interpreted as painful, because they were recognised as normal and being within the ''limits of autoregulation''. Operative Neuromodulation could be defined as a process aiming to re-establish the lost autoregulation of neural systems. Notably, the first and most widely applied type of neuromodulation has been the management of chronic pain. In Operative Neuromodulation, we alter the signal transmission by implanted devices in order to re-establish the lost normal ''range of autoregulation''. In this therapeutic context, we modulate neural networks in order to re-regulate them. The implanted devices become part of the system and act to allow the system to regain a new functional ''range of autoregulation''.

Emerging applications and future prospects

Neuromodulation is an area of intersection, exchange and cross-fertilization of ideas from many disciplines. In order to offer high-quality services to patients and

cost-effective solutions to society for the problems of those who suffer from chronic neurological diseases we must face many challenges. The most widely used types of electrical stimulation of the brain, so far, are vagus nerve stimulation (VNS), deep brain stimulation (DBS), and motor cortex stimulation (MCS); these have proved effective for carefully selected groups of patients. Our first challenge, on the basis of the most successful brain stimulation devices is to investigate the potential benefits from a judicious, sound but bold expansion of their indications. Our next big challenge is to integrate stimulation technology with human neurobiology, neuroplasticity, and neural repair, and explore the potential neuroprotective effects of neuromodulation. Some of the above issues that are of great concern to the future of neuromodulation, and neurosurgery in general, will be briefly described below.

Deep brain stimulation

DBS is a field that has great potential. It is widely acknowledged that the list of DBS indications is going to expand. Currently, DBS is being used or tested for efficacy in dystonia, pain, Tourette syndrome, epilepsy, stroke, persistent vegetative states, obsessive-compulsive disorder (OCD) and depression. The thalamocortical loops targeted in Parkinson disease run parallel to those implicated in OCD. DBS can modulate the activity of many neural circuits that are important in psychopathologic states [6]. The outcome of DBS is likely to improve. Improved high-resolution magnetic resonance images after implantation and more standardised reporting of lead locations in published series will ultimately improve the outcome for patients. This brings forward the issue of earlier recommendation of DBS treatment in the course of neurological disorder. In the field of movement disorders, there is a hint that DBS may slow the progression of Parkinson's disease. There is a ''catch-22,'' of course, in that unless DBS is applied earlier such evidence will not be available [22]. From a technological perspective, progress is expected in many critical areas including the introduction of telemetric implantable pulse generators, the extension of battery life and the production of rechargeable batteries. DBS may be brought to another level if we develop electrodes that stimulate and monitor neuronal activity from multiple regions of the brain simultaneously and generate ''network level'' representations. Research has shown that self-timed movements are preceded by increased activity in the parietal cortex and sensorimotor putamen [16]. A ''closed loop'' DBS which will be activated by control signals derived from brain structures could be much more effective. Another great development would be the creation of DBS microelectrodes embedded with microactuators that will enable precise electrode insertion; the time required for surgery would be significantly reduced and it would be possible to easily adjust the position of the electrode tip after implantation.

Progress may also come from application of novel stimulation waveforms and the construction of ''smart stimulators'' that have the capability for dynamic internal adjustments [16]. Exciting work is conducted at the NASA Ames Research Center on the development of nanoelectrode arrays utilising aligned carbon nanofibers; with such technology, our ability to offer precise complex patterns of stimulation may be enhanced and it will become possible to perform not only electrical microrecording but also electrochemical recording, and stimulation [12]. Nanomaterials interact much more closely with cells than currently available materials. Carbon nanofibers can act as minimally traumatic CNS electrodes. Any neurological disorder that has altered electrical conductivity could potentially be helped through such materials [26]. Ultimately, the big objective is to understand DBS mechanism of action. In this, we will be undoubtedly helped by the above progress and also by the development of implantable *chronic recording microelectrode arrays* that incorporate on board amplification, spike detection and wireless transmission of data and power [16]. Finally, we should overcome the current problems and make feasible the application of DBS in children.

Cortical stimulation and vagus nerve stimulation

Currently, the main indication of cortical stimulation is central neuropathic pain but the list of indications is growing to include sensory cortex stimulation for pain or tinnitus, cerebellar stimulation for epilepsy and epileptogenic cortex stimulation for the control of seizures. It remains to be clarified whether it would be preferable, in selected conditions, to perform intradural rather than epidural stimulation (the latter is currently practised much more widely), whether stimulation should be anodal or cathodal and many other issues. Cortical stimulation may become more effective by many of the technological developments described in the previous and following sections. In VNS, the challenge is also multi-fold. Again, the first issue is the better understanding of its action on epilepsy and the efficacious application in other

conditions notably depression, addictive states and potentially Alzheimer's disease. Many of the above technological developments will provide novel ways to address such issues. An area of expected progress is the field of ''closed loop'' systems, i.e. devices capable of ''responsive neurostimulation''. These are not applied on a fixed schedule, as in movement disorders, but the stimulator is triggered by intrinsic brain activity. This will affect the application of both cortical and vagus nerve stimulation. Closed-loop, on demand, VNS stimulation, triggered by the electrical changes that precede a seizure may need to be prioritised as one of the first lines of research. It is highly likely that it will improve VNS efficacy and prolong the duration of useful function of the device; this is particularly important in epileptic patients who are frequently young adolescents or children.

Direct relay of hearing or visual information into the cerebral cortex

A few of the most intriguing neural prostheses projects aim to artificially relay environmental sensory information directly into the human cerebral cortex. The best known struggle in this area has the ambitious goal of conveying visual perception by implanting stimulation electrodes into the visual cortex of blind volunteers [23]. In fields of both auditory and visual prostheses, it can be argued that an effective prosthetic device could be ''plugged in'' anywhere along the central auditory or visual system. However, viewed strictly from the anatomical and surgical safety perspectives, the cerebral cortex is likely to be a much more attractive implantation site compared to brainstem or other deep brain sites. One of the most difficult aspects of this work may ultimately prove to be the encoding of environmental sound or vision into the parameters of the electrical stimulus. Auditory cortex neural prosthesis research has shown that patients with profound auditory loss can discriminate between electrical stimuli based on the differences in the parameters of the stimulation current with the level of the electric current being correlated to the sound loudness and the frequency of the electric current being correlated to the sound pitch. Following this discovery and taking advantage of the subject's discriminatory ability, it was possible to *encode* relevant environmental sound features using the fundamental parameters of the electrical stimulus and, thus, to design and construct effective speech processors; these devices receive input from an external microphone and then electrically encode this acoustic information in a manner specifically designed to exploit optimally the patient's ability to perceive differences in certain electrical stimulus parameters [8]. For all the above reasons, the speech processor is the component that had the greatest impact in the success of cochlear and auditory implants.

The most widely applied and tested visual cortical prosthesis consists of implanted arrays of penetrating intracortical microelectrodes whose superstructures ''tile'' the surface of the cortex, with electrode lead wires connected to fully implanted electronic stimulator modules [23]. A key component is again an advanced computerised processing system of the environmental image that converts, or more precisely encodes, the patient's visual field images into sequences of electrical stimuli with specific parameters that could evoke a visual perception. It is important, therefore, in such applications to develop suitable interfaces that will allow us to ''communicate'' with the human cerebral cortex. A relevant and important finding is that deaf patients do not appear to sustain deafferentation changes that would preclude the ''reactivation'' of normal auditory processing by the prosthetic device [8] and a similar phenomenon could be expected to occur in the visual cortex and pathway of blind patients. It is also encouraging that the cerebral cortex seems to have the ability to adapt and to interpret in an efficient manner electrical information that is applied with the right sequences and within a proper range by a large intracortical array. A significant discovery that resulted from this research is that penetrating electrodes into the cerebral cortex are greatly superior in delivering more precisely the electrical stimulation compared to those electrodes that are placed in contact with the cortical surface. This opens the possibility of another field of therapeutic cortical stimulation namely this of *deep cortical stimulation* (via an array of penetrating recording and stimulating electrodes); this application of brain stimulation should be distinguished from both the *surface cortical stimulation* (*epidural or subdural*) and also the *deep brain stimulation* which is applied in basal ganglia, limbic or other deeply located structures. Undoubtedly, in all such applications, advanced imaging and electrophysiological recordings are of paramount importance in helping us to identify the best location in the cortex for the implantation of the neuroprosthesis.

Microelectrode arrays, cultured neural probes and hybrid neural interfaces

Great progress is likely to occur in research aiming to improve the neuroelectronic interfaces based on advanced

sophisticated technological solutions and a better understanding of neural growth. Some of these devices are briefly described below. *Microelectrode arrays* (MEAs) are special types of micro-hardware constructed by using microfabrication and micro-electronics by thin-film based planar and 3D-arrays of substrate microelectrodes in vitro coupled to populations of cultured neurons [20]. *Hybrid neural interfaces* are designed to make connections and communicate with regenerating neurons. *Cultured neural probes* are hybrid neural information prosthetic transducers for stimulation and/or recording of neural activity in the brain or the spinal cord. Each consists of a *microelectrode array* on a planar substrate, where each electrode is being covered and surrounded by a locally confined network of cultured neurons, obtained by chemical patterning of the substrate. The development of such neuronal cultures includes the outgrowth and retraction of neurites (axons and dendrites) in order to establish a network of synaptically connected neurons. The purpose of the cultured cells is that they act as intermediaries for collateral sprouts from the in vivo system, thus allowing for an effective and selective neuron electrode interface. This allows the interconnection of neural networks with chemically patterned electrode arrays [17].

Neuromimetics

There are limitations of current neuroprostheses, which challenge the scientific and engineering community in identifying directions for continued research and development. An exciting field of great interest is biomimetic science. This is based on the widely accepted fact that biological systems solve problems that current technical systems cannot tackle. The biomimetic approach is the attempt to apply solutions, developed by evolution, to technical problems. *Neuromimetics* is part of biomimetics and can be defined as the art and science of designing and constructing human-made processes, substances, compounds, devices, or systems that mimic or imitate natural neurological materials, structures, forms or processes. A neuromimetic apparatus is of special interest to researchers in nanotechnology, robotics, artificial intelligence, medical industry, and military. Characteristic examples of biomimetics are the development of integrated silicon sensors that estimate visual motion using architecture derived from the neural circuitry that extracts motion information from the fly optic lobe [7].

Brain computer interface

A *brain computer interface* (BCI) can be defined as electronic brain implant that translates the intention to either communicate or move into communication through the movement of a robotic device or computer cursor or into actual movement of paralyzed limbs. This represents a combined application of functional neuroprostheses with assistive technology [18]. A BCI can detect changes in the user's brain activity and convert them into commands for a computer application. This is achieved through the application of signal processing techniques to the signals that the patient is still able to control. The key element in a BCI is a decoding algorithm that converts the main electrophysiological signal into an output that is suitable to control an external device. The interfaces rely on the natural adaptive ability of the human brain. The users have to learn to adapt their biological response, i.e. change the amplitude or frequency of the signal monitored. Undeniably, developments in BCI technology will open new possibilities for operative neuromodulation [1, 25].

Computer modelling

Computer modelling of the bioelectrical and statistical aspects of neural recording and neurostimulatory recruitment is another promising area where great developments are likely to occur. One example is the development of novel mathematical models that encode the nonlinear dynamics of hippocampal neuronal networks. It has been demonstrated that it is possible to replicate some of the hippocampal functions with a microchip implementation of the predictive mathematical models. This work aims to develop a microchip that captures the three-dimensional neuronal behaviour of a particular hippocampal region. It holds the promise that individuals with damaged areas of the brain could be helped by such computational methods and that the use of neural interfaces could enhance normal or impaired neural function [2].

Neural engineering and neurotechnology

Neural engineering includes many fields. Developments in some of them are likely to influence the practice of neuromodulation such as neural network architecture software and hardware, neuromorphic and neuromimetic engineering, neural control interfaces, and neural computation and cortical coding. The latter applies system science and non-linear dynamics to model and

simulate biological neural systems, decipher neural decoding and understand neural plasticity and adaptation. *Bio-Micro-ElectroMechanical Systems* (*Bio-MEMS*) is a field of development of multi-functional, chronic neural implants aiming to obtain and control a signal extracted from cerebral cortical activity in order to offer or enhance capabilities such as move a prosthetic arm with near natural performance. Finally, another line of research aims to augment cognition by developing advanced sensor technologies and cognitive state classification algorithms for integration within training systems.

Neuromodulation of cognition and emotion

Today, convergent data obtained using multiple neuroscientific methods indicate that a wide range of illnesses can be understood as dysfunction of specific neuronal circuits (networks), which follow defined anatomical pathways and rely on specific neurotransmitters [4]. The processes that underlie thought and emotion are rooted in the physical biology of the brain; abnormalities in this biology ranging from genetic mutations to structural malformations can give rise to psychiatric symptoms. With these insights into the function of the human brain as well as the feverish pace of technological innovation in imaging and surgical methods, the road is being paved for future neurosurgeons (or neuromodulation practitioners) to have a direct impact on the mind as well as the brain [4]. It will, however, be necessary to have a thorough understanding of the underlying mechanisms of psychiatric disorders; this will help neurosurgeons and other (neuromodulation) physicians to face the ethical, social, and technical challenges that are sure to lie ahead as modern science continues to unlock the secrets of the brain and mind [4].

Neurotrophic electrostimulation and integration with biological therapies

This is another important field because it highlights the great potential of combining stimulation and regenerative methods. Studies on cochlear implants in animals have provided evidence that electrical stimulation promotes the survival of auditory neurons [24]. The combination of advanced electrical stimulation combined with neural engineering and regenerative therapies (gene therapy, stem cell transplants) and pharmacological approaches is likely to provide significant benefits to patients. The most effective treatment strategies will be based on a convergence and integration of neural prostheses and electrical stimulation with restorative techniques and other biological therapies that will interact and amplify the effectiveness of each other in order to maximize the restoration of function after CNS damage.

Epilogue

Undeniably, based on what we have achieved and on what is currently taking place in centers around the world, we can envision a new era of breakthroughs. The collective future of neuromodulation will be great if we succeed in identifying the major challenges that need to be overcome and make great leaps forward in functionality, acceptability and profitability of neuromodulation devices and neuroprostheses. We should be aware that technologies that work today may need to be redesigned to become more complex and intelligent systems in order to better serve the population. Such advanced designs will be characterized by miniaturization, extreme integration of information-technology and information exchange between the neuromodulation device and the patient's body. From a socioeconomic perspective, it is expected that there will be a shift from external therapeutic devices towards implanted therapeutic devices, and an increase in the use of the more cost-effective aids and therapies. Progress in microsystems technologies, microelectronics, nanotechnologies, etc. is likely to create new opportunities for helping patients and new fields of clinical practice and research. The future of neuromodulation, however, concerns more than simply a prediction of exciting technological developments. What actually happens will be the result of a complex interaction between: a shift in mindset away from a dependence upon pharmacological treatment, better awareness and understanding of existing indications and applications, introduction of new indications, better understanding of mechanisms of action, improved case selection, more mature assessment of outcome and better evidence regarding efficacy [21]. Engineering and digital technologies will continue to provide new designs and construct materials for implantable neuromodulatory or neuroprosthetic devices to improve the functional state of patients with neurological disorders. Nowadays, we are privileged that the great resource of modern neurosurgery is available to us which has made it feasible to operate safely in the most deep or difficult locations in the human brain. If we cherish, enhance and utilise the above great resource and exploit the technological advances

in other fields, we can start from what was previously unimaginable and make it first possible and later routine, and in this process, offer great benefits to patients. In this book, we wish to highlight the immense therapeutic potential which may arise from the convergence of efforts and close collaboration of biomedical scientists and biotechnological engineers in order to re-engineer deranged neurological function. The articles in this volume hope to contribute towards a constructive integrative relationship between all the biomedical and technological fields involved in neuromodulation, a world-wide dissemination of authoritative information regarding this scientific field, and an expansion of current medical practice and research into this area.

References

1. Angelakis E, Hatzis A, Panourias IG, Sakas DE (2007) Brain computer interface: a reciprocal self-regulated neuromodulation. Acta Neurochir Suppl 97: 555–559
2. Berger TW, Ahuja A, Courellis SH, Deadwyler SA, Erinjippurath G, Gerhardt GA, Gholmieh G, Granacki JJ, Hampson R, Hsaio MC, LaCoss J, Marmarelis VZ, Nasiatka P, Srinivasan V, Song D, Tanguay AR, Wills J (2005) Restoring lost cognitive function. IEEE Eng Med Biol Mag 24: 30–44
3. Farah MJ (2005) Neuroethics: the practical and the philosophical. Trends Cogn Sci 9: 34–40
4. Feldman RP, Alterman RL, Goodrich JT (2001) Contemporary psychosurgery and a look to the future. J Neurosurg 95: 944–956
5. Fellous J-M, Linster C (1998) Computational models of neuromodulation. Neural Comput 10: 771–805
6. Greenberg BD (2002) Update on deep brain stimulation. J ECT 18: 193–196
7. Harrison R (2000) Fly-inspired VLSI vision sensors in Neurotechnology for Biomimetic Robots. The North Eastern University Conference Proceedings, East Point, Nahant, MA (May 14–16, 2000), p 17
8. Howard MA, Volkov IO, Noh D, Garell C, Abbas PJ, Rubinstein JT, Ganz BJ, Baken HE (2000) Auditory cortex neural prosthetic devices. In: Maciunas RJ (ed) Neural prostheses. American Association of Neurological Surgeons Publications, Park Ridge, Illinois, pp 273–286
9. Hille B (2001) Ion channels of excitable membranes, 3rd edn. Mass. Sinauer Associates Inc., Sunderland
10. Katz PS (1995) Intrinsic and extrinsic neuromodulation of motor circuits. Curr Opin Neurobiol 5: 799–808
11. Krames ES (2006) Neuromodulation devices are part of our ''tools of the trade''. Pain Med 7(S1): S3–S5
12. Li J, Andrews RJ (2006) Trimodal nanoelectrode array for precise deep brain stimulation: prospects of a new technology based on carbon nanofiber arrays. Acta Neurochir Suppl (in press)
13. Marder E, Thirumalai V (2002) Cellular, synaptic and network effects of neuromodulation. Neural Netw 15: 479–493
14. McCormick DA, Pape HC (1990) Properties of a hyperpolarization-activated cation current and its role in rhythmic oscillation in thalamic relay neurons. J Physiol 431: 291–318
15. North R (2006) Definition of neuromodulation. E-mail communication, copy circulated to the Executive Committee members of the International Neuromodulation Society (www.neuromodulation.com, August 10, 2006)
16. Pancrazio JJ, Chen D, Fertig SJ, Miller RL, Oliver E, Peng GCY, Shinowara NL, Weinrich M, Kleitman N (2006) Towards neurotechnology innovation: report from the 2005 Neural Interfaces Workshop. An NIH-sponsored event. Neuromodulation 9: 1–7
17. Rutten WLC, Ruardij TG, Marani E, Roelofsen BH (2006) Neural networks on chemically patterned electrode arrays, towards a cultured probe. Acta Neurochir Suppl (in press)
18. Sakas DE, Panourias IG, Simpson BA, Krames ES (2007) An introduction to operative neuromodulation and functional neuroprosthetics, the new frontiers of clinical neuroscience and biotechnology. Acta Neurochir Suppl 97: 3–10
19. Sakas DE, Panourias IG, Singounas E, Simpson BA (2006) Neurosurgery for psychiatric disorders: from the excision of brain to the chronic electrical stimulation of neural networks. Acta Neurochir Suppl (in press)
20. Sanguineti V, Giugliano M, Grattarola M, Morasso P (2003) Neuro-engineering: from neural interfaces to biological computers. In: Riva G, Davide F (eds) Communications through virtual technology: identity community and technology in the internet age. IOS Press, Amsterdam, pp 233–246
21. Simpson BA (2006) Challenges for the 21st century: the future of electrical neuromodulation. Pain Med 7(S1): S191–S194
22. Simpson BA (2006) The role of neurostimulation: the neurosurgical perspective. J Pain Symptom Manage 31 Suppl 4: S3–S5
23. Troyk P, Bak M, Berg J, Bradley D, Cogan S, Erickson R, Kufta C, McCreery D, Schmidt E, Towle V (2003) A model for intracortical visual prosthesis research. Artifical Organs 27: 1005–1015
24. Vollmer M, Leake PA, Beitel RE, Rebscher SJ, Snyder RL (2005) Degradation of temporal resolution in the auditory midbrain after prolonged deafness is reversed by electrical stimulation of the cochlea. J Neurophysiol 93: 3339–3355
25. Warwick K, Gasson MN, Spiers AJ (2006) Therapeutic potential of computer to cerebral cortex implantable devices. Acta Neurochir Suppl (in press)
26. Webster TJ, Waid MC, McKenzie JL, Price RL, Ejiofor JU (2004) Nano-biotechnology: carbon nanofibers as improved neural and orthopaedic implants. Nanotechnology 15: 48–54

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Management of chronic severe pain: cerebral neuromodulatory and neuroablative approaches

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Summary

Two approaches are utilized when targeting the brain to treat pain. The first, a non-destructive approach, uses either electrical stimulation of brain targets thought to modulate the process of pain perception, or pharmacological agents are introduced into ventricular spaces to target pain modulating receptors. Electrical stimulation targets include; the thalamic nuclei, the periventricular and periaqueductal grey (PVG and PAG) matter or the motor cortex. Currently, the pharmacological agent of choice for intracerebroventricular injection is morphine. In general, electrical stimulation is used for nonmalignant type pain, and pharmacological modulation for malignant type pain. The second, a destructive approach, is usually employed with the goal of interrupting the signals that lead to pain perception at various levels. Neuroablation is usually performed on cellular complexes such as ''nuclei, or gyri'' or on tracts with the aim of disrupting the sensory and limbic pathways involved in the emotional processes associated with pain. Specific cerebral neuroablation targets include; the thalamic medial group of nuclei, the cingulated gyrus, and the trigeminal nucleus and tract. There are fewer reports in the literature detailing the brain, when compared to the spine, as a target to treat pain, and further research is required.

Keywords: Neuromodulation; cerebral chronic pain; central pain; neuropathic pain; neuroablation; neurostimulation; review.

Introduction

The introduction of neuromodulation techniques to treat chronic severe pain has contributed considerably to the pain specialist's armamentarium. Based on topographic action, neuromodulation techniques can be categorized as; cerebral or cranial, and extracranial, which includes spinal and peripheral. Cerebral neuromodulatory techniques currently available include; deep brain stimulation (DBS), motor cortex stimulation (MCS), and the use of intraventricular narcotics. Examples of neuroablative cerebral procedures used to treat chronic pain include; thalamotomy, cingulotomy, and midbrain tractotomy. Targeting of the brain to control pain has a long history in neurological surgery, for example, surgical treatment of trigeminal neuralgia was first established in the 1900s [79]. However, sectioning a brain pathway or center to treat pain elsewhere in the body was not performed until the 1930s [68]. At this time Sjoqvist sectioned the trigeminal tract of the brain stem to treat facial pain. Later the concept of stereotactic trigeminal tractotomy and caudalis dorsal root entry zone (DREZ) were born from Sjoqvist's [68] work. In 1949, Spiegel and Wycis first introduced human stereotaxis [69], and performed what was most likely one of the first stereotactic procedures to treat human pain, mesencephalotomy, used to treat ''intractable'' facial pain [70]. With the advent of stereotactic procedures, various methods to treat pain by targeting deeper brain nuclei soon followed.

Since the 1950s, stereotactic procedures have focused on various targets, including; both neuroablative and deep brain stimulation approaches, the pontine spinothalamic tract [6, 28, 29], prefrontal white matter [80], mesencephalic spinothalamic and trigeminothalamic tract [70], pulvinar [13, 82], posteromedial thalamus [10, 64], hypophysis [48], centrum medianum-parafascicularis [52, 77, 83], nucleus ventralis posterior medialis (VPM) and nucleus ventralis posterior lateralis (VPL) of the thalamus, and periventricular and periaquiductal grey matter [23]. The two techniques of interest that evolved during the quest to treat pain via the cerebrum are; MCS and intraventricular opioid administration. These two techniques are discussed in detail later in this chapter. Currently, and despite the replacement of neuroablative by neuroaugmentative procedures to treat pain and

other indications, cerebral neuromodulation remains in its infancy compared to spinal neuromodulation. Deep brain stimulation used to treat pain has yet to receive Federal Drug Administration (FDA) approval, in the US, and final efficacy and best indications for cerebral neuromodulation have yet to be determined.

Cerebral neurostimulation to control pain

Electrical neuromodulation

Deep brain stimulation

In the 1950s, while performing psychosurgery, Pool observed and reported on analgesic effects as a consequence of septal stimulation in the front and lateral forniceal columns [57]. Later, Pool and Heath re-reported the pain relieving effect of septal and near-septal stimulation in non-psychiatric patients [26, 56]. The first pain relieving effect due to thalamic stimulation was reported by Mazars *et al*. in 1960 [44, 59]. It is interesting to note that contrary to the spinal cord as a target for pain control, neurostimulation of the brain to relieve pain was observed at approximately the same time that stereotactic neuroablation was first performed [70]. However, these early reports regarding pain relief resulting from deep white matter stimulation did not contribute to the current applications of DBS for pain relief. In fact at the time, Melzack and Wall's gate theory [45] was credited with providing the logical rationale for DBS of the sensory thalamus to control pain. In the late 1960s and as a direct outgrowth of gate theory, Reynolds reported on the analgesic effect of focal brain stimulation in rats [59]. In the early 1970s, Hosobushi *et al*. [32, 33] and Richardson [61, 62] were the first to report on the stimulation of the human thalamus, and the periventricular and periaqueductal grey (PVG and PAG) matter. Stimulation of the thalamic sensory nuclei produced paresthesias in painful areas, and can be explained by gate theory. An additional region reported to evoke paresthesias when stimulated is the internal capsule, and Fields and Adams [3, 11] implanted electrodes in the posterior limb of the internal capsule. Stimulation of the PVG and PAG typically does not produce paresthesias but may induce unpleasant sensations. A further nonparesthetic dependant target of DBS, is the centromedian-parafascicular complex, which has been targeted by Andy [4] to treat painful dyskinesia.

Many reports discuss the use of DBS to treat chronic pain. However, wide spread adoption of the modal has been prevented mainly due to, total numbers of patients treated remaining low, inconsistent target localization, and treatment of various pain syndromes. The mechanism of DBS pain relief is site dependant. The thalamus and PVG/PAG are the most commonly [70] targeted sites of DBS and are currently associated with the largest number of patients treated. Hosobushi *et al*. [32] suggested that the pain-relieving effect of PVG/PAG stimulation is opioid dependant, based on studies where the pain-relieving effect was reversed by naloxone. Mixed evidence exists regarding opioid mediated analgesia due to PAG/PVG stimulation. Some investigators support the notion while others disagree. Currently, it is accepted that the pain-relieving effect of PAG/PVG stimulation is due to activation of multiple supraspinal descending pain modulatory systems, both opioid and biogenic amine dependant [78]. Pain relief resulting from stimulation of the VPL/VPM, the major sensory nuclei of the thalamus, is poorly understood. It has been proposed to be due to inhibition of spinothalamic tract neurons [17]. Activation of dopaminergic mechanisms has also been proposed [75]. Currently, the accepted hypothesis is that thalamic stimulation may activate the nucleus raphe magnus of the restroventral medulla resulting in activation of the descending endogenous inhibitory pain pathways [78].

Major determinates that dictate the response and outcome of DBS for pain relief are adequate patient selection and meticulous assignment of a pain syndrome with a DBS target. In general, pain can be classified as nociceptive or neuropathic. Numerous clinical observations suggest that PVG/PAG stimulation is effective in treating somatic nociceptive pain, which conceptually is reasonable given the proposed opioid mediated effect of PAG/PVG [30]. It has been suggested that VPL/VPM stimulation is more effective in treating neuropathic pain [30]. However as mentioned earlier, the total number of patients treated by DBS is small and, in the absence of controlled trials to prove the assumption, any definitive conclusions regarding the ideal target for any particular pain syndrome remains elusive. Furthermore many patients present with an assorted pain syndrome, which dictates that the DBS target be individualized according to the patient. Some authors suggest placing two electrodes simultaneously in the sensory thalamic nucleus and in the PVG [49]. For some pain syndromes e.g. thalamic infarction induced pain, target selection is simpler given thalamic stimulation is not possible [49]. Chronic neuropathic pain conditions treated by, but not limited to DBS include; anesthesia dolorosa, post-stroke pain, thalamic pain, brachial plexus avulsion, post herpetic neuralgia, postcordotomy dysesthesia, spinal cord

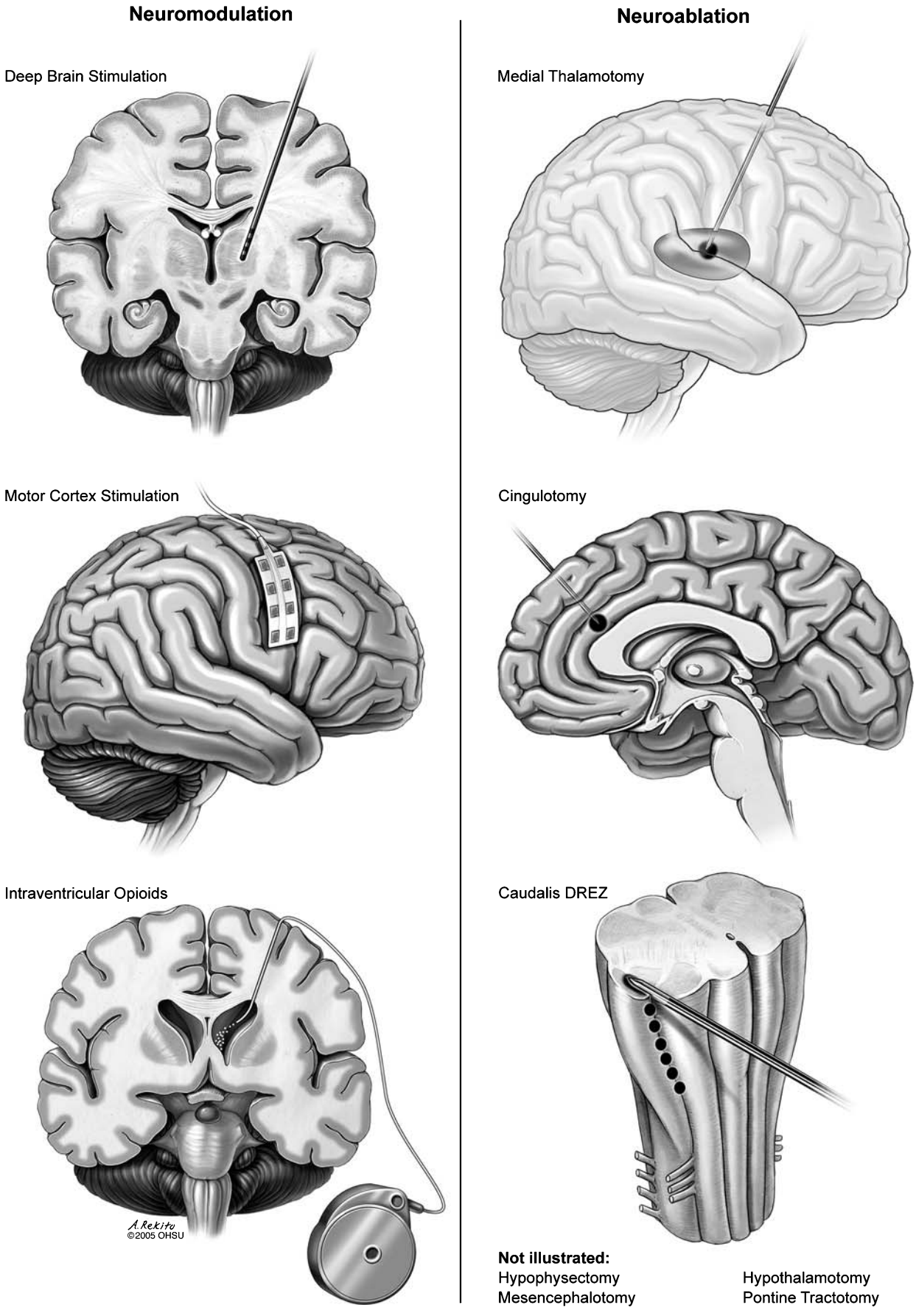

Fig. 1. Diagrammatic representation of cerebral neuromodulation and neuroablation procedures

Table 1. *Deep brain stimulation pain relief outcome data from different studies and for various pain indications*

Pain syndrome	Range of successful pain control (%)
Peripheral neuropathy [42, 72]	37–69
Brachial plexus injury [20, 31]	33–55
Amputation pain [20, 66]	20–67
Anesthesia dolorosa [42, 66]	18–46
Thalamic pain [42, 46]	24–56
Spinal cord injury pain [66, 72]	0–80

injuries and peripheral neuropathy pain. Nociceptive pain conditions treated by, but not limited to DBS include; failed back surgery syndrome, osteoarthritis and cancer pain [60].

Technically, DBS to treat chronic pain is similar to that of DBS in other surgical settings and surgeons have access to a wide spectrum of preferences, options, and tools best used to approach deep brain nuclei (Fig. 1). Deep brain stimulation targets are usually derived from a Schaltenbrand and Bailey atlas and further confirmed intraoperatively, either by macrostimulation or microrecording techniques. To best judge the benefits of stimulation and to help fine tune stimulation parameters following final electrode implantation, a trial period of approximately one week is usually a prerequisite. A summary of DBS pain relief outcome data from different studies and for various pain indications can be found in Table 1 [78]. Complications of DBS for pain relief are similar to those of movement disorders or other indications. Typically, they are related to either: (1) neural injury from bleeding or inadvertent trauma due to electrode insertion, (2) infection, (3) hardware failure, and (4) transient side effects related to over-stimulation or unintentional stimulation of neighboring areas, which may cause diplopia, seizure, nausea, paresthesia, electric shocks or headaches. Overall, DBS surgery is a safe procedure with a low possibility of side effects. Currently, DBS is a modal reserved to treat only a few chronic pain conditions. Considerable debate remains regarding the precise efficacy and indications in terms of which pain syndromes respond to which target? These limitations precluded DBS being approved for use in the US by the FDA.

Motor cortex stimulation

One of the earliest reports regarding the involvement of the motor cortex in sensory phenomena was by the eminent neurosurgeon Penfield, who together with Jasper while performing epilepsy surgery observed that stimulation of the precentral gyrus elicited sensory responses when the corresponding portion of the adjacent postcentral gyrus had previously been resected [53]. Both neurosurgeons treated burning pain on one side of the body by postcentral gyrectomy and when pain recurred they performed a precentral gyrectomy, which then controlled the pain. Independently, White and Sweet attempted surgical resection of the postcentral gyrus for relief of central pain and reported 13% pain relief [76]. Not until 1971 and after the publication of gate theory did Lende and his co-workers re-explored the cortex as a potential site for pain control. Inspired by Penfield's work and in an attempt to treat central neuropathic facial pain and provide long-term pain relief [41] they performed two cases of pre and postcentral gyrectomy of the facial cortex. These reports constitute the backbone of research regarding the pre and postcentral areas and a link with pain control, and it could be argued ultimately paved the way for MCS. By the 1980s, and mainly due to the constraints and inefficiencies of ablative procedures available to treat certain pain syndromes especially those neuropathic in nature, and the inconsistency of target results and indications of DBS for chronic pain, a persistent quest to locate another target along the sensory pathway was a driving force behind the evolution of MCS.

Logically, sensory rather than motor cortex stimulation to achieve pain control would have been a next step and would have been in line with an adoption of gate theory thinking. However, in 1985 Hardy, stimulated the rat medial prefrontal cortex with a resultant significant elevation of nociceptive response latency; he concluded that stimulation of the medial prefrontal cortex produced analgesia [21, 22]. Following the inconsistent results of DBS of the thalamus and other deep brain targets, altering the level of stimulation to cortical and subcortical areas was a next step, and Hosobushi implanted electrodes in subcortical somatosensory areas for control of dysesthetic pains. From this study, he concluded that somatosensory stimulation works well for leg pain [31]. In 1991, Tsubokawa *et al.* first introduced stimulation of the epidural motor cortex as an option to treat central deafferentation pain. This group soon realized that postcentral gyrus stimulation was either ineffective or exacerbated the pain. During procedures, they discovered that epidural motor cortex stimulation inhibited thalamic burst activity with increased regional blood flow to the cortex and thalamus [73]. Tsubokawa *et al*. was a leader in the use of this particular modal showing that it was safe, and that there was no clinical or electrical seizure activity related to motor cortex stimulation as the pain

control threshold required was less than that required for muscular activity. Primarily, Tsubokawa *et al*. used MCS for central deafferentation pain syndromes such as post-stroke pain [73, 74].

The mechanism of action of MCS is poorly understood; however, the work of Garcia-Larrea [15, 16], and Peyron [54] and co-workers shed some light on the mechanism of action of MCS. Positron emission tomography (PET) and electrophysiological studies showed that cortical stimulation increased blood flow to the ipsilateral thalamus, cingulated gyrus, orbitofrontal cortex, insula and the brain stem with some correlation between increased thalamic and brain stem flow and longevity of pain relief. The increased flow to the ipsilateral sensory thalamus was greater than that to the motor (ventrolateral) thalamus, furthermore an intact somatosensory pathway was not absolutely necessary for the changes to take effect nor for the clinical benefits [15, 16, 54]. Chronic stimulation of the motor cortex produces the phenomenon of habituation, which is particularly likely with use of high frequency stimulation and can further provoke epileptogenic activities. The patient selection process is paramount for all pain patients destined for pain relieving surgery and in the case of MCS the debate continues. It is clear that neurogenic rather than nociceptive pain conditions should be treated. In an attempt to predict the best candidates for MCS, Yamamoto *et al.* proposed a pharmacological classification of post-stroke patients. The classification relies on the pain relief response to escalating doses of both intravenous thiamylal and morphine, and concluded that patients with a good response to thiamylal or ketamine and a poor response to morphine are the best candidates for MCS [81].

Several neurogenic pain syndromes have been treated by MCS including; thalamic pain, bulbar post stroke pain, which typically occurs with ''Wallenberg's syndrome'', facial neuropathic and deafferentation pain, and phantom and brachial plexus avulsion pain [7]. Central post-stroke pain following thalamic infarction, or thalamic or putamenal bleeding were reported by Tsubokawa *et al*. with good to excellent pain control in 65% of cases (more than 12 months), and no seizures were observed [73, 74]. Katayama extended the indications to include bulbar pain due to ''Wallenberg's syndrome'' and reported on four patients initially treated with VPL thalamic stimulation that resulted in increased pain. Three of these patients were later treated by MCS with greater than 60% pain reduction in two patients and greater than 40% in one patient [36]. Treatment of neuropathic facial pain appears to be one of the most promising indications for MCS, and may be related to the breadth of facial representation over the motor cortex. Several reports include neuropathic facial pain treatment by MCS. Meyerson, Nguyen, Rainov, Ebel and Herregodts all treated trigeminal neuropathic pain with MCS and reported pain relief in approximately 60% of patients for periods up to 12 months [9, 27, 47, 50, 51, 58]. Peripheral deafferentation pain as well as brachial plexus avulsion has also been treated by MCS, with variable results. Motor cortex stimulation has been shown to produce improvement in symptoms of; thalamic hand syndrome, action tremors, intention myoclonus, and Parkinson's disease. This is an active area of observation and ongoing MCS research [7].

Technically, MCS involves implantation of epidural electrodes in the motor cortex (Fig. 1) which can be localized by either: a) radiological landmarks of the central sulcus, b) intraoperative somatosensory evoked potential (SSEP) with observation of ''phase reversal'' over the central sulcus, c) intraoperative stimulation of the cortex after muscle relaxation discontinuation to localize the motor cortex as well as to determine the seizure threshold, and possibly d) use of neuronavigation systems to localize the central sulcus. Some authors recommend the use of functional magnetic resonance imaging (fMRI) in the targeting paradigm especially with infarctions involving the motor cortex where neural plasticity may be involved in redistribution of the motor cortical functions [63]. A trial period is followed by implantation of a permanent system. Complications of MCS include; intraoperative seizures, stimulator pocket infection, epidural bleeding, subdural effusion, tolerance and diminished benefit over time. Diminished benefit over time is the major concern regarding this modal in the long term.

Pharmacological cerebral neuromodulation

Intraventricular opioids

Human intracerebroventricular use of morphine was first reported by Leavens *et al.* in 1982 [40], and was a result of earlier studies that showed the direct analgesic effects of opioids applied in the ventricular region and around the medulla of the cerebrospinal fluid (CSF) [5, 8]. Powerful demonstrations of the analgesic response to intrathecal morphine coupled with its widespread clinical use demonstrated the need for injection sites to control pain involving the head, neck and upper extremities regions other than the lumbar or thoracic spine. Care needs

to be taken to avoid respiratory depression and sedation associated with high spinal intrathecal opioid injection. The intracerebroventricular route of opioid delivery allows for small morphine doses to be delivered in close proximity to head and neck cancers. This provides adequate pain relief with minor and no respiratory side effects. Target opioid receptors are those around the wall of the third ventricle and the aqueduct in the midbrain where opioid receptors are abundant in the PVG and PAG matter. The opioid mediated action explains why this modal is better suited to treat nociceptive type pain, and is an excellent choice for cancer pain. In Leaven's *et al*. 1982 report, morphine was strictly used to treat patients with intractable cancer pain, 1 mg of morphine was administered with profound analgesia and no respiratory depression or neurological changes [40].

Lazorthes in a report of 82 patients recommended the use of intracerebroventricular morphine for: 1) chronic pain secondary to inoperable malignant tumors in terminal cancers, 2) pain not relieved by medical treatment, and in particular, development of serious side effects from using oral or systemic morphine, 3) intractable bilateral, midline, or diffuse pain beyond the possibilities of percutaneous or open surgical interruption of nociceptive pathways, 4) chronic pain of somatic nociceptive origin (neurogenic pain is a contraindication), 5) upper body pain topography secondary to cervicothoracic cancers, 6) chronic pain of the lower half of the body (subdiaphragmatic) only after failure and/or contraindication of intrathecal spinal administration, 7) absence of general risks of complications, such as coagulation disturbances, cutaneous infection, and septicemia, 8) informed consent from patient and family, and 9) presence of favorable domestic environment (e.g., physician, nurse, or family) for ambulatory surveillance and chronic intracerebroventricular morphine treatment. When the topography of pain involves a transitional area, e.g. lower thoracic, diaphragmatic, or upper abdominal, intracerebroventricular morphine indication is confirmed after a negative small dose of morphine (2.5–5 mg, maximum) trial by lumbar intrathecal injection [38].

The surgical technique involves implantation of a ventricular catheter into the lateral ventricle near the foramen of Monroe for drug delivery near target receptors around the aqueductal wall in the midbrain (Fig. 1). Analgesic latency is between 15 and 30 mins and the effect can last for a mean of 28 hours. Results of intracerebroventricular morphine administration, for excellent or good pain relief, range from greater than 50 to 97%. Tolerance was reported by Lazorthes *et al*. in 3 of 82 patients [38]. Side effects of intracerebroventricular morphine administration include; somnolence, nausea, confusion or respiratory depression. Side effects are generally transient and improve after readjustment of the morphine dosage. Despite limited use in the last few years, probably due to the increased effectiveness of oral opioids, the technique is relatively simple and effective. This technique remains a viable option for patients with intractable pain of malignant etiology, following oral opioid failure, and when pain is diffuse or cephalic in topography [37].

Cerebral neuroablation for chronic pain

Neuroablation of the nervous system to treat pain is a well known procedure and has been in use for over 100 years, e.g. treatment of trigeminal neuralgia by either nerve section or alcohol injection [79]. However, aided by the introduction of human stereotaxis [69] and resultant deep brain targeting, destruction of brain pain pathways/centers as a treatment was not introduced until the late 1930s [68]. Several targets along the body and face sensory pathways together with several thalamic and other deep brain targets have been approached for lesioning and include: the medullary trigeminal tract [68], pontine spinothalamic tracts [6, 28, 29] midbrain spinothalamic tract [70], medial [64] and sensory [23] thalamus, medial frontal lobe [80], pulvinar [13, 82], hypophysis [48] and cingulate gyrus [34].

Before further discussing lesioning of the thalamus, cingulated gyrus and trigeminal tract nucleus, it is important to outline the following: 1) DBS and neuroablation of the same target does not produce similar effects, ablation effects are temporary, and mechanisms of action of DBS are quite different from those of neuroablation; hence, for chronic pain, targets for DBS are not the same as those of neuroablative thalamic procedures, 2) to quote Tasker's [72] statement concerning the outcome of surgical procedures for pain "it must be clear that success is usually partial and limited except in special situations such as *tic douloureux*", and 3) in general and due to the wide spread use of neuromodulative techniques, neuroablative procedures whether spinal or cerebral, to control chronic pain are in decline.

Medial thalamotomy

Stereotactic thalamic neuroablative pain surgery is a procedure of preference mainly due to its relative safety

in relation to deep brain stem structures and because of the wide involvement of many thalamic nuclei in pain processing [23]. The main sensory nucleus, the Vc nucleus as defined by Hassler [25], was the first structure targeted by neuroablation, however it was soon recognized that Vc nucleus ablation was associated with significant deafferentation phenomena. The work of Mark *et al.* lead to the belief that targeting the medial thalamic nuclei was more effective in pain management [43]. Neuroablation nuclei targets in medial thalamotomy are; the centralis lateralis (CL), centrum medianum (CM), and parafascicularis (PF). These nuclei process nociceptive information, therefore, it is rational to assume that medial thalamotomy would be more effective as a treatment for nociceptive rather than neuropathic pain. However, in reality, several pain syndromes have successfully been treated by medial thalamotomy including: cancer pain, central and peripheral deafferentation pain, spinal cord injury, malignancy, arthritis, and the neurogenic pains associated with Parkinson's disease [2]. The overall success of medial thalamotomy as reported by Frank *et al*., in a comparison with mesencephalic tractotomy, was 52% [14], cancer pain was the main diagnosis treated. Two recent studies regarding medial thalamotomy by, Jeanmonod *et al*. [35] and Young *et al*. [83] who used radiofrequency and gamma knife, respectively reported a 60% success rate in achieving neurogenic pain control. The ideal target lying between the three main medial thalamic nuclei has yet to be determined, (the CM nucleus is the most frequently targeted).

From a technical stand point, stimulation of the medial nuclei does not usually produce a conscious or objective sensory response, lesioning does not induce sensory loss, and identifying cellular activity in the region of the medial thalamus for the purpose of guidance is not reported by all authors. Additionally, there is no consensus about whether this cellular activity is naturally occurring or due to thalamic deafferentation [71]. Reports in the literature regarding medial thalamotomy procedures are inconsistent in terms of the target, the guidance technique, the patient population, and the lesioning method used. Therefore, definitively describing the success of medial thalamotomy as a neuroablative procedure is difficult. However, the general perception is that the procedure is effective in treating nociceptive pain with recent data pointing to success with neuropathic pain. The procedure is safer than mesencephalic tractotomy and the ideal target has yet to be determined.

Stereotactic cingulotomy

The term cingulotomy refers to stereotactic lesioning of the anterior cingulate gyrus. The cingulate gyrus has been a target to treat pain since the 1950s when Le Beau performed an open cingulectomy to treat intractable pain [39]. It is thought that cingulotomy initiates relief by significantly altering the patient's emotional reaction to his/her painful situation by interruption of the limbic system Papez circuit [24] and by increasing tolerance to the subjective and emotional feelings of pain [12, 65]. This procedure is performed using standard stereotactic protocols, under general anesthesia. Bilateral lesions are usually performed in the anterior aspect of the cingulate gyrus, and the amount of cingulum destroyed is related to the procedure success rate [1] (Fig. 1). A suitable candidate for stereotactic cingulotomy is a terminally ill patient with wide spread metastatic disease that has spread into the musculoskeletal system, where administration of intrathecal or intraventricular opiates is difficult. Moreover, the presence of emotional factors accompanying the pain would favor a stereotactic cingulotomy procedure. Of note, stereotactic cingulotomy has been used by some authors to treat non-malignant pain with a success rate of approximately 25% [34]. Stereotactic cingulotomy involves ablation of sufficient anterior cingulate gyrus volume. This is usually achieved by producing at least two lesions using a wide surface area uninsulated tip electrode. The procedure is generally safe with few and minor side effects. In a relatively recent series with 12 patients, Pillay and Hassenbusch reported that 7 patients had satisfactory pain relief and 5 patients found it not useful [55]. Despite cingulotomy being a well established limbic system surgery for pain, the procedure is rarely used today, mainly due to the narrow indication, advances in medical management of terminal cancer patients, and the wide spread use of neuroaugmentative procedures.

Caudalis DREZ

The caudalis DREZ procedure was first reported by Siqueira with two patients [67]. Gorecki, Nashold and colleagues at Duke University [18, 19] pioneered the technique and introduced several indications. Open ablative brain and brain stem surgeries were largely abandoned following the introduction of stereotaxis in the 1960s. The caudalis DREZ procedure is intended to destroy the nucleus caudalis portion of the spinal trigeminal nucleus with the overlying trigeminal tract. The objective, similar to spinal DREZ surgery, is to destroy

the cells of second order neurons thought to function abnormally in deafferentation pain, and postherpetic neuralgia, thus achieving pain relief (Fig. 1). The caudalis DREZ procedure is valuable and effective in treating postherpetic neuralgia and modestly effective for anesthesia dolorosa. These two conditions are difficult to treat and in a situation, where either DBS or MCS are ineffective, caudalis DREZ represents a last resort for neuropathic facial pain otherwise nonresponsive to neuromodulation. Procedure outcomes are variable and potential risks include ataxia and motor neurological deficits.

Conclusions

Whether the approach to surgically treat pain is neuroaugmentative or neuroablative there is a paucity of consistent data defining absolute indications and benefits derived from any one procedure. The brain and brain stem as targets for pain treatment remain a second choice with the spinal cord the preferred target. Reversible non-destructive procedures are of course a first clinical choice but in certain situations neuroablation may be the only viable option.

References

1. Abdelaziz O, Cosgrove G (2002) Stereotactic cingulotomy for the treatment of chronic pain. In: Burchiel K (ed) Surgical management of pain. Thieme Medical Publishers Inc., New York, pp 812–820
2. Abosch A, Lozano A (2005) Stereotactic ablative procedures for pain relief. In: Fisher W, Burchiel K (eds) Seminars in neurosurgey pain management for the neurosurgeon: part 2/3, vol 2/3. Thieme Medical Publishers Inc., New York, pp 195–202
3. Adams JE, Hosobuchi Y, Fields HL (1974) Stimulation of internal capsule for relief of chronic pain. J Neurosurg 41: 740–744
4. Andy OJ (1980) Parafascicular-center median nuclei stimulation for intractable pain and dyskinesia (painful-dyskinesia). Appl Neurophysiol 43: 133–144
5. Atweh SF, Kuhar MJ (1977) Autoradiographic localization of opiate receptors in rat brain. II. The brain stem. Brain Res 129: 1–12
6. Barbera J, Barcia-Salorio JL, Broseta J (1979) Stereotaxic pontine spinothalamic tractotomy. Surg Neurol 11: 111–114
7. Brown JA, Barbaro NM (2003) Motor cortex stimulation for central and neuropathic pain: current status [see comment]. Pain 104: 431–435
8. Dickenson AH, Le Bars D (1983) Morphine microinjections into periaqueductal grey matter of the rat: effects on dorsal horn neuronal responses to C-fibre activity and diffuse noxious inhibitory controls. Life Sci 33 [Suppl 1]: 549–552
9. Ebel H, Rust D, Tronnier V, Boker D, Kunze S (1996) Chronic precentral stimulation in trigeminal neuropathic pain. Acta Neurochir (Wien) 138: 1300–1306
10. Fairman D (1973) Stereotactic hypothalamotomy for the alleviation of pain in malignant tumors. J Surg Oncol 5: 79–84
11. Fields HL, Adams JE (1974) Pain after cortical injury relieved by electrical stimulation of the internal capsule. Brain 97: 169–178
12. Foltz EL, White LE Jr (1962) Pain "relief" by frontal cingulumotomy. J Neurosurg 19: 89–100
13. Fraioli B, Guidetti B (1975) Effects of stereotactic lesions of the pulvinar and lateralis posterior nucleus on intractable pain and dyskinetic syndromes of man. Appl Neurophysiol 38: 23–30
14. Frank F, Fabrizi AP, Gaist G, Weigel K, Mundinger F (1987) Stereotactic mesencephalotomy versus multiple thalamotomies in the treatment of chronic cancer pain syndromes. Appl Neurophysiol 50: 314–318
15. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Bonnefoi F, Mauguiere F, Laurent B, Sindou M (1997) Positron emission tomography during motor cortex stimulation for pain control. Stereotact Funct Neurosurg 68: 141–148
16. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
17. Gerhart KD, Yezierski RP, Fang ZR, Willis WD (1983) Inhibition of primate spinothalamic tract neurons by stimulation in ventral posterior lateral (VPLc) thalamic nucleus: possible mechanisms. J Neurophysiol 49: 406–423
18. Gorecki JP, Nashold BS (1995) The Duke experience with the nucleus caudalis DREZ operation. Acta Neurochir Suppl 64: 128–131
19. Gorecki JP, Nashold BS Jr, Rubin L, Ovelmen-Levitt J (1995) The Duke experience with nucleus caudalis DREZ coagulation. Stereotact Funct Neurosurg 65: 111–116
20. Gybels J, Kupers R (2000) Brain stimulation in the management of persistent pain. In: Schmidek H (ed) Operative neurosurgical techniques. WB Saunders Philadelphia, pp 1639–1651
21. Hardy SG (1985) Analgesia elicited by prefrontal stimulation. Brain Res 339: 281–284
22. Hardy SG, Haigler HJ (1985) Prefrontal influences upon the midbrain: a possible route for pain modulation. Brain Res 339: 285–293
23. Hariz MI, Bergenheim AT (1995) Thalamic stereotaxis for chronic pain: ablative lesion or stimulation? Stereotact Funct Neurosurg 64: 47–55
24. Hassenbusch S (1996) Intracranial ablative procedures for pain. In: Youman J (ed) Neurological surgery. WB Saunders Philadelphia, pp 3541–3551
25. Hassler R, Riechert T (1959) Clinical and anatomical findings in stereotactic pain operations on the thalamus. Arch Psychiatr Nervenkr 200: 93–122
26. Heath R, Mickle W (1960) Evaluation of 7 years' experience with depth electrode studies in human patients. In: Ramey E, O'Doherty D (eds) Electrical studies in unanethetized brain. Harper & Brothers New York, pp 214–217
27. Herregodts P, Stadnik T, De Ridder F, D'Haens J (1995) Cortical stimulation for central neuropathic pain: 3-D surface MRI for easy determination of the motor cortex. Acta Neurochir Suppl 64: 132–135
28. Hitchcock E, Kim MC, Sotelo M (1985) Further experience in stereotactic pontine tractotomy. Appl Neurophysiol 48: 242–246
29. Hitchcock ER (1973) Stereotaxic pontine spinothalamic tractotomy. J Neurosurg 39: 746–752
30. Hosobuchi Y (1983) Combined electrical stimulation of the periaqueductal gray matter and sensory thalamus. Appl Neurophysiol 46: 112–115
31. Hosobuchi Y (1986) Subcortical electrical stimulation for control of intractable pain in humans. Report of 122 cases (1970–1984). J Neurosurg 64: 543–553

32. Hosobuchi Y, Adams JE, Linchitz R (1977) Pain relief by electrical stimulation of the central gray matter in humans and its reversal by naloxone. Science 197: 183–186
33. Hosobuchi Y, Adams JE, Rutkin B (1973) Chronic thalamic stimulation for the control of facial anesthesia dolorosa. Arch Neurol 29: 158–161
34. Hurt RW, Ballantine HT Jr (1974) Stereotactic anterior cingulate lesions for persistent pain: a report on 68 cases. Clin Neurosurg 21: 334–351
35. Jeanmonod D, Magnin M, Morel A (1993) Thalamus and neurogenic pain: physiological, anatomical and clinical data [erratum appears in Neuroreport 1993 (8): 1066]. Neuroreport 4: 475–478
36. Katayama Y, Tsubokawa T, Yamamoto T (1994) Chronic motor cortex stimulation for central deafferentation pain: experience with bulbar pain secondary to Wallenberg syndrome. Stereotact Funct Neurosurg 62: 295–299
37. Lazorthes Y, Sallerin B, Verdie J, Sol J (2002) Intrathecal and intracerebroventricular opioids: past uses and current indications. In: Burchiel K (ed) Surgical management of pain. Thieme Medical Publishers Inc., New York, pp 625–632
38. Lazorthes YR, Sallerin BA, Verdie JC (1995) Intracerebroventricular administration of morphine for control of irreducible cancer pain. Neurosurgery 37: 422–428; discussion 428–429
39. Le Beau J (1954) Anterior cingulectomy in man. J Neurosurg 11: 268–276
40. Leavens ME, Hill CS Jr, Cech DA, Weyland JB, Weston JS (1982) Intrathecal and intraventricular morphine for pain in cancer patients: initial study. J Neurosurg 56: 241–245
41. Lende RA, Kirsch WM, Druckman R (1971) Relief of facial pain after combined removal of precentral and postcentral cortex. J Neurosurg 34: 537–543
42. Levy RM, Lamb S, Adams JE (1987) Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. Neurosurgery 21: 885–893
43. Mark VH, Ervin FR, Yakovlev PI (1961) Correlation of pain relief, sensory loss, and anatomical lesion sites in pain patients treated with stereotactic thalamotomy. Trans Am Neurol Assoc 86: 86–90
44. Mazars G, Roge R, Mazars Y (1960) Results of the stimulation of the spinothalamic fasciculus and their bearing on the physiopathology of pain. Rev Prat 103: 136–138
45. Melzack R, Wall PD (1965) Pain mechanisms: a new theory. Science 150: 971–979
46. Meyerson BA (1980) Recent advances in neurosurgical treatment of chronic pain. Acta Neurol Scand Suppl 78: 15–23
47. Meyerson BA, Lindblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir Suppl 58: 150–153
48. Moricca G, Arcuri E, Moricca P (1981) Neuroadenolysis of the pituitary. Acta Anaesthesiol Belg 32: 87–99
49. Nandi D, Aziz TZ (2004) Deep brain stimulation in the management of neuropathic pain and multiple sclerosis tremor. J Clin Neurophysiol 21: 31–39
50. Nguyen JP, Keravel Y, Feve A, Uchiyama T, Cesaro P, Le Guerinel C, Pollin B (1997) Treatment of deafferentation pain by chronic stimulation of the motor cortex: report of a series of 20 cases. Acta Neurochir Suppl 68: 54–60
51. Nguyen JP, Lefaucheur JP, Le Guerinel C, Fontaine D, Nakano N, Sakka L, Eizenbaum JF, Pollin B, Keravel Y (2000) Treatment of central and neuropathic facial pain by chronic stimulation of the motor cortex: value of neuronavigation guidance systems for the localization of the motor cortex. Neurochirurgie 46: 483–491
52. Niizuma H, Kwak R, Ikeda S, Ohyama H, Suzuki J, Saso S (1982) Follow-up results of centromedian thalamotomy for central pain. Appl Neurophysiol 45: 324–325
53. Penfield W, Jasper H (1954) Epilepsy and the functional anatomy of the human brain. Little, Brown Boston
54. Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguiere F, Laurent B (1995) Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain 62: 275–286
55. Pillay PK, Hassenbusch SJ (1992) Bilateral MRI-guided stereotactic cingulotomy for intractable pain. Stereotact Funct Neurosurg 59: 33–38
56. Pool J, Clark W, Hudson P, Lombardo M (1956) Hypothalamic-hypophyseal interrelationships. Charles C Thomas Springfield
57. Pool JL (1954) Psychosurgery in older people. J Am Geriatr Soc 2: 456–466
58. Rainov NG, Fels C, Heidecke V, Burkert W (1997) Epidural electrical stimulation of the motor cortex in patients with facial neuralgia. Clin Neurol Neurosurg 99: 205–209
59. Reynolds DV (1969) Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science 164: 444–445
60. Rezai A, Lozano A (2002) Deep brain stimulation for chronic pain. In: Burchiel K (ed) Surgical management of pain. Thieme Medical Publishers Inc., New York, pp 565–576
61. Richardson DE, Akil H (1977) Pain reduction by electrical brain stimulation in man. Part 1: Acute administration in periaqueductal and periventricular sites. J Neurosurg 47: 178–183
62. Richardson DE, Akil H (1977) Pain reduction by electrical brain stimulation in man. Part 2: Chronic self-administration in the periventricular gray matter. J Neurosurg 47: 184–194
63. Roux FE, Ibarrola D, Tremoulet M, Lazorthes Y, Henry P, Sol JC, Berry I (2001) Methodological and technical issues for integrating functional magnetic resonance imaging data in a neuronavigational system. Neurosurgery 49: 1145–1156; discussion 1156–1147
64. Sano K, Sekino H, Hashimoto I, Amano K, Sugiyama H (1975) Posteromedial hypothalamotomy in the treatment of tractable pain. Confin Neurol 37: 285–290
65. Sharma T (1973) Absence of cognitive deficits from bilateral cingulotomy for intractable pain in humans. Tex Med 69: 79–82
66. Siegfried J (1991) Therapeutical neurostimulation – indications reconsidered. Acta Neurochir Suppl 52: 112–117
67. Siqueira JM (1985) A method for bulbospinal trigeminal nucleotomy in the treatment of facial deafferentation pain. Appl Neurophysiol 48: 277–280
68. Sjogvist O (1938) Studies on pain conduction in the trigeminal nerve. A contribution to the surgical treatment of facial pain. Acta Psychiatr Neural Scand Suppl XVII. Mercators Tryckeri Helsingfors, pp 93–122
69. Spiegel EA, Wycis H (1949) Pallidothalamotomy in chorea. Philadelphia Neurological Society
70. Spiegel EA, Wycis HT (1953) Mesencephalotomy in treatment of intractable facial pain. AMA Arch Neurol Psychiatry 69: 1–13
71. Tasker R (2002) Stereotactic medial thalamotomy for chronic pain: is it an effective procedure? In: Burchiel K (ed) Surgical management of Pain. Thieme Medical Publishers Inc., New York, pp 805–811
72. Tasker RR (1994) The recurrence of pain after neurosurgical procedures. Qual Life Res 3 Suppl 1: S43–S49
73. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl 52: 137–139
74. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
75. Tsubokawa T, Yamamoto T, Katayama Y, Moriyasu N (1982) Clinical results and physiological basis of thalamic relay nucleus

stimulation for relief of intractable pain with morphine tolerance. Appl Neurophysiol 45: 143–155
76. White J, Sweet W (1955) Pain: its mechanisms and neurosurgical control. Charles C Thomas, Springfield
77. Whittle IR, Jenkinson JL (1995) CT-guided stereotactic anteromedial pulvinotomy and centromedian-parafascicular thalamotomy for intractable malignant pain. Br J Neurosurg 9: 195–200
78. Whitworth L, Fernandez J, Feler C (2005) Deep brain stimulation for chronic pain. In: Fisher W, Burchiel K (eds) Seminars in neurosurgey pain management for the neurosurgeon: part 2/3. Thieme, New York, pp 183–193
79. Wilkins R (1999) Historical overview of surgical techniques for trigeminal neuralgia. Techniques Neurosurg 15: 202–217
80. Winter A (1972) Depression and intractable pain treated by modified prefrontal lobotomy. J Med Soc N J 69: 757–759
81. Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T (1997) Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy [see comment]. Pain 72: 5–12
82. Yoshii N, Fukuda S (1976) Several clinical aspects of thalamic pulvinotomy. Appl Neurophysiol 39: 162–164
83. Young RF, Jacques DS, Rand RW, Copcutt BC, Vermeulen SS, Posewitz AE (1995) Technique of stereotactic medial thalamotomy with the Leksell Gamma Knife for treatment of chronic pain. Neurol Res 17: 59–65

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Extradural cortical stimulation for central pain

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Summary

Central pain results from a central nervous system injury and represents a challenge for the pain therapist. Human studies have shown that motor cortex stimulation (MCS), i.e. the placement of a stimulating plate on the dura overlying the motor cortex can relieve brain central pain. Studies suggest that MCS directly affects activity in the first and second order somatosensory areas, thalamic nuclei and also inhibits spinal primary afferents and spinothalamic tract neurons. The following factors have been found to predict analgesia by MCS: intact or almost intact corticospinal motor function, mild or negligible sensory loss, absence of thermal sensory threshold alteration within the painful area, positive response to the barbiturate and/or ketamine test, positive response to the propofol test, positive response to transcranial magnetic stimulation (TMS). The targeting of the cortical area is made by anatomical localization by computed tomography (CT), magnetic resonance imaging (MRI), neuronavigation, intraoperative neurophysiological recordings, functional MRI (fMRI), and intraoperative clinical assessment. We perform the procedure under local anaesthesia. We describe in detail our surgical technique and stimulation protocol. Furthermore, we review the most important studies with respect to their results, the observed side effects and complications. The future prospects and likely developments of MCS for central pain are also discussed.

Keywords: Neuromodulation; motor cortex stimulation; central pain; neuronavigation; MCS.

Introduction

Central pain (CP), i.e. pain following central nervous system injury, represents a challenge for the pain therapist. However, progress has been made recently in this field [2, 5, 10, 14]. Among the most effective recent additions is extradural cortical stimulation (CS), in which a stimulating paddle is positioned on the dura overlying the cortex in order to apply motor (MCS) or sensory (SCS) cortical stimulation.

Historical note

In 1989, Tsubokawa's group in Japan first reported that positioning of a stimulating plate on the dura overlying the motor cortex (Brodmann's area 4), i.e. motor cortex stimulation (MCS), could relieve brain central pain [31]. In 1993, Meyerson's group reported extradural cortical stimulation effects in patients with neuropathic peripheral pain [8] and in 1995, we introduced the propofol test [3] and proved, contrary to current belief, that stimulation of the first somatosensory area (SI) (Brodmann's areas 3,1,2) can have analgesic effects [4]. MCS gained wide acceptance and several hundred patients have been implanted with extradurally stimulating electrodes up to now [6, 8, 10, 11].

Mechanism of action

The analgesic effect of CS appears to have a somatotopic organization. Animal studies suggest that MCS directly affects activity in the first and second somatosensory areas (SI and SII), several thalamic (specific and non-specific), hypothalamic and brainstem nuclei and inhibits spinal primary afferents and spinothalamic tract neurons. In particular, the thalamic sensory nuclei both receive and project to the first motor area (MI) [23]; in man, MI may be activated by painful stimuli [16]. According to Tsubokawa's original view, there is a highly organized set of reciprocal connections between the motor cortex and the sensory cortex, which appear to carry primarily nonnoxious information. MCS activates non-nociceptive neurons in SI selectively, either through orthodromic activation of neuronal chains to SI or antidromic activation of axons projecting from SI. This nonnoxious stimulation activates surround inhibition in SI that quenches hyperactivity of nociceptive cells. In contrast, postcentral stimulation produces nonselective activation of all elements within the sensory cortex including the hyperactive nociceptive neurons. This theory

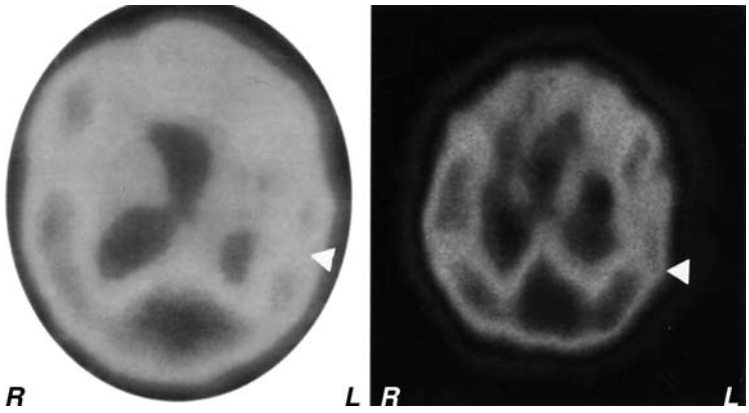

Fig. 1. SPECT pre- (*left*) and post-cortical stimulation (*right*) showing renormalization of SI rCBF

is disproven by the fact that SI stimulation can have analgesic effects [8] and Tsubokawa later rejected his original idea. Recently, a study concluded that MCS acts by reducing neuronal hyperactivity interfering with sensory processing and thus, relieves both pain and sensory discrimination. MCS reinforces the control of non-nociceptive sensory inputs on nociceptive systems, at least when these sensory afferents are partially preserved (implying that lemniscal fibers inhibit spinothalamic tract (STT) fibers) [15]. However, a patient was described by the Lyon group (see patient 1 in Ref. [8]) who had clearly abnormal lemniscal somatosensory evoked potentials (SEPs) and was relieved by MCS; this implies that a normal lemniscal system is not required to obtain good MCS results.

Cortical stimulation changes local cortical SI-MI and thalamic rCBF [4, 7, 32], even bilaterally [28] (Figs. 1, 2). It is known that a relatively high stimulation frequency can induce a tonic depolarization and cortical inactivation effect, which is known to inhibit thalamic relays. We argue that MCS may act locally by modulating the MI/SI dipole and a long thalamocortical reverberating loop, resetting disrupted oscillation and/or temporal synchronization [2, 4]. Tsubokawa and colleagues noted that 3 of 38 patients who were submitted to either thalamic or motor cortex stimulation became pain-free without stimulation for at least 2 years; after that, they obtained excellent pain relief and the intervals between intermittent stimulation increased progressively [33]. They concluded that brain stimulation appears to cause reorganization of neural circuits in the SI cortex, which sometimes can suppress or alleviate CP. Some authors believe that MCS does not act at cortical levels below the electrode, but through descending axons; in 1974, Adams stimulated pyramidal fibers in the internal capsule to relieve human pain.

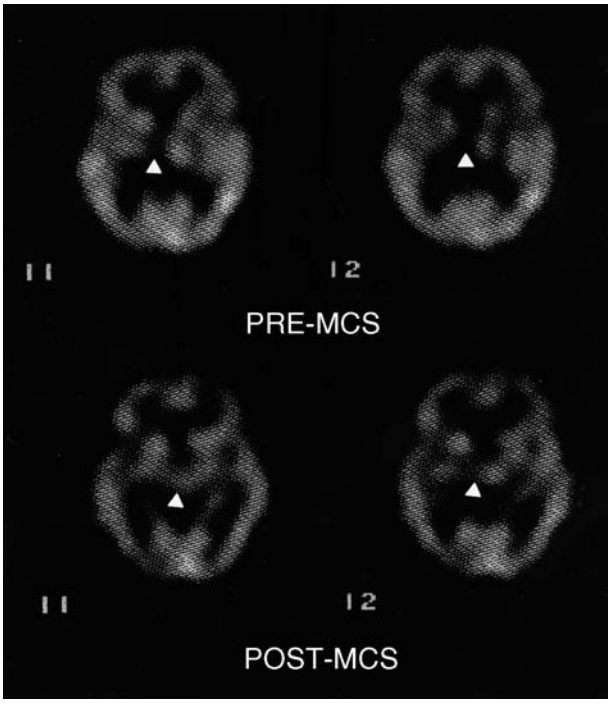

Fig. 2. SPECT pre- (*top*) and post-cortical (*bottom*) stimulation showing renormalization of thalamic rCBF

Prognostic factors

The following factors have been found to predict analgesia by CS:

1) intact or almost intact corticospinal motor function [20],
2) mild or no sensory loss, and in particular absence of thermal sensory threshold alteration within the painful area [15],
3) positive response to the barbiturate and/or ketamine test [36],
4) positive response to the propofol test [3, 12, 22],
5) positive response to transcranial magnetic stimulation (TMS) [6, 9, 10, 13].

Currently, criteria 1–3 are no longer considered reliable. Most importantly, patients suffering from CP can be categorized according to drug susceptibility. It seems that responsiveness to GABA distinguishes groups that are likely to have a favorable response to stimulation (Class A central pain) [5, 10, 23]. Patients with thalamic stroke may experience more pronounced benefit than patients with suprathalamic strokes [36].

Targeting of the cortical area

The rolandic fissure is generally localized externally by using the Taylor-Haughton lines, although both MI and SI gyri have a variable position and configuration. Because of interindividual variability of cortical anatomy, individual anatomic maps must be created for each patient. To overcome inconsistencies in electrode placement, both anatomic and functional techniques for localization of MI have been explored. The most useful are described below.

Anatomical localisation by computed tomography (CT), magnetic resonance imaging (MRI) and neuronavigation

Several anatomical methods on imaging modalities such as CT or MR have been established to detect the central sulcus (CS) (lateral axial, medial axial, lateral sagittal, midline sagittal). In all of them, the CS is defined in relation to other anatomical structures, assuming that these landmarks can be identified reliably. Unfortunately, the interobserver agreement is not absolute [1, 18]. At the superior axial levels of the brain, the precentral sulcus can be easily identified as the sulcus forms a right angle with the superior frontal sulcus. The next posterior sulcus is the CS. On these reconstructions, the central, sylvian, interhemispheric, superior and inferior frontal sulci can be clearly identified. The arm area is about 2 cm in length, having the upper limit of 5 cm above the lateral sulcus (sylvian); the hand area is found at the intersection between the precentral gyrus and the superior frontal sulcus or between the superior and inferior frontal sulci. The face is found 3 cm above the lateral sulcus (sylvian) and does not exceed the inferior frontal sulcus. The neck and nape are slightly above the inferior frontal sulcus (between the arm and leg area). The pelvis-thorax area is small and slightly above the superior frontal sulcus. The leg area is usually found in the medial surface of the hemisphere, but this area can extend largely onto the lateral aspect of the hemisphere in 30–40% of the patients, and in some it can be restricted to the lateral surface only.

Imaging data have been uploaded onto neuronavigation systems for guidance and reformatted for integration in the radiological atlas of Talairach and Tournoux. Several techniques have been explored; these are based on either triaxial images lacking true 3-D visualization, on surface-rendered 3-D images [17] or on volumetric image rendering that facilitates true 3-D gyral visualization of the cortical anatomy through opacity modulation, thus allowing for visualization of electrode orientation according to the twisted shape of the precentral gyrus. Current image guidance systems can integrate preoperatively generated functional data derived from functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) [24]. Despite their undoubted esthetic and technological appeal, we find that simple paramagnetic skin fiducials and their positioning in the MR suite under imaging conditions is usually equally adequate. In fact, neuronavigation appears to add little in terms of better results [25, 35].

Localisation by intraoperative neurophysiological recordings

Intraoperative epidural cortical mapping of MI-SI, including recording of sensory evoked potentials (SEPs) and bipolar epidural stimulation, is considered the most accurate method to localize the central sulcus (CS) and the cortical area to be stimulated. Experience, however, shows otherwise; cortical mapping with intracranial SEP is frequently compromised and sometimes impossible to obtain because of electrical artifacts, anesthesia, somatosensory wave attenuation, diffuse responses, or sensorimotor disconnection as a result of paraplegia or amputation. Under SEP guidance, the contacts record a negative wave (N20) over the sensory cortex and a positive wave (P20) over the motor cortex 20 msecs after the stimulation of the trigeminal, median or posterior tibial nerve. The position of the central sulcus is confirmed when an inversion of this wave is observed between two adjacent contacts. However, N20 is not always recordable, even in awake or mildly sedated patients, or can be severely attenuated by the CNS lesion causing central pain; furthermore, the wave reversal is often inaccurate, in particular, but not exclusively, when the part of the gyrus representing the face or leg is searched for. Considerable experience is required and usually the surgical procedure is unnecessarily prolonged.

Other authors use, as a guide, muscle contraction plus electromyogram (EMG) recordings in response to bipolar stimulation, but this may be either not elicited even after extensive attempts to determine appropriate stimulation sites (both in the awake state and more frequently under general anesthesia), or be difficult to interpret. Moreover, motor effects can be obtained by stimulation applied anteriorly as well as posteriorly to the central sulcus, and large zones of both MI and SI are able to give identical motor responses after stimulation [26]. Lower-threshold EMG activation usually is attained with the anode located inferior to the target and cathode superior and parallel to the central sulcus. If performed epidurally under general anesthesia, stimulation intensity of more than 15 mA is often required and yields diffused peripheral responses, especially in plegic or amputated patients. Electrical artifacts from the operating room environment can also be a problem. Some authors temporarily implant a subdural multipolar (16–40 contacts) electrode grid in order to explore a wider cortical field in search for an analgesic location; the cortical map obtained by recording SEP through the plate electrode placed at different locations on the dural surface over the CS region, instead of using a large grid, is just as useful. Despite extensive in-depth assessment, there are patients who draw no benefit, others who draw benefit only from stimulation of a very restricted area and others still in whom the effective area is wide. Finally, the results from these different methods for localizing the CS, even when repeated, do not often match precisely. Therefore, the target defined for cortical stimulation may be unreliable or ambiguous in a sizable proportion of cases.

Localisation by intraoperative clinical assessment

Intraoperative clinical assessment of the awake patient helps to increase precision of the electrode placement. However, under the stressful situation of being subjected to surgery, a patient is rarely capable to report on the intensity of pain. Moreover, waiting for an analgesic effect takes minutes and is time consuming and essentialy useless.

Localisation by functional MRI (fMRI)

Functional MR (fMR) has been explored extensively in terms of functional localization and appears to be superior to the competing methods described above [27–30]; in particular, correspondence between contours of fMR activation areas and results from cortical mapping is high (94%), with a mean interdistance between targets defined by both techniques of 4 mm; considering that an electrode has an activation area of 5 mm, this is accurate enough. fMRI examinations depend on the affected body region and include repetitive contraction of the lips, cyclic finger tapping of the contralateral hand, or flexion-and-extension of the toes of the contralateral foot at a rate of 1 Hz after a training session before image acquisition. Blocks of 30 secs alternating activation and rest are repeated a few times. Generally, a focal cortical activation area (diameter 5–10 mm) after hand motor tasks is localized to contralateral MI, but differences in surface and minor displacement of the precentral activation area between both sides are frequently observed. The central sulcus veins are a more stable landmark than the parenchymal motor hand area found with fMR; however, these veins are found deep in the sulcus and are not recognizable by inspecting the cortical surface. fMRI is particularly useful in amputees or plexus avulsion patients; mental and virtual movements of the missing or paralytic limb easily induce contralateral SI/MI activations. Unfortunately, fMRI suffers from certain limitations: 1) lack of cooperation from some patients, requiring repeat scanning, 2) activation areas vary dramatically with different task paradigms and thresholding, 3) weak sensitivity, 4) incompletely understood principles of the blood oxygenation level dependence, 5) false activation foci from large draining veins or aberrant blood vessel anatomy, 6) contamination from motion artifacts, 7) unstandardized activation protocols, 8) intrinsic distortion of echo planar images, and 9) difficulty in detecting cortical activity down in the sulci and fissures.

In summary, the accuracy of neuronavigational methodologies using integrated fMRI depends heavily on the protocols for fMRI data acquisition and its subsequent analysis.The image fusion and the registration of fMRI data in navigation software are sources of potential inaccuracy and functional mislocalization; overall reliability depends on the precision of registration with anatomic images, the signal processing during the fMRI study, the significance of the functional activation signals and the deviation during the image-fusion studies. Thus, detection of the exact borders of fMRI activation has all the artifacts and errors of stereotactic localization. In light of this, we conclude that integrated neuronavigation is not infallible, and, based on a comparison of published series, it does not improve the results in a clear-cut fashion. Anatomic MRI based approaches are sufficient

after considering the degree of somatotopic precision that may be required. MR axonography may also be valuable [19]. Cortical thermography is indicated for subdural approaches [34].

Surgical technique

All patients undergo a preoperative (MRI/fMRI) study after placement of fiducial paramagnetic markers on the skin along the CS projection obtained from the Haughton-Taylor lines. The outline of the incision is adjusted in the scanner until the fiducial and the identified CS match. Local anesthesia should always be employed; during intraoperative stimulation, the intensity can be kept lower than under general anesthesia reducing the risk of epileptic fits. We never fix the patient's head in a Mayfield clamp, as we find this useless; if well positioned, the patients generally stay still during the whole procedure (approximately 45 min). We make an oblique linear skin incision (6–10 cm) parallel to and 1 cm ahead of or behind the projection of the central sulcus and then drill two burr holes at a distance of 2–4 cm. An 4-electrode plate is inserted from the edge of one burr hole into the epidural space overlying the contralateral MI or SI of the painful area. The bony bridge between the two holes will hold the plate in place. Some authors prefer to place the stimulator perpendicular – or almost so – to the rolandic fissure, for its supposed improved selectivity, but results appear not to differ between these two approaches. A few place the grid directly into the central sulcus subdurally; however, this is more invasive and its superiority to epidural procedures is doubtful. If a flap craniotomy ($4–5 \times 4–5$ cm) is chosen, the electrode is fixed to the outer layer of the dura with two stitches and the dura is stretched to avoid an extradural clot. A few authors place a second electrode subdurally over the medial aspect of the precentral cortex to cover the leg area and a dual stimulating device in cases of hemisoma pain. Intraoperative bipolar stimulation is performed until satisfactory motor or sensory responses are obtained; if no response is observed, the plate is left on the site of the original projection. We never employ EMG recordings or SEPs. For facial or leg pain, targeting of the hand area may be used and an approach to the motor area of the face or the foot, by displacing the electrode caudally by 20 mm or rostrally by 20 mm along the CS. Although considered a best guess, studies show an acceptable correspondence between this method and fMRI targeting. At the same time, repositioning under neuronavigation is also ''blind'' and approximate, as the navigator probe does not see the actual poles during surgery. The electrode array is then connected to an extension lead that is tunneled externally, and connected to an external stimulus generator worn by the patient. If analgesia is obtained after a test period (days to several weeks), a pulse generator is pocketed subclavicularly and connected with the stimulating plate via a percutaneously implanted cable (Fig. 3).

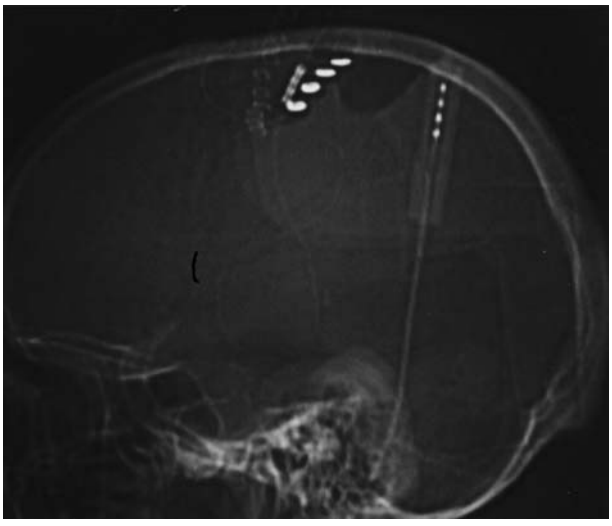

Fig. 3. Radiograph showing a motor cortex stimulator in place. A posterior craniectomy is seen where a parietal cortical stimulator had previously provided a similar degree of analgesia

Stimulation protocol

As each patient appears to be different, only general indications are possible [8, 11]. The stimulating electrode is placed at a site eliciting muscle contraction of the painful area with the lowest threshold. Motor contractions are obtained at 1–2 Hz and 400–800 msecs with bipolar stimulation at increasing voltage; analgesia, when seen, always occurs below motor threshold. Chronic stimulation usually exploits the following ranges: monophasic stimulation, 25–60 Hz (but it may be more or less), 60–200 msecs (max. 450), 1–4 V (max. 10 in atrophic brains), bipolar stimulation (negative pole over selected area of MI, positive pole over other area of MI or SI), electrode coupling depending on spatial pain extent, with a 0/3 pairing for extensive coverage, cyclical (ON: minutes-hours, OFF: same or more, stimulator switched on or off at night) or continuous mode and mean impedance 900–1200 ohms. Increasing voltage can increase analgesia at the expense of intolerable sensory effects. Anodal, instead of cathodal, stimulation might work best for MCS. It is possible that impedance

increases over time, requiring voltage adjustment. In some patients, pain can be relieved or improved almost immediately during intraoperative stimulation for periods ranging from several minutes to hours to days (about 3) without further stimulation. For instance, one patient reported more than 24 hour-long analgesia after 4 h of continuous stimulation. This so-called posteffect (which is also seen after propofol infusion) may influence the choice of stimulation parameters, but it has a tendency to abate over time, and by the second month it may stabilize at several minutes to a few hours. It is a common experience that optimal pain relief is often achieved at an interelectrode distance of 30 mm. Actually, this wide internodal bipolar stimulation is similar to monopolar stimulation and activates corticospinal tract neurons that originate from deep layers and extend perpendicular to the cortex. Thus, precise, somatotopic localization of the electrode may not be required after all. In several patients, analgesia fades over time (perhaps due to tolerance or fatigue); in some cases, the benefit may be restored by repositioning the electrode or by intensive reprogramming of parameters. In others, removal of the epidural scar may be necessary to restore the benefit.

Results

The analgesic effect of MCS appears to have a somatotopic organization and best results are usually seen when the stimulating poles overlie parts of cortex corresponding to painful body parts. Finding the appropriate target area – not necessarily BA4 – appears to be the key to successful stimulation; almost 1 out of 5 patients may have to undergo repositioning, because of inaccurate electrode positioning. However, variability of results is more often due to poor patient selection and inadequate electrical field activation than related to difficulty in identifying the appropriate target area. The assessment of results at follow-up periods shorter than at least 1 year is of limited relevance. The most important article providing conclusive evidence about the role of electrical neurostimulation for CP is that of Katayama and colleagues [21]. These authors analyzed a series of 45 patients with central poststroke pain (CPSP), all tested with percutaneous SCS. Satisfactory analgesia was set at $\geq$60% reduction on Visual Analogue Scale (VAS) scale. In the long-term, only 7% achieved satisfactory analgesia. Of the remaining 42, 12 underwent Vc deep brain stimulation (DBS) (in 7 also of IC and/or medial lemniscus) and 25% obtained satisfactory relief in the long term; 31 patients in whom spinal cord stimulation (SCS) was ineffective underwent MCS (1 underwent both MCS and Vc DBS) and 48% obtained long-term relief. In particular, 9% thalamic-infrathalamic and 0% suprathalamic, 0% suprathalamic and 30% thalamic-infrathalamic and 33% suprathalamic and 52% thalamic-infrathalamic cases obtained long-term relief from respectively SCS, DBS and MCS. The success rate of stimulation techniques, particularly MCS, is also appreciably better than that of destructive procedures. Globally, half (or more according to some estimates) of central pain patients benefit at 4 years follow-up (see Table 1).

Physiological effects of stimulation

MCS does not generally induce any motor activation, even at high voltage, or any sensory phenomena in most patients. Thus, blinded, controlled studies are feasible. The conclusion is that cortical stimulation does not act through a placebo effect. In some patients, a sensation of tingling or mild vibration projected to the same area of the pain distribution could be induced by MCS at intensities below the threshold for muscle contraction. Similar paresthesias may be induced in some patients in whom moderate or severe weakness is present and muscle contraction is not inducible on MCS. Some of these patients report paresthesias even with low-frequency or single-pulse stimulation such as that used intraoperatively, unlike patients without pain, suggesting plastic changes in MI and not SI activation. Satisfactory analgesia may be achieved without stimulation-induced paresthesias in some patients, whereas stimulation-induced paresthesias may be obtained without satisfactory analgesia in others. SI stimulation may be accompanied by paresthesias. In 12 Japanese patients, high-frequency stimulation of SI exacerbated the central pain while SI stimulation is in fact as analgesic as MCS, particularly in GABA responsive patients. In three patients, MCS at an intensity higher than 3 mA, induced dysesthesias appearing right from the start of stimulation and resolving after the stimulator was stopped (see review in [8, 10]).

Side effects and complications

Complications with cortical stimulation are minimal (less than 1%). These include extradural or subdural clots generally without sequelae, few system failures, wound dehiscence and infections requiring temporary system explantation [8]. MCS can occasionally induce

Table 1. *Results of motor cortex stimulation (MCS) in central pain (CP)*

Pain syndrome	Number of patients	% of pts with excellent/good pain relief	Follow-up	Other findings	References (sorted by date)
''Deafferentation pain secondary to lesions within the CNS'' [1]	25 [1] 7 [2] 12 [3] 11 [4]	100% [2, 21, 46C, 49E] 85% [17i] ≈75% [1, 4, 6a, 8∗c, 14i, 27, 29§, 30§, 33§, 34§, 40]	>7 mos. [1] >1 yr [3] 2 yr [4] 4 mos. [5]	first report of MCS for CP [1] stimulation of ipsilateral BA 4 effective [4, 20] SI-SII stimulation effective [13, 15, 19]	[1] Tsubokawa *et al.* Pain 1990; Suppl 5: S491 (abs.952) [2] Tsubokawa *et al.* Pacing Clin Electrophysiol 1991; 14: 131–134 [3] Tsubokawa *et al.* Acta Neurochir Suppl (Wien) 1991; 52: 137–139 [4] Tsubokawa *et al.* J Neurosurg 1993; 78: 393–401 [5] Katayama *et al.* Stereotact Funct Neurosurg 1994; 62: 295–299 [6] Yamamoto *et al.* Pain 1997; 72: 5–12 [7] Katayama *et al.* Stereotact Funct Neurosurg 1997; 69: 73–79 [8] Katayama *et al.* J Neurosurg 1998; 89: 585–591 [9] Katayama *et al.* Stereotact Funct Neurosurg 2001; 77: 159–162 [10] Katayama *et al.* Stereotact Funct Neurosurg 2001; 77: 183–186 [11] Fukaya *et al.* Neurol Res 2003; 25: 153–156 [12] Katayama *et al.* Acta Neurochir Suppl. 2003; 87: 121–123 [13] Canavero and Bonicalzi. J Neurosurg 1995; 83: 1117; [14] Canavero *et al.* J Neurosurg 1999; 91: 121–123; [15] Canavero and Bonicalzi. Clin J Pain 2002; 18: 48–55 [16] Migita *et al.* Neurosurgery 1995; 36: 1037–1040 [17] Fuji *et al.* No Shinkei Geka. 1997; 25: 315–319 [18] Saitoh *et al.* J Neurosurg 2000; 92: 150–155 [19] Kuroda *et al.* Stereotact Funct Neurosurg 2000; 74: 226 [20] Saitoh *et al.* Acta Neurochir Suppl. 2003; 87: 149–152 [21] Saitoh *et al.* J Neurosurg 2004; 100: 935–939 [22] Tani *et al.* J Neurosurg. 2004; 101[4]: 687–689 [23] Parrent and Tasker. Acta Neurochir (Wien) 1992; 117: 89 [24] Hosobuchi Stereotact Funct Neurosurg 1992; 59: 76–83 [25] Henderson *et al.* Stereotact Funct Neurosurg. 2004; 82(5–6): 207–213 [26] Brown and Pilitsis. Neurosurgery. 2005; 56(2): 290–297 [27] Peyron *et al.* Pain 1995; 62: 275–286 [28] Nguyen *et al.* Acta Neurochir Suppl (Wien) 1997; 68: 54–60 [29] Garcia-Larrea *et al.* Stereotact Funct Neurosurg 1997; 68: 141–148
Thalamic pain [2, 17, 18, 42]	6 [5] 39 [6§] 42 [7b] 31 [8§) .. [9d]	≈65% [3, 5, 32§, 35§, 37§, 44, 47D, 47]	1 yr [6] ≥2 yrs [8] 2 yrs [13] 5 wks [14]	pain relief at stimulus intensities below movements treshold [3, 15]	
CP (thalamic and extrathalamic lesions) [3, 4, 6–11, 13–16, 19–21, 23–25, 27–31, 33–39, 41, 43–49]	45 [10] 31 [11§] 2 [13] 1 [14] 8 [15] 2 [16] 7 [17] 8 [18] 1 [19] 19 [20]	≈45–50% [4∗, 5, 6∗, 8∗c, 10e, 12g, 16m, 18o, 20q, 29§, 36§, 38∗, 39, 40∗, 42∗, 45] ≈40% [13h, 15l, 31§]	4 yrs [15] 1 yr [16] 1–3 mos [17]	almost immediate pain relieving effect [2, 15, 47] (One week) test period [4, 6, 17] fair and poor responders not implanted [4, 17] effective in ketamine (K)/thyiamylal (T) sensitive & morphine resistant pts [3, 4, 6, 16, 20]	
Lateral medullary infarct [5, 8, 13, 26]	1 [21] 1 [22] 1 [23r]	<40%[9d, 15l, 17∗n, 28u29§, 33§, 34§, 36∗§, 37§, 39∗, 48]	17 mos [18] <1 yr [24]	(un)effective in propofol (in)sensitive pts [13, 14, 39, 45]	
SCI [22, 28, 30, 33–35, 37]	2 [24] 1 [25s] 1 [26t] 2 [27] 12 [28] 6 [29§v] 18 [30§w] 7 [31§x] 20 [32§z] 16 [33§y] 16 [34§y] 27 [35§z] 8 [36§] 13 [37§A] 6 [38] 6 [39] 3 [41] 2 [42] 1 [43] 1 [44] 3 [45] 5 [46] 9 [47D] 1 [48] 4 [49]	0% [11f, 13h, 16m, 19p, 26t, 41B, 43] ref.35: 70–99% pain relief: 3pts 40–69% pain relief: 10pts 0–39% pain relief: 14pts	9 wks–22 mos. [27] 3–50 mos. [30] 2–6 mos [31] 12–74 mos [32] 27 mos. [33] 27 mos [34] 2–104 mos [35] 3 wks–31 mos [38] 2 wks 4 yrs [39] 2 yrs [44] 4–60 mos [47] 4–60 mos [48] 6–40 mos [49]	intermittent stimulation effective [2, 8, 22] tests with phentolamine, lidocaine, ketamine, thiopental, (morphine), placebo [18, 20, 22] no correlation between tests results and MCS effectiveness [18, 22] nonpainful paresthesias unrelieved [4] no seizures at therapeutic level [3, 34] stimulation of areas rostral to MI ineffective [4] high frequency postcentral stimulation ineffective or pain worsening [4, 10] increase in cortical and/or thalamic rCBF [2, 21, 29] increase in skin temperature (painful zones) [2] MCS more effective than thalamic stimulation [1, 5] bilateral stimulation effective [22] unsuccessful previous DBS or SCS [5, 8, 28, 38] gradual effect reduction [4, 13, 15, 28, 30, 34, 36, 42] reappearance of analgesia after electrode repositioning [3, 30, 34] long-term analgesia without stimulation [8, 9, 27, 39] abnormal pain sensations [11]	

(*continued*)

Table 1 (*continued*)

Pain syndrome	Number of patients	% of pts with excellent/good pain relief	Follow-up	Other findings	References (sorted by date)
				experience of supernumerary painful phantom arm [14] adverse cognitive effects [36] no prognostic sign found, 10–39% relief may be acceptable for some patients [35	[30] Nguyen *et al.* Pain 1999; 82: 245–251 [31] Garcia-Larrea *et al.* Pain 1999; 83: 259–273 [32] Mertens *et al.* Stereotact Funct Neurosurg 1999; 73: 122–125 [33] Nguyen *et al.* Neurochirurgie 2000; 46: 483–491 [34] Nguyen *et al.* Arch Med Res 2000; 31: 263–265 [35] Nuti *et al.* Pain 118: 43–52, 2005 [36] Montes *et al.* Neurophysiol Clin 2002; 32: 313–325 [37] Drouot *et al.* Brain 2002; 125: 1660–1664 [38] Carroll *et al.* Pain 2000; 84: 431–437 [39] Nandi *et al.* J Clin Neurosci 2002; 9: 557–561 [40] Nandi and Aziz. J Clin Neurophysiol 2004; 21: 31–39 [41] Meyerson *et al.* Acta Neurochir Suppl (Wien) 1993; 58: 150–153 [42] Herregodts *et al.* Acta Neurochir Suppl (Wien) 1995; 64: 132–135 [43] Barraquer-Bordas *et al.* Rev Neurol 1999; 29(11): 1044–1048 [44] Franzini *et al.* J Neurosurg 2000; 93: 873–875 [45] Franzini *et al.* Neurol Res 2003; 25: 123–126 [46] Tirakotai *et al.* Minim Invasive Neurosurg 2004; 47(5): 273–277 [47] Pirotte *et al.* Neurosurgery 2005; 56(2 Suppl): 344–359 [48] Slawek *et al.* Neurol Neurochir Pol 2005; 39(3): 237–240 [49] Gharabaghi *et al.* Neurosurgery 2005; 57(1 Suppl): 114–120

* Long-term results; § pts also reported elsewhere or duplicate paper.

[a] Excellent/good results in 71% of T+ or K+ and M− pts, in 50% of T+ or K+ and M+ pts, in 13% of T− and K− and M− pts and 0% of T− and K− and M+ pts; [b] Study on MCS effects on post-stroke involuntary and voluntary movement disorders during stimulation for pain control.; [c] excellent/good results in 72% of pts with no or mild motor weakness, 15% of pts with moderate or severe motor weakness, 70% of pts with inducible muscle contractions, 9% of pts without inducible motor contractions (difference statistically significant). No relationship between pain control and presence of hypesthesia, dysesthesia, hyperpathia, allodynia or disappearance of SSEP N20 wave plus stimulation-induced paresthesias, or motor performance improvement [d] SCS vs DBS (thal. VC n.) vs MCS. SCS first, if failed, then DBS and/or MCS. DBS and MCS in 4 pts: better result: MCS 1/4 pts; DBS 2/4 [e] SCS vs DBS (thal. VC n.) vs MCS. DBS and cortical pre- post-central or pre-frontal stimulation can produce painful sensations, [f] Experimental study on conscious somatosensory responses. MCS unsuccessful in 2 pts reporting abnormal pain sensation after stimulation, [g] Review on DBS and MCS for post-stroke movement disorders an post-stroke pain. [h] Pain relief only in syringomyelia pt with parietal somatosensory stimulation. Contralateral spreading of pain and vanishing of analgesia at 2 yrs. [i] Short-term (5 wks) pain relief (allodynia disappearance, 50% reduction of burning pain). Experience of painful supernumerary phantom arm during MCS (lasting 6 mos. after stimulator was switched off) [l] Effective SI stimulation in 1 pts (MCS responsive too). Overall efficacy: 3/7 CP pts, all propofol-responsive. Ineffective in 4/7 CP pts, all propofol-unresponsive, 16 [m] TMS study; MCS effective in a barbiturate and morphine unresponsive pt, uneffective in a barbiturate responsive, morphine unresponsive pt [n] satisfactory/unsatisfactory results [o] fair to good results. +4 PNP pts. Electrode placement: subdural in 5 pts, interhemispheric in 3 pts. Dual devices driving 2 electrodes in 2 pts. [p] MCS ineffective. Later SI/SII CS effective for 4 years [q] Modified MCS protocol: subdural MCS within the central sulcus. Implants in: interhemispheric fissure: 5 pts (lower limb pain), within central sulcus: 5 pts (area 4 and area 3b stimul) + surface of the precentral gyrus. Area 4 within central sulcus optimal stimulation point [r] pain relief with ipsilateral to pain BA4 stimulation [s] +5 PNP pts; Evaluation of intensive reprogramming for recapture of the beneficial effects of MCS [t] +9 PNP pts; MCS ineffective in CP [t] I pt 70% pain reduction in the right arm + hemi-trunk; no pain relief on the right leg; 1 pt 20–60% pain relief in leg (subdural medial MCS) [u] Best results in pts with parietal lobe infarct, thalamic abscess/infarct pts (almost normal life, drugs markedly reduced). Pain relief <40% in SCI [v] +3 PNP pts. Correlation rCBF increase/analgesic efficacy [w] +12 PNP pts. [x] Investigational study on rCBF/electrophysiology [y] identical patients [z] some pts already reported [A] +18 PNP pts. MCS effective in pts with normal or quite normal non-nociceptive thermal threshold within the painful area or in pts with improved sensory thresholds during MCS [B] no effect In spite of multipolar electrode grid or paddle relocation [C] Evaluation of clinical usefulness of a frameless stereotactic system, neuronavigation, single burr hole and vacuum headrest [D] including syrinx pts. +9 PNP pts [E] + PNP pta. Description of an integrated protocol for precise electrode placement, combining functional image guidance and intraoperative electrical stimulation in the awake patient.

short-lasting, focal or generalized seizures; hence, antiepileptic drugs are usually administered to all patients for the duration of the test period and then gradually are discontinued. These episodes happen exclusively during trial stimulation at intensities above muscle contraction threshold with high-frequency pulses and no consequences have been thus far reported. Neither kindling of a permanent epileptic state with long-term stimulation, nor EEG signs of epileptic ''irritability'', even at high voltages (9–10 V) have been reported [8]. Up to 5% of patients may complain of headache and/or local tenderness and hypersensitivity over the electrode site; this probably represents localized dural current spread. Reduction of stimulation parameters without loss of analgesia may or may not relieve these symptoms. Some cases of headache may actually be due to contraction of the temporalis muscle from stimulation of the face area. In Wallenberg's syndrome, local pain may be relieved by incision and resuturing of the dura around the electrode. Temporary speech disorders have been reported in a few patients.

Bizarre phenomena

The following bizarre phenomena have been rarely reported during CS [8]: 1) a very unpleasant pain in the same area of the original pain, 2) analgesia via ipsilateral stimulation, 3) bilateral analgesia (or sensory effects) from unilateral CS, and 4) induced sensation of supernumerary phantom arm [7].

Future prospects and developments

CS should be pursued by a functional neurosurgeon with experience in the field of pain. CP patients should be submitted to propofol or barbiturate tests and all patients to TMS for optimal surgical selection. All patients should be evaluated with validated scales and good responders be submitted to sham stimulation. MCS can control both spontaneous and evoked pains or, rarely, only evoked pain whilst non-painful paresthesias are resistant. Both MI and SI CS may achieve control of CP. Even when stimulation parameters are sought carefully, some may exacerbate the pain, and several patients can lose benefit, generally in the first few months. At this time, MCS is the technique of choice for patients with CP who do not respond to an adequate course of drug therapy (including lamotrigine, high dose gabapentin and mexiletine), with a better morbidity/mortality profile than competing techniques.

There is a tendency in recent studies to perform a small craniotomy because this allows an extended functional exploration of the region of interest; the surgical approach is believed by some to play a role in the accuracy of the targeting and that trephination is superior to a single burr hole. However, the burr hole approach also allows surgery to be performed under local anesthesia. Two burr holes allow repositioning of the electrode up to 5 mm below the bone. This is an advantage because it improves the possibility to evoke muscular activation by high intensity, low frequency stimulation, which can be quite difficult to achieve under general anesthesia. We strongly advise against the use of: a) general anesthesia, b) craniotomy, c) grids, and d) multi-step procedures. In case of failure, contralateral stimulation, perhaps based on TMS and/or neurometabolic findings, should be attempted, as the generator of pain may have shifted contralaterally [2]. All this should be tempered by our ignorance of long-term efficacy ($\geq$5 years) and the lack of randomized controlled trials addressing the many questions raised by this new technique. Questions remain regarding in which direction to orient the electrode, whether specifically designed multiple electrodes might provide better electrical field coverage, and whether subdural electrodes might provide more effective stimulation, especially for the lower extremity.

References

1. Berger MS, Cohen WWA, Ojemann GA (1990) Correlation of motor cortex brain mapping data with magnetic resonance imaging. J Neurosurg 72: 383–387
2. Canavero S (1994) Dynamic reverberation. A unified mechanism for central and phantom pain. Med Hypotheses 42: 203–207
3. Canavero S, Bonicalzi V, Pagni CA, Castellano G, Merante R, Gentile S, Bradac GB, Bergui M, Benna P, Vighetti S, Coletti Moia M (1995) Propofol analgesia in central pain: preliminary clinical observations. J Neurol 242: 561–567
4. Canavero S, Bonicalzi V (1995) Cortical stimulation for central pain. J Neurosurg 83: 1117
5. Canavero S, Bonicalzi V (1998) The neurochemistry of central pain: evidence from clinical studies, hypothesis and therapeutic implications (review). Pain 74: 109–114
6. Canavero S, Bonicalzi V, Paolotti R, Cerutti A (1999) Extradural cortical stimulation for neurogenic pain and Parkinson's disease. The Turin experience. In: Meadows P (ed) IFESS Conference Proceeding: 1996–1998. Electronic edition. La Canada Flintrige (CA): IFESS CD
7. Canavero S, Bonicalzi V, Castellano G, Perozzo P, Massa-Micon B (1999) Painful supernumerary phantom arm following motor cortex stimulation for central post-stroke pain. J Neurosurg 91: 121–123
8. Canavero S, Bonicalzi V (2002) Therapeutic extradural cortical stimulation for central and neuropathic pain: a review. Clin J Pain 18: 48–55

9. Canavero S, Bonicalzi V, Dotta M, Vighetti S, Asteggiano G (2003) Low-rate repetitive TMS allays central pain. Neurol Res 25: 151–152
10. Canavero S, Bonicalzi V (2003) Neuromodulation for central pain. Expert Rev Neurotherapeutics 3: 591–607
11. Canavero S, Bonicalzi V (2004) Motor cortex stimulation for central and neuropathic pain. Pain 108: 199–200
12. Canavero S, Bonicalzi V (2004) Intravenous subhypnotic propofol in central pain. A double-blind, placebo-controlled, Crossover Study. Clin Neuropharmacol 27: 182–186
13. Canavero S, Bonicalzi V (2005) Transcranial magnetic stimulation for central pain. Curr Pain Headache Rep 9: 87–89
14. Canavero S, Bonicalzi V (2007) Central pain syndrome. Cambridge University Press
15. Drouot X, Nguyen JP, Peschanski M, Lefaucheur JP (2002) The antalgic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone. Brain 125(Pt 7): 1660–1664
16. Gelnar PA, Szeverenyi NM, Apkarian AV (1995) Cortical response to painful thermal stimuli in humans using functional MRI. J Neurosurg 82: 372–373
17. Herregodts P, Stadnik T, Deridder F, Dhaens J (1995) Cortical stimulation for central neuropathic pain: 3-D surface MRI for easy determination of the motor cortex. Acta Neurochir Suppl 64: 132–135
18. Iwasaki S, Nagakawa H, Fukusumi A, Kichikawa K, Kitamura K, Otsuji H, Uchida H, Ohishi H, Yaguchi K, Sumie H (1991) Identification of pre- and postcentral gyri on TC and MR images on the basis of the medullary pattern of cerebral white matter. Radiology 179: 207–213
19. Kamada K, Houkin K, Iwasaki Y, Takeuchi F, Kuriki S, Mitsumori K, Sawamura Y (2002) Rapid identification of the primary motor area by using magnetic resonance axonography. J Neurosurg 97: 558–567
20. Katayama Y, Fukaya C, Yamamoto T (1998) Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. J Neurosurg 89: 585–591
21. Katayama Y, Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C (2001) Motor cortex stimulation for post-stroke pain: comparison of spinal cord and thalamic stimulation. Stereotact Funct Neurosurg 77: 183–186
22. Meyerson BA (1997) Guest editorial. Pharmacological tests in pain analysis and in prediction of treatment outcome. Pain 72: 1–3
23. Meyerson BA, Linderoh B (2001) Brain stimulation: intracerebral and motor cortex stimulation. In: Loeser JD (ed) Bonica's management of pain, 3rd edn. Lippincott Williams & Wilkins, Baltimore, pp 1877–1889
24. Nimsky C, Ganslandt O, Kober H, Moller M, Ulmer S, Tomandl B, Fahlbusch R (1999) Integration of functional magnetic resonance imaging supported by magnetoencephalography in functional neuronavigation. Neurosurgery 44: 1249–1255
25. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
26. Nii Y, Uematsu S, Lesser RP, Gordon B (1996) Does the central sulcus divide motor and sensory functions? Cortical mapping of human hand areas as revealed by electrical stimulation through subdural grid electrodes. Neurology 46: 360–367
27. Pirotte B, Voordecker P, Neugroschl C, Baleriaux D, Wikler D, Metens T, Denolin V, Joffroy A, Massager N, Brotchi J, Levivier M (2005) Combination of functional magnetic resonance imaging-guided neuronavigation and intraoperative cortical brain mapping improves targeting of motor cortex stimulation in neuropathic pain. Neurosurgery 56 ONS Suppl 2: 344–359
28. Roux FE, Ibarrola D, Lazorthes Y, Berry I (2001) Chronic motor cortex stimulation for phantom limb pain: a functional magnetic resonance imaging study: technical case report. Neurosurgery 48: 681–688
29. Roux FE, lbarrola D, Tremoulet M, Lazorthes Y, Henry P, Sol JC, Berry L (2001) Methodological and technical issues for integrating functional magnetic resonance imaging data in a neuronavigational system. Neurosurgery 49: 1145–1157
30. Sol JC, Casaux J, Roux FE, Lotterie JA, Bousquet P, Verdie JC, Mascott C, Lazorthes Y (2001) Chronic motor cortex stimulation for phantom limb pain: correlations between pain relief and functional imaging studies. Stereotact Funct Neurosurg 77: 172–176
31. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1990) Motor cortex stimulation for control of thalamic pain. Pain Suppl 5: S491
32. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Treatment of thalamic pain by chronic motor cortex stimulation. PACE 14: 131–134
33. Tsubokawa T, Katayama Y, Yamamoto T, Maejima S, Koshinaga M (1996) Effective mechanisms and follow-up results of chronic motor cortex stimulation for relief of central deafferentation pain. Abstracts, III International Congress of the International Neuromodulation Society, Orlando, p 123
34. Ueda M, Sakurai T, Kasai K, Ushikubo Y, Samejima H (1997) Localisation of sensory motor cortex during surgery by changes of cortical surface temperature after median nerve stimulation. Lancet 350: 561
35. Velasco M, VeLisco F, Brito F, Velasco AL, Nguyen JP, Marquez L, Boleaga B, Keravel Y (2002) Motor cortex stimulation in the treatment of deafferentation pain: Part 1-Localization of the motor cortex. Stereotact Funct Neurosurg 79: 146–167
36. Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T (1997) Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy. Pain 72: 5–12

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Motor cortex stimulation for neuropathic pain

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Summary

Since the initial publication of Tsubokawa in 1991, epidural motor cortex stimulation (MCS) is increasingly reported as an effective surgical option for the treatment of refractory neuropathic pain although its mechanism of action remains poorly understood. The authors review the extensive literature published over the last 15 years on central and neuropathic pain. Optimal patient selection remains difficult and the value of pharmacological tests or transcranial magnetic stimulation in predicting the efficacy of MCS has not been established. Pre-operative functional magnetic resonance imaging (fMRI), 3-dimensional volume MRI, neuronavigation and intra-operative neurophysiological monitoring have contributed to improvements in the technique for identifying the precise location of the targeted motor cortical area and the correct placement of the electrode array. MCS should be considered as the treatment of choice in post-stroke pain, thalamic pain or facial anesthesia dolorosa. In brachial plexus avulsion pain, it is preferable to propose initially dorsal root entry zone (DREZ)-tomy; MCS may be offered after DREZotomy has failed to control the pain. In our experience, the results of MCS on phantom limb pain are promising. In general, the efficacy of MCS depends on: a) the accurate placement of the stimulation electrode over the appropriate area of the motor cortex, and b) on sophisticated programming of the stimulation parameters. A better understanding of the MCS mechanism of action will probably make it possible to adjust better the stimulation parameters. The conclusions of multicentered randomised studies, now in progress, will be very useful and are likely to promote further research and clinical applications in this field.

Keywords: Neuromodulation; neuropathic pain; motor cortex stimulation; MCS; pain; post-stroke pain; facial anesthesia dolorosa; brachial plexus avulsion; phantom limb pain.

Introduction

Neuropathic types of pain (NP) are considered as difficult to treat, heterogeneous clinical syndromes that are secondary to a wide variety of peripheral and/or central nervous system injuries [2]. Currently, the pathophysiological mechanisms of neuropathic pain are much better understood [2, 16]; however, since the introduction of anticonvulsant and tricyclic antidepressant drugs in the management of NP, little progress has been made in the pharmacological treatment of this condition [44].

As early as late 1960s, the neuromodulation-based concept of the ''gate control theory'', was followed by the development of minimally invasive and reversible neurostimulation techniques; this represented a major step forward in the treatment of intractable neuropathic pain. Chronic spinal cord stimulation (SCS) is a minimally invasive percutaneous, epidural and increasingly adjustable technique because it is performed with multipolar and multichannel electrodes; however, it will control only pain secondary to incomplete peripheral nerve damage [20]. Deep brain stimulation (DBS) of the sensory thalamic nuclei has offered disappointing long-term results, especially in central pain [23]. This explains the interest aroused by motor cortex stimulation (MCS); this alternative treatment was proposed, in 1991, by Tsubokawa *et al.* [50] and was based on data derived from experiments in animal models of central sensory deafferentation pain. MCS inhibits the spontaneous thalamic neuronal hyperactivity induced by spinothalamic tractotomy [40]. The first clinical benefits were seen in cases of thalamic pain [51] or neuropathic facial pain [29].

The action mechanism of MCS remains poorly understood. It has been proposed that it may be related to the inhibition of nociceptive ascending pathways at the thalamic [3, 47, 48], or spinal level [43]. These scientific data have not been validated in humans. Furthermore, they do not explain the observed prolonged antinociceptive effects. Other proposed mechanisms involve supraspinal structures, namely the cingulate gyrus, orbitofrontal cortex, and brainstem [12, 35]. There are many unclear or unsettled issues that must be addressed. These include

the action mechanism, the best possible electrode structure, the optimum stimulation parameters, and the correct stimulation depth; the latter should be determined after taking into account the cortex layers and the orientation of the fibers in the motor cortex. Despite all these uncertainties, nearly 300 cases have been reported describing MCS applications to most types of intractable peripheral and central neuropathic pain [1, 3, 6, 47]. Many clinical studies have reported beneficial effects, but in several reports, the results were contradictory [18]. Similarly to all other neuromodulation techniques, the patients must be strictly selected; this is especially important in MCS because the optimum indications are not yet fully determined. Many studies [32, 33, 36, 45] have emphasized that the degree and duration of the analgesic effect depend on the accuracy of electrode placement on the motor cortical area that corresponds ideally to the somatic area of pain. This objective is difficult to achieve because: a) the patient does not feel any stimulation-induced paraesthesias, and b) the sensory deafferentation is often associated with cortical reorganization [11, 28, 37, 56].

Patient selection criteria

The diagnosis of neuropathic pain (NP) must be confirmed by a multidisciplinary evaluation. The pain should: a) be localized in an area of extensive sensory deafferentation (hypoaesthesia), b) be secondary to either a peripheral nerve damage or a central nervous system lesion (or malfunction) which can be demonstrated by neuroimaging, electrophysiology or surgical exposure, and c) be a symptom of a non-progressive condition. Furthermore, it should be possible for the pain to be classified definitively as NP according to the classification proposed by Rasmussen *et al.* [39]. NP should have an intense character and a chronic progression for over 6 months and should be intractable to pharmacological or physical treatments. It is important to investigate whether the patient has received any benefits from properly prescribed and observed anticonvulsant or antidepressant treatments. The development of new anticonvulsants has prolonged the period of medical treatment before NP is recognized as being refractory [2, 39, 44]. Some authors [8, 47, 58] have attributed predictive value to certain pharmacological tests such as the lack of response to morphine, the attenuation of pain by barbiturates and the response to transcranial magnetic stimulation (TMS) [7, 22, 30, 34]. The predictive value of these tests has not been established [42].

Targeting and surgical technique

The first objective of the procedure is to define accurately the motor cortex area that corresponds to the somatic area of pain and should be stimulated. Current neuroimaging techniques allow us to determine directly the anatomical position of the central sulcus (CS) and indirectly the somatotopic representation of the motor homunculus (Area 4) in the precentral gyrus. The theoretical cortical target to be identified and stimulated depends on the size of the somatic region of pain. The main body segments and their respective motor cortex areas to be stimulated are described below:

1) face: lower part of the central gyrus,
2) upper limb and hand: middle part of the central gyrus between the inferior frontal sulcus and the superior frontal sulcus, and
3) lower limb and trunk: upper part of the central gyrus between the superior frontal sulcus and the interhemispheric fissure.

The distal part of the lower limb lies on the inner surface of the hemisphere, and therefore, it cannot be directly stimulated epidurally; this limb representation, however, can be extended to the upper part of the motor gyrus [55]. With current neuronavigation methods, it is possible to reconstruct three-dimensionally the cortex from morphological MRI data and identify these anatomical structures precisely. These topographical data can be subjected to image fusion with functional MRI (fMRI) data obtained during an actual motor task [31, 36, 38, 45] or a virtual motor task [41, 45]; the latter should correspond to the pain territory in a painful phantom limb, or to the neighbouring territory in cases of complete motor deficits (upper limb following brachial plexus avulsion). This correlation is particularly useful because the deafferentation may have reorganized the motor cortex and therefore reduced or displaced the target area that should be stimulated. Some authors use TMS to identify the motor cortex and then combine TMS with neuronavigation [34] and PET data [35, 45].

Intraoperative techniques

Craniotomy

The initial procedure by Tsubokawa consisted of a simple burr hole under local anaesthesia. This has been replaced by a small craniotomy [10, 32–35], which offers the advantage of better intraoperative neurophysiological exploration and minimizes the risk of a post-operative

epidural haematoma. The location and borders of the craniotomy are defined by neuronavigation analysis of the preoperative targeting data. A 4–5-cm sized bone flap is sufficient; alternatively, a 5-cm-diameter trephine craniotomy may be done when the target lies on the outer surface of the hemisphere (face or upper limb).

Intraoperative neurophysiological exploration

The first stage consists of pinpointing the CS on the dural surface. In practice, neuronavigation is sufficient but, if there is doubt, target confirmation can be done by recording somatosensory evoked potentials (SEPs) after stimulation of the contralateral median nerve at the wrist [33, 55]. The SEPs are recorded using an electrode grid with multiple poles (20–40) or the 4-contact plate electrode with contacts 4 mm in diameter spaced 10 mm apart (Resume®, Medtronic Inc., Minneapolis, USA). Many studies have provided evidence of a relationship between the location of the CS and the location of the N20/P20 phase reversal [47, 53]. The N20 is elicited in the motor gyrus area that corresponds to the hand, i.e. in front of the CS. In several NP conditions that are accompanied by severe sensory deafferentation (e.g. brachial plexus avulsion), the intraoperative SEPs cannot be used. Furthermore, the intraoperative SEPs recorded after trigeminal or tibial nerve stimulation are often difficult to interpret. Therefore, it is useful to check the quality of SEPs intra-operatively.

The second stage is critical. It consists of localising accurately the targeted cortical area by MCS. It may be difficult to induce transdurally muscle contractions in the somatic area of pain because: 1) the dura-to-cortex distance is affected by the variable thickness of the subarachnoid space or the presence of cortical atrophy, 2) the stimulation delivered by the neurostimulators is not intense (10 mA max), and 3) the suppression of neuronal activity by general anaesthesia [33, 34]. In practice, it is possible to use the final quadripolar electrode (Resume®) to perform this motor stimulation test and to couple the electrical stimulation (pulse width: 1 msec, low frequency: 1–3 Hz, intensity: 5–10 mA, monophasic pulse) with electromyographic (EMG) recording of the activity of the appropriate muscles. Thus, it is possible to detect a subclinical response without necessarily inducing muscle contraction.

Placement of the electrode array

Based on the intraoperative electrophysiological data and the extent of the pain territory, one or two quadripolar plate electrodes (Resume®) are sutured to the dura either perpendicularly or parallel to the SC; the electrode orientation depends on surgeon's preference but it is important to have at least two poles over the targeted motor cortex. The electrode extensions are tunnelled and connected to an implantable pulse generator (IPG), (ITREL 3® or SYNERGY®, Medtronic Inc., Minneapolis, USA) which is inserted in the subclavicular or the lateral thoracic region. Experience has shown that it is not worthwhile to perform a prolonged percutaneous stimulation test intraoperatively; the identification of the optimal stimulation parameters may require multiple adjustments because the patient usually does not feel any MCS-induced paraesthesias or sensations. The parameters are selected empirically and usually are: amplitude: 2 V (1–4 V), frequency: 40 Hz (25–55 Hz), pulse width: 120 μsec (60–180 μsec).

It is important that the negative contact (cathode) is placed over the motor cortex area that corresponds ideally to the territory of somatic pain. Most surgeons prefer bipolar stimulation with the negative contact (cathode) over the motor area and the positive contact (anode) over the sensory area [47]. In bipolar stimulation, both cathode and anode electrode contacts are active and their position can be relevant to the clinical effects of MCS [26]. The response of any cortical fiber varies and depends on its orientation in the stimulation-induced field [15]. An interpolar distance of 20–30 mm is preferred in order to cover widely the motor cortex area. It is possible to apply bipolar stimulation using the ITREL 3® system. The time course of the analgesic effect is variable. Under optimal neuroanatomical conditions, Tsubokawa [47] reported that the pain begins to decrease 5 minutes after the start of MCS and disappears completely after 10–20 minutes; after stimulation is stopped, there is a 2- to 6-hour post-MCS effect. Based on these observations, he recommended intermittent stimulations with a rate of 5–7 per day. Conversely, Nguyen *et al.* [34] underlined the latency of the analgesic effect, which is rarely immediate but may last for several days. Very often, it is found that the intensity must be increased in order to keep the stimulation efficacious; this can be explained by an increase in the impedance of the ''electrode to dura'' contact.

Results

A literature review in the Pubmed beginning in 1991 identified 29 publications, describing over 251 patients [3, 6, 34, 47]. It is difficult to compare their results

because most studies are retrospective and use different assessment scales. No prospective studies have been published and the number of available controlled studies is limited. A randomized (on/off) multicentered study is currently being conducted in France.

Central pain

Thalamic pain syndromes are intractable, disabling, and particularly resistant to medical and conservative treatments. The long-term failure of DBS in this type of NP has been verified. Tsubokawa *et al.* [49] reported disappointing results following stimulation of the sensory nuclei of the thalamus; although the initial effect was satisfactory in certain patients, tolerance to stimulation developed in a few months and, after 2 years the stimulation was efficacious only in 38% of the cases. More recently, following a literature review of long-term results, Levy *et al.* [23] reported that, in 24 cases, the DBS improvement rate was only 24%; the complications were uncommon (5.3%) but serious (5 cerebral haemorrhages). The main indication of MCS is post-stroke pain [50, 51]. Nguyen *et al.* [34] estimated that our experience on the treatment of this condition by MCS is based on over 159 cases of central pain secondary to ischaemic or haemorrhagic stroke; the MCS success rate was 52% (83/159). Table 1 summarizes the results of the main published series on MCS. Several authors [18, 34] have underlined that the association of pain with a major motor deficit is a poor prognostic indicator. Nevertheless, the management of central pain by MCS should be considered as an alternative treatment of confirmed efficacy.

Trigeminal neuropathic pain

Trigeminal neuropathic pain is one of the most common indications of MCS. This type of NP is most often secondary to an iatrogenic injury to the roots of the trigeminal nerve (thermocoagulation or conventional surgery). MCS has replaced the chronic stimulation of the Gasserian ganglion in the treatment of trigeminopathic pain. In the latter procedure, it is possible to perform not only a prolonged percutaneous test-stimulation but also a long-term stimulation of the ganglion [19]; there is, however, a serious risk of late dislodgment of the percutaneously inserted electrode. The alternative method of electrode implantation through a temporal approach is a major surgical procedure. This technique has been abandoned gradually, although its results were satisfactory in facial neuropathic pain of central or peripheral origin [46]. The results of thalamic stimulation were disappointing [23]; in 12 cases of anaesthesia dolorosa, the long-term success rate was only 18%. With regard to MCS, 47 cases have been reported in the literature; the success rate was high with the average

Table 1. *Published series on the results of MCS on central neuropathic pain*

Authors (reference number)	Patients number/ age range (years)	Follow-up in months	Success rate at latest follow-up (≥50% analgesia)
Tsubokawa *et al.* [51]	11/52–72	≥24	45% (5/11)
Nguyen *et al.* [34]	18	46 (mean)	marked improvement (>60%): 7 satisfactory improvement (40–60%): 8 failure (<40%): 3
Meyerson *et al.* [29]	3	–	0%
Yamamoto *et al.* [57]	28/35–72	≥12	46%
Mertens *et al.* [27]	16/29–78	23 (mean)	67%
Saitoh *et al.* [42]	8	26 (mean)	25% (2/8)
Caroll *et al.* [9]	5		40% (2/5)

Table 2. *Published series on the results of MCS on trigeminal neuropathic pain*

Authors (reference number)	Patients number/ age range (years)	Follow-up in months	Success rate at latest follow-up (≥50% analgesia)
Meyerson *et al.* [29]	5/44–71	4–28	100% (5/5)
Herregodts *et al.* [14]	5/40–45	15 (mean)	88% (4/5)
Ebel *et al.* [10]	7/37–81	5–24	43% (3/7)
Nguyen *et al.* [32, 34]	22		marked improvement (>60%): 59% (13/22) satisfactory improvement (40–60%): 23% (5/22)
Brown and Barbaro [3]	8/37–73	10 (mean)	75%

Table 3. *Published series on the results of MCS in neuropathic limb pain*

Authors (reference number)	Indications	Patients number	Mean follow-up in months (range)	Success rate at latest follow-up (%)
Nguyen *et al.* [33]	brachial plexus avulsion	2		50%
Mertens *et al.* [27]	brachial plexus avulsion	4		50%
Saitoh *et al.* [42]	brachial plexus avulsion	4	19	25%
	phantom limb pain	2	20	50%
Sol *et al.* [45]	phantom limb pain	3	27.3	67%
Caroll *et al.* [9]	phantom pain	3	–	67%
Pirotte *et al.* [36]	plexus avulsion	3	–	33%
Lazorthes *et al.* [21]	phantom	7	42 (6–76)	85%
Katayama *et al.* [18]	phantom limb pain	5	>24	20%

long-lasting improvement being evaluated as greater to 50% in 73–75% of the cases (Table 2).

Neuropathic limb pain

In this group, MCS may be indicated only after SCS either has failed or is contraindicated. This category includes patients with NP secondary to complete sensory deafferentation after either brachial plexus avulsion or limb amputation (phantom limb pain). Table 3 summarizes the main published series. In brachial plexus injuries, the results are not satisfactory (average success rate 40%). In this condition, it is not feasible to identify the CS by intraoperative SEP monitoring. Therefore, it is preferable to perform a DREZotomy as the first procedure of choice. In phantom limb pain, the results are variable with an average success rate of 55% [9, 33, 34, 42]. We have reported comparable results [41, 45]. In a recent retrospective study [21], in 7 patients with a mean follow-up of 42 months (range: 6–76), the success rate was 85% (excellent: 3, significant: 3, failure: 1). Conversely, Katayama *et al.* [18] reported conflicting results; he achieved a lasting analgesic effect in 6 of 19 patients with painful phantom limbs after SCS. Of 10 patients who did not respond to SCS, he reported lasting improvement after thalamic DBS (nucleus ventralis caudalis) in 6 cases (60%), whereas only 1 out of 5 patients treated by MCS had a lasting improvement (success rate: 20%). In this article, there was little information on the pre- and intraoperative identification of the motor cortex target; in addition, 3 of the 5 patients who received MCS had brachial plexus avulsion without being clear whether this was associated with an amputated upper limb. MCS represents the preferred treatment in phantom limb pain which is otherwise considered intractable and irreversible. The historical failures of sensory cortex removals are well-known [24, 25, 52]. In a literature review, Levy *et al.* [23] reported 5 cases of periventricular gray matter (PVG) DBS who had an initial good response (4 of 5 improved) but a disappointing long-term response (only 1 of 5 improved); this was not confirmed by the recent study of Katayama *et al.* [18].

Table 4. *Published series on the results of MCS in post-spinal lesion pain*

Author (reference number)	Indication	Patients number	Success rate at latest follow-up (%)
Nguyen *et al.* [33]	post-trauma paraplegia	4	75
Mertens *et al.* [27]	post-trauma	3	100

Post-spinal lesion pain

This type of NP, particularly in the lower limbs, represents a very difficult problem because the pain is bilateral and the cortical target area is located near the midline. To overcome this difficulty, surgeons have implanted the electrodes interhemispherically [42]; this, however, induces an increased risk of complications. Paradoxically, Nguyen [33] has reported that unilateral cortical stimulation can have a bilateral effect (Table 4).

Side effects and complications

Complications are uncommon and of moderate severity. The most serious are epilepsy, and epidural or subdural haematomas; they occur approximately in 3% of the cases.

Stimulation-induced seizures

These have been seen mostly during the test-stimulation period [29]. Their incidence during chronic MCS is very low if the stimulation intensity remains below the motor threshold. The incidence can become higher after ''intense reprogramming'' [13, 34].

Epidural haematoma

Theoretically, if the dura is correctly secured around the edges of the craniotomy, the risk is negligible. However, several cases have been reported, especially during the early period of MCS, when the electrodes were inserted through a single burr hole [29, 51].

Skin ulceration and infection

This is a common risk which is associated with the implantation of any stimulation device. In the literature, the frequency is estimated between 0.7 and 2.2%. Any implantation should be postponed as long the patient has untreated urinary, pulmonary or other infections.

Loss of efficacy

After the initial benefit, which may last for several months, some authors have reported a tolerance-like phenomenon [10]. In such cases, the efficacy can be restored by replacing the electrode on a more optimal cortical target [33, 45, 51]. Sometimes, a simple increase in the electrode-dural impedance is required by either increasing the stimulation intensity or changing the bipolar configuration. A loss of efficacy secondary to neural plasticity and reorganization of the deafferentated cortical area is another possibility; this hypothesis led Henderson *et al.* to perform ''intensive reprogramming'' in order to restore the initial efficacy [13].

Conclusions

Neuropathic pain (NP) is considered as a difficult-to-treat clinical condition which is associated with various lesions in the peripheral or central nervous system. Antidepressant and anticonvulsant medications are considered as the primary treatment and offer satisfactory relief to most patients [2, 44]. Over the last few years, a new approach to the treatment of NP has developed; this is based on the current understanding of pain mechanisms and aims to target specifically these mechanisms [54]. This rational approach cannot yet be implemented widely because of difficulties in converting our understanding of the pathophysiological mechanisms, obtained from animal studies, to treatment protocols in patients [16]. Nevertheless, chronic motor cortex stimulation (MCS) is no more just a promising method; it has gained an established role in the treatment of chronic intractable pain secondary to sensory deafferentation. It provides a therapy to a category of pain which until now has been proved resistant to any other treatment. In certain types of central neuropathic pain, such as post-stroke pain, MCS constitutes the first-choice therapeutic alternative after the failure of medical and conservative treatments. The same applies to facial anaesthesia dolorosa. Conversely, in pain secondary to brachial plexus avulsion, it is preferable to propose first selective ablative surgery, such as DREZotomy. Other indications need to be confirmed, even if lasting efficacy has been reported by various authors in ''phantom limb pain'' or paraplegia-related pain.

The efficacy of MCS depends directly on the accurate placement of the stimulation electrode over the appropriate area of the motor cortex. The primary motor cortex that corresponds to the somatic area of pain may have been displaced because of either brain plasticity or cortical reorganization secondary to the sensory deafferentation or to the causal lesion in the nervous system. Brain mapping using fusion of three-dimensional volume MRI with fMRI in combination with intraoperative electrophysiology is a valid technique for identifying the precise location of the targeted motor cortex. There are still many unclear issues such as which neurons or axons should be stimulated, which cortical afferents or efferents are stimulated by MCS, and whether antidromic stimulation contributes to the clinical effects. Multicenter prospective studies are being conducted. They will describe larger clinical series with a ''study design'' of MCS that includes ''on/off'' sequences evaluated in a ''blind'' manner. Hence, the conclusions of these studies are expected to be of particular significance. A better understanding of MCS mechanisms of action will probably make it possible to program better the stimulation parameters; currently, the programming remains empirical and is based on practical clinical observations. Experimental studies predicting the bioelectrical effects of MCS by computer modelling [26] and more sophisticated neuronal fiber models are in the stage of development and are likely to promote further research and clinical applications in this field.

References

1. Bonicalzi V, Canavero S (2004) Motor cortex stimulation for central and neuropathic pain. Pain 108: 199–200
2. Bouhassira D, Attal N (2004) Novel strategies for neuropathic pain. In: Villanueva L, Dickenson A, Ollat H (eds) The pain system in normal and pathological states: a primer for clinicians. IASP Press, Seattle, pp 299–309
3. Brown JA, Barbaro NM (2003) Motor cortex stimulation for central and neuropathic pain: current status. Pain 104: 431–435

4. Brown JA, Pilitsis JG (2005) Motor cortex stimulation for central and neuropathic facial pain: a prospective study of 10 patients and observations of enhanced sensory and motor function during stimulation. Neurosurgery 56: 290–297
5. Canavero S (1995) Cortical stimulation for central pain. J Neurosurg 83: 1117
6. Canavero S, Bonicalzi V (2002) Therapeutic extradural cortical stimulation for central and neuropathic pain: a review. Clin J Pain 18: 48–55
7. Canavero S, Bonicalzi V, Dotta H, Vighetti S, Asteggiano G (2003) Low role repetitive TMS allays central pain. Neurol Res 23: 151–152
8. Canavero S, Bonicalzi V, Pagni CA, Castellano G, Merante R, Gentile S, Bradac GB, Bergui M, Benna P, Vighetti S (1995) Propofol analgesia in central pain: preliminary clinical observations. J Neurol 242: 561–567
9. Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ (2000) Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. Pain 84: 431–437
10. Ebel H, Rust D, Tronnier V, Böker D, Kunze S (1996) Chronic precentral stimulation in trigeminal neuropathic pain. Acta Neurochir (Wien) 138: 1300–1306
11. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E (1995) Phantom limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 357: 482–484
12. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
13. Henderson JM, Boongird A, Rosenow JM, Lapresto E, Razai AR (2004) Recovery of pain control by intensive reprogramming after loss of benefit from motor cortex stimulation for neuropathic pain. Stereotac Funct Neurosurg 82: 207–213
14. Herregodts P, Stadnik T, De Ridder F, D'Haens J (1995) Cortical stimulation for central neuropathic pain: 3-D surface MRI for easy determination of the motor cortex. Acta Neurochir Suppl 64: 132–135
15. Holsheimer J, Manola L (2005) Differential effects of cathodal and anodal stimulation in MCS. 7th INS Meeting, Rome (Proceedings)
16. Jensen TS, Baron R (2003) Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 102: 1–8
17. Katayama Y, Fukaya C, Yamamoto T (1998) Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favourable response. J Neurosurg 89: 585–591
18. Katayama Y, Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C (2001) Motor cortex stimulation for phantom limb pain: a comprehensive therapy with spinal cord and thalamic stimulation. Stereotact Funct Neurosurg 77: 159–161
19. Lazorthes Y, Armengaud JP, Da Motta M (1987) Chronic stimulation of the gasserian ganglion for the treatment of atypical facial neuralgia. Pacing Clin Electrophysiol 10: 257–265
20. Lazorthes Y, Verdié JC, Sol JC (2005) Spinal cord stimulation for neuropathic pain. Handbook of clinical neurology's volume on pain. Elsevier (in press)
21. Lazorthes Y, Sol JC, Cintas P, Lotterie JA, Verdie JC, Fowo S, Berta S, Aryan HE, Park SM, Meltzer HS (2005) Chronic motor cortex stimulation for phantom pain control. 55th Annual Meeting, Congress of Neurological Surgeons (CNS), Boston, MA (Proceedings)
22. Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP (2001) Pain relief induced by repetitive transcranial magnetic stimulation of précentral cortex. Neuroreport 12: 1–3
23. Levy RM, Lamb S, Adams JE (1987) Treatment of chronic pain by deep brain stimulation: long-term follow-up and review of the literature. Neurosurgery 21: 885–893
24. Lewin W, Phillips CG (1952) Observation on partial removal of the post-central gyrus for pain. J Neurol Neurosurg Psychiatry 15: 143–147
25. Mahoney CGdeG (1944) The treatment of painful phantom limb by removal of post-central cortex. J Neurosurg 1: 156–162
26. Manola L, Roelofsen BH, Holsheimer J, Harani E, Geelen J (2005) Modelling motor cortex stimulation for chronic pain control: electrical potential field, activating functions and responses of simple nerve fibre models. Med Biol Eng Comput 43: 335–343
27. Mertens P, Nuti C, Sindou M, Guenot M, Peyron R, Garcia-Larrea L, Laurent B (1999) Precentral cortex stimulation for the treatment of central neuropathic pain. Stereotact Funct Neurosurg 73: 122–125
28. Merzenich MM, Nelson RI, Stryker MP, Cynader MS, Schoppmann A, Zool JM (1984) Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol 224: 391–405
29. Meyerson BA, Lindblom U, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir Suppl 58: 150–153
30. Migita K, Tohru U, Kazunori A, Shuji M (1995) Transcranial magnetic cord stimulation in patients with central pain: technique and application. Neurosurgery 76: 1037–1040
31. Mogilner AY, Rezai AR (2001) Epidural motor cortex stimulation with functional imaging guidance. Neurosurg Focus 11: E4
32. Nguyen JP, Keravel Y, Feve A, Uchiyama T, Cesaro P, Le Guerinel C, Pollin B (1997) Treatment of deafferentation pain by chronic stimulation of the motor cortex: report of a series of 20 cases. Acta Neurochir Suppl 68: 54–60
33. Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central of neuropathic pain: correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
34. Nguyen JP, Lefaucheur JP, Moubarak K, Cesaro P, Palfi S, Keravel Y (2004) Novel strategies for modern Neurosurgery. In: Villanueva L, Dickenson A, Ollat H (eds) The pain system in normal and pathological states: a primer for clinicians. IASP Press, Seattle, pp 311–326
35. Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguiere F, Laurent B (1995) Electrical stimulation of précentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain 62: 275–286
36. Pirotte B, Woordecker Ph, Neugroschl C, Baleriaux D, Wilker D, Metens Th, Denolin V, Joffroy A, Massager N, Brotchi J, Levivier M (2005) Combination of functional magnetic resonance image-guided neuronavigation and intraoperative cortical brain mapping improves targeting of motor cortex stimulation in neuropathic pain. Neurosurgery Suppl 2 56: 344–359
37. Pons TP, Garrahty PE, Ommaya AK, Kaas JH, Taub E, Mishkin M (1991) Massive cortical reorganisation after sensory deafferentation in adult macaques. Science 252: 1857–1860
38. Rao SM, Binder JR, Hammeke TA, Bandettini PA, Bobholz JA, Frost JA, Myklebust BM, Jacobson RD, Hyde JS (1995) Somatotopic mapping of the human primary motor cortex with functional magnetic resonance imaging. Neurology 45: 919–924
39. Rasmussen PV, Sindrup SH, Jensen TS, Bach FW (2004) Symptoms and signs in patients with suspected neuropathic pain. Pain 110: 461–469
40. Rinaldi PC, Young RF, Albe-Fessard D, Chodakiewitz J (1991) Spontaneous neuronal hyperactivity in the medial and intralaminar thalamic nuclei of patients with deafferentation pain. J Neurosurg 74: 415–421
41. Roux FE, Ibarrola D, Lazorthes Y, Berry I (2001) Chronic motor cortex stimulation for phantom limb pain: a functional magnetic resonance imaging study: technical case report. Neurosurgery 48: 681–688

42. Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Yoshimine T (2000) Motor cortex stimulation for central and peripheral déafférentation pain. J Neurosurg 92: 150–155
43. Senapati AK, Huntington PJ, Peng YP (2005) Spinal dorsal horn neuron response to mechanical stimuli is decreased by electrical stimulation of the primary motor cortex. Brain Research 1036: 173–179
44. Sindrup SH, Jensen TS (1999) Efficacy of pharmacological treatment of neuropathic pain: an update and effect related to mechanism of drug action. Pain 81: 389–400
45. Sol JC, Casaux J, Roux FE, Lazorthes Y (2001) Chronic motor cortex stimulation for phantom limb pain: correlations between pain relief and functional imaging studies. Stereotact Funct Neurosurg 77: 172–176
46. Taub E, Munz M, Tasker RR (1997) Chronic electrical stimulation of the gasserian ganglion for the relief of pain in a series of 34 patients. J Neurosurg 86: 197–202
47. Tsubokawa T (2002) Motor cortex stimulation for relief of central deafferentation pain. In: Burchiel KJ (ed) Surgical management of pain. Thieme, New York, pp 555–564
48. Tsubokawa T, Katayama Y (1998) Motor cortex stimulation in persistent pain management. In: Gildenberg PL, Tasker RR (eds) Textbook of stereotactic and functional neurosurgery. Mc Graw Hill, New York, pp 1547–1556
49. Tsubokawa T, Katayama Y, Yamamoto T *et al* (1985) Deafferentation pain and stimulation of thalamic sensory relay nucleus. Appl Neurophysiol 48: 166–171
50. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl 52: 137–139
51. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
52. White JC, Sweet WH (1969) Pain and neurosurgeon: a forty-year experience. Charles C. Thomas, Springfield IL, p 401
53. Wood CC, Spencer DD, Allison T, McCarthy G, Williamson PD, Goff WR (1988) Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. J Neurosurg 68: 98–111
54. Woolf CJ, Max MB (2001) Mechanism-based pain diagnosis: issues for analgesic drug development. Anesthesiology 95: 241–249
55. Woolsey CN, Erickson TC, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg 51: 476–506
56. Wu CWH, Kaas JH (1999) Reorganization in primary motor cortex of primates with long-standing therapeutic amputation. J Neurosci 19: 7679–7697
57. Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T (1997) Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy. Pain 72: 5–12
58. Yamamoto T, Katayama Y, Tsubokawa T, Koyama S, Maejima S, Hirayama T (1991) Usefulness of the morphine/thiamylal test for the treatment of deafferentation pain. Pain Res (Tokyo) 6: 143–146

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Motor cortex stimulation for chronic non-malignant pain: current state and future prospects

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Summary

Motor cortex stimulation (MCS) was proposed by Tsubokawa in 1991 for the treatment of post-stroke thalamic pain. Since that time, the indications have been increased and included trigeminal neuropathic pain and later other types of central and peripheral deafferentation pain. The results reported in the literature are quite good; the mean long-term success rate is 80% in facial pain and 53% in non-facial pain. Our own results are less impressive: 4 of 14 patients (28%) experienced a greater than 40% pain relief, but in 2 of them the effect faded with time. Only few minor complications have been reported. The accurate placement of the epidural electrode over the motor cortex that somatotopically corresponds to the painful area is believed to be essential for pain relief. Predictive factors included the response to pharmacological tests, the relative sparing from the disease process of the cortico-spinal tract and the sensory system, and the analgesic response achieved during the test period of MCS. A possible predictive factor might be a test of repetitive transcranial magnetic stimulation (rTMS) of the motor cortex. MCS may act by rebalancing the control of non-nociceptive sensory inputs over nociceptive afferents at cortical, thalamic, brainstem and spinal level. In addition, it may interfere with the emotional component of nociceptive perception. Biochemical processes involving endorphins and GABA may also be implicated in the mechanism of MCS. It is time for a large multicenter prospective randomized double blind study evaluating not only the effect of MCS on pain (based on the available guidelines for assessment of neuropathic pain), but also the optimal electrode placement and stimulation parameters, and the possible relationship with the response to rTMS. New electrode design and a new generation of stimulators may help in improving the results.

Keywords: Neuromodulation; epidural motor cortex stimulation; chronic non-malignant pain; neuropathic pain; central pain; intraoperative neurophysiological monitoring.

Introduction

Motor cortex stimulation (MCS) was introduced in the treatment of central and neuropathic pain in the early nineties. This type of pain is defined by the International Association for the Study of Pain (IASP) as pain initiated or caused by a lesion (or dysfunction) of the central or peripheral nervous system; in spite of the advances in pharmacological treatment, it still represents a challenge to pain specialists and particularly to neurosurgeons. Tsubokawa and colleagues [27, 28] observed hyperactivity of low threshold mechanoreceptor thalamic neurons after spino-thalamic tractotomy in a cat model, and found that MCS inhibited the abnormal firing whereas sensory cortex stimulation (SCS) had no effect. On this basis, they proposed MCS for the treatment of thalamic pain. They treated 11 patients with epidural MCS and reported the long-term results [28]. Eight patients obtained an excellent pain relief during the one week test period and, hence, they underwent chronic stimulation. At 2 years, in 5 cases the results were unchanged (greater than 80% pain relief), while, in the remaining 3 cases, the effect of MCS decreased gradually over several months. The stimulation was subthreshold for muscle contraction and no complications were described. In 1993, Meyerson published his experience on ten patients [16]. Five of them complained of trigeminal neuropathic pain and all achieved more than 50% pain relief. Stimulation was subthreshold for movement in these cases as well, and it was used for 20–30 minutes, one to six times a day. Since then, an exponentially increasing number of cases have been described over the following years, supporting the use of MCS in the treatment of central and peripheral neuropathic pain syndromes.

Clinical indications

MCS has been used so far for central and peripheral neuropathic pain; there is no experience on chronic benign nociceptive pain. The indications have increased

from the original post-stroke central pain and trigeminal neuropathic pain, and include postherpetic neuralgia, peripheral deafferentation pain syndromes such as brachial plexus and roots avulsions, spinal cord injury pain, phantom limb and stump pain, and complex regional pain syndrome (CRPS) [2–4, 7, 10, 14, 17–19, 22, 23, 26]. The best results were obtained in trigeminal pain (more than 80% of successful results); the large somatotopic facial representation on the motor cortex compared to the other body regions, may be an explanation for these particularly good results in facial neuropathic pain.

Surgical technique

The key point of surgery is the accurate placement of the electrode over the motor cortex that somatotopically corresponds to the painful area [17]. A multicontact strip electrode is usually placed in the epidural space; subdural placement has been used in the interhemispheric fissure for lower limbs pain and was advocated by Saitoh for a more stable motor cortex activation [24]. There is general agreement that the best electrode orientation is perpendicular to the central sulcus. The location of the motor cortex has been identified by morphological craniometer landmarks, using fiducial markers and MRI neuronavigation, integrating functional MRI (fMRI) into the targeting plan [21]; however, a precise neurophysiological localisation is mandatory. We use the phase reversal technique to identify the central sulcus. We stimulate the controlateral median nerve at the wrist and record from each contact of the strip electrode. A cortical N20 potential is recorded over the sensory cortex and a cortical P20 potential is recorded over the motor cortex; the central sulcus is found between the two contacts showing the phase reversal. The motor mapping is obtained by motor cortex focal anodal stimulation through two adjacent contacts of the same strip electrode with a short train of stimuli (5 stimuli, 0.5 ms, ISI 4 ms, 10–30 mA). Muscle responses are recorded from muscle bellies of the controlateral hemibody, with needle electrodes. This mapping technique allows the use of general anaesthesia (totally intravenous anaesthesia with Propofol and Remifentanyl, and no muscle relaxants after intubation) and has a very low rate of inducing epileptic seizures (less than 4%) compared to the classical so called ''Penfield's technique'' for motor cortex mapping. In contrast to other authors [1], we feel that a neurophysiological precise localisation of the motor cortex is essential. In the past, we placed the electrode through a simple burr hole, but with experience we prefer a small craniotomy; it allows an easier and more extensive cortical mapping and the placement of 2 electrode paddles when the region of pain is extensive and, consequently, the cortical area to be covered is wide.

Stimulation parameters

An empirical approach is used to select the optimal stimulation parameters by adjusting the combination of contacts, polarity, frequency, pulse width and, to a lesser extent, amplitude, according to the patient's pain relief. Stimulation is always subthreshold for muscle contraction or any sensation. This makes possible double blind studies. Manola *et al.* published the results of a computer modelling study on MCS [13]. They studied the electrical potential field characteristics and the initial response of single fibre models to stimulation of the precentral gyrus by an epidural multicontact electrode. They concluded that the amount of the cerebrospinal fluid (CSF) between the dura and the cortex underneath the stimulating electrode is the most important factor affecting the distribution of the electrical field; when the CSF layer increases in thickness from 0 to 2.5 mm, the load impedance decreases by 28%, and the stimulation amplitude increases by 6.6 V for each mm of CSF. Both anode and cathode should be considered active because of the large anode-cathode distance (<10 mm). Anodal fields preferentially excite fibres perpendicular to the electrode surface, whereas cathodal fields excite fibres running parallel to the electrode surface. Therefore, anodal stimulation over the precentral gyrus preferentially activates pyramidal axons; cathodal precentral stimulation, used in most of the published clinical reports, preferentially excites fibres parallel to the brain surface, i.e. connecting interneurons or horizontal braches of cortical afferents and efferents.

Assessment of the results

Guidelines have been published for the assessment of neuropathic pain and its response to treatment [5]. The most reliable assessment measures are the visual analogue scale (VAS) (not the percentage of pain relief) and the global impression of change (GIC), which can be implemented utilizing multidimensional scales such as the SF-36 or the Owenstry questionnaire. Many articles report only the percentage of pain relief, some report the VAS score and a few utilize multidimensional scales. A pain relief of 50% is the usual cut-off for success, but

recently also pain relief of 40% or even 30% during medical treatment, has been considered sufficient to define a treatment as effective for neuropathic pain.

Clinical results

The clinical results in patients complaining of trigeminal neuropathic pain are reported in Table 1 [3, 7, 15, 17, 18, 22]. The long-term success rate (greater than 40% pain relief) ranged from 40 to 100%. In these 7 published series, 47 patients were submitted to MCS and 38 (80%) reported a fair to excellent pain relief. The clinical results in patients complaining of central or peripheral deafferentation pain are reported in Table 2; six published series are analysed [4, 9, 18, 19, 24, 28]. The long-term success rate ranged from 40 to 77%. Overall, 56 of 104 patients (53%) experienced long-term fair to excellent pain relief. Our personal results are less impressive. We submitted to MCS 14 patients (Table 3); in 8 cases, the pain was due to trigeminal neuropathy (4 post-traumatic, 2 post-herpetic, 1 post-trigeminal surgical lesion, and 1 multiple sclerosis), in 4 to an ischemic stroke (3 thalamic, 1 bulbar), and in the remaining 2 to a spinal cord lesion. Only 2 patients (14%) reported a stable long-term pain relief (greater than 50%); one patient reported a 40% pain relief for a few months, but then the effect gradually faded; another patient initially was a failure, then gained a 50% pain relief after an aggressive reprogramming of the stimulator, but the effect decreased over few weeks. Ten patients are considered as failures.

Table 1. *Effect of MCS on facial neuropathic pain*

Author	Patients	Acute responders (%)	Long-term responders (%)	Follow up
Meyerson *et al.* [16]	5	100	100	
Herrengodts *et al.* (1995)	5		80	
Nguyen *et al.* [17]	7	100	100	
Rainov *et al.* [22]	2	100	100	18 months
Ebel *et al.* [7]	7		43	
Nguyen *et al.* [18]	12		83	27 months
Brown and Barbaro [2]	9	88	75	10 months

Recently, commenting on an article published in Neurosurgery [3], Kanpolat wrote ''We are reluctant to mention our hesitation regarding the effectiveness of MCS, but it seems that only series with good results have been reported . . . and most of the failures seem to remain unreported''. Regarding the same article, Broggi commented [3]: ''My experience with MCS has been that patients with neuropathic facial pain . . . experience poor and transient results as measured by quality of life''. The same sort of scepticism is expressed by Meyerson in his editorial published in Pain [15]: ''MCS . . . should not be considered an established method of pain control . . . . It may seem that the results of MCS are not impressive but it must be remembered that the forms of pain for which MCS may be effective, . . . are those for which there are no or little other treatment''

Complications

Complications such as haematomas either epidural or subdural, infections and other minor problems, are reported in a small percentage of patients, but they do not produce neurological deficits. Epileptic seizures occasionally occurred during the motor mapping, but chronic seizures have never been reported.

Table 2. *Effect of MCS on central and peripheral neuropathic pain (non-trigeminal)*

Author	Patients	Type/cause of pain	Acute responders (%)	Long-term responders (%)	Follow up
Tsubokawa *et al.* [28]	11	thalamic	73	45	24 months
Katayama *et al.* [19]	31	post-stroke		48	>24 months
Carrol *et al.* [4]	10	5 post-stroke 3 phantom limb 2 various	50	40	1–31 months
Nguyen *et al.* [18]	13	central pain		77	27 months
Saitoh *et al.* [24]	8	4 thalamic 4 peripheral deafferentation	75	75	6–26 months
Nuti *et al.* [19]	31	22 poststroke 4 brachial plexus 5 variuos		52	48 months

Table 3. *Personal experience*

Type/cause of pain	Patients	Long-term results
Trigeminal neuropathy	8	1 S 1 F, then S, then F 6 F
Post-stroke	4	1S then F 3 F
Spinal cord lesion	2	1S 1F

S Success (>40% pain relief), *F* failure (<40% pain relief).

Predictive factors

Pharmacological tests have been proposed in order to predict the efficacy of MCS. Yamamoto *et al.* correlated the percentage of pain relief obtained with different drugs with that of MCS in post-stroke patients [29]. The regression analysis showed a significant correlation between the MCS effect and the effect of the Thiamytal test or the Ketamine test, but not with the Morphine test. These results have not been duplicated [24]. Katayama stressed the importance of a relative integrity of the cortico-spinal tract [9]; only 15% of 13 patients reported a satisfactory pain relief when a moderate to severe motor weakness was present, and only 9% reported a benefit when motor contraction could not be elicited. The success rate was 73% when a mild or absent motor impairment was present [9]. Drouot *et al.* [6] noticed that the antalgic efficacy of MCS was related to sensory changes in the painful zone. Favourable prognostic factors were the absence of alteration of non-nociceptive sensory modalities within the painful area, or an abnormal sensory threshold that could be improved by MCS (a better sensory discrimination by switching on the stimulator). Katayama *et al.* [9] on the other hand, reported no correlation between sensory symptoms, somatosensory evoked potentials (SEPs) and the MCS effect.

Nuti *et al.* published the 4-years outcome in 31 patients and studied the possible predictors of efficacy [19]. There was no statistical correlation between the long-term outcome and any of the following variables: pre-operative motor status, pain semeiology, type or site of the lesion that causes pain, quantitative sensory testing, and SEPs. Notably, the patients who had a normal motor function showed a tendency towards a significantly decreased analgesic drug intake; this finding is in agreement with the observations of Katayama. The pain relief obtained at the end of the first month of MCS was the only factor that had a strong statistical correlation with the long term pain relief [19]. There are many reports on the analgesic effect of repetitive transcranial magnetic stimulation (rTMS) over the motor cortex at subthreshold intensities [11, 12], but so far there is no evidence of a significant correlation of the response to rTMS with the efficacy of MCS. The parameters used for rTMS are very different from those used for MCS, apart from the intensity, which is subthreshold for muscle contraction in both electrical and magnetic stimulation.

Mechanisms of action

According to Tsubokawa's hypothesis [28], under normal conditions noxious and non-noxious inputs from the thalamus converge at cortical level and the non-noxious stimulus is able to inhibit the noxious afferences. When such an inhibitory mechanism is lost as a consequence of a thalamic lesion, MCS can antidromically and orthodromically activate large fibres reciprocal connections between the motor and the sensory cortex, and then activate non-noxious, fourth order sensory neurones restoring the inhibitory control over the nociceptive inputs. PET studies demonstrated a significant increase in cerebral blood flow in the ipsilateral lateral thalamus, but also in the brainstem, cingulate gyrus, anterior insula, and orbito-frontal cortex, during MCS, in patients reporting a good pain relief [8, 20, 23]. MCS may reinforce the control of non-nociceptive sensory inputs on nociceptive systems not only at the thalamic level, but also at the brainstem and at the spinal cord level. Indeed, in experimental models of deafferentation pain, MCS reduces the hyperactivity of thalamic neurones as well as the hyperactivity at dorsal columns nuclei. An attenuation of flexion reflexes (R III) has been shown during MCS in cases of good analgesic effect [8]. The changes in these polysynaptic reflexes during MCS suggest that a descending inhibitory mechanism at spinal level may be involved in mediating the effect of MCS. A recent experimental study in rats by Senapati *et al.* [25], has shown that MCS produced significant inhibition of wide dynamic range dorsal horn neuron activity in response to high intensity mechanical painful stimuli but not to innocuous stimuli. MCS may also reduce the emotional component of chronic pain by activating the anterior cingulate cortex and the anterior insula as demonstrated by PET studies [8, 20, 23]. Biochemical processes such as action on the endorphin sites in the brainstem or control on the GABAergic interneurons at cortical level, may also be implicated, in the mechanisms of MCS.

Future prospects

In our opinion, it is time for a prospective multicenter randomized double blind study. Electrode placement should be precisely documented (both topographically and neurophysiologically), different stimulation parameters should be tested, pain relief assessment should follow the existing guidelines, and the predictive value of rTMS should be studied. Technical advances such as new electrode designs, covering a larger area of the motor cortex may be helpful in improving the clinical results. The new generation of neurostimulators may reduce the need for time consuming multiple programming visits.

References

1. Brown JA (2001) Motor cortex stimulation. Neurosurg Focus 11: E5
2. Brown JA, Barbaro NM (2003) Motor cortex stimulation for central and neuropathic pain: current status. Pain 104: 431–435
3. Brown JA, Pilitis JG (2005) Motor cortex stimulation for central and neuropathic facial pain: a prospective study of 10 patients and observation of enhanced sensory and motor function during stimulation. Neurosurg 56: 290–297
4. Carroll D, Joint C, Martens N, Shlugman D, Stein J, Aziz TZ (2000) Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 patients. Pain 84: 431–437
5. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Hanpaa M, Jorum E, Serra J, Jensen TS (2004) EFNS guidelines on neuropathic pain assessment. Eur J Neurol 11: 153–162
6. Drouot X, Nguyen JP, Pescanski M, Lefaucheur JP (2002) The antalgic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone. Brain 125: 1660–1664
7. Ebel H, Rust D, Tronnier V, Boker D, Kunze S (1996) Chronic pre central stimulation in trigeminal neuropathic pain. Acta Neurochir (Wien) 138: 1300–1306
8. Garcia-Larrea L, Pyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of the motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–277
9. Katayama Y, Fukaya C, Yamamoto T (1998) Poststroke pain control by motor cortex stimulation: neurological characteristics predicting a favourable response. J Neurosurg 89: 585–591
10. Katayama Y, Tsubokawa T, Yamamoto T (1994) Chronic motor cortex stimulation for central deafferentation pain: experience with bulbar pain secondary to Wallenberg syndrome. Stereotact Funct Neurosurg 62: 295–299
11. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC (2005) Long lasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 76: 833–838
12. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib D, Cesaro P, Keravel Y, Nguyen JP (2005) Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry 75: 612–616
13. Manola L, Roelofsen BH, Holsheimer J, Marani E, Geelen J (2005) Modelling motor cortex stimulation for chronic pain control: electrical potential field, activating functions and responses of simple nerve fibre models. Med Biol Eng Comput 43: 335–343
14. Meglio M, Cioni B, Montano N (2005) Motor cortex stimulation for pain control In: Meglio M (ed) Proceedings of the 14th Meeting of the World Society for Stereotactic and Functional Neurosurgery. Medimond, Bologna, pp 175–181
15. Meyerson B (2005) Motor cortex stimulation-effective for neuropathic pain but the mode of action remains illusive. Pain 118: 6–7
16. Meyerson B, Lindblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir Suppl 58: 150–153
17. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugières P, Pollin B, Fève A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlation between clinical, electrophysiological and anatomical data. Pain 82: 245–251
18. Nguyen JP, Lefaucheur JP, Le Guerinel C, Eizenbaum JF, Nakano N, Carpentier A, Brugières P, Pollin B, Rostaign S, Keravel Y (2000) Motor cortex stimulation in the treatment of central and neuropathic pain. Arch Med Res 31: 263–265
19. Nuti C, Peyron R, Garcia-Larrea L, Brunon J, Laurent B, Sindou M, Mertens P (2005) Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. Pain 118: 43–52
20. Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguière F, Laurent B (1995) Electrical stimulation of the precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain 62: 275–286
21. Pirotte B, Voordecker P, Neugroschi C, Baleriaux D, Wikler D, Metens T, Denolin V, Joffroy A, Masseger R, Brotchi J, Levivier R (2005) Combination of functional magnetic resonance imaging-guided neuronavigation and intraoperative cortical brain mapping improves targeting of motor cortex stimulation in neuropathic pain. Neurosurg 56: ONS344–ONS359
22. Rainov NG, Fels C, Heidecke V, Burkert W (1997) Epidural electrical stimulation of the motor cortex in patients with facial neuralgia. Clin Neurol Neurosurg 99: 205–209
23. Saitoh Y, Osaki Y, Nishimura H, Hirano S, Kato A, Hashikawa K, Hatazawa J, Yoshimine T (2004) Increased regional cerebral blood flow in the controlateral thalamus after successful motor cortex stimulation in a patient with post-stroke pain. J Neurosurg 100: 935–939
24. Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Yoshimine T (2000) Motor cortex stimulation for central and peripheral deafferentation pain. J Neurosurg 92: 150–155
25. Senapati AK, Huntington PJ, Peng YB (2005) Spinal dorsal horn neurone response to mechanical stimuli is decreased by electrical stimulation of the primary motor cortex. Brain Res 1036: 173–179
26. Son BC, Kim MC, Moon DE, Kang JK (2003) Motor cortex stimulation in a patient with intractable complex regional pain syndrome type II with hemibody involvement. J Neurosurg 98: 175–179
27. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl 52: 137–139
28. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
29. Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T (1997) Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy. Pain 72: 5–12

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Stimulation of primary motor cortex for intractable deafferentation pain

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Summary

The stimulation of the primary motor cortex (M1) has proved to be an effective treatment for intractable deafferentation pain. This treatment started in 1990, and twenty-eight studies involving 271 patients have been reported so far. The patients who have been operated on were suffering from post-stroke pain (59%), trigeminal neuropathic pain, brachial plexus injury, spinal cord injury, peripheral nerve injury and phantom-limb pain. The method of stimulation was: a) epidural, b) subdural, and c) within the central sulcus. Overall, considering the difficulty in treating central neuropathic pain, trigeminal neuropathic pain and certain types of refractory peripheral pain, the electrical stimulation of M1 is a very promising technique; nearly 60% of the treated patients improved with a higher than 50% pain relief after several months of follow-up and sometimes of a few years in most reports. The mechanism of pain relief by the electrical stimulation of M1 has been under investigation. Recently, repetitive transcranial magnetic stimulation (rTMS) of M1 has been reported to be effective on deafferentation pain. In the future, rTMS may take over from electrical stimulation as a treatment for deafferentation pain.

Keywords: Neuromodulation; motor cortex stimulation; primary motor cortex; repetitive transcranial magnetic stimulation (rTMS); deafferentation pain; navigation.

Introduction

Deafferentation pain is one of the most difficult types of pain to treat and is usually refractory to medical treatment. In 1990, Tsubokawa *et al.* found that pain can be reduced by motor cortex stimulation (MCS) in patients suffering from post-stroke pain [39]. In 1993, pain due to trigeminal peripheral lesion was successfully treated with MCS [18]. Phantom-limb pain and brachial plexus injuries also responded to MCS well. Other studies have shown that MCS can provide pain relief in 50–75% of patients with deafferentation pain [14, 18, 20, 31].

Twenty-eight studies involving 271 patients have been reported from Japan ($n = 112$) [12, 13, 32, 39], France ($n = 97$) [17, 20, 24, 36], Belgium ($n = 19$) [8, 25], USA ($n = 11$) [7, 10], Sweden ($n = 10$) [18], U.K. ($n = 10$) [2], Germany ($n = 9$) [4, 27, 28], and Italy ($n = 3$) [1, 5]. This selection includes only original publications with new cases and no duplicate publications on the same patients. All these trials followed an open methodology; no controlled double blind study has been performed so far. Several indications have been studied including most neuropathic pains, but one is clearly far ahead from all others, this of post-stroke pain (59% of all published cases) followed by trigeminal neuropathic pain (17%). All other indications represent less than 10% each. The two exceptions are combinations of central pain and movement disorders. Both publications report a surprising improvement of movement disorders related to MCS, which was initially intended to treat only severe pain [21].

Recently, repetitive transcranial magnetic stimulation (rTMS) has been applied in the treatment of neuropathic pain. The area of stimulation was the primary motor cortex (M1).

Motor cortex stimulation (MCS)

Pharmacological tests (drug challenge tests: DCT)

To clarify pathophysiological mechanisms and to allow patient choice, pharmacological tests, or drug challenge tests (DCT) have been done in two institutes. One study included 39 central post-stroke pain patients who had intractable hemibody pain with dysesthesias. The correlation between the response to pharmacological treatment and the effect of MCS therapy was examined. Yamamoto *et al.* reported that thiopental- and ketamine-

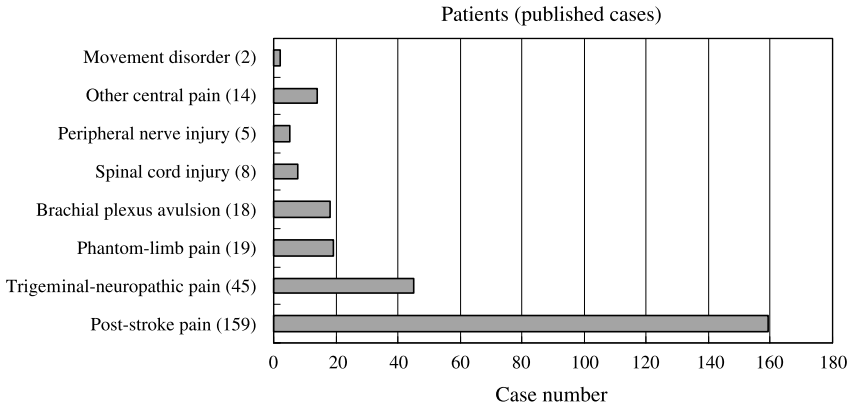

Fig. 1. Published cases of deafferentation pain treated by MCS; 67% central pain and 32% peripheral pain. The two exceptions are combinations of central pain and movement disorders (listed here as movement disorders)

responsive and morphine-resistant patients displayed long-lasting pain reduction after long-term use of MCS. Their DCT showed that definite pain reduction occurred in 20% by the morphine test, 56% by the thiopental test, and 48% by the ketamine test. On the basis of these DCT's assessments, it was concluded that there was no obvious difference between thalamic ($n = 25$) and suprathalamic pain ($n = 14$) [41]. Saitoh *et al.* performed DCT including thiopental, ketamine, phentolamine, lidocaine, morphine, and placebo in 18 cases. Of 18 cases in DCT, eight cases scoring "excellent" or "good" pain relief by MCS were found to be sensitive to morphine ($n = 5$), ketamine ($n = 4$), thiopental ($n = 4$) or lidocaine ($n = 3$). The other 10 cases scoring "fair" or "poor" pain relief had morphine ($n = 4$) or thiopental ($n = 2$) sensitivity. No relationship was found between morphine sensitivity and pain relief following MCS, and none of the patients was found to be sensitive to phentolamine. Several of the excellent MCS responders had not responded to any drug. The investigators concluded that ketamine might be a useful drug for patient selection [32].

Patients

The most common type is post-stroke pain, which is also the most difficult to treat. All cases, except two, had a severe neuropathic pain history, 67% central and 32% peripheral deafferentation pain. The two exceptions were combinations of central pain and movement disorders. The other reported cases included brachial plexus injury, spinal cord injury, trigeminal neuropathic pain, peripheral nerve injury, and phantom-limb pain (Fig. 1).

Surgical methods

Previous reports have described the implantation of epidural electrodes over the precentral gyrus [1, 3, 4, 8, 9, 10, 18, 20, 22, 23]. A small craniotomy, 3–4 cm in diameter, was performed around the central sulcus and an electrode array with four-plate electrodes (diameter 5 mm, model 358; Medtronic Inc., Minneapolis, MN, USA) was inserted in the epidural space. The best location and orientation of the electrode array were, therefore, determined in such a way that bipolar stimulation was offered with an appropriate pair of electrodes. Tsubokawa reported no polarity-related differences in pain relief for most patients [39]. Nguyen *et al.* reported the use of navigation for performing the craniotomy and electrode implantation in the epidural space. The center of the flap should correspond to the target as determined by imaging. Sensory evoked potential (SEP) are recorded from the grid electrode applied on the dura mater. The exact site where the four-plate electrode should be placed depends on the results from the electrophysiological study. They placed the electrode perpendicular to the central sulcus in a parietal-to-frontal lobe direction [22]. Such an epidural approach might not provide optimal pain relief since both the method and the area of test stimulation were restricted by a brief operative period under local anesthesia. Saitoh *et al.* reported that the subdural implant or implant within the central sulcus seemed to be more effective than the epidural implant, because this application make it possible to stimulate M1 more directly. A 20-grid electrode (4×5 array; 0.3 cm electrode diameter; 0.7 cm separation; Unique Medical Co., Tokyo, Japan) was placed subdurally to confirm the locations of the central sulcus by the SEP measurement. For hand or face pain in selected patients, 4-plate electrode was implanted within the central sulcus, and for foot pain, in the interhemispheric fissure in addition of the grid electrode. After implantation of the test electrodes, electrical stimuli were delivered to various areas. Final Resume (Medtronic, Inc., Minneapolis, MN) was implanted after the definition of the best location for pain relief [31, 32].

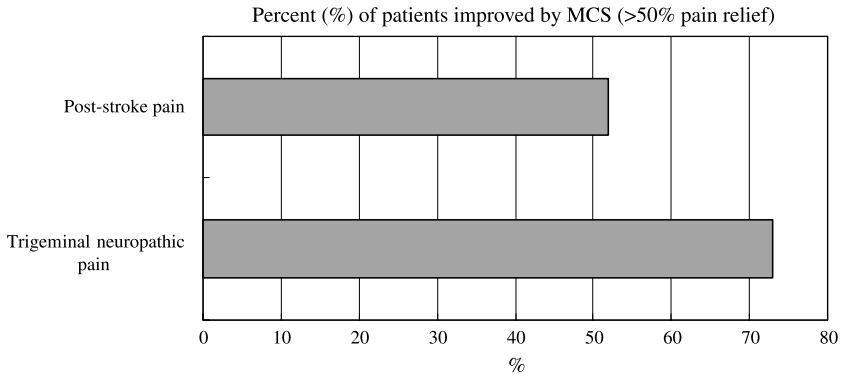

Fig. 2. Cases of post-stroke pain and trigeminal neuropathic pain; these two conditions can be considered as valid indications for MCS. 82 of 159 (52%) of post-stroke pain patients showed pain relief (>50%), and 33 of 45 (73%) of trigeminal neuropathic pain patients showed improvement

Results of motor cortex stimulation (MCS)

If one considers the difficulty in treating central neuropathic pain, trigeminal neuropathic pain and certain types of refractory peripheral pain, MCS appears to be a very promising technique with nearly 60% of the patients being improved with a higher than 50% pain relief after several months of follow-up and sometimes of a few years in most reports. Considering the number of cases published and their outcome, post-stroke pain and trigeminal neuropathic pain are the only conditions with significant improvement and, hence, these can be considered as valid indications for MCS (Fig. 2).

The relatively big number of patients with post-stroke pain who have been treated by MCS can be explained by two factors: a) post-stroke pain is the biggest patients category with deafferentation pain, and b) the therapeutic options for this condition are very limited. The numbers are smaller in trigeminal neuropathic pain but the results are excellent and very consistent in most reports with more than 70% of the patients being good responders [4, 8, 18, 21, 22]. Other types of central pain and traumatic spinal cord injury have responded with promising results but more studies are needed in order to assess more precisely the efficacy of MCS (Fig. 3). Brachial plexus avulsion pain does not seem to respond well (less than 50% of responders) [7, 22, 32, 36]; results for phantom-limb pain [2, 29, 30, 32] are better but they tend to vary from one report to the other, and the treated cases are few to draw any conclusions. In peripheral nerve injury where spinal cord stimulation (SCS) usually fails, the results of MCS are excellent [2, 18]. If these excellent results were confirmed, the therapeutic strategy of selecting between SCS and MCS should be reconsidered. More studies with rigorous methodology are needed to validate the indications. rTMS trials have a potential in predicting the effectiveness of MCS in the treatment of deafferentation pain [16, 19, 34]. Usually intermittent MCS trial stimulations were performed. The pain relief induced by a period of MCS is temporary. The longest MCS effect was 24 hours after 30 minutes of stimulation. Some patients had pain relief for only one hour after stimulation. In general, the obtained pain relief by a period of MCS lasts for 3–5 hours [31]. In some cases we observed a decrease of the MCS effectiveness after implantation; however, the cause of this decrease in efficacy has remained unknown. The stimulation parameters were usually as follows: a) relatively low frequency (25–50 Hz), b) impedance between 900 and 1500 ohm, and c) amplitude subthreshold of this that induces muscle twitch.

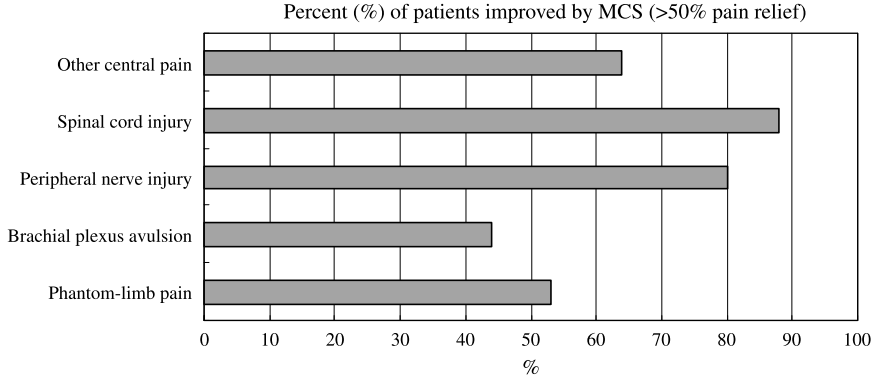

Fig. 3. Other types of central pain and traumatic spinal cord injury that have provided promising responses to MCS. 10 of 19 (53%) of phantom-limb pain patients showed pain relief (>50%), 8 of 18 (44%) of brachial plexus avulsion, 4 of 5 (80%) of peripheral nerve injury, 7 of 8 (88%) of spinal cord injury, and 9 of 14 (64%) of other types of central pain

Complications

Epileptic seizures have been reported during test stimulation; this was probably due to the variability of test conditions. Paresthesia, dysesthesia and chronic contraction during test stimulation are more common. Speech disorders have also been observed but rarely. The low rate of epileptic seizures during chronic stimulation (0.7%) means that stimulation of M1 with the correct range of parameters is reasonably safe. Paresthesia and dysesthesia have been documented in a small percentage (2.2%) of the published cases. In total, 11.4% of the published cases were associated with an adverse effect. The most serious complications were epi- or subdural hematoma, epileptic seizures, and aphasia or dysphasia and represented 3.6% of the reported cases. The larger craniotomy should decrease the risk of epi- or sub-dural hematoma and their consequences; a larger craniotomy allows better visual control of the lead, makes less likely the accidental removal of the grid or lead, and reduces the risk of inadvertent opening of the dura [20, 31, 32]. The risk of peri-operative hemorrhage is lower compared to DBS.

In one study, two major adverse effects occurred during a long follow-up [32]. Two patients developed cerebral hemorrhage; one died and the other remained in a vegetative state. None of these major complications can be linked to the MCS procedure itself or the chronic stimulation, but they are more closely related to the medical history of the patients. This is especially true in patients with post-stroke pain. It has already been demonstrated than stroke patients are likely to develop a second stoke in the years that follow the first stroke.

Pain relief mechanism with MCS

Tsubokawa *et al.* proposed that in patients with central deafferentation pain, activation of hypothetical sensory neurons by MCS might inhibit deafferentation nociceptive neurons within the cortex [39]. The mechanism of phantom-limb pain is unknown; however, both hyperactivity of peripheral nerves and sensitization of spinal neurons may play a part [3, 38].

So far, positron emission tomography (PET) studies, using ^{15}O-labeled water, have shown no significant rCBF change in the right primary sensory cortex and the M1 close to the location of MCS electrode [23, 33]. Therefore, it was speculated that MCS does not reduce pain by stimulating either of these cortices directly. Tsubokawa's hypothesis is that MCS activates non-nociceptive fourth-order sensory neurons, which in turn inhibit hyperactive nociceptive neurons in the sensory cortex [39]. However, no significant changes were induced in the parietal cortex, thus indicating that the sensory cortex is probably not the key structure in MCS-induced pain reduction. A model of MCS action was proposed by Garcia-Larrea *et al.* whereby activation of thalamic nuclei directly connected with motor and premotor cortices would entail a cascade of synaptic events in pain-related structures receiving afferents from these nuclei, including the medial thalamus, anterior cingulate and upper brainstem. MCS could influence the affective-emotional component of chronic pain by cingulate-orbitofrontal activation, and lead to descending inhibition of pain impulses by activation of the brainstem; this is also suggested by the attenuation of spinal flexion reflexes [6]. Ipsilateral thalamic hypometabolism has been reported in cases of central pain. Increased rCBF demonstrated by PET indicates increased synaptic activity, which can subserve either excitatory or inhibitory mechanisms. Thalamic CBF changes may reflect the activation of inhibitory processes; this is in agreement with animal studies showing that pathologically hyperactive thalamic neurons are inhibited by MCS [11]. The mechanisms of deafferentation pain and that of MCS efficacy have been under investigation, and will probably be better understood in the near future.

rTMS

Recently, rTMS has been applied in the treatment of psychiatric and neuro-degenerative diseases such as depression [15], dystonia [35], schizophrenia, Parkinson's disease, and epileptic seizures [40]. Based on the experience with MCS, rTMS is now beginning to be applied in cases of intractable deafferentation pain [16, 26]. Hirayama *et al.* [9] applied rTMS precisely to M1 using navigation-guided figure-of-eight coil. Effective treatment was defined as a VAS improvement of more than 30%. Ten of 20 patients (50%) showed significant reductions in pain on the VAS following the stimulation of M1. Five Hertz stimulation of M1 reduced intractable deafferentation pain in approximately one every two patients. The pain reduction continued to be significant for three hours. Lefaucheur *et al.* [16] reported that 10 Hz rTMS of the motor cortex resulted in a significant but transient relief of chronic pain; this was influenced by pain origin and pain site. The factors most favorable for rTMS treatment are a trigeminal nerve lesion and the presence of sensation in the painful zone. The factors least favorable are brainstem stroke, limb pain, and

severe sensory loss. A few other reports have also supported the effectiveness of rTMS on pain [37]. rTMS may be a good predictor of MCS efficacy; Saitoh *et al.* suggested that MCS can be recommended to patients who had good results following rTMS [34]. In the future, it is possible that rTMS could take over from MCS as a treatment for deafferentation pain.

References

1. Canavero S, Bonicalzi V (1995) Cortical stimulation for central pain. J Neurosurg 83: 1117
2. Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ (2000) Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. Pain 84: 431–437
3. Coghill RC, Sang CN, Maisog JM, Iadarola MJ (1999) Pain intensity processing with in the human brain: a bilateral distributed mechanism. J Neurophysiol 82: 1934–1943
4. Ebel H, Rust D, Tronnier V, Boker D, Kunze S (1996) Chronic precentral stimulation in trigeminal neuropathic pain. Acta Neurochir (Wien) 138: 1300–1306
5. Franzini A, Ferroli P, Servello D, Broggi G (2000) Reversal of thalamic hand syndrome by long-term motor cortex stimulation. J Neurosurg 93: 873–875
6. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
7. Henderson JM, Boongird A, Rosenow JM, LaPresto E, Rezai AR (2004) Recovery of pain control by intensive reprogramming after loss of benefit from motor cortex stimulation for neuropathic pain. Stereotact Funct Neurosurg 82: 207–213
8. Herregodts P, Stadnik T, De Ridder F, D'Haens J (1995) Cortical stimulation for central neuropathic pain: 3-D surface MRI for easy determination of the motor cortex. Acta Neurochir [Suppl] 64: 132–135
9. Hirayama A, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, Kato A, Yoshimine T (2006) Reduction of intractable deafferentation pain with navigation-guided repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex. Pain 122: 22–27
10. Hosobuchi Y (1993) Motor cortex stimulation for control of central deafferentation pain. Electrical and magnetic stimulation of the brain and spinal cord, Raven Press, New York
11. Iadarola MJ, Max MB, Berman KF, Byas-Smith MG, Coghill RC, Gracely RH, Bennett GJ (1995) Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. Pain 63: 55–64
12. Katayama Y, Fukaya C, Yamamoto T (1998) Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. J Neurosurg 89: 585–591
13. Katayama Y, Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C (2001) Motor cortex stimulation for post-stroke pain: comparison of spinal cord and thalamic stimulation. Stereotact Funct Neurosurg 77: 183–186
14. Katayama Y, Yamamoto T, Kobayashi K, Oshima H, Fukaya C (2003) Deep brain and motor cortex stimulation for post-stroke movement disorders and post-stroke pain. Acta Neurochir [Suppl] 87: 121–123
15. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, Repella JD, Danielson AL, Willis MW, Benson BE, Speer AM, Osuch E, George MS, Post RM (1999) Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry 46: 1603–1613
16. Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, Keravel Y, Nguyen JP (2004) Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry 75: 612–616
17. Mertens P, Nuti C, Sindou M, Guenot M, Peyron R, Garcia-Larrea L, Laurent B (1999) Precentral cortex stimulation for the treatment of central neuropathic pain: results of a prospective study in a 20-patient series. Stereotact Funct Neurosurg 73: 122–125
18. Meyerson BA, Lindblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir [Suppl] 58: 150–153
19. Migita K, Uozumi T, Arita K, Monden S (1995) Transcranial magnetic stimulation of motor cortex in patients with central pain. Neurosurg 36: 1037–1040
20. Nguyen JP, Keravel Y, Feve A, Uchiyama T, Cesaro P, Le Guerinel C, Pollin B (1997) Treatment of deafferentation pain by chronic stimulation of the motor cortex: report of a series of 20 cases. Acta Neurochir [Suppl] 68: 54–60
21. Nguyen JP, Pollin B, Feve A, Geny C, Cesaro P (1998) Improvement of action tremor by chronic cortical stimulation. Mov Disord 13: 84–88
22. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
23. Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguiere F, Laurent B (1995) Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain 62: 275–286
24. Peyron R, Laurent B, Garcia-Larrea (2000) Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 30: 263–288
25. Pirotte B, Voordecker P, Neugroschl C, Baleriaux D, Wikler D, Metens T, Denolin V, Joffroy A, Massager N, Brotchi J, Levivier M (2005) Combination of functional magnetic resonance imaging-guided neuronavigation and intraoperative cortical brain mapping improves targeting of motor cortex stimulation in neuropathic pain. Neurosurgery 56 [Suppl 2]: 344–359
26. Pleger B, Janssen F, Schwenkreis P, Volker B, Maier C, Tegenthoff M (2004) Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neurosci Lett 356: 87–90
27. Rainov NG, Fels C, Heidecke V, Burkert W (1997) Epidural electrical stimulation of the motor cortex in patients with facial neuralgia. Clin Neurol Neurosurg 99: 205–209
28. Rainov NG, Heidecke V (2003) Motor cortex stimulation for neuropathic facial pain. Neurol Res 25: 157–161
29. Roux FE, Ibarrola D, Tremoulet M, Lazorthes Y, Henry P, Sol JC, Berry I (2001) Methodological and technical issues for integrating functional magnetic resonance imaging data in a neuronavigational system. Neurosurgery 49: 1145–1156
30. Saitoh Y, Shibata M, Sanada M, Mashimo T (1999) Motor cortex stimulation for phantom limb pain. Lancet 353: 212
31. Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Kato A, Yoshimine T (2000) Motor cortex stimulation for central and peripheral deafferentation pain. J Neurosurg 92: 150–155
32. Saitoh Y, Kato A, Ninomiya H, Baba T, Shibata M, Mashimo T, Yoshimine T (2003) Primary motor cortex stimulation within the central sulcus for treating deafferentation pain. Acta Neurochir [Suppl] 87: 149–152

33. Saitoh Y, Osaki Y, Nishimura H, Hirano S, Kato A, Hashikawa K, Hatazawa J, Yoshimine T (2004) Increased regional cerebral blood flow in the contralateral thalamus after successful motor cortex stimulation in a patient with poststroke pain. J Neurosurg 100: 935–939
34. Saitoh Y, Hirayama A, Kishima H, Oshino S, Hirata M, Kato A, Yoshimine T (2006) Stimulation of primary motor cortex for intractable deafferentation pain. Acta Neurochir Suppl 99: 1–3
35. Siebner HR, Filipovic SR, Rowe JB, Cordivari C, Gerschlager W, Rothwell JC, Frackowiak RS, Bhatia KP (2003) Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. Brain 126: 2710–2725
36. Sol JC, Casaux J, Roux FE, Lotterie JA, Bousquet P, Verdie JC, Mascott C, Lazorthes Y (2001) Chronic motor cortex stimulation for phantom limb pain: correlations between pain relief and functional imaging studies. Stereotact Funct Neurosurg 77: 172–176
37. Tamura Y, Okabe S, Ohnishi T, N Saito D, Arai N, Mochio S, Inoue K, Ugawa Y (2004) Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. Pain 107: 107–115
38. Tasker RR (1984) Deafferentation. In: Wall PD, Melzack R (eds) Textbook of pain. Churchill Livingstone, Edinburg, pp 119–132
39. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
40. Wassermann EM, Lisanby SH (2001) Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 112: 1367–1377
41. Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T (1997) Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy. Pain 72: 5–12

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Cathodal, anodal or bifocal stimulation of the motor cortex in the management of chronic pain?

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Summary

The conditions of motor cortex stimulation (MCS) applied with epidural electrodes, in particular monopolar (cathodal or anodal) and bipolar stimulation, are discussed. The results of theoretical studies, animal experiments and clinical studies lead to similar conclusions. Basically, cortical nerve fibres pointing at the epidural electrode and those normal to this direction are activated by anodal and cathodal stimulation, respectively. Because MCS for the relief of chronic pain is generally applied bipolarly with electrodes at a distance of at least 10 mm, stimulation may actually be bifocal. The polarity and magnitude of a stimulus needed to recruit cortical nerve fibres varies with the calibre and shape of the fibres, their distance from the electrode and their position in the folded cortex (gyri and sulci). A detailed analysis of intra-operative stimulation data suggests that in bipolar MCS the anode of the bipole giving the largest motor response in the pain region is generally the best electrode for pain management as well, when connected as a cathode. These electrode positions are most likely confined to area 4.

Keywords: Motor cortex stimulation; anodal stimulation; cathodal stimulation; bipolar stimulation; computer modelling; motor evoked potential.

Abbreviations

MCS Motor cortex stimulation; *SCS* spinal cord stimulation; *PNS* peripheral nerve stimulation; *PG* precentral gyrus; *PoG* postcentral gyrus; *CS* central sulcus (central fissure); *MEP* motor evoked potential; *CSF* cerebro-spinal fluid; *D-wave* direct wave (non-synaptic); *I-wave* indirect wave (mono-/polysynaptic).

Introduction

Motor cortex stimulation (MCS) has been introduced by Tsubokawa *et al*. [32] as a treatment modality in the management of medically refractory neuropathic pain of central origin, in particular central post-stroke pain. Apart from central pain [14, 19], trigeminal (facial) neuropathic pain [20, 27] and other central and peripheral deafferentation pain syndromes [4, 21] have been shown to be good indications for MCS treatment as well.

Following a craniotomy, an electrode lead for spinal cord stimulation (SCS) is placed on the dura mater over the appropriate somatotopic part of the sensory-motor cortex. This lead (Resume, Medtronic, Minneapolis, MS) consists of a linear array of 4 disc electrodes (4 mm diameter, 10 mm center separation) mounted on a flexible paddle (∼38 mm long) and powered by an Itrel 3 pulse generator (Medtronic). Some neurosurgeons employ two leads in parallel, driven by a pulse generator having 8 output connections (Synergy, Medtronic). To allow sufficient flexibility in positioning the lead(s), the craniotomy should have a diameter of about 5 cm.

Although in some centres the electrode array is placed on the precentral gyrus (PG) parallel to the central sulcus (CS), it is now believed that most pain relief can be obtained when the lead is placed across CS and stimulation is applied bipolarly with the negative pole (cathode) anteriorly over motor area 4 on PG and the positive pole posteriorly over CS or the postcentral gyrus (PoG, somatosensory cortex, area 3). In chronic stimulation the pulse amplitude is generally less than 50% of the threshold magnitude of a motor-evoked potential (MEP) in the painful body region. The stimulus pulse parameters for chronic stimulation have the following values: amplitude: 2–7 V, duration: 30–450 msec and rate: 20–110 pps. In contrast to SCS, MCS is not accompanied by the perception of paresthesia, thus allowing the performance of double blind studies.

Theoretical aspects

Cathodal and anodal stimulation

Although in MCS bipolar stimulation is considered to be superior to monopolar cathodal stimulation, it was believed that the anode is an indifferent electrode, unable to evoke any neuronal activity in the underlying cortex. This assumption was based on the role of anodes in peripheral nerve stimulation (PNS) and SCS. In these applications nerve fibres are oriented either parallel to the electrode array (peripheral nerves, dorsal columns), or tangential (dorsal spinal roots). These axons are depolarized and eventually excited near a cathode and hyperpolarized near an anode [11, 18, 28]. Although excitation of these fibres can be obtained by anodal stimulation as well, the current needed is 3–7 fold the cathodal threshold current [3], which is far beyond the clinical amplitude range in SCS [10] and PNS [33].

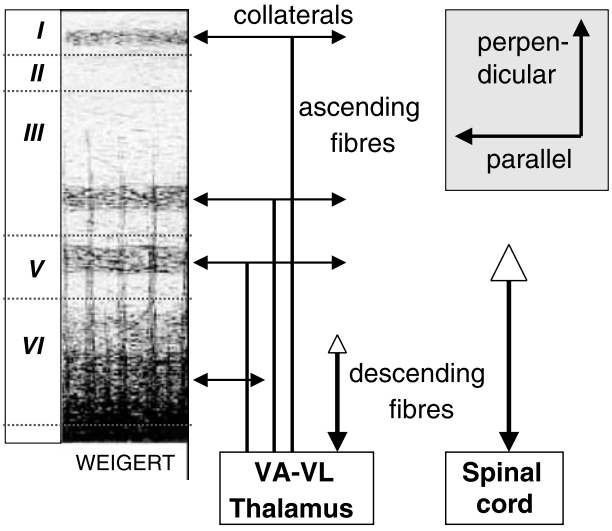


Fig. 1. Weigert-stained microscopic cortex slice showing the orientation of ascending and descending 'perpendicular' fibre tracts and 'parallel' fibres (collaterals and other intracortical connections in parallel to the cortical layers)

Mathematical models of neurostimulation

In 1879 Fritsch and Hitzig [5] were the first to report on the superior excitability of the cerebral cortex in surface anodal stimulation. This early finding has been confirmed both by mathematical modelling and experimental studies.

Struijk *et al*. [31] used a simple analytical model employing cathodal and anodal point source electrode(s) in a homogeneous conducting medium to predict the response of myelinated nerve fibres having different orientations to an SCS electrode array. They modelled monopolar cathodal and anodal, as well as bi-, tri- and quadrupolar stimulation. More recent models included point source stimulation of complete neuron models [17, 29] instead of myelinated axon models with sealed ends, and an inhomogeneous model of human motor cortex with realistic geometry and electrode dimensions [15]. All these models led to the prediction that *cathodal* stimulation on the distal side of the dendritic tree of e.g., a pyramidal tract neuron will depolarize (the distal parts of) the dendritic tree and hyperpolarize the initial segment and proximal part of their axon. *Anodal* stimulation has the opposite effect and may thus result in action potential generation and propagation along the corticospinal tract [2].

Nerve fibre orientation and effect of stimulation

Most cortical nerve fibres are present in bundles perpendicular to the cortical surface and in layers parallel to this surface and will be indicated accordingly in this chapter (see Fig. 1). 'Perpendicular' axons constitute the ascending (thalamo-cortical, cortico-cortical, etc.) and descending pathways (cortico-spinal, cortico-thalamic, cortico-cortical etc.), whereas 'parallel' fibres include their collaterals and intracortical connections. In the convexity of a cortical gyrus these axons are either parallel to the plane of the overlying (epidural) electrode array, or pointing (on their dendritic side) towards an overlying electrode.

In accordance to the modeling predictions focal *cathodal* stimulation on the surface of a gyrus will activate 'parallel' fibres and inactivate (hyperpolarize) 'perpendicular' fibres in the underlying cortex, whereas *anodal* stimulation will activate 'perpendicular' fibres and hyperpolarize 'parallel' fibres. The effects of cathodal and anodal monopolar stimulation are summarized in Fig. 2.

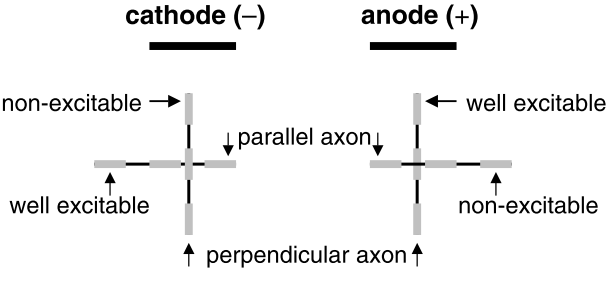


Fig. 2. Response of 'perpendicular' and 'parallel' cortical fibres to focal cathodal and anodal stimulation on the convexity of a gyrus; well excitable and non-excitable indicates that the fibre membrane is depolarized and hyperpolarized, respectively

Bipolar and bifocal stimulation

In *MCS*, pulses are generally applied bipolarly with two adjacent disc electrodes having a center separation of 10 mm. Amassian *et al*. [1] assumed that a major difference in current distribution would exist between mono- and bipolar stimulation, the latter favoring the activation of nerve fibres parallel to the bipole axis (particularly in layer I) rather than 'perpendicular' fibres. Using their computer model of motor cortex with realistic geometry and tissue conductivities, Manola *et al*. [15] calculated the electrical fields evoked by stimulation with two adjacent epidural electrodes. They concluded that an electrode distance of 10 mm allows only minor mutual influence of the cathodal and anodal fields in the underlying cortex, so that the cathode and the anode can be considered as virtual monopoles. Since both the cathode and the anode are capable of recruiting (different types of) cortical nerve fibres, bipolar stimulation should be considered as potentially *bifocal* stimulation.

Whether nerve fibres are actually stimulated near the cathode, the anode or both depends primarily on the cathodal and anodal threshold stimuli needed for their activation. Thereby, it should be considered that the magnitude of the anodal and cathodal electrical fields in the cortex and thus the threshold stimuli, are strongly influenced by the thickness of the well-conducting cerebrospinal fluid (CSF) separating each electrode and the cortex. If e.g., the thickness of the CSF-layer under the anode and the cathode would be similar, stimulation might be bifocal, whereas a different thickness would result in stimulation near the electrode with the smallest CSF-layer only. A smaller CSF-layer is accompanied by a higher current density in the cortex and thus a lower threshold current. The effect of the CSF-layer thickness (0–2.5 mm) on the depth of the electrical field in a gyrus when a stimulus of 1 V is applied is illustrated in Fig. 3.

When a stimulating electrode is centered above the convexity of PG, some 'perpendicular' fibres are pointing towards this electrode, as indicated by fibre 1 in Fig. 4. These fibres will be activated at anodal stimulation only. In contrast, 'parallel' fibres are likely to be most excitable when stimulated with a cathode. This simple principle, however, only holds for nerve fibres in the convexity of a gyrus.

Stimulation applied over a sulcus wall or lip

Due to the presence of cortical sulci, the previously introduced rule is not appropriate for cortical regions in a sulcus wall or its lip. The orientation of, e.g., the motor

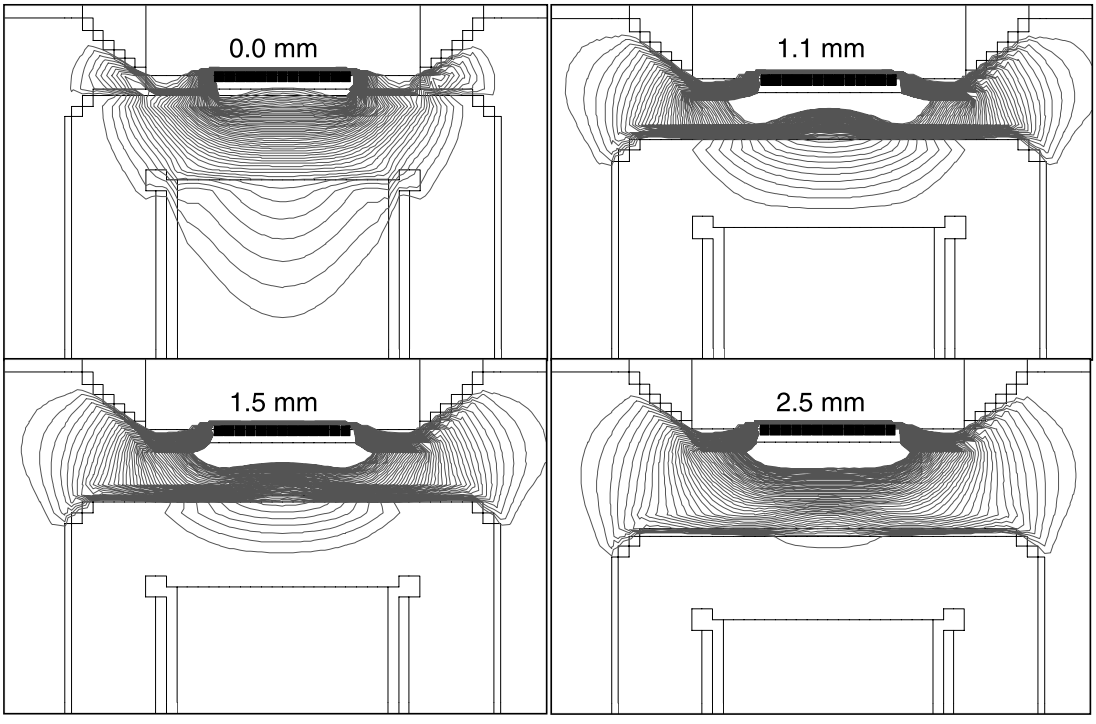


Fig. 3. Current-density fields calculated in computer models of MCS; monopolar stimulation at 1 V by a 4 mm disc electrode in the epidural space, centered on the convexity of the gyrus; models with cerebro-spinal fluid layers 0–2.5 mm; 55 equidistant iso-current density lines 5–60 $\mu A/mm^2$

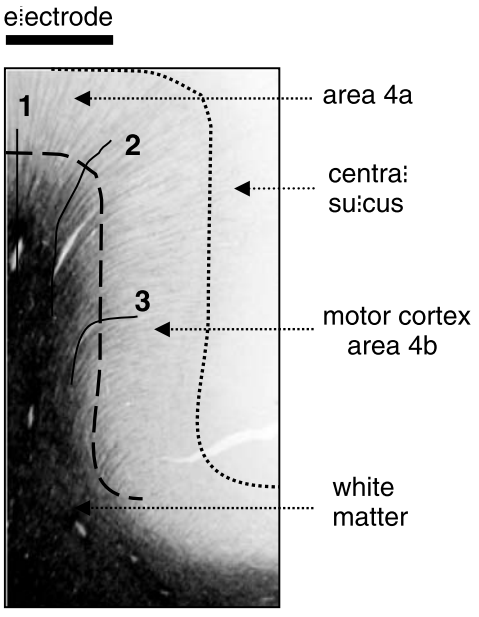


Fig. 4. 'Perpendicular' fibres originating at different positions in the precentral gyrus; *fibre 1* in the center, *fibre 2* in the lip of the anterior wall, and *fibre 3* deep in the anterior wall of the central sulcus

cortex in the anterior wall of CS (area 4b) and all corresponding nerve fibres is changed relative to the overlying epidural electrode. Because the stimulus-induced field has changed as well [16], the stimulation conditions of all fibre types are different. Because the initial part of the 'perpendicular' fibres (within the gray matter) is still positioned almost normal to the cortical layers, these fibres have different orientations according to their position (ranging from the convexity of PG to deep in CS). In contrast to fibre 1 in Fig. 4, pointing towards the electrode and being excitable by anodal pulses only, the proximal (intracortical) segment of fibre 3 (in the anterior wall of CS) is almost parallel to the epidural disc electrode and needs less current for its activation when the electrode is a cathode. The 'perpendicular' fibre in the anterior lip of CS (fibre 2 in Fig. 4) has an intermediate orientation and may be activated by both anodal and cathodal stimulation. Due to the favorable orientation of its proximal segment it is predicted that fibre 3 needs less cathodal current for its excitation than fibre 2, despite its larger distance from the electrode [15]. Similarly, 'parallel' fibres (of the same calibre) in the anterior wall of CS, need least current for their activation when stimulated anodally. The various nerve fibre types in the motor cortex should, therefore, not be considered as uniform populations regarding their response to epidural stimulation, because their excitability varies with their position.

In the next sections, electrophysiological studies on motor cortex stimulation in cats and monkeys and in chronic pain patients treated with MCS are discussed and compared with predictions arising from the theoretical approach presented in this section.

Experimental studies

Direct (D-wave) and indirect (I-wave) responses

In various electrophysiological studies on both cats and monkeys it has been shown that focal, monopolar stimulation with single stimuli on the surface of the exposed PG may result in two types of responses as recorded from the corticospinal tract: 1) a short latency, direct response (D-wave) resulting from direct activation of pyramidal axons either at their initial segment or at a proximal node of Ranvier in the subcortical white matter; 2) longer latency, indirect responses (I-waves) most likely resulting from indirect, mono- or polysynaptic activation of pyramidal tract cells [1, 6, 9, 23–25]. I-waves generally constitute a complex of several consecutive MEPs at intervals corresponding to the synaptic delays. In cats and monkeys, the response to anodal stimulation was a short latency D-wave, whereas cathodal stimulation initially evoked a polyphasic I-wave complex with a longer delay and a higher threshold. When stimulating the hand region of the baboon in the convexity of PG with a cathode, Hern *et al.* [9] reported that the threshold to activate pyramidal tract cells was about 50–400% higher than in anodal stimulation and that this difference is inversely related to the anodal threshold amplitude. Gorman [6] observed that in focal cathodal stimulation at the surface of the cat motor cortex, the I-wave had a lower threshold than the D-wave. In several studies, the response of pyramidal tract cells to cortical surface stimulation was recorded intracellularly. Purpura and McMurtry [26] reported that, in cats, these neurons were depolarized by an anodal stimulus, whereas a cathodal stimulus caused their hyperpolarization. Rosenthal *et al.* [30] recorded pyramidal cell responses in cat motor cortex and observed that the I-wave was preceeded by an EPSP, delaying the response by 0.9 msec. In contrast to pyramidal cells, non-pyramidal cells in the superficial cortical layers were usually hyperpolarized by anodal stimulation [26].

These studies generally confirm the hypotheses that in the convexity of PG: (1) cortico-spinal tract ('perpendicular') fibres approximately pointing at the overlying electrode are excited at a lower magnitude in anodal than

in cathodal stimulation, thereby evoking a D-wave and an I-wave complex, respectively; (2) at supra-threshold anodal stimulation the D-wave may be followed by an I-wave complex, whereas in cathodal stimulation a D-wave may follow the initial I-wave(s); (3) 'parallel' fibres, running almost normal to the cortico-spinal tract fibres (and thus almost parallel to the plane of the epidural electrode) are more likely excited at cathodal stimulation. The latter fibres have both mono- and poly-synaptic connections with cortico-spinal tract fibres [1]. Their (cathodal) stimulation may thus result in consecutive responses of corticospinal tract fibres (MEPs) with increasing delays instead of a non-synaptic, direct response following anodal stimulation.

Because the architecture of the motor cortex is more complex than the simplified models, the responses to focal anodal and cathodal surface stimulation on the convexity of PG cannot be defined so strictly. Only within a limited anodal current range pyramidal tract fibres are recruited selectively. At higher intensities the D-wave is followed by an I-wave complex. The opposite happens in cathodal stimulation: the initial I-wave is accompanied by an earlier D-wave at a slightly suprathreshold stimulus magnitude. Accordingly, the stimulus amplitude ratio D/I is generally higher in anodal than in cathodal surface stimulation [1].

Contrary to model predictions, Hern *et al.* [9] reported that the region of the cat motor cortex with the lowest threshold for anodal surface stimulation was always centered on the anterior lip of CS, whereas the region of minimum threshold in cathodal stimulation was more anteriorly in PG, but still overlapping the 'anodal' area. This inconsistency may be explained by the abnormal architecture of large cortico-spinal tract cells in the uppermost part of CS, having a reversed orientation with respect to the exposed surface of the brain [1, 8].

Bipolar stimulation

Because bipolar MCS can actually be considered as bifocal stimulation [1, 25], it can be predicted from the experimental and modelling studies which category of cortical nerve fibres ('parallel' or 'perpendicular') is most likely recruited in the vicinity of either the cathode or the anode, or both. It has been shown that in the convexity of PG the threshold stimulus for the recruitment of ('perpendicular') corticospinal tract fibres, evoking a D-wave, is minimal in anodal stimulation [9, 15]. Furthermore, the threshold stimulus for the recruitment of 'parallel' fibres, evoking I-waves, is lowest in cathodal stimulation, but higher than in anodal stimulation of 'perpendicular' fibres [6, 23]. When increasing the amplitude in bipolar stimulation, pyramidal tract fibres near the anode will generally be recruited first. At a somewhat higher magnitude, 'parallel' fibres will be recruited in the vicinity of the cathode. Finally, either 'parallel' fibres near the anode or 'perpendicular' fibres near the cathode, or both, may be recruited as well. As discussed earlier in this chapter, the recruitment order will be affected by the thickness of the CSF-layer below the anode and the cathode. The only certainty is that in bipolar stimulation the cathodal and anodal currents are identical.

Clinical studies

Cathodal and anodal stimulation

The localization of a specific somatotopic area in the motor cortex is the initial step in several neurosurgical procedures, such as cortical ablation and neuromodulation. In MCS, a craniotomy is made around PG and a linear-electrode array is placed either epidurally or subdurally over a cortical region including PG. Single stimuli are generally applied monopolarly by each cortical electrode and/or bipolarly by various electrode combinations. Electrodes for surface electromyographic (EMG) recording are placed over one or more muscles in the painful body area. The recorded MEPs are generally characterized by a few parameters, including their peak–peak amplitude. In some studies evoked responses of the corticospinal tract have been utilized [12].

Katayama *et al*. [12] stimulated various cortical sites of the exposed brain in 20 patients under general anesthesia to identify the motor cortex. The stimulating electrode had four disc contacts of 5 mm diameter and 10 mm center-to-center spacing. Single pulses were applied either monopolarly, or bipolarly with various anode–cathode combinations. The responses evoked in the cortico-spinal tract were recorded with wire electrodes placed in the spinal epidural space. Katayama *et al*. reported that the evoked potentials had similar characteristics as the D-wave in cats and monkeys. The stimulus-response delays were so short that the responses could not be mediated by one or more synapses, whereas the threshold current was generally lower in anodal than in cathodal monopolar stimulation. When stimuli of the same magnitude were applied monopolarly, the evoked potential was slightly larger in anodal than in cathodal stimulation [12, 13]. Katayama *et al*. [12] also reported

that the amplitude of the D-wave increased when the bipolar distance was increased (from 10 up to 30 mm). (See also Final remarks: Effect of bipole distance on MEP amplitude.) Moreover, when applying a stimulus of high amplitude they observed that in some patients the D-wave was followed by up to 3 waves resembling the synaptically mediated I-waves evoked in animals. Katayama *et al*. also observed that D-waves are resistant to anesthesia and muscle relaxants, whereas I-waves are vulnerable to the depth of anesthesia and that their shape is affected by the modality of stimulation (cathodally, anodally or bipolarly).

Bipolar stimulation

Generally, the initial response to bipolar stimulation of the motor cortex will be elicited near the anode. Some conditions may, however, favor an initial response evoked near the cathode [7, 12]. This could happen when the anode is situated near or above CS and the cathode is above the convexity of PG, or when the thickness of the CSF-layer in the vicinity of the two electrodes (separated by 10–30 mm centre–centre) is different. If under the anode the thickness of this layer would exceed the value below the cathode, the threshold amplitude of the latter might become lower than the anodal one.

When stimuli are suprathreshold, cortical nerve fibres in the vicinity of both the anode and the cathode may evoke a response (bifocal stimulation). Because the electrodes constituting a bipole are at least 10 mm apart, the anode and the cathode may either stimulate parts of the same somatotopic region or representations of different body areas, thus complicating the localization of a target area. A simple way to avoid this problem is by stimulating monopolarly (anodally) instead of bipolarly.

Nguyen *et al*. [21, 22] placed one quadrupolar SCS lead (Resume) or two leads in parallel on the exposed dura mater in the target region as identified by fMRI. The electrode arrays were placed across CS, thus covering part of motor area 4 and premotor area 6 (together constituting PG) and area 3 (PoG). Single pulses of the same magnitude and duration were applied bipolarly with 14 different cathode–anode pairs and MEPs were recorded from a few muscles in the painful body area(s). Those bipolar combination(s) generating MEPs with the largest peak–peak amplitude were assumed to be closest to the cortical somatotopic representation of the corresponding muscle. Surgery was completed when an adequate muscle response was obtained. In the following days, the analgesic effect of stimulation was tested with various bipolar combinations at a stimulus magnitude of 20–30% of the MEP threshold. Generally, the most pain relieving combination had the cathode on PG and the anode at the adjacent electrode on the posterior side, being either above CS or PoG.

The bipoles giving the largest intra-operative motor responses and those giving most pain relief in a series of 19 patients are represented by the positions of their cathodes in Fig. 5a and b, respectively. In each figure, the spatial distribution is in accordance with the somatotopy of the sensorimotor cortex: from the face on the inferior side via the hand, upper limb, thorax, abdomen and pelvis to the lower limb on the superior side. When, however, the distributions of the cathodes representing the bipoles evoking the largest MEPs and those giving most pain relief are compared, an obvious difference in their distribution can be observed. The cathode positions

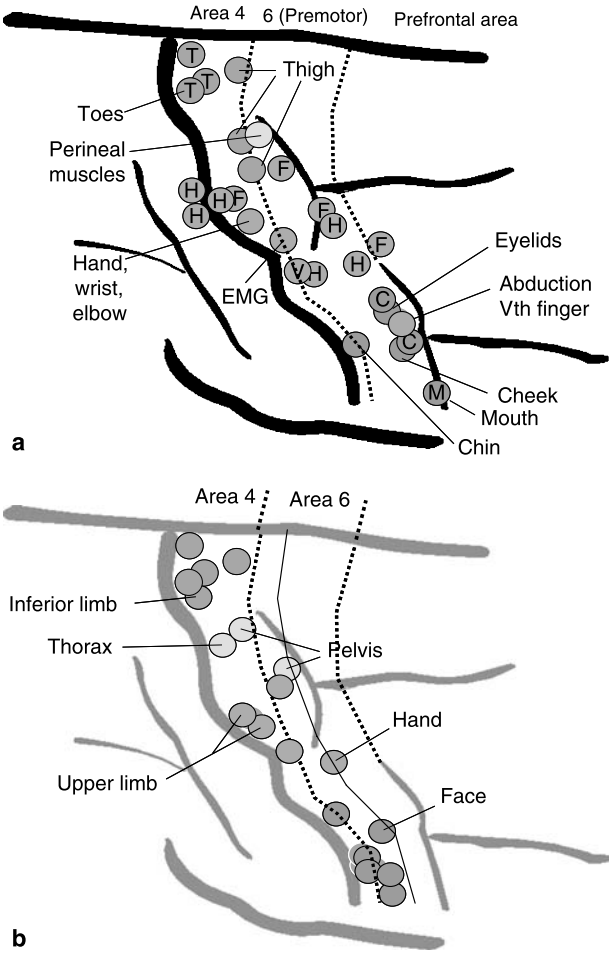
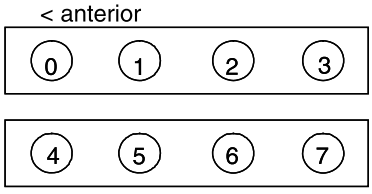


Fig. 5. Positions of the cathode in bipolar motor cortex stimulation in 19 patients: (a) corresponding to largest MEPs in intra-operative target localization; (b) corresponding to most relief of chronic pain in post-operative stimulation; reproduced with permission from Nguyen *et al*. [22]



a

Bipoles		V_{p-p}	
Cathode	Anode	[μV]	%
0	1	19	21
1	2	52	57
2	3	14	15
0	2	91	100
1	3	34	37
4	6	50	55
5	7	22	25
2	6	55	60

b

Bipoles		V_{p-p}	
Cathode	Anode	[μV]	%
5	6	56	20
6	7	278	100
0	2	14	5
4	6	237	85
5	7	179	64
2	6	44	16
3	7	110	40

Fig. 6. Bipolar combinations eliciting *MEPs* in deltoid (a) and first interosseus muscle (b) in a patient during intra-operative testing; cathode and anode numbers correspond to electrode numbers 0–7 on top of this Fig. V_{p-p}: peak–peak amplitude of *MEP* in microVolt and percentage of highest value of each muscle

evoking the largest motor effects (Fig. 5a) are present in most parts of motor area 4 and premotor area 6, and a few posterior to CS in somatosensory area 3. In contrast, the cathode positions inducing the analgesic effect (Fig. 5b) are generally confined to motor area 4, although they seem to extend in the adjacent (posterior) part of area 6. (See also Final remarks: How well can a cortical target be covered by MCS.) The large difference in cathode distributions shown in Fig. 5a and b suggests that the cathode position of a bipole evoking the largest MEPs is unlikely to be a reliable predictor of the cathode position inducing a satisfactory analgesic effect in the same somatotopic area.

In the previous sections it has been shown that the recruitment of a muscle may result from both cathodal and anodal stimulation on the cortical surface, or epidurally. A larger stimulus is, however, needed in cathodal than in anodal stimulation to elicit an I-wave (if evoked at all under general anesthesia [12]) and a D-wave, respectively. Because stimulation was applied bipolarly and the cathodal and anodal currents have the same magnitude, it is most probable that MEPs are generated primarily near the anode of a bipole. This hypothesis was tested in a detailed analysis of the intra-operative MEPs elicited by supra-threshold pulses of the same magnitude (30–40 mA) and duration (2 msec) applied with 14 different cathode–anode combinations in each of five patients.

In Fig. 6 all bipoles evoking a MEP in the deltoid (a) and first dorsal interosseus muscle (b) of a patient, as well as the corresponding peak–peak amplitudes (V_{p-p}) of the MEPs are shown. The electrode numbers are indicated on top of this table and V_{p-p} is given in both microVolts and as a percentage of the largest MEP recorded from the same muscle. The cortical representation of a body area will generally coincide with the cathode or anode position providing the largest MEP in that area (V_{max}), whereas V_{p-p} will decrease with increasing distance from this location. To determine whether MEPs of the two muscles tested in each patient were elicited by cathodal or anodal stimulation, we allocated the V_{p-p} values exceeding 70% of V_{max} to the cathode and anode positions of the corresponding bipoles. In Fig. 7a and b, the data of two patients are shown in four 2×4 electrode arrays: the upper and lower ones for the cathodes and anodes, respectively, and the left and right ones for one muscle each. Two ranges of V_{p-p} values are distinguished: 70–90% and 90–100% of V_{max}, and the corresponding electrodes are gray and black, respectively. Moreover, the approximate position of CS with respect to the 2×4 electrode array is indicated by a straight line and the most likely position of a muscle's somatotopic representation by a gray oval, generally overlapping two adjacent electrodes.

The distributions of the cathodal and anodal electrodes with V_{p-p} 70–100% of 5 patients were evaluated according to the following criteria: (i) each muscle is represented by a unique (or 2 adjacent) electrode(s); (ii) the cathodes and/or anodes have a similar distribution as the cathodes in chronic stimulation for pain management as shown in Fig. 5b. The *anodes* related to 8 out of 9 muscles were uniquely located immediately anterior to CS (3 cases) or on both sides at adjacent electrodes (5 cases), as shown by the black and gray circles surrounded by gray ovals in Fig. 7. Only 2 out of 9 muscles were represented by a *cathode* close to CS, one of them not being unique but accompanied by a second one anteriorly (electrodes 2–3 and 4–5 in Fig. 7b, fdi-muscle). As shown in Fig. 7c most *cathodal* representations were on the frontal side of the electrode array (most likely on area 6), whereas *anodal* representations were lacking on that side.

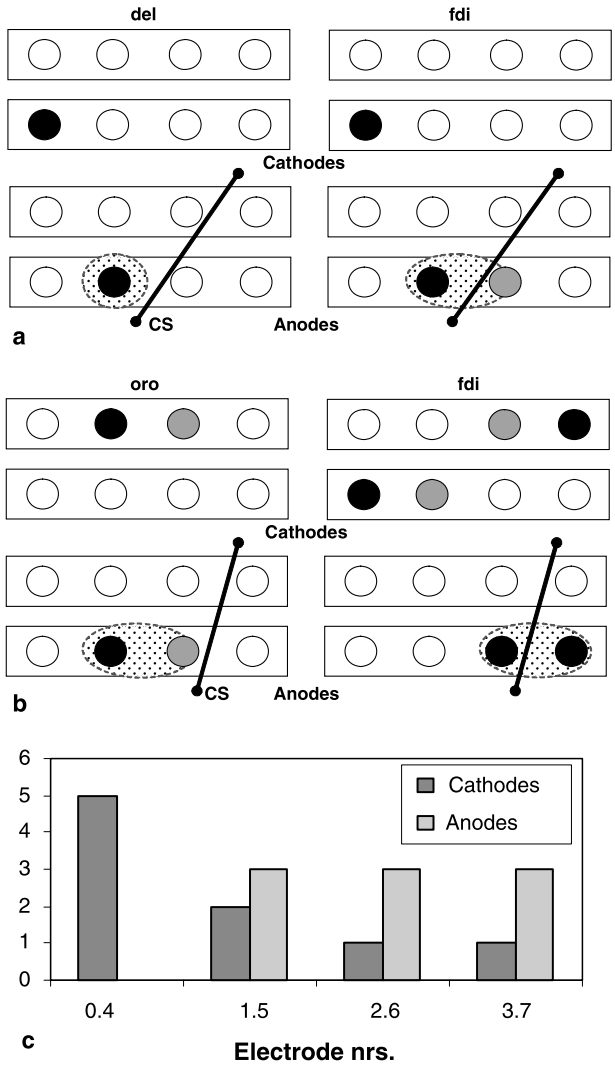


Fig. 7. Electrodes of 2×4 arrays and related MEP amplitudes when used as cathodes (top rows) and anodes (lower rows) of different bipoles in 2 patients (a and b) and 2 muscles each (left and right); electrode numbers shown on top of Fig. 6 (nrs. 0 and 4 on frontal side); amplitudes indicated as % of highest value of each muscle: 0–70% – white, 70–90% – gray, 90–100% – black; CS approximate position of central sulcus; oval area: approximate cortical region giving largest MEP; *del* deltoid muscle; *fdi* first dorsal interosseus muscle; *oro* orbicularis oris muscle; c distribution of largest cathodal and anodal MEPS of all 9 muscles

Finally, the positions of the *anodes* giving the largest MEPs have been compared with the *cathodal* position(s) selected postoperatively for maximum pain relief by each patient. The results shown in Table 1 clearly indicate that the anodal and cathodal positions correspond well, although the cathode selected for pain relief sometimes correspond with an adjacent anode eliciting a MEP with a somewhat smaller V_{p-p} (<100%). The most probable explanation is that V_{p-p} varies with the anode-cathode distance in bipolar stimulation (see Closing remarks: Effect of bipole distance on MEP amplitude). It is concluded that the *anodal* electrode eliciting the largest MEP in the painful body region is most likely providing most pain relief when programmed as a *cathode*.

Table 1. *Cathode giving most pain relief and anode(s) eliciting largest MEPs in 5 patients; cathode and anode numbers correspond to electrode numbers 0–7 (top of Fig. 6)*

Patient	Pain relief	MEPs		
	Cathode(s)	Anode(s)	V_{p-p} in %	Muscle
1	2	2 & 6	100 & 94	fdi
2	6	6 & 7	99 & 100	fdi
3	2	2 & 6	75 & 100	fdi
4	2 & 6	2 & 6	100 & 60	del
5	2	2 & 5	67 & 100	del

Closing remarks

How well can a cortical target be covered by MCS

The optimal condition for MCS is that, one of the active electrodes is centered on the cortical area to be stimulated, because the efficacy of stimulation decreases when the distance between the electrode and the cortical target is increased. Taking into account that a 6 mm space is present between the edges of the 4 mm wide disc electrodes, the probability that the centre of a cortical target area coincides with one of the electrodes is low.

The target may as well be centered in the 6 mm wide space between adjacent electrodes or aside the electrode array where cortical tissue needs a higher stimulus to be activated. When the target would be centered exactly between adjacent electrodes on a lead, anodal (or cathodal) stimulation by each one would ideally give the same response. When instead, the target is more than 5 mm apart from the centre of one electrode and less than 5 mm from the adjacent one, the effect of stimulation by the latter will most probably be strongest. When the stimulus applied is sufficiently large, the effective radius of a stimulating electrode may exceed the radius of the electrode (2 mm), thus making the electrode position less critical. The precision of MCS would, however, be enhanced when the average distance between the stimulating electrode and the cortical target would be reduced. Another benefit of a smaller contact spacing would be a reduction of the energy consumption by the pulse generator.

Although several cathodes shown in Fig. 5b are situated on premotor area 6, most are centered less than 5 mm anterior to the boundary between areas 4 and 6

(as indicated in Fig. 5b by the thin line 5 mm anterior to this boundary). Therefore, the pain relieving targets of these electrodes may still be located exclusively in motor area 4.

Effect of bipole distance on MEP amplitude

Katayama *et al*. [12] reported that the amplitude of the D-wave increased when the anode–cathode distance was increased from 10 to 30 mm (center-to-center). Our data on 5 patients generally support this observation, but only if the anode is kept in place and the cathode is displaced. As shown in Fig. 6a anode 2 evokes a larger V_{p-p} in combination with electrode 0 (91 μV) than with electrode 1 (52 μV) as the cathode, and anode 3 gives a larger V_{p-p} with electrode 1 (34 μV) than with electrode 2 (14 μV) as the cathode. From Fig. 6b it is shown that anode 6 evokes a larger V_{p-p} when electrode 4 is the cathode (237 μV) than with 5 (56 μV) or 2 (44 μV). This observation also provides additional evidence for the previous conclusion that MEPs are elicited by the anode of a bipole.

Because the magnitude of a MEP varies with the size of the stimulating bipole and since the set of bipoles for intra-operative stimulation generally includes different anode–cathode distances, the bipole eliciting the largest MEP may not be the optimal choice for therapeutic stimulation. A second disadvantage of bipolar stimulation is the probability of bifocal stimulation. To identify the best electrode unambiguously, monopolar cathodal and anodal stimulation should be applied.

Which cortical nerve fibres mediate the analgesic effect of MCS

The data presented in this chapter may be helpful to unravel which cortical nerve fibres will most likely be activated in order to bring about pain relief. It has been shown that anodal epidural stimulation of any part of motor area 4 results in a low threshold, direct (non-synaptically mediated) MEP of the corresponding muscle(s), whereas cathodal stimulation at the same location and a 50–70% lower magnitude results in pain relief. Abundant evidence is present to confirm that epidural anodal stimulation immediately activates descending corticospinal nerve fibres originating from primarily large pyramidal (Betz) cells in layer V of motor area 4. Conversely, cathodal stimulation activates most probably large myelinated fibres parallel to the cortical layers, including: (i) collaterals of specific thalamocortical projections from ventrolateral-ventral anterior (VL-VA) thalamic nuclei, (ii) collaterals of cortico-cortical projections, particularly from the postcentral and premotor cortex, (iii) intrinsic cortical connections in parallel to the cortical layers (1). Those 'parallel' nerve fibres activated at a low stimulus level (20–50% of the motor threshold) constitute most likely the initial link of the neuronal chain(s) finally resulting in the relief of pain perception.

The main parameters determining the excitability of a nerve fibre are its diameter and shape, as well as its position with respect to the stimulating electrode [15]. Fibres with a low threshold when stimulated epidurally with a cathode would most likely be large diameter 'parallel' fibres in layers I, V or VI of motor area 4. However, almost no morphometric data on the diameter distributions of these fibres could be found in the literature. The largest nerve fibres are of particular interest because they will generally be activated by the weakest stimulus.

Finally, it should be considered that nerve fibre action potentials elicited by electrical stimulation will generally propagate both orthodromically and antidromically. If, for example, large fibres of a specific thalamocortical projection from VL-VA thalamic nuclei would be activated by MCS, these fibres might antidromically impose an effect on VL-VA thalamic nuclei via the intrathalamic collaterals of these fibres.

References

1. Amassian VE, Stewart M, Quirk GJ, Rosenthal JL (1987) Physiological basis of motor effects of a transient stimulus to cerebral cortex. Neurosurg 20: 74–93
2. Basser PJ, Roth BJ (2000) New currents in electrical stimulation of excitable tissues. Ann Rev Biomed Eng 2: 377–397
3. BeMent SL, Ranck JB (1969) A quantitative study of electrical stimulation of central myelinated fibers with monopolar electrodes. Exp Neurol 24: 147–170
4. Brown JA, Barbaro NM (2003) Motor cortex stimulation for central and neuropathic pain: current status. Pain 104: 431–435
5. Fritsch G, Hitzig E (1879) Über die elektrische Erregbarkeit des Grosshirns. Arch anat physiol Wiss Med 37: 300–332
6. Gorman ALF (1966) Differential patterns of activation of the pyramidal system elicited by surface anodal and cathodal cortical stimulation. J Neurophysiol 29: 547–564
7. Hanajima R, Ashby P, Lang AE, Lozano AM (2002) Effects of acute stimulation through contacts placed on the motor cortex for chronic stimulation. Clin Neurophysiol 113: 635–641
8. Hassler R, Muhs-Clement K (1964) Architektonischer Aufbau des sensomotorischen und parietalen Cortex der Katze. J Hirnforsch 6: 377–420
9. Hern JEC, Landgren S, Phillips CG, Porter R (1962) Selective excitation of corticofugal neurones by surface-anodal stimulation of the baboon's motor cortex. J Physiol 161: 73–90

10. Holsheimer J (2002) Which neuronal elements are activated directly by spinal cord stimulation. Neuromodulation 5: 25–31
11. Holsheimer J (2003) Principles of neurostimulation. In: Simpson BA (ed) Electrical stimulation and the relief of pain. Pain research and clinical management, vol. 15. Elsevier Science, Amsterdam, pp 17–36
12. Katayama Y, Tsubokawa T, Maejima S, Hirayama T, Yamamoto T (1988) Corticospinal direct response in humans: identification of the motor cortex during intracranial surgery under general anaesthesia. J Neurol Neurosurg Psychiatry 51: 50–59
13. Kombos T, Suess O, Kern B-C, Funk T, Hoell T, Kopetsch O, Brock M (1999) Comparison between monopolar and bipolar electrical stimulation of the motor cortex. Acta Neurochir (Wien) 141: 1295–1301
14. Katayama Y, Kukaya C, Yamamoto T (1998) Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. J Neurosurg 89: 585–591
15. Manola LJ, Roelofsen BH, Holsheimer J, Marani E, Geelen J (2005) Modelling motor cortex stimulation for chronic pain control: electrical potential field, activating functions and responses of simple nerve fibre models. Med Biol Eng Comput 43: 335–343
16. Manola LJ, Holsheimer J (2007) Motor cortex stimulation: role of computer modelling. In: Sakas DE, Simpson BA (eds) Operative neuromodulation, vol. 2: neural networks surgery. Acta Neurochir Suppl 97: 497–503
17. McIntyre CC, Grill WM (1999) Excitation of central nervous system neurons by nonuniform electric fields. Biophys J 76: 878–888
18. McNeal DR (1976) Analysis of a model for excitation of myelinated nerve. IEEE Trans Biomed Eng 23: 329–337
19. Mertens P, Nuti C, Sindou M, Guenot M, Peyron R, Garcia-Larrea L, Laurent B (1999) Precentral cortex stimulation for the treatment of central neuropathic pain. Stereotact Funct Neurosurg 122–125
20. Meyerson BA, Lindblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir [Suppl] 58:150–153
21. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugière P, Pollin B, Fève A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
22. Nguyen JP, Lefaucheur JP, Keravel Y (2003) Motor cortex stimulation. In: Simpson BA (ed) Electrical stimulation and the relief of pain. Pain research and clinical management, vol. 15. Elsevier Science, Amsterdam, pp 197–209
23. Patton HD, Amassian VE (1954) Single- and multiple-unit analysis of cortical stage of pyramidal tract activation. J Neurophysiol 17: 345–363
24. Phillips CG (1956) Cortical motor threshold and the thresholds and distribution of excited Betz cells in the cat. Quart J Exp Physiol 41: 70–84
25. Phillips CG, Porter R (1962) Unifocal and bifocal stimulation of the motor cortex. J Physiol 162: 532–538
26. Purpura DP, McMurtry JG (1965) Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 28: 166–185
27. Rainov NG, Heidecke V (2003) Motor cortex stimulation for neuropathic facial pain. Neurol Res 25: 157–161
28. Ranck JB (1975) Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 98: 417–440
29. Rattay F (1998) Analysis of the electrical excitation of CNS neurons. IEEE Trans Biomed Eng 45: 766–772
30. Rosenthal J, Waller HJ, Amassian VE (1967) An analysis of the activation of motor cortical neurons by surface stimulation. J Neurophysiol 30: 844–858
31. Struijk JJ, Holsheimer J, van Veen BK, Boom HBK (1991) Epidural spinal cord stimulation: calculation of field potentials with special reference to dorsal column nerve fibers. IEEE Trans Biomed Eng 38: 104–110
32. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
33. Wee AS (2001) Anodal excitation of intact peripheral nerves in humans. Electromyogr Clin Neurophysiol 41: 71–77

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Somatosensory cortex stimulation for deafferentation pain

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Summary

Functional neuroimaging has demonstrated that a relationship exists between the intensity of deafferentation pain and the degree of deafferentation-related reorganization of the primary somatosensory cortex. It has also revealed that this cortical reorganization can be reversed after the attenuation of pain. Deafferentation pain is also associated with hyperactivity of the somatosensory thalamus and cortex. Therefore, in order to suppress pain, it seems logical to attempt to modify this deafferentation-related somatosensory cortex hyperactivity and reorganization. This can be achieved using neuronavigation-guided transcranial magnetic stimulation (TMS), a technique that is capable of modulating cortical activity. If TMS is capable of suppressing deafferentation pain, this benefit should be also obtained by the implantation of epidural stimulating electrodes over the area of electrophysiological signal abnormality in the primary somatosensory cortex. The first studies demonstrated a statistically significant pain suppression in all patients and a clinically significant pain suppression in 80% of them. This clinical experience suggests that somatosensory cortex stimulation may become a neurophysiology-based new approach for treating deafferentation pain in selected patients. In this chapter, we review the relevant recent reports and describe our studies in this field.

Keywords: Neuromodulation; deafferentation pain; neurostimulation; phantom limb pain; somatosensory cortex; transcranial magnetic stimulation; TMS; stimulation.

Introduction

Any lesion along the somatosensory tract can cause deafferentation and lead to the generation of peripheral or central neuropathic pain. Deafferentation leads to phantom sensations in 90–98% of limb amputees [71]. The sensations arise immediately in 75% of the patients, as soon as anesthesia wears of, or they are delayed by two to three weeks in the remaining 25% [71]. Phantom pain, a particular type of phantom sensation, is present in 70% of limb amputees [81]. Even though in 14% of the patients the pain decreases in time [81], it is generally accepted that once the pain continues for more than 6 months it becomes difficult to treat [71]. Several treatments are used with variable success and include medications [30, 63], transcutaneous electrical nerve stimulation, nerve root stimulation, regional nerve blocks, epidural treatments [30], motor cortex stimulation (MCS) [4, 62, 93], and thalamic stimulation [38, 41, 45]. Neurobiological [36, 55], neurophysiological [23, 52] and functional neuroimaging data [10, 23, 50, 52, 66, 70] demonstrate that mechanisms of cortical plasticity are activated and lead to somatosensory cortex reorganization and the associated phantom sensations.

Plasticity in the auditory and somatosensory system

Focal parenchymal development and reorganization in all areas of adult sensory cortex is governed by common mechanisms of synaptic plasticity [6, 21, 77, 92]. These processes have been studied extensively in the auditory system and auditory cortex and they could serve as a model for understanding plasticity in other areas of the sensory cortex. The auditory system develops in two stages [37, 99]. The first stage of synapse or auditory tract formation seems to be genetically determined [83] and requires the release of a chemotropic factor [37, 84]. This is followed by fine-tuning of the synapses leading to the formation of a tonotopic structure [78]. In animals that have been born deaf, the auditory system has a rudimentary tonotopic organization [32, 42]. The development of finely tuned tonotopy, however,

requires electrical activity from auditory input during a critical period [31, 82]. It is the product of self-organization [18] via apoptotic resorption of surplus synapses and neurons [79, 84]. The auditory input only influences the development of tonotopy, but the electrical stimulation of the cochlea can modify the rudimentary tonotopic organization in animals that never had any auditory input [39, 40]. The mature auditory system demonstrates strong capacity for reorganization, adjusting itself to any change in the auditory environment [25, 87]. The tonotopic maps are not rigid and may be altered or reorganized by: a) normal physiological stimuli (such as learning), b) relevant environmental stimuli [25, 74, 97], c) sound overexposure [9], d) partial unilateral hearing loss [19, 31], e) focal electrical auditory cortex stimulation [87, 88], and f) tinnitus [61]. The tonotopic map can, however, also be reorganized via direct cortical stimulation as it has been demonstrated in the big brown bat. Electrical auditory cortex stimulation can change the tonotopic map in the cortex [7], thalamus [104], and inferior colliculus [25, 104] suggesting that the corticofugal pathway is involved in this tonotopical reorganization [87].

The above apply to the somatosensory system as well; the development of somatotopy depends on incoming somatosensory input [101]; any alteration of somatosensory input, whether physiological (discrimination training) [73] or pathological [36] will induce cortical reorganization in the developing or adult somatosensory cortex. The somatotopic map can also be reorganized by direct cortical stimulation [72]. Peripherally induced and maintained reorganization is initiated immediately after injury or training [20, 100]. This first stage lasts from minutes to weeks and leads to axonal growth and synaptic sprouting. If this process is maintained by chronic peripheral input, permanent connections (cortical, thalamothalamic or corticothalamic) develop in the second stage [67, 100] leading to intractable phantom limb pain. Subsequent changes in the peripheral input do not affect the changes of the second stage [100]. This explains why phantom pain becomes very difficult to treat once it has been present for more than 6 months [71]. If phantom limb pain is related causally with cortical reorganization, one would expect the reversal of this reorganization in patients whose neuropathic pain has been treated successfully. This re-reorganization has been demonstrated by magnetoencephalography (MEG) in patients suffering from neuropathic or complex regional pain who become pain free after spinal cord stimulation [53, 89].

Clinical analogy between tinnitus and phantom pain

In addition to the developmental and reorganizational processes, additional common features exist between phantom pain and tinnitus [56, 58, 59, 91]. Both symptoms are wholly subjective sensations that may change in character and quality. Both can be suppressed or relieved by electrical stimulation and both exhibit residual inhibition. Transection of an afferent nerve usually does not help in relieving tinnitus or chronic pain. In both conditions, the ascending system is modified by a descending counterpart, and in both systems ascending and descending fibers make connections with the thalamus and cortex. This leads to similar characteristic symptoms in both tinnitus and phantom pain [58, 59, 91]. A normal stimulus to the skin in patients with phantom pain can create a painful sensation (allodynia), in the same way, patients with tinnitus can perceive a sound as unpleasant or painful. A painful stimulus in patients with phantom pain often generates an explosive and prolonged reaction to the stimulus (hyperpathia) similarly to the hyperacusis in tinnitus patients [57]. The ''wind-up phenomenon'', a worsening of the pain sensation with repeated stimuli of the same intensity is also seen in tinnitus, and the patients describe an increasing unpleasant sensation on repetition of the same sound [58, 59]. Furthermore, a feeling of anxiety, nausea and stress response are often encountered in both phantom pain and tinnitus [58, 59].

Rationale for somatosensory cortical stimulation in deafferentation pain

The neurobiological, pathophysiological and clinical analogies between deafferentation tinnitus and deafferentation pain [33, 56, 58, 59, 91] suggest that the treatment strategy that has been developed recently for treating tinnitus (see chapter on auditory cortex stimulation for tinnitus), could be applied to deafferentation pain as well. This basic strategy can be summarized as follows: 1) phantom phenomena are caused by cortical hyperactivity and reorganization, 2) hyperactivity and reorganization can be demonstrated by functional neuroimaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) or magnetic source imaging (MSI), 3) the area of hyperactivity and reorganization can be influenced by neuronavigated TMS, and 4) if pain is successfully suppressed by TMS, a stimulating electrode can be implanted epidurally over the area of cortical hyperactivity and reorganization, in order to suppress the pain.

Phantom phenomena and cortical hyperactivity and reorganization

The electroencephalogram (EEG) power spectrum (firing rate) and the level of consciousness are correlated [103]; the higher the frequency and the lower the amplitude are, the higher the level of consciousness is. Delta waves (1–3 Hz) are recorded in deep sleep, anaesthesia and coma, and theta waves (4–7 Hz) are noted in light sleep. Alpha waves (8–12 Hz) are detected from sensory areas in resting state with the eyes closed and beta waves (13–30 Hz) are detected frontally when people attend to something; beta waves provide an excitatory background for the appearance of gamma-band oscillations (30–45 Hz) [2]. The synchronization of separate gamma band activities, present in different corticothalamic columns [86], is proposed to bind [28, 29] the dispersed neural gamma activity into one coherent sensory percept [14, 17, 35, 46, 47, 64, 75, 90]. Stimulus-related gamma band activity is similar in the somatosensory and auditory systems (see chapter on auditory cortex stimulation for tinnitus); a first phase locked gamma activity arises as early as 30–70 ms from stimulus onset. The cortical processing of consciously perceived and unperceived somatosensory stimuli is thought to be identical during the first 100–120 ms after stimulus onset [64]. Subsequent (>200 ms), nonstimulus-locked gamma band (28–50 Hz) oscillatory activity reflects consciously perceived stimuli. Somatosensory event-related and phase-ordered gamma oscillations (38–42 Hz), are elicited by the onset of painful stimuli over the corresponding scalp site, and are linearly related to pain perception [16]; gamma2 (38–42 Hz) and gamma3 (42–46 Hz) bands have significant predictive value of pain ratings during pain induction [17]. In other words, synchronized gamma band activity seems to be a necessary prerequisite for the conscious perception of pain [1, 16, 17, 48, 49, 80].

Deafferentation pain is associated with hyperactivity at the somatosensory thalamic [11, 49, 76] and cortical levels [11, 49], and bursting activity at theta frequencies (4–7 Hz) at the thalamic and cortical levels [27, 34, 44]. This coherent thalamic and cortical theta activity is due to the generation of low-threshold calcium spike bursts by thalamic cells [34]. It has been suggested that the

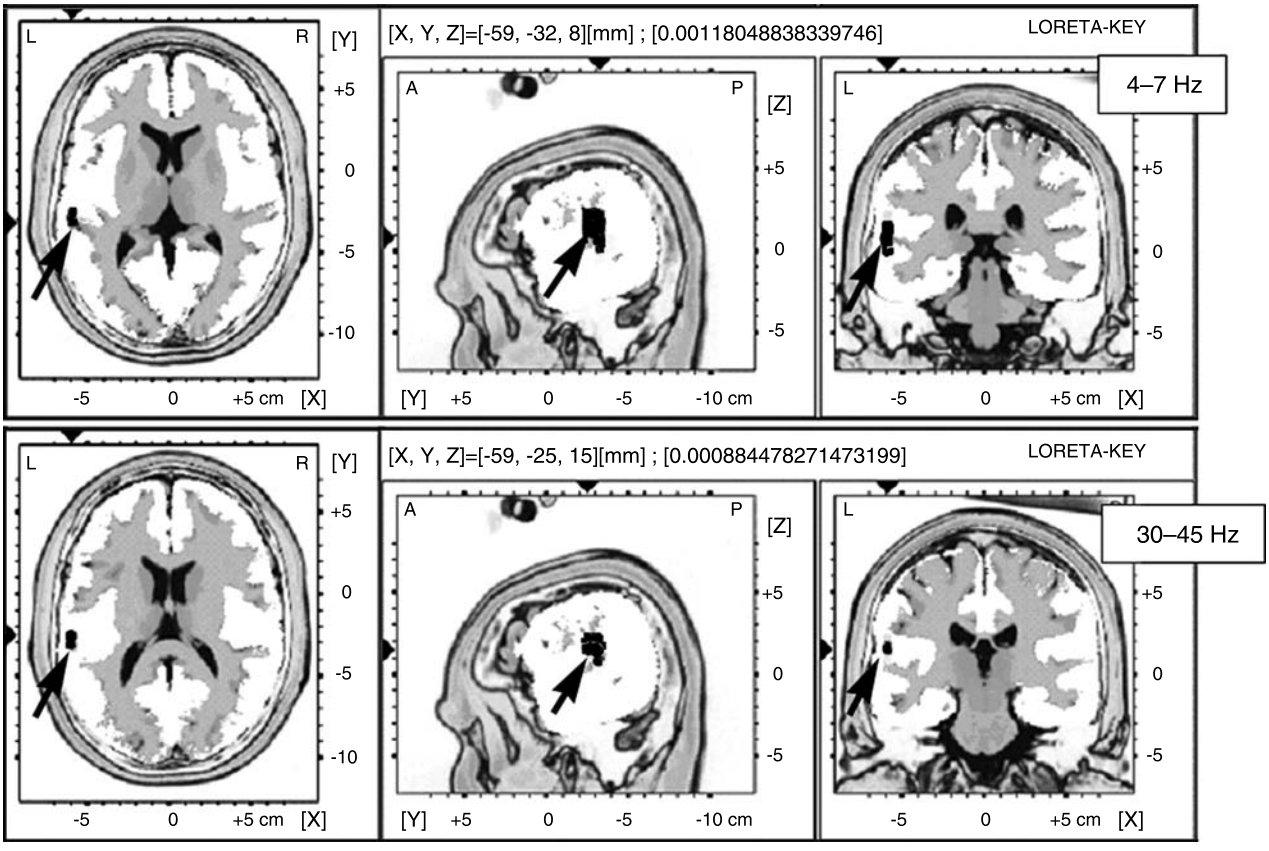

Fig. 1. Loreta transformation [65] of filtered theta and gamma band activity demonstrate thalamocortical dysrhythmia [48, 49] in a patient suffering from unilateral deafferentation pain in the right upper limb region. Note that only in the lower part of the contralateral somatosensory cortex, more pronounced theta and gamma band activity is present

emergence of pain results from ectopic gamma band activation (edge effect) in accordance with the ''thalamocortical dysrhythmia'' model of deafferentation pain [48, 49]. Gamma band activity is normally present in the sensory cortex in locally restricted areas for short times [13, 51]. It has been proposed that this temporal coherence establishes feature specification and cognitive binding through synchronization [11, 29, 85]. The synchronized gamma oscillations, however, persist focally in a pathological state, which is associated with deafferentation pain. This can be detected by quantitative EEG recordings, when filtered at theta and gamma bands. Furthermore, performing low resolution tomographic (loreta) transformations [65] of these filtered EEG data creates a functional image of the spontaneous electrical activity of the brain, depicting the location of the spontaneous ''thalamocortical dysrhythmic hyperactivity'', which is associated with deafferentation pain.

Reorganization of the somatosensory cortex has been visualized using magnetic source imaging (MSI), and a very strong direct relationship ($r = 0.93$) between the amount of cortical reorganization and the intensity of phantom limb pain has been demonstrated [23, 52]. Furthermore, pain related primary somatosensory cortex reorganization [52] reverses simultaneously with clinical improvement [53]. Reorganization and synchronized hyperactivity are most likely related to each other. It has been suggested that synchronized hyperactivity leads to reorganization, based on Hebbian mechanisms (neurons that fire together, wire together) [22]. Thus, deafferentation pain-related synchronized gamma band activity [1, 16, 17, 48, 49, 80] could result in cortical reorganization by stabilizing synchronously firing axons (Hebbian) and segregating non-synchronized thalamocortical input (anti-Hebbian).

Hyperactivity and reorganization on functional neuroimaging

PET [5], fMRI [10, 50] or MSI [23, 52, 98] can demonstrate cerebral alterations in metabolism, blood oxygenation, and magnetic activity, respectively, which are associated with physiological or pathological activity. Event-related synchronization in the gamma band (32–38 Hz) correlates with the BOLD effect on fMRI [3, 24], suggesting that fMRI can visualize the gamma band synchronized activity that is associated with deafferentation pain. fMRI studies in neuropathic pain demonstrate activation in the contralateral primary somatosensory cortex, parietal association cortex, inferior frontal cortex and in the anterior cingulate gyrus, as well as bilateral activation in the secondary somatosensory cortex and the insula [54, 66, 68, 69, 102]. Furthermore, it seems that there is a linear relationship between the intensity of pain and the amplitude of the BOLD signal [60, 69]; however, only the contralateral primary somatosensory cortex can discriminate intensity differences (of 1° centigrade) of small noxious stimuli [60].

Effects of neuronavigated TMS on hyperactivity and reorganization

TMS is an accepted method to study cortical plasticity [12, 94, 95]. It delivers electrical current of up to 8 Amp at the coil and induces a magnetic field pulse of up to 2.5 Tesla. The changing magnetic field creates an electrical field of 500 V/m resulting in neural activity [96]. The area influenced directly by TMS depends on the coil configuration, but averages to a diameter of 3 cm [8]. On initiating the TMS study, the motor cortex is localized by high intensity stimulation, and by decreasing the stimulus intensity to the level that no more contractions of the opponens pollicis can be elicited (motor threshold, MT). Subsequently, the somatosensory cortex is localized by fMRI-based neuronavigation, and magnetic pulses at different frequencies (1, 5, 10 and 20 Hz) are delivered at 90% of MT. Using this technique, 8 patients underwent a fMRI for localizing the area of cortical reorganization. The target was located on the somatosensory cortex, at a site corresponding to the area of pain hyperactivity.

Neuronavigation-guided TMS was able to suppress deafferentation pain (in a placebo-controlled study) in

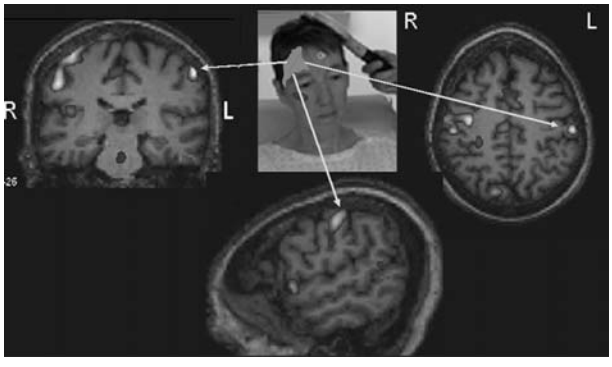

Fig. 2. fMRI-guided TMS for deafferentation pain. The red area corresponds to the deafferented painful area. Green arrows point at the corresponding somatosensory cortex activation area. Note the activation of the anterior cingulated area, bilateral insula periaquaductal grey and contralateral motor cortex area. This motor cortex activation is due to the patient rubbing her right forehead with her left hand in the MRI scanner (Publication of picture with patient's approval)

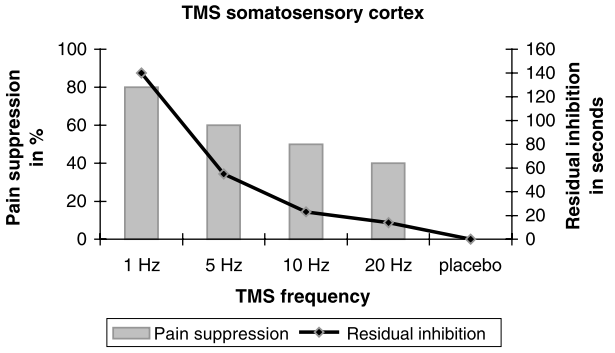

Fig. 3. Illustrative case of TMS effect on the somatosensory cortex; it demonstrates a dose response curve both for pain suppression and residual inhibition. The lower the frequency is the longer the clinical effect on pain suppression lasts

5 of 8 patients. The TMS results of a representative case are shown in Fig. 3 and demonstrate a dose-response curve, for both pain suppression and residual inhibition.

Most TMS studies target the motor cortex. There are multiple arguments for this motor cortex – centered approach. Penfield observed sensory responses during electrical stimulation of the motor cortex in a patient who underwent previously surgical resection of the corresponding somatosensory cortex for treatment of epilepsy [43]. Clinical and experimental data demonstrate the existence of hyperactive thalamic neurons in patients with deafferentation pain compared to controls. These neurons can be inhibited by motor cortex stimulation (MCS); however, somatosensory cortex stimulation had no effect [44, 76, 93]. First clinical experiences with somatosensory cortical stimulation showed either an increase of pain or had no effect [93]. Notably, cortical stimulation with low parameters, both low amplitude and low frequency, prevents the iatrogenic induction of pain or paresthesias by TMS in these patients and is capable of suppressing the deafferentation pain.

Cortical hyperactivity and reorganization: successful pain suppression by TMS and epidural cortical electrode lead

The underlying mechanism of cortical stimulation is not known; it may be related to activation of descending corticofugal axons that cause an increased synaptic activity in the thalamus rather than an activation of apical dendrites in the cortex; this has been demonstrated by PET in humans suffering from pain [26]. Thus, cortical stimulation can activate and increase the firing rate in deafferented neurons, which are normally firing at low frequencies (4–7 Hz); this results in more pronounced lateral inhibition [48] of gamma band hyperactivity, at the lesion margin and, similarly to tinnitus suppression, it deactivates the neural substrate which is responsible for the deafferentation pain (see chapter on auditory cortex stimulation for tinnitus). In 5 patients with deafferentation pain who were treated with somatosensory cortex stimulation, we observed a significant improvement [15]. One advantage somatosensory cortical stimulation might have over MCS is that changing the stimulation parameters has an immediate effect (within seconds), whereas MCS has a delayed effect; this makes the former a lot easier and less time-consuming in programming the stimulation parameters. On the basis of the above findings, it is evident that an important field for investigation will be whether somatosensory cortex stimulation could be capable of treating the same patients as MCS or different categories of patients suffering from phantom pain.

Conclusion

Somatosensory cortex stimulation could become a novel approach for deafferentation pain, and is worthy of further investigation. In order to select patients with pain, who are the right candidates for this procedure, fMRI-based and neuronavigation-guided TMS could be used as non-invasive preoperative tools with potentially prognostic value.

References

1. Babiloni C, Babiloni F, Carducci F, Cincotti F, Rosciarelli F, Arendt-Nielsen L, Chen AC, Rossini PM (2002) Human brain oscillatory activity phase-locked to painful electrical stimulations: a multi-channel EEG study. Hum Brain Mapp 15: 112–123
2. Bekisz M, Wrobel A (1999) Coupling of beta and gamma activity in corticothalamic system of cats attending to visual stimuli. Neuroreport 10: 3589–3594
3. Brookes MJ, Gibson AM, Hall SD, Furlong PL, Barnes GR, Hillebrand A, Singh KD, Holliday IE, Francis ST, Morris PG (2005) GLM-beamformer method demonstrates stationary field, alpha ERD and gamma ERS co-localisation with fMRI BOLD response in visual cortex. Neuroimage 26: 302–308
4. Brown JA, Barbaro NM (2003) Motor cortex stimulation for central and neuropathic pain: current status. Pain 104: 431–435
5. Bruehlmeier M, Dietz V, Leenders KL, Roelcke U, Missimer J, Curt A (1998) How does the human brain deal with a spinal cord injury? Eur J Neurosci 10: 3918–3922
6. Buonomano DV, Merzenich MM (1998) Cortical plasticity: from synapses to maps. Annu Rev Neurosci 21: 149–186
7. Chowdhury SA, Suga N (2000) Reorganization of the frequency map of the auditory cortex evoked by cortical electrical stimulation in the big brown bat. J Neurophysiol 83: 1856–1863
8. Cohen LG, Roth BJ, Nilsson J, Dang N, Panizza M, Bandinelli S, Friauf W, Hallett M (1990) Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. Electroencephalogr Clin Neurophysiol 75: 350–357

9. Cohen YE, Saunders JC (1994) The effect of acoustic overexposure on the tonotopic organization of the nucleus magnocellularis. Hear Res 81: 11–21
10. Condes-Lara M, Barrios FA, Romo JR, Rojas R, Salgado P, Sanchez-Cortazar J (2000) Brain somatic representation of phantom and intact limb: a fMRI study case report. Eur J Pain 4: 239–245
11. Contreras D, Llinas R (2001) Voltage-sensitive dye imaging of neocortical spatiotemporal dynamics to afferent activation frequency. J Neurosci 21: 9403–9413
12. Corthout E, Uttl B, Walsh V, Hallett M, Cowey A (2000) Plasticity revealed by transcranial magnetic stimulation of early visual cortex. Neuroreport 11: 1565–1569
13. Crone NE, Miglioretti DL, Gordon B, Lesser RP (1998) Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. Brain 121 (Pt 12): 2301–2315
14. Crone NE, Boatman D, Gordon B, Hao L (2001) Induced electrocorticographic gamma activity during auditory perception. Brazier Award-winning article, 2001. Clin Neurophysiol 112: 565–582
15. De Mulder G, De Ridder D, Sunaert S, Moller A (2005) Somatosensory cortex stimulation for deafferentation pain: report on 5 cases. Neurosurgery (in press)
16. De Pascalis V, Cacace I, Massicolle F (2004) Perception and modulation of pain in waking and hypnosis: functional significance of phase-ordered gamma oscillations. Pain 112: 27–36
17. De Pascalis V, Cacace I (2005) Pain perception, obstructive imagery and phase-ordered gamma oscillations. Int J Psychophysiol 56: 157–169
18. Deacon T (1997) Evolution and intelligence: beyond the argument from design. In: Scheibel A, Schopf J (eds) The origin and evolution of intelligence. Jones and Bartlett, Boston, pp 103–136
19. Dietrich V, Nieschalk M, Stoll W, Rajan R, Pantev C (2001) Cortical reorganization in patients with high frequency cochlear hearing loss. Hear Res 158: 95–101
20. Doetsch GS, Harrison TA, MacDonald AC, Litaker MS (1996) Short-term plasticity in primary somatosensory cortex of the rat: rapid changes in magnitudes and latencies of neuronal responses following digit denervation. Exp Brain Res 112: 505–512
21. Donoghue JP (1995) Plasticity of adult sensorimotor representations. Curr Opin Neurobiol 5: 749–754
22. Eggermont JJ, Roberts LE (2004) The neuroscience of tinnitus. Trends Neurosci 27: 676–682
23. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E (1995) Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 375: 482–484
24. Foucher JR, Otzenberger H, Gounot D (2003) The BOLD response and the gamma oscillations respond differently than evoked potentials: an interleaved EEG-fMRI study. BMC Neurosci 4: 22
25. Gao E, Suga N (1998) Experience-dependent corticofugal adjustment of midbrain frequency map in bat auditory system. Proc Natl Acad Sci USA 95: 12663–12670
26. Garcia-Larrea L, Peyron R, Mertens P, Laurent B, Mauguiere F, Sindou M (2000) Functional imaging and neurophysiological assessment of spinal and brain therapeutic modulation in humans. Arch Med Res 31: 248–257
27. Gorecki J, Hirayama T, Dostrovsky JO, Tasker RR, Lenz FA (1989) Thalamic stimulation and recording in patients with deafferentation and central pain. Stereotact Funct Neurosurg 52: 219–226
28. Gray CM, Konig P, Engel AK, Singer W (1989) Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature 338: 334–337
29. Gray CM, Singer W (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proc Natl Acad Sci USA 86: 1698–1702
30. Halbert J, Crotty M, Cameron ID (2002) Evidence for the optimal management of acute and chronic phantom pain: a systematic review. Clin J Pain 18: 84–92
31. Harrison RV, Ibrahim D, Mount RJ (1998) Plasticity of tonotopic maps in auditory midbrain following partial cochlear damage in the developing chinchilla. Exp Brain Res 123: 449–460
32. Hartmann R, Shepherd RK, Heid S, Klinke R (1997) Response of the primary auditory cortex to electrical stimulation of the auditory nerve in the congenitally deaf white cat. Hear Res 112: 115–133
33. Jastreboff PJ (1990) Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res 8: 221–254
34. Jeanmonod D, Magnin M, Morel A (1996) Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. Brain 119 (Pt 2): 363–375
35. Joliot M, Ribary U, Llinas R (1994) Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. Proc Natl Acad Sci USA 91: 11748–11751
36. Kaas JH, Merzenich MM, Killackey HP (1983) The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. Annu Rev Neurosci 6: 325–356
37. Kandel ER (1991) Cellular mechanisms of hearing and the biological basis of individiuality. In: Kandel E, Schwartz J, Jessell T (eds) Principles of neural science. Appleton & Lange, Norwalk, Connecticut, pp 1009–1031
38. Katayama Y, Yamamoto T, Kobayashi K, Kasai M, Oshima H, Fukaya C (2001) Motor cortex stimulation for phantom limb pain: comprehensive therapy with spinal cord and thalamic stimulation. Stereotact Funct Neurosurg 77: 159–162
39. Kral A, Hartmann R, Tillein J, Heid S, Klinke R (2002) Hearing after congenital deafness: central auditory plasticity and sensory deprivation. Cereb Cortex 12: 797–807
40. Kral A, Tillein J, Heid S, Hartmann R, Klinke R (2005) Postnatal cortical development in congenital auditory deprivation. Cereb Cortex 15: 552–562
41. Kumar K, Toth C, Nath RK (1997) Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery 40: 736–746; discussion 746–747
42. Leake PA, Snyder RL, Rebscher SJ, Moore CM, Vollmer M (2000) Plasticity in central representations in the inferior colliculus induced by chronic single- vs. two-channel electrical stimulation by a cochlear implant after neonatal deafness. Hear Res 147: 221–241
43. Lende RA, Kirsch WM, Druckman R (1971) Relief of facial pain after combined removal of precentral and postcentral cortex. J Neurosurg 34: 537–543
44. Lenz FA, Garonzik IM, Zirh TA, Dougherty PM (1998) Neuronal activity in the region of the thalamic principal sensory nucleus (ventralis caudalis) in patients with pain following amputations. Neuroscience 86: 1065–1081
45. Levy RM (2003) Deep brain stimulation for the treatment of intractable pain. Neurosurg Clin N Am 14: 389–399, vi
46. Llinas R, Ribary U, Joliot M, Wang X (1994) Content and context in temporal thalamocortical binding. In: Buzsaki G, Llinas R, Singer W (eds) Temporal coding in the brain. Springer, Berlin, pp 251–272
47. Llinas R, Ribary U, Contreras D, Pedroarena C (1998) The neuronal basis for consciousness. Philos Trans R Soc Lond B Biol Sci 353: 1841–1849
48. Llinas R, Urbano FJ, Leznik E, Ramirez RR, van Marle HJ (2005) Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci 28: 325–333
49. Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP (1999) Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci USA 96: 15222–15227

50. Lotze M, Flor H, Grodd W, Larbig W, Birbaumer N (2001) Phantom movements and pain. An fMRI study in upper limb amputees. Brain 124: 2268–2277
51. MacDonald KD, Barth DS (1995) High frequency (gamma-band) oscillating potentials in rat somatosensory and auditory cortex. Brain Res 694: 1–12
52. Maihofner C, Handwerker HO, Neundorfer B, Birklein F (2003) Patterns of cortical reorganization in complex regional pain syndrome. Neurology 61: 1707–1715
53. Maihofner C, Handwerker HO, Neundorfer B, Birklein F (2004) Cortical reorganization during recovery from complex regional pain syndrome. Neurology 63: 693–701
54. Maihofner C, Schmelz M, Forster C, Neundorfer B, Handwerker HO (2004) Neural activation during experimental allodynia: a functional magnetic resonance imaging study. Eur J Neurosci 19: 3211–3218
55. Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM (1984) Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol 224: 591–605
56. Moller A (2006) Neural plasticity and disorders of the nervous system, Cambridge University Press, Cambridge (in press)
57. Moller A (2006) Hearing: its physiology and pathophysiology, 2nd edn. Elsevier Science, Amsterdam
58. Moller AR (1997) Similarities between chronic pain and tinnitus. Am J Otol 18: 577–585
59. Moller AR (2000) Similarities between severe tinnitus and chronic pain. J Am Acad Audiol 11: 115–124
60. Moulton EA, Keaser ML, Gullapalli RP, Greenspan JD (2005) Regional intensive and temporal patterns of functional MRI activation distinguishing noxious and innocuous contact heat. J Neurophysiol 93: 2183–2193
61. Muhlnickel W, Elbert T, Taub E, Flor H (1998) Reorganization of auditory cortex in tinnitus. Proc Natl Acad Sci USA 95: 10340–10343
62. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
63. Nikolajsen L, Jensen TS (2001) Phantom limb pain. Br J Anaesth 87: 107–116
64. Palva S, Linkenkaer-Hansen K, Naatanen R, Palva JM (2005) Early neural correlates of conscious somatosensory perception. J Neurosci 25: 5248–5258
65. Pascual-Marqui RD, Michel CM, Lehmann D (1994) Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 18: 49–65
66. Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 30: 263–288
67. Pons TP, Garraghty PE, Ommaya AK, Kaas JH, Taub E, Mishkin M (1991) Massive cortical reorganization after sensory deafferentation in adult macaques. Science 252: 1857–1860
68. Porro CA (2003) Functional imaging and pain: behavior, perception, and modulation. Neuroscientist 9: 354–369
69. Porro CA, Lui F, Facchin P, Maieron M, Baraldi P (2004) Percept-related activity in the human somatosensory system: functional magnetic resonance imaging studies. Magn Reson Imaging 22: 1539–1548
70. Ramachandran VS (1993) Behavioral and magnetoencephalographic correlates of plasticity in the adult human brain. Proc Natl Acad Sci USA 90: 10413–10420
71. Ramachandran VS, Hirstein W (1998) The perception of phantom limbs. The D. O. Hebb lecture. Brain 121 (Pt 9): 1603–1630
72. Recanzone GH, Merzenich MM, Dinse HR (1992) Expansion of the cortical representation of a specific skin field in primary somatosensory cortex by intracortical microstimulation. Cereb Cortex 2: 181–196
73. Recanzone GH, Merzenich MM, Jenkins WM, Grajski KA, Dinse HR (1992) Topographic reorganization of the hand representation in cortical area 3b owl monkeys trained in a frequency-discrimination task. J Neurophysiol 67: 1031–1056
74. Recanzone GH, Schreiner CE, Merzenich MM (1993) Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. J Neurosci 13: 87–103
75. Ribary U, Ioannides AA, Singh KD, Hasson R, Bolton JP, Lado F, Mogilner A, Llinas R (1991) Magnetic field tomography of coherent thalamocortical 40-Hz oscillations in humans. Proc Natl Acad Sci USA 88: 11037–11041
76. Rinaldi PC, Young RF, Albe-Fessard D, Chodakiewitz J (1991) Spontaneous neuronal hyperactivity in the medial and intralaminar thalamic nuclei of patients with deafferentation pain. J Neurosurg 74: 415–421
77. Robertson D, Irvine DR (1989) Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. J Comp Neurol 282: 456–471
78. Rubsamen R (1992) Postnatal development of central auditory frequency maps. J Comp Physiol [A] 170: 129–143
79. Sanes DH, Song J, Tyson J (1992) Refinement of dendritic arbors along the tonotopic axis of the gerbil lateral superior olive. Brain Res Dev Brain Res 67: 47–55
80. Sauve K (1999) Gamma-band synchronous oscillations: recent evidence regarding their functional significance. Conscious Cogn 8: 213–224
81. Sherman RA, Sherman CJ, Parker L (1984) Chronic phantom and stump pain among American veterans: results of a survey. Pain 18: 83–95
82. Sininger YS, Doyle KJ, Moore JK (1999) The case for early identification of hearing loss in children. Auditory system development, experimental auditory deprivation, and development of speech perception and hearing. Pediatr Clin North Am 46: 1–14
83. Snyder RL, Leake PA (1997) Topography of spiral ganglion projections to cochlear nucleus during postnatal development in cats. J Comp Neurol 384: 293–311
84. Staecker H, Galinovic-Schwartz V, Liu W, Lefebvre P, Kopke R, Malgrange B, Moonen G, Van De Water TR (1996) The role of the neurotrophins in maturation and maintenance of postnatal auditory innervation. Am J Otol 17: 486–492
85. Steriade M, Amzica F, Contreras D (1996) Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation. J Neurosci 16: 392–417
86. Steriade M (2000) Corticothalamic resonance, states of vigilance and mentation. Neuroscience 101: 243–276
87. Suga N, Gao E, Zhang Y, Ma X, Olsen JF (2000) The corticofugal system for hearing: recent progress. Proc Natl Acad Sci USA 97: 11807–11814
88. Suga N, Ma X (2003) Multiparametric corticofugal modulation and plasticity in the auditory system. Nat Rev Neurosci 4: 783–794
89. Theuvenet PJ, Dunajski Z, Peters MJ, van Ree JM (1999) Responses to median and tibial nerve stimulation in patients with chronic neuropathic pain. Brain Topogr 11: 305–313
90. Tiitinen H, Sinkkonen J, Reinikainen K, Alho K, Lavikainen J, Naatanen R (1993) Selective attention enhances the auditory 40-Hz transient response in humans. Nature 364: 59–60
91. Tonndorf J (1987) The analogy between tinnitus and pain: a suggestion for a physiological basis of chronic tinnitus. Hear Res 28: 271–275

92. Trojan S, Pokorny J (1999) Theoretical aspects of neuroplasticity. Physiol Res 48: 87–97
93. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl 52: 137–139
94. Walsh V, Ashbridge E, Cowey A (1998) Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. Neuropsychologia 36: 45–49
95. Walsh V, Ashbridge E, Cowey A (1998) Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. Neuropsychologia 36: 363–367
96. Walsh V, Rushworth M (1999) A primer of magnetic stimulation as a tool for neuropsychology. Neuropsychologia 37: 125–135
97. Weinberger NM, Bakin JS (1998) Learning-induced physiological memory in adult primary auditory cortex: receptive fields plasticity, model, and mechanisms. Audiol Neurootol 3: 145–167
98. Weiss T, Miltner WH, Huonker R, Friedel R, Schmidt I, Taub E (2000) Rapid functional plasticity of the somatosensory cortex after finger amputation. Exp Brain Res 134: 199–203
99. Whitehead MC, Morest DK (1985) The development of innervation patterns in the avian cochlea. Neuroscience 14: 255–276
100. Wiech K, Preissl H, Lutzenberger W, Kiefer RT, Topfner S, Haerle M, Schaller HE, Birbaumer N (2000) Cortical reorganization after digit-to-hand replantation. J Neurosurg 93: 876–883
101. Woolsey TA, Wann JR (1976) Areal changes in mouse cortical barrels following vibrissal damage at different postnatal ages. J Comp Neurol 170: 53–66
102. Youell PD, Wise RG, Bentley DE, Dickinson MR, King TA, Tracey I, Jones AK (2004) Lateralisation of nociceptive processing in the human brain: a functional magnetic resonance imaging study. Neuroimage 23: 1068–1077
103. Zeman A (2002) Consciousness, a user's guide. Yale University Press, New Haven
104. Zhang Y, Suga N (2000) Modulation of responses and frequency tuning of thalamic and collicular neurons by cortical activation in mustached bats. J Neurophysiol 84: 325–333

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Localization of precentral gyrus in image-guided surgery for motor cortex stimulation

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Summary

According to recent clinical data, motor cortex stimulation (MCS) is an alternative treatment for central pain syndromes. We present our minimal invasive technique of image guidance for the placement of motor cortex stimulating electrode and assess the clinical usefulness of both neuronavigation and vacuum headrest. Neuronavigation was used for identification of precentral gyrus and accurate planning of the single burr-hole. The exact location was reconfirmed by intraoperative phase reversal of somatosensory evoked potential (SSEP) and clinical response after electrical stimulation test. Implementation of navigation technique facilitated localization of the precentral gyrus with a high degree of accuracy. Determination of stimulating electrode placement was possible in every case. Postoperative clinical and neuroradiological evaluations were performed in each patient. All patients experienced postoperative relief from pain. Our preliminary series may confirm image guidance as a useful tool for surgery of MCS. Additionally, minimal and safe exposure can be performed using a single burr-hole and vacuum head rest.

Keywords: Central pain; motor cortex stimulation; intra-operative somatosensory; neuronavigation; thalamic pain.

Introduction

Motor cortex stimulation (MCS) is a neurosurgical intervention using epidural electrode placement over the motor cortex to treat complex central and neuropathic pain disorders. Although the scientific basis for pain relief with this technique remains obscure, the available literature proposes that at least part of the effect may be mediated via the inhibition of thalamic pain pathways [1, 3, 9, 13, 19]. Tsubokawa and colleagues reported their first clinical experience of MCS in central pain syndrome patients in 1991, after discovering that MCS profoundly inhibited the abnormal firing of thalamic neurons in their cat model of spinothalamic tractotomy [34, 35]. Subsequently, MCS has been used increasingly in patients with central pain after putaminal or thalamic stroke [15, 16, 22, 23, 29, 33] and for pain originating from trigeminal system structures for which no other effective surgical option is available [7, 15, 20, 22, 24, 26, 33].

Operative technique

Localization of the motor cortex

Numerous successful operations of motor cortex stimulation for central and neuropathic pain have been published during the past two decades [6, 23, 29, 34]. However, precise localization of precentral gyrus remains the meaningful step of this procedure; many techniques have been applied to determine this cortical landmark [8, 17, 22, 31], but these techniques have not been systemically compared [37]. Some neurosurgeons used external bony landmarks for exact positioning of the cranial burr-holes [31]. Others relied on phase reversal of the N20-P20 somatosensory evoked potential (SSEP) at the Rolandic fissure (RF) [17, 38]. Most investigators create a craniotomy when performing motor cortex stimulation for correct placement of the grid electrode [22, 25, 27, 30]. Nguyen *et al.* are the pioneers who introduced a planning technique for motor cortex stimulation using frame-based stereotaxy [22]. In recent years, neuronavigation has gained increasing significance in planning craniotomies and localizing small, deep-seated pathological lesions [11, 12, 28, 32]. Neuronavigation is employed in MCS surgery in order to localize precisely the motor cortex and reduce the operation time. The image guidance system also provides ongoing feedback to the surgeon on the cortical structures encountered

during electrode placement. Imaging transfer of MRI is convenient, and anatomical localization of the central sulcus can be obtained readily, so that the single precentral burr-hole can be performed following morphologic recognition of the precentral gyrus. SSEP and intraoperative stimulation tests are other combined modalities, which are definitely useful and countercheck the correct and suitable site for placement of the stimulating electrode. Surgeons should place the electrode in a way as to cover the cortical area representing the corresponding somatotopic area of pain [33]. Recently, image guidance using functional magnetic resonance imaging (fMRI) data was employed to monitor positioning of the electrode array according to the capability of generating somatotopic patterns of the primary motor cortex in individual patients [10].

Preoperative preparation and image-guided data acquisition

An antiepileptic drug was administered preoperatively and continued for three days postoperatively in order to prevent the risk of seizures. In our neurosurgical department, VectorVision 2 image guidance (BrainLab AG, Munich, Germany) was used to localize the central sulcus. Technical details concerning the VectorVision system have been published elsewhere [12]. Before acquiring image-guided data, MRI-compatible fiducial markers were spherically distributed around the precentral gyrus, prior to scanning. MRI type data was used for navigation. The motor cortex could be outlined and reconstructed in any plane or in 3D mode. MRI data were transferred to the neuronavigation system by intranet or zip disc.

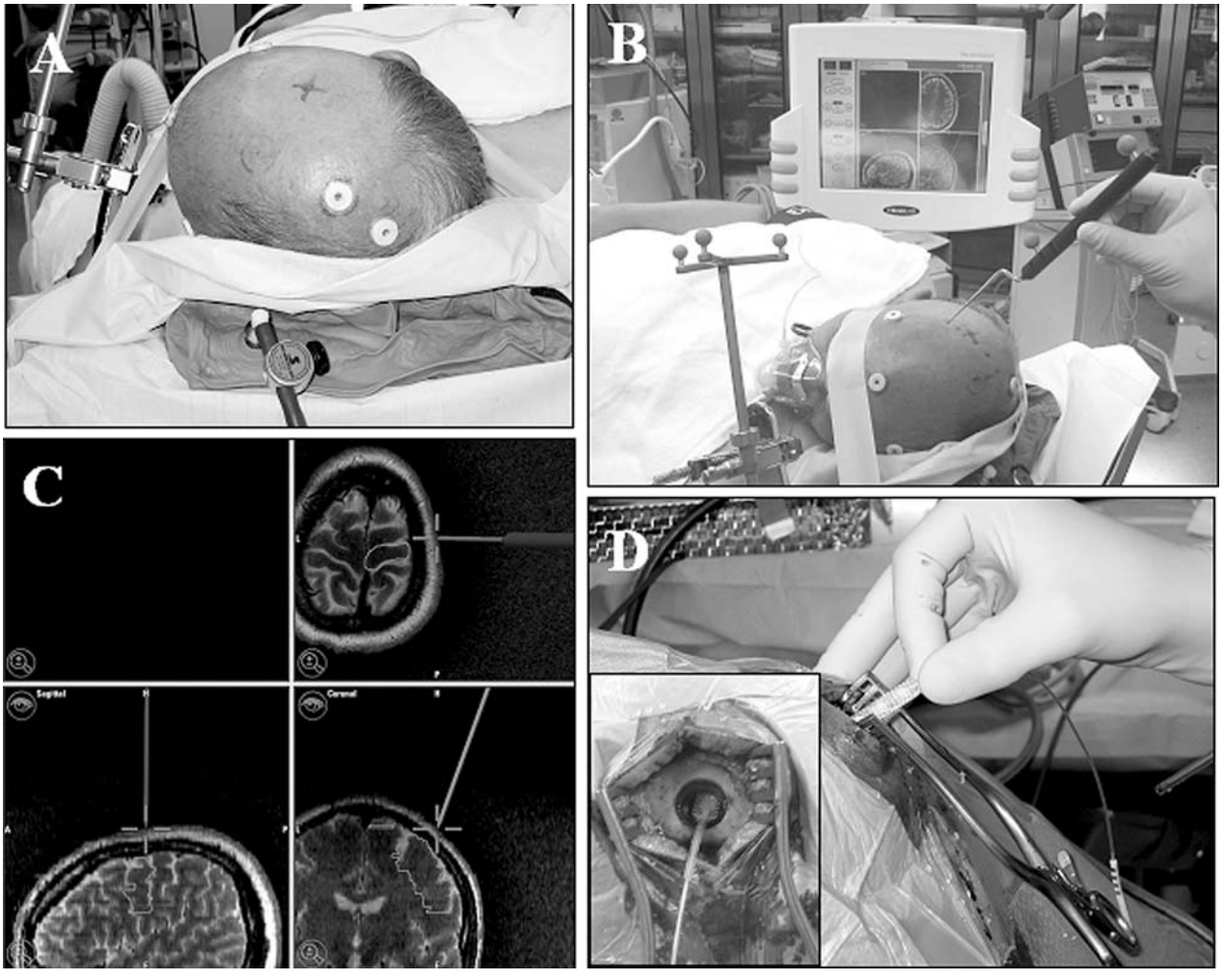

Fig. 1. (A) Photographs showing the patient's position; the head is turned approximately 80° to the left side and is securely affixed in a vacuum head rest. (B) The central sulcus is localized using image guided neuronavigation. (C) Triplanar MRI scans; the navigation monitor displays gray crosses, which represent the target area. The straight line shows the preplanned vector and the possible site for single burr-hole. (D) Intraoperative image showing the cranial burr-hole and the placement of monitoring electrode

Intraoperative procedure

The procedure is performed under local anesthesia. A vacuum headrest may be used in MCS surgery in order to avoid a head-pin fixation. This headrest was found useful and suitable for endoscopically treated colloid cyst patients and other single burr-hole procedures [2, 14, 32]. After fitting the patient with an appropriately sized headrest, the air in the headrest is removed to create a vacuum; simultaneously the headrest is reshaped according to the individual head contour of the patient. Subsequently, the head is additionally secured using strap tape (Fig. 1A).

For patient's registration in the navigation system a non-sterile pointer is used to locate the adhesive skin fiducials. During registration, the data acquired are matched to the patient's head position. Afterwards, we verify the accuracy of navigation data by testing the positions of recognizable anatomical landmarks, such as nasion and mastoid tip or others. The central sulcus is localized using image guided neuronavigation (Fig. 1B, C). Then, a small burr-hole is created

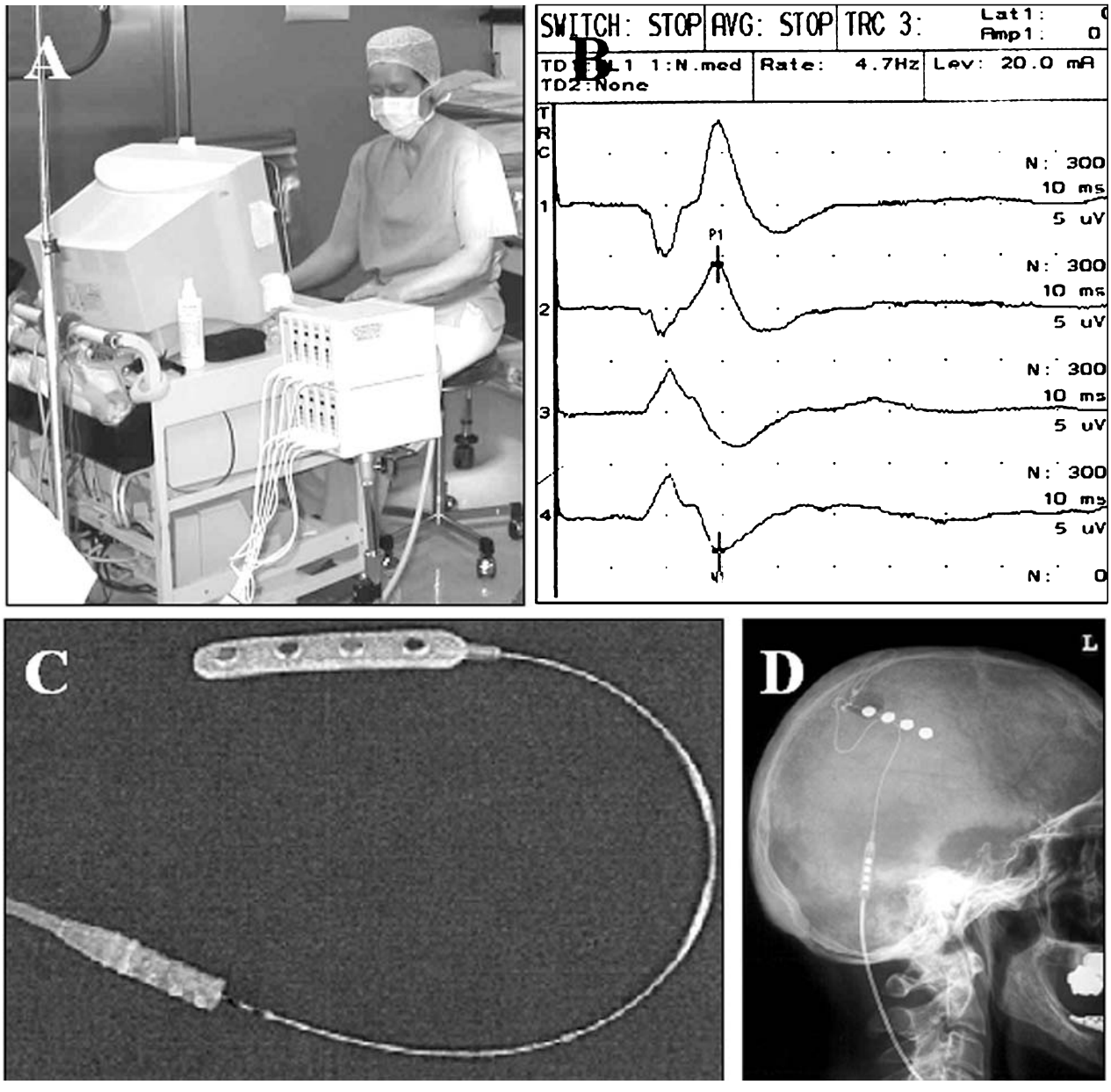

Fig. 2. (A) Intraoperative electrophysiological monitoring. (B) The position of the central sulcus is confirmed from phase reversal of the N20 component with median nerve stimulation. (C) Photograph of a flat quadripolar lead (Resume®, Medtronic Inc., Minneapolis, USA). (D) Postoperative lateral skull film demonstrates the position of stimulating electrode

Table 1. *Clinical characteristics of 9 patients with central pain operated on with image-guided neuronavigation MCS*

Age/sex	Pain origin	Somatotopic target	Pain relief (VAS)	Outcome (6–42 months)
46, m	insular infarction	right upper limb	85	excellent
68, m	anaesthesia dolorosa	left face	90	excellent
62, m	syringomyelia	right face	90	excellent
72, f	brainstem (postoperative brainstem cavernoma)	right side	75	good
64, m	thalamic infarction	right upper limb	40	fair
35, m	spinal bleeding	right upper limb	40	fair
57, m	thalamic bleeding	right upper limb	65	good
78, f	anaesthesia dolorosa	left face	40	fair
59, m	thalamic infarction	left upper limb	70	good

f Female, *m* male, *VAS* visual analog scale.

according to the desired target of motor cortex (Fig. 1D). The exact site of electrode placement is verified by intraoperative electrophysiology (Fig. 2A) and cortical stimulation testing. Somatosensory evoked potentials are recorded with a four-contact electrode after stimulation of the median and posterior tibial nerves. The position of the central sulcus can therefore be confirmed by phase reversal of the N20 component after median nerve stimulation or the N40 component after tibial nerve stimulation. Inversion of this wave is observed between two adjacent electrode contacts (Fig. 2B). After removal of the monitoring electrode, a flat quadripolar lead (Resume®, Medtronic Inc., Minneapolis, USA) (Fig. 2C) is introduced extradurally through the burr-hole and positioned in such a way as to cover the cortical area representing the corresponding somatotopic area of pain. Then, intraoperative stimulation test is carried out by a screening device (Medtronic 8214 screener) with a wide range of the following controlled parameters: e.g. frequency (Hz), pulse width (msec), and intensity (mA). Normally, stimulation frequencies for MCS range between 40 and 100 Hz, and amplitudes vary from 1.5 to 10 V. Pulse width can be adjusted from 90 to 450 msec. Patients are asked to report vibrating or tingling sensations as well as relief in the painful area after stimulation over several minutes. Minimal stimulation above the threshold of muscle contractions is also performed in order to verify the exact location for electrode placement.

Changes in pain level were evaluated in each patient. Pain assessment according to the visual analogue scale (VAS) was performed before and after motor cortex stimulation. Effects of stimulation with regard to pain relief were classified into four categories: excellent, reduction of pain level by 80–100%; good, 60–79% reduction; fair, 40–59% reduction; and poor, less than 40% reduction. The postoperative test phase was continued for three days. Only those patients with at least 50% pain reduction underwent implantation of permanent pulse generator (IPG, Itrel III, Medtronic Inc.).

Results and complications

Results of MCS are usually more favourable in the treatment of patients with neuropathic facial pain rather than central pain. Similar results were also seen in our patients (Table 1). A possible explanation for the particularly excellent results in facial pain syndrome is that the facial somatotopic representation on the motor cortex is large compared to that of other body regions [4]. Clinical response of MCS does not appear to be specific to any particular chronic pain condition [6]. Some positive results of preoperative testing might be predictive factors for the efficacy of MCS. For instance, barbiturate sensitivity and opioid insensitivity have been suggested as possible predictors of response [5, 36, 39]. Repetitive transcranial magnetic stimulation has been shown to be a very useful tool in predicting the effect of implanted electrodes [5, 18, 21]. Severe sensory deafferentation is considered a poor prognostic factor [24].

In published series, morbidity directly related to the MCS procedures included intraoperative seizures, headache, epidural hematoma, subdural effusion, stimulator-pocket infection and dehiscence of the stimulator pocket [4, 23, 30, 36]. Although these complications appear to be rare, a cautious technique during operation is required. Therefore, we would recommend epidural electrode placement via a single burr-hole approach under neuronavigational guidance as a minimally invasive procedure for motor cortex stimulation.

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References

1. Adams JE, Hosobuchi Y, Fields HL (1974) Stimulation of internal capsule for relief of chronic pain. J Neurosurg 41: 740–744
2. Alberti O, Riegel T, Hellwig D, Bertalanffy H (2001) Frameless navigation and endoscopy. J Neurosurg 95: 541–543
3. Andersen P, Eccles JC, Sears TA (1962) Presynaptic inhibitory action of cerebral cortex on the spinal cord. Nature 194: 740–741
4. Brown JA, Barbaro NM (2003) Motor cortex stimulation for central and neuropathic pain: current status. Pain 104: 431–435
5. Canavero S, Bonicalzi V (1995) Cortical stimulation for central pain. J Neurosurg 83: 11–17
6. Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ (2000) Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. Pain 84: 431–437
7. Ebel H, Rust D, Tronnier V, Boker D, Kunze S (1996) Chronic precentral stimulation in trigeminal neuropathic pain. Acta Neurochir (Wien) 138: 1300–1306
8. Franzini A, Ferroli P, Dones I, Marras C, Broggi G (2003) Chronic motor cortex stimulation for movement disorders: a promising perspective. Neurol Res 25: 123–126
9. García-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguière F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
10. Gharabaghi A, Hellwig D, Rosahl SK, Shahidi R, Shrader C, Freund HJ, Samii M (2005) Volumetric image guidance for motor cortex stimulation: integration of three-dimensional cortical anatomy and functional imaging. Neurosurgery Suppl 57: 114–120
11. Grunert P, Muller-Forell W, Darabi K, Reisch R, Busert C, Hopf N, Perneczky A (1998) Basic principles and clinical applications of neuronavigation and intraoperative computed tomography. Comput Aided Surg 3: 166–173
12. Gumprecht HK, Widenka DC, Lumenta CB (1999) BrainLab VectorVision neuronavigation system: technology and clinical experiences in 131 cases. Neurosurgery 44: 97–105
13. Gybels J, Kuypers R (1995) Subcortical stimulation in humans and pain. In: Desmedt JE, Bromm B (eds) Pain and the brain. Series: advances in pain research and therapy. Raven, New York, pp 187–199
14. Hellwig D, Bauer BL, Schulte DM, Gatscher S, Riegel T, Bertalanffy H (2003) Neuroendoscopic treatment for colloid cysts of the third ventricle: the experience of a decade. Neurosurgery 52: 525–532
15. Herregodts P, Stadnik T, De Ridder F, D'Haens J (1995) Cortical stimulation for central neuropathic pain: 3-D surface MRI for easy determination of the motor cortex. Acta Neurochir Suppl (Wien) 64: 132–135
16. Katayama Y, Fukaya C, Yamamoto T (1998) Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. J Neurosurg 89: 585–591
17. King RB, Schnell GR (1987) Cortical localization and monitoring during cerebral operations. J Neurosurg 67: 210–219
18. Lefaucheur JP, Drouot X, Keravel Y, Nguyen JP (2001) Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport 12: 1–3
19. Lindblom U, Ottosson JO (1957) Influence of pyramidal stimulation upon the relay of coarse cutaneous afferents in the dorsal horn. Acta Physiol Scand 38: 309–318
20. Meyerson BA, Linblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir Suppl 58: 250–153
21. Migita K, Uozumi T, Arita K, Monden S, Burchiel KJ, Young RF (1995) Transcranial magnetic coil stimulation of motor cortex in patients with central pain. Neurosurgery 36: 1037–1040
22. Nguyen JP, Keravel Y, Fève A, Uchiyama T, Cesaro P, Le Guerinel C, Pollin B (1997) Treatment of deafferentation pain by chronic stimulation of the motor cortex: report of a series of 20 cases. Acta Neurochir Suppl 68: 54–60
23. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugières P, Pollin B, Fève A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlation between clinical, electrophysiological and anatomical data. Pain 82: 245–251
24. Nguyen JP, Lefaucheur JP, Le Guerinel C, Fontaine D, Nakano N, Sakka L, Eizenbaum JF, Pollin B, Keravel Y (2000) Treatment of central and neuropathic facial pain by chronic stimulation of the motor cortex: value of neuronavigation guidance systems for the localization of the motor cortex. Neurochirurgie 46: 483–491
25. Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguiere F, Laurent B (1995) Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. Pain 62: 275–286
26. Rainov NG, Fels C, Heidecke V, Burkert W (1997) Epidural electrical stimulation of the motor cortex in patients with facial neuralgia. Clin Neurol Neurosurg 99: 205–209
27. Rainov NG, Heidecke V (2003) Motor cortex stimulation for neuropathic facial pain. Neurol Res 25: 157–161
28. Reinhardt HF, Trippel M, Westermann B, Horstmann GA, Gratzl O (1996) Computer assisted brain surgery for small lesions in the central sensorimotor region. Acta Neurochir (Wien) 138: 200–205
29. Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Yoshimine T (2000) Motor cortex stimulation for central and peripheral deafferentation pain. Report of 8 cases. J Neurosurg 92: 150–155
30. Saitoh Y, Shibata M, Hirano S, Kato A, Kishima H, Hirata M, Yamamoto K, Yoshimine T (2001) Motor cortex stimulation for deafferentation pain. Neurosurg Focus 11: 1–5
31. Taylor J, Haughton AM (1990) Determination of the Rolandic and Sylvian fissure. Trans Acad Ireland 18: 511–526
32. Tirakotai W, Riegel T, Sure U, Bozinov O, Hellwig D, Bertalanffy H (2004) Clinical application of neuro-navigation in a series of single burr-hole procedures. Zentralbl Neurochir 65: 1–8
33. Tirakotai W, Riegel T, Sure U, Rohlfs J, Gharabaghi A, Bertalanffy H, Hellwig D (2004) Image-guided motor cortex stimulation in patients with central pain. Minim Invas Neurosurg 47: 273–277
34. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl 52: 137–139
35. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Treatment of thalamic pain by chronic motor cortex stimulation. Pacing Clin Electrophysiol 14: 131–134
36. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
37. Velasco M, Velasco F, Brito F, Velasco AL, Nguyen JP, Marquez I, Boleaga B, Keravel Y (2002) Motor cortex stimulation in the treatment of deafferentation pain. I. Localization of the motor cortex. Stereotact Funct Neurosurg 79: 146–167
38. Wood CC, Spencer DD, Allison T, McCarthy G, Williamson PD, Goff WR (1988) Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. J Neurosurg 68: 99–111
39. Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T (1997) Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy. Pain 72: 5–12

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Anatomical and physiological basis, clinical and surgical considerations, mechanisms underlying efficacy and future prospects of cortical stimulation for pain

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Summary

The analgesic efficacy of cortical stimulation on refractory neuropathic pain has been established. Although it offers pain relief to 45–75% of the patients, this technique remains under evaluation and the definitive protocol for its application has not been established yet. The mechanisms underlying the analgesic efficacy of cortical stimulation are still largely unknown. Successive technical adaptations have been proposed and tried in order to reduce the number of non-responding patients. In this chapter, we summarize the limited amount of crucial information that has been acquired so far on pain processing in the central nervous system, on the functional pathophysiology of neuropathic pain and on the mechanisms underlying the efficacy of cortical stimulation. We also discuss key issues that could help to increase the success rate and enhance the future prospects of the technique.

Keywords: Neuromodulation; neuropathic pain; cortical brain mapping; functional magnetic resonance imaging; positron emission tomography; motor cortex; stimulation; navigation; thalamus.

Introduction

The analgesic efficacy of chronic epidural motor cortex stimulation (MCS) on refractory central and neuropathic pain (NP) has been confirmed by many studies after the first report in 1991 [1, 5, 15, 17, 18, 25]. The application of MCS in NP increased rapidly despite the lack of an understanding of the mechanisms underlying its analgesic efficacy. The technique remains currently under evaluation and a definitive surgical protocol has not been established yet.

The recommended procedure of MCS has undergone successive adaptations following various attempts to improve the success rate of the technique and reduce the number of non-responding patients. Of the stimulated patients, 45–75% experience pain relief. The patients may expect such excellent results from MCS but the clinical management of non-responders can be a very frustrating problem. Frustration is experienced physically and emotionally by the patient, and intellectually by the attending staff. The important question is why many NP patients, although they have been rigorously selected respond so differently to the same stimulation procedure? The answer should undoubtedly be found in the diversity and the heterogeneity of the clinical syndromes of NP and in the various areas of imprecision in the stimulation technique. This latter issue makes it necessary to improve our understanding and refine the technical approach of MCS. The present article does not aim to describe extensively the surgical technique for implantation of a MCS device but to describe in a succinct manner certain key issues that could help to improve the technique's success rate.

Anatomical and physiological basis

Nociceptive pain

The ascending nociceptive and sensory pathways are separate and specific, but deeply interconnected. Under physiological circumstances, noxious stimuli activate high-threshold primary sensory neurons. The dorsal horn of the spinal cord represents the first stage of integration; segmental afferent and descending sensory pathways produce a robust long-term depression of primary afferent nociceptive transmission (inhibitory gating mechanisms). Ascending nociceptive imputs project to the brainstem, thalamic nuclei and to post-central primary

cortex (SI) where their somatotopic distribution runs in parallel with the ''homunculus'' in the pre-central gyri. The secondary (or associated) sensory cortex, involves the posterior parietal gyri (SII), cingular, orbitofrontal, thalamic and brainstem structures and represents the second stage of integration of nociceptive imputs (central processing). The understanding of the central mechanisms of nociceptive pain has progressed following the application of brain imaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). Recent findings, obtained by these techniques, suggest that different structures in the central pain network (pain matrix) subserve the sensory, affective, cognitive and attentional aspects of pain perception and tune the pain of each individual patient [2, 4, 6–8, 10, 12, 19–21, 23, 24].

Neuropathic pain

In contrast to nociceptive pain, NP results from damage to the peripheral (PNS) or central nervous system (CNS). It is characterized by a complex combination of sensory deficits including partial or complete loss of sensation and dysesthesia or paresthesia. Injury to the PNS or CNS is reflected by neuroplasticity adaptive changes in the dorsal root ganglion cells and central neurons. NP is probably not the result of a single pathophysiological mechanism, but the final product of an altered peripheral, spinal, and supraspinal signal processing. In the dorsal horn of the spinal cord, synaptic plasticity may be involved in the transition from acute to chronic pain as well as in the pathophysiology of NP. Moreover, environmental and psychological factors may contribute to a functional and structural reorganization of cortical sensory maps. These neuroplasticity changes in function, chemistry and organization of the central pain-processing system may be influenced by genetic factors. Genetic disposition can alter pain susceptibility; this explains why individuals with apparently similar lesions develop different pain syndromes. It is known that CNS adapts to both peripheral and central injury, frequently in a beneficial way, but sometimes such a neuronal reorganization can be maladaptive. The understanding of the pathophysiology of NP is further complicated by new information indicating that pain and pain modulation are mediated, not by a single pathway with a few central nodes, but by a network of multiple interacting modules of neuronal activity [2]. Although the definitive protocol regarding the patient selection and the surgical technique has not been established yet, a degree of consensus has been reached on certain clinical and surgical issues.

Clinical considerations

Degree of deafferentation

Since MCS is neither a brain-invasive nor a neuroablative procedure, the selection criteria of MCS could theoretically be extended to include any refractory and severe pain syndrome. However, it is reasonable to contain the indications of MCS only to patients presenting a serious degree of chronic deafferentation secondary to a lesion in the somatosensory pathways. Mild or deep cutaneous hypoesthesia, allodynia and hyperesthesia are frequently seen in these patients. Fluctuations in the intensity of pain are a common finding and are induced by activities of daily living and various factors such as season, weather, food, smoking, alcohol consumption, quality of sleep, social life, etc. The resistance of pain to morphine and its qualitative description as ''burning'' or ''electrical'' differentiate it from nociceptive pain and make it compatible with the criteria for being treated by MCS. NP should be refractory to extensive oral or intrathecal pharmacotherapy and severe enough to justify a surgical intervention; notably, such patients have often been subjected to various neurosurgical procedures unsuccessfully.

Somatic distribution

The pain that could be treated by MCS presents typically a lateralized somatic distribution limited in one segment such as a hand, forearm, arm, lower limb, hemiface, one trigeminal branch or it can affect a more extended area of a body segment and limb i.e. face and upper limb, hemitrunk, an upper and a lower limb, both lower limbs or rarely the hemibody.

Underlying lesion

NP syndromes may have different underlying conditions, either central or peripheral. The central lesions include ischemic or hemorrhagic stroke or focal trauma in any of the following areas: parietal cortex, internal capsule, thalamus, brainstem or spinal cord. Syrinx cavity in the medulla or spinal cord can also be a cause of central NP. The peripheral lesions can be ischemic, traumatic or inflammatory and include limb amputation, post-radiation or herpetic plexopathy and root avulsion

or section. Many such lesions can be mixed, i.e. central and peripheral; this category includes iatrogenic or post-herpetic trigeminal neuropathy and brachial plexus avulsion. The phantom pain observed in paralytic or amputated limbs represents a very challenging NP syndrome that can be subjected to treatment by MCS.

Corticospinal impairment

A high degree of corticospinal impairment may be a predictor of a poor clinical response to MCS [11]. Therefore, patients who do not have hemi- or monoplegia may be better candidates for MCS compared to the ones who do.

Condition of the cortex

Electrical stimulation of the cortex may not be feasible in patients with a large destroyed cortical surface (stroke) and in those in whom the subarachnoid space between the cortex and the inner dural surface is relatively wide as in the case of a subdural hygroma.

Surgical considerations

Navigation-based craniotomy

In the early nineties, the MCS procedure was done through a trephination in the ''estimated motor area'' but currently, in order to remain ''minimally invasive'', the procedure has been reduced to a single burr hole. Subsequently, navigational image-based guidance was introduced to improve the targeting of the central sulcus (CS) [9, 17]. In the current procedure, an epidural MCS device is implanted, under general anesthesia, using a frameless navigation system. The patient's head is fixed in a headholder clamp suitable for neuronavigation. Our preferred position is the lateral decubitus (''park bench''); this allows the horizontal orientation of the operative field and an easy access to the contralateral upper limb under the operating table [18]. We recommend a $4 \times 4\,cm^2$ craniotomy rather than a burr-hole. Indeed, considering the expected analgesic improvement, issues such as the amount of hair shaving, the length of the skin incision, or the duration of the surgical procedure (4-hour-long) have limited importance for such disabled patients. The craniotomy is centered on the cortical projection area of the painful somatic segment, parasagittal for lower limb pain and temporo-frontal for facial pain.

Functional targeting method

Functional areas that correspond to the face and the hand are represented extensively on the CS; however, in chronic NP, functional reorganization in the primary cortical areas may develop. Therefore, CT or MRI-based image-guided navigation may not reflect accurately the functional target which should be stimulated. For accurate electrode positioning, a functional method for the identification of the target is required.

Cortical brain mapping

Since 1991, intraoperative epidural cortical brain mapping (iCM) of the primary sensorimotor cortex [including intraoperative recording of somatosensory evoked potentials (iSEP) and bipolar stimulodetection (iBS)] is used as the most accurate method for localizing the CS and the functional target to be stimulated on the motor cortex [18, 19, 25]. Such ''iCM-guided MCS procedures'' combine iCM recordings and epidural fixation of the stimulation electrode in a single stage. Some authors [21] implant a grid for cortical brain mapping, record SEP for one week and fix the stimulation electrode in a separate surgical procedure. For iCM, a grid (or the electrode which is intended to be used for chronic MCS) is placed at different locations on the dural surface over the CS region. The coordinates of every iSEP recording contact that covers the CS region are registered in the navigation workstation. The CS and the motor target of the hand are defined by means of the N20-P30 wave phase reversal (confirmed on 3 repeated recordings) according to a technique described previously [14, 18, 26]. iSEP after facial stimulation are used for facial pain. Peripheral stimulation of the median, tibial or trigeminal nerves are efficient for studying each segment. However, systematic median nerve stimulation is recommended in all pain distribution patterns; in this way, a ''hand'' target is obtained. This target is highly reproducible and can be helpful as a reference target when recordings after lower limb or facial stimulation give ambiguous data [18]. The location of the motor target can be confirmed by iBS through the stimulation electrode (5 mm space tips bipolar stimulator probe; isolated square-wave pulses with a duration of 1 ms; 60 Hz; from 5–20 mA) [18].

Epidural electrode for stimulation

Once the motor target has been identified, the stimulation electrode is fixed epidurally, perpendicular to the CS with 3 poles anterior to the CS. Very careful hemostasis

is highly recommended for avoiding epidural infectious or hemorrhagic complications. Superficial denervation of the dura by bipolar coagulation can reduce the post-operative local pain described by many patients when switching the stimulation on. The test-procedure consists of stimulating the patient for 1 hour every 4 hours (monophasic square wave pulses; frequency 40 Hz; duration 100 μs; amplitude 1–5 V), with many bipolar combinations and the negative pole located over the motor cortex. Excellent and good responders are implanted with a subcutaneous stimulator for long-term stimulation.

Clinical observations after MCS

Postoperatively, MCS induces significant, reproducible and long-lasting pain relief occurring from 10 to 15 minutes after the start of stimulation and lasting for 15–120 minutes after stimulation is switched off [18]. Some patients report that pain relief can remain stable for more than 24 hours if the initial stimulation period is longer than 4 hours. It has also been described that severe pain recurs when the stimulation is switched off for more than 2 days. In other patients, no analgesic effect is observed, whatever combination of stimulation parameters is tested. In the majority of patients, the electrical stimulation of the parietal cortex, strongly increases the burning or tingling sensation and pain in general. Some patients mention a transient painful sensation (reported as a painful ''clic'') centered on the craniotomy when stimulation is switched on; this is probably due to direct stimulation of the dura.

Mechanisms underlying the efficacy of MCS

The mechanisms underlying the analgesic efficacy of MCS remain largely unknown. Some clinical, electrophysiological and functional observations have, however, allowed a limited understanding of the conditions that are necessary for obtaining analgesia.

Descending effect from the pre-central cortex

All observations show that pain relief is obtained after stimulation of the pre-central cortex only. This suggests that MCS, i.e. stimulation above the level of the lesion, may be effective by a descending modulation on the cortical projection of pain. According to our clinical experience, this descending effect may occur after stimulation of the motor cortex (in some patients) or the pre-motor cortex (in others).

Inhibition or activation of the thalamus?

Functional neuroimaging studies have showed abnormal metabolism in the thalamus contralateral to the painful segment. PET studies (using fluorodeoxyglucose as radiotracer) showed a reduced metabolism in the thalamus on the affected side [12] and other studies (using 0^{15}-labelled water) showed a significantly increased regional cerebral blood flow (rCBF) after MCS compared to the non-stimulated state [7]; this was independent from analgesic effect and was restricted in a set of ipsilateral cortical and subcortical regions of which the most significant are the ventral and lateral (VL) thalamus, orbito-frontal cortex, anterior cingulate gyrus and upper part of the brainstem. Some of the modifications observed may not be related directly to the analgesic efficacy of MCS. However, all rCBF changes occurred far from the somatosensory areas and no evidence was found on a potential MCS-related activation of the sensory cortex. VL and ventral anterior are the only thalamic nuclei that are connected directly with the motor and premotor cortices. These thalamic regions are not involved in pain integration; cells in the VL thalamus are somatotopically arranged as are their projections to the pre-motor cortex [7]. Other regions in which the rCBF increases after MCS include the medial thalamus, orbito-frontal cortex, anterior cingular gyrus and upper part of the brainstem which are known to be involved in pain processing and control. These areas have strong interconnections and are also connected to the medial and anterior thalamus. The modulation by MCS might be effective by suppressing either the intensity of the conscious sensation or at least the distressful reaction to pain.

The functional hypothesis of MCS efficacy

The MCS-induced rCBF increases in the VL thalamus and other secondary regions may be functionally related. A degree of motor thalamic activation at a certain threshold might be a necessary stage for the activation of other structures which would allow the analgesic effect of MCS to be expressed. The lack of clinical effect may result from a failure to reach such a threshold [7]. The observation that a high degree of corticospinal impairment may be a predictor of a poor clinical response to MCS supports this hypothesis [11].

The contralateral hemisphere

Changes in rCBF have also been observed in the hemisphere contralateral to the MCS. It is unclear whether a relationship exists between the rCBF changes and the mechanisms of analgesic effect. However, contralateral interferences implicating multiple structures such as the anterior cingulate gyrus, upper brainstem and contrateral thalamus has been repeatedly confirmed [7, 8, 21], especially in patients who have cortico-subcortical lesions involving the hemisphere where MCS is applied [7]. It has been suggested that such lesions affect the bilateral balance of thalamo-parietal circuits which is important for pain relief; consequently, the thalamic pain syndrome could be considered as a bilateral disorder of functional plasticity [8].

The level and nature of the underlying lesion

The clinical practice clearly shows that the success rate of MCS strongly depends on patient selection and, therefore, on the underlying lesion of the NP syndrome. Patients suffering from central poststroke pain or trigeminal neuropathy have better results than others. This suggests that the neuronal circuitry which is activated in deafferentation, the functional plasticity and the pathogenesis of NP may not be related to similar mechanisms in patients with cortical stroke, thalamic stroke or limb amputation.

Precise electrode positioning

The clinical practice has also showed that the analgesic efficacy of MCS strongly depends on the position of the electrode. In order to induce pain relief, MCS should respect the somatotopic projection of the painful segment on motor cortex. In other words, an accurate targeting of the somatotopic projection of the painful area on the CS is crucial for obtaining pain relief. This must be the main goal of the surgical procedure and should be achieved prior to fixing the electrode to the dura.

Functional plasticity

In NP, the electrode positioning, although it is assisted by cortical brain mapping, can be functionally inaccurate. A degree of functional reorganization or plasticity may take place as a result of deafferentation [10, 20]. This has not been studied extensively. However, fMRI studies of ''mental movements'' in amputees have collected interesting data. The neural mechanisms involved in the mental representation of an action and in its execution remain the same and the cortical areas, which correspond to the missing limb, seem to persist and get activated for several years after amputation [20]. Some adaptation does occur and marked reorganization of motor and somatosensory cortices has been seen in amputees with upper limb phantom pain in which the activated areas in fMRI were displaced compared to their expected location [10].

Clinical and technical limitations

Variable success rates

The success rate of long-term pain relief ranges from 45 to 75% [5, 15, 17]. The best success rates have been observed in central poststroke pain and particularly, in trigeminal neuropathy (>90%). Patients who have been operated on many times for trigeminal neuralgia develop non-paroxysmic, lancinating pain or even deep ''anesthesia dolorosa''. In brachial plexus avulsion or amputation, the results are variable with the success rate lower than 60%. In patients with pain in the lower limbs, after central subcortical stroke, the MCS has a success rate inferior to 50%.

Electrical intraoperative cortical mapping (iCM)

iCM represents the most direct, reliable and precise functional technique for recording neuronal activity in the primary cortical areas; unfortunately, in NP, iCM may have limitations that reduce significantly the quality of this targeting method. In marked deafferentation, iCM may show wave attenuation, diffused motor response, increased sensitivity to electrical artifacts or lack of reproducibility. In a personal series of 18 patients, iCM was highly accurate in localizing the functional target in 9 cases (50%) and provided an approximate target in 3 (17%) and a non-reproducible target in 6 cases (33%) [18].

Future prospects

The frustrating situations of non-responding patients raise a series of questions among which the accuracy of the *electrode positioning* is the most serious. Other important issues are the *patient selection* and the *method used to stimulate the cortex.* Progress in all these areas is likely to be based on future developments that will improve the technique's success rate and reduce the number of non-responding patients.

Patients selection

The variability of the published results suggests that the success rate depends on the type of lesion that underlies NP. Identifying predictors of a good response could improve the MCS success rate. Various techniques have been proposed in order to predict the response to epidural MCS and improve patient selection [7, 11]. These include the barbiturates and morphine tests and the response to transcranial magnetic stimulation (TMS) of the motor cortex [3, 13, 16]. It is not clear, however, whether TMS should be applied more widely in the selection of the potentially good responders. Furthermore, many functional changes that have been observed by fMRI, PET or magnetoencephalography (MEG) may not be related to the analgesic efficacy of MCS; it is not clear, therefore, whether functional imaging could allow better selection of the potential good-responders.

Accurate electrode positioning

The variability of the reported results could also be related to inaccurate electrode positioning in some patients. Therefore, the actual efficacy of MCS might be underestimated. Appropriate targeting along the CS is a crucial step in obtaining pain relief; therefore, the accuracy of electrode's position should be questioned first in non-responders. The following adjunctive measures have been proposed in order to improve the targeting method.

Awake surgery

If patients are kept awake during the procedure, the quality of iCM may improve because the amplitude of the evoked potentials is increased, the electrophysiological data are more reproducible and the sensitivity of the iCM to the electrical artefacts is reduced. Awake surgery represents a valid approach for MCS but requires training and experience for keeping the complication rate (subdural hemorrhage, seizures, infection) low. One must keep in mind, however, that awake surgery does not allow an assessment of the analgesic efficacy of MCS because the level of consciousness of the patient is depressed. Furthermore, contrary to patients who are operated on awake for brain tumors, chronic NP patients often present with a poor level of cooperation, and are affected by their pain, the uncomfortable position, and the analgesic drugs that reduce their ability to understand and sustain their concentration on simple tasks. Nevertheless, awake surgery can improve at least the functional targeting method used for electrode positioning.

Combination of functional techniques

The combination of functional techniques may increase the accuracy of functional cortical targeting. The navigation system is a precious tool for integrating intraoperatively different targeting methods such as iCM, PET, fMRI or MEG [2, 6, 7, 23, 24]. The contribution of fMRI to the functional cortical mapping during the procedure of MCS has been evaluated [19, 20], but certain technical and methodological issues must be addressed prior to its reliable application. In 18 patients, fMRI-guidance was combined with iCM. iCM-guided MCS was performed under stereotactic image-guidance using a frameless neuronavigation system; the data obtained by iCM and fMRI were compared intraoperatively. Correspondence between contours of fMRI activation areas and iCM in the precentral gyrus was found in almost all patients. Furthermore, fMRI appeared to be less altered by artefacts and provided data, which were more unambiguous than those of iCM. fMRI also has the great advantage that it can be performed in amputated patients in whom iCM is not feasible. As fMRI is still under evaluation, fMRI-guidance must be used and validated in combination with iCM to improve the functional targeting in MCS procedures. Correct targeting is crucial for obtaining pain relief; therefore, this combination of fMRI with iCM may increase the analgesic efficacy of MCS [19]. fMRI is, however, a time consuming technique that requires training and engineering support (statistical parametric mapping, spatial and functional validation) prior to a regular application in stereotactic procedures.

Technical advances in both fMRI, PET and MEG have improved their spatial and temporal resolution. Further advances may be expected in the near future in the study of normal and pathological pain, and of the nociceptive and non-nociceptive sub-regions in the somatosensory cortex and subcortical regions [6, 23, 24]. MRI techniques such as fMRI and diffusion tensor imaging (DTI) may also be combined for anatomical-functional correlations. This may be a helpful adjunctive method for localising the activated motor area [22] and for enhancing the topographical definition of the damage in the thalamoparietal fibers (Fig. 1). Such combinations could confirm or improve the accuracy of the targeting data of fMRI and iCM. Finally, the combination of different functional methods may reduce the number of recommendations made to non-responding patients for reoperation in order to reposition the cortical electrode in an attempt to define an alternative target.

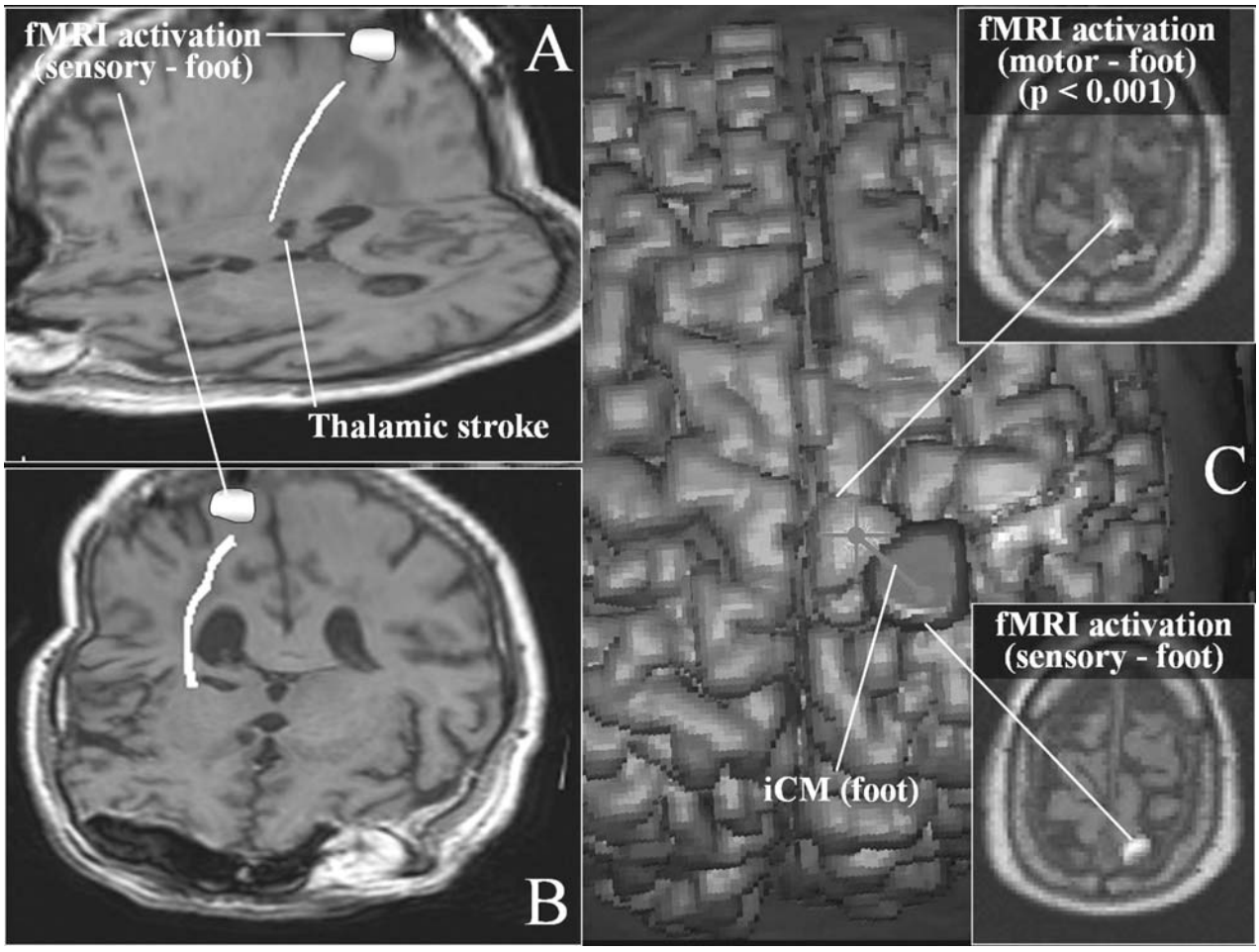

Fig. 1. Combination in the 3D-navigational planning of data from both functional magnetic resonance imaging (*fMRI*) and diffusion tensor imaging (*DTI*) for anatomo-functional correlations in a patient with central poststroke pain. Structural MRI *left lateral view* (A) and *anterior view* (B) showed a small residual cavity (thalamic stroke) confined to the right thalamic ventral posterolateral nucleus and the adjacent posterior arm of the internal capsule. DTI maps showed selective reduction of right sensory thalamocortical fibers (A and B). fMRI, performed with different sensory and motor task paradigms (*foot*) showed cortical areas of activation projected within the target obtained by intraoperative cortical brain mapping (*iCM*) (C)

Optimizing the method of cortical stimulation

Motor vs premotor stimulation

It was mentioned above that pain relief occurs in some patients when the negative pole of the stimulation electrode is over the premotor rather than the motor area of the pre-central cortex. This observation requires to keep a large part of the electrode in a location that covers both motor and premotor gyri because both receive somatotopic projection of pain. Therefore, a single quadripolar electrode should be orientated perpendicular to the CS.

Electrode orientation

When the functional targeting method provides ambiguous data (e.g. in targeting facial areas), we do not recommend orientating a single electrode vertically along the CS over the motor strip. Finding the functional target along the CS is crucial in obtaining pain relief [17, 18] and this should be achieved prior to fixing the electrode to the dura. The orientation of the electrode in a direction perpendicular to the CS allows the stimulation of both motor and premotor gyri. The use of two electrodes (positioned side by side and orientated perpendicular to the CS) may offer better vertical cover of the motor and premotor gyri along the CS.

Subdural electrode positioning

The opening of the dura may offer certain advantages but it constitutes a more invasive approach. First, subdural iCM recordings provide a more precise functional targeting because they are associated with an increase in the iSEP wave amplitude. Second, the subdural position

of the electrode allows the decrease of the intensity of cortical stimulation. Third, direct observation of the cortical gyri allows to control better the location of the CS by direct correlation with the navigation images. However, subdural MCS remains disputable and, in general, it is not recommended for several reasons: a) it does not increase the technique's success rate, b) it increases significantly the risk of seizures that can be induced by stimulation and c) it might contribute to scar tissue formation, cortical lesioning, empyema, secondary gliosis, and chronic seizures.

Large electrode

The use of double or multiple electrodes, separated or combined in a newly-designed enlarged silicone plate is a valid alternative that may increase the stimulated cortical surface and the chances of obtaining an analgesic effect.

Conclusion

The technique of cortical stimulation remains under evaluation because the underlying mechanisms are still essentially unknown. Indeed, pain and pain modulation are mediated by a network of multiple interacting modules (sensory, affective, cognitive and attentional) of neuronal activity. The understanding of the central mechanisms of nociceptive and neuropathic pain has progressed based on the application of brain imaging techniques such as PET, fMRI and MEG. Successive technical adaptations have been proposed to reduce the number of non-responding patients to MCS. The accuracy of the electrode position is undoubtedly a crucial factor in obtaining pain relief. The combination of different functional imaging methods with intraoperative cortical mapping may improve the quality of cortical targeting. Future developments are needed in order to improve the patient selection process, the methods used for cortical stimulation and the success rate of MCS.

References

1. Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ (2000) Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. Pain 84: 431–437
2. Casey KL (2000) Concepts of pain mechanisms: the contribution of functional imaging of the human brain. Prog Brain Res 129: 277–287
3. Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, Rothwell JC (1999) Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. Exp Brain Res 124: 520–524
4. Duffau H (2001) Acute functional reorganisation of the human motor cortex during resection of central lesions: a study using intraoperative brain mapping. J Neurol Neurosurg Psychiatry 70: 506–513
5. Ebel H, Rust D, Tronnier V, Boker D, Kunze S (1996) Chronic precentral stimulation in trigeminal neuropathic pain. Acta Neurochir (Wien) 138: 1300–1306
6. Ferretti A, Del Gratta C, Babiloni C, Caulo M, Arienzo D, Tartaro A, Rossini PM, Romani GL (2004) Functional topography of the secondary somatosensory cortex for nonpainful and painful stimulation of median and tibial nerve: an fMRI study. Neuroimage 23: 1217–1225
7. Garcia-Larrea L, Peyron R, Mertens P, Grégoire MC, Lavenne F, Le Bars D, Convers P, Mauguière F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
8. Helmchen C, Lindig M, Petersen D, Tronnier V (2002) Disappearance of central thalamic pain syndrome after contralateral parietal lobe lesion: implications for therapeutic brain stimulation. Pain 98: 325–330
9. Herregodts P, Stadnik T, De Ridder F, D'Haens J (1995) Cortical stimulation for central neuropathic pain: 3-D surface MRI for easy determination of the motor cortex. Acta Neurochir Suppl 64: 132–135
10. Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H (2001) Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci 21: 3609–3618
11. Katayama Y, Fukaya C, Yamamoto T (1998) Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. J Neurosurg 89: 585–591
12. Laterre EC, De Volder AG, Goffinet AM (1988) Brain glucose metabolism in thalamic syndrome. J Neurol Neurosurg Psychiatry 51: 427–428
13. Lee L, Siebner HR, Rowe JB, Rizzo V, Rothwell JC, Frackowiak RSJ, Friston KJ (2003) Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23: 5308–5318
14. McCarthy G, Alisson T, Spencer DD (1993) Localization of the face area of human sensorimotor cortex by intracranial recording of somatosensory evoked potentials. J Neurosurg 79: 874–884
15. Meyerson BA, Lindblom U, Linderoth B, Lind G, Herregodts P (1993) Motor cortex stimulation as treatment of trigeminal neuropathic pain. Acta Neurochir Suppl 58: 150–153
16. Migita K, Uozumi T, Arita K, Monden S, Lindblom U, Linderoth B (1995) Transcranial magnetic coil stimulation of motor cortex in patients with central pain. Neurosurgery 36: 1037–1040
17. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
18. Pirotte B, Voordecker P, Neugroschl C, Baleriaux D, Wikler D, Metens T, Denolin V, Joffroy A, Massager N, Brotchi J, Levivier M (2005) Combination of functional MR-guided neuronavigation and intraoperative cortical brain mapping improves targeting of motor cortex stimulation in neuropathic pain. Neurosurgery 2 Suppl 56: 344–359
19. Pirotte B, Neugroschl C, Metens T, Wikler D, Denolin V, Voordecker P, Joffroy A, Massager N, Brotchi J, Levivier M, Baleriaux D (2005) Comparison of functional MRI-guidance to electrical cortical mapping for targeting selective motor cortex areas in neuropathic pain: a study based on intraoperative stereotactic navigation. AJNR Am J Neuroradiol (in press)
20. Roux FE, Ibarrola D, Tremoulet M, Lazorthes Y, Henry P, Sol JC, Berry I (2001) Methodological and technical issues for integrating

functional magnetic resonance imaging data in a neuronavigational system. Neurosurgery 49: 1145–1156
21. Saitoh Y, Osaki Y, Nishimura H, Hirano S, Kato A, Hashikawa K, Hatazawa J, Yoshimine T (2004) Increased regional cerebral blood flow in the contrealateral thalamus after successful motor cortex stimulation in a patient with poststroke pain. J Neurosurg 100: 935–939
22. Seghier ML, Lazeyras F, Vuilleumier P, Schnider A, Carota A (2005) Functional magnetic resonance imaging and diffusion tensor imaging in a case of central poststroke pain. J Pain 6: 208–212
23. Torquati K, Pizzella V, Babiloni C, Del Gratta C, Della Penna S, Ferretti A, Franciotti R, Rossini PM, Romani GL (2005) Nociceptive and non-nociceptive sub-regions in the human secondary somatosensory cortex: an MEG study using fMRI constraints. Neuroimage 26: 48–56
24. Tran TD, Hoshiyama M, Inui K, Kakigi R (2003) Electrical-induced pain diminishes somatosensory evoked magnetic cortical fields. Clin Neurophysiol 114: 1704–1714
25. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
26. Wood CC, Spencer DD, Alisson T, McCarthy G, Williamson PD, Goff WR (1988) Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. J Neurosurg 68: 99–111

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Chronic electrostimulation of the trigeminal ganglion in trigeminal neuropathy: current state and future prospects

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Summary

Over two decades ago, the electrostimulation of the trigeminal ganglion (TGES) was established as a treatment option for patients with trigeminopathic pain due to a (iatrogenic) lesion of the trigeminal nerve, on whom the other therapeutic methods, either neurosurgical or conservative have very limited efficacy and usually are associated with a poor outcome. The technique of TGES which uses the setup also used for the thermocoagulation lesion for trigeminal neuralgia was first published by Steude in 1984 and has not been altered substantially. After a percutaneous puncture with a 16 gage needle of the oval foramen, a monopolar electrode (diameter 0.9 mm, custom-made) is placed in the postganglionic trigeminal nerve. After a successful test-stimulation phase, a permanent electrode pulse generator system is implanted. Our experience includes more than 300 patients with a minimum follow-up of one year. Of these patients, 52% showed a good to excellent analgesic effect. The TGES-induced analgesia was persistent in long term-follow-up in all patients. The impact of TGES on cerebral pain modulation was proven by electrophysiology and PET. TGES is an effective, minimally invasive and reversible treatment option in selected patients with trigeminopathic pain; it should, therefore, always be considered as the primary treatment-option. Electrodes with two leads and a diameter not exceeding the 0.9 mm, allowing bipolar stimulation might enhance the neuromodulatory efficacy and options of TGES.

Keywords: Neuromodulation; trigeminal ganglion; trigeminopathic pain; electrostimulation; TGES.

Background and indications

Despite the continuous development of new and refined medical approaches as well as surgical techniques over the recent decades, the management of patients with trigeminal neuropathy still remains a challenge. There are highly effective neurosurgical treatments for typical trigeminal neuralgia (tic douloureux) i.e. microvascular decompression or percutaneous thermocoagulation (in selected cases). However, patients with trigeminopathic pain, also described as ''atypical trigeminal neuralgia'' suffer from a severe pain syndrome of partial deafferantation that is hardly alleviated by any therapeutic approach. In trigeminal neuropathy, patients are characteristically affected by a continuous burning pain sensation accompanied by hypesthesia along one or more trigeminal divisions without the stabbing pain attacks typical of tic douloureux. Multiple maxillofacial interventions, dental extractions, orthodontic interventions and destructive procedures in the Gasserian ganglion are frequently part of the medical history of these patients. Over the last thirty years, various ablative neurosurgical procedures such as percutaneous thermocoagulation, electrocoagulation, glycerol rhizotomy and retrogasserian rhizotomy have been applied in trigeminal neuropathy. These approaches did not show any beneficial effect and even led to worsening of pain in 73–78% of the patients as it has been shown by Sweet [10], Siegfried [5] and our group [9]. Hence, nowadays, destructive procedures do not play a major role in the treatment of trigeminal neuropathy, and, in our opinion, they are contraindicated in these patients.

After the effectiveness of therapeutic neuromodulation, based on the gate-control theory by Melzak and Wall [2], had been proven in the spinal cord, this approach was also applied to the trigeminal ganglion. In 1974, the first procedures of electrostimulation of the trigeminal nerve were done in our institution using subdural floating electrodes inserted between C1 and C2 according to the procedure established for percutaneous cordotomy [6]. Electrodes were guided under fluoroscopic control to the other side, through the foramen magnum and were finally placed in the region of the

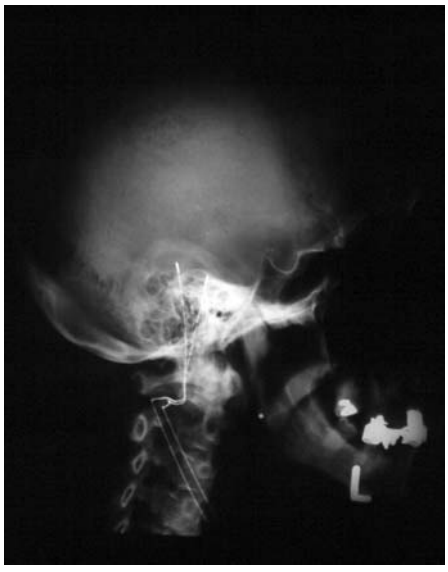

Fig. 1. Conventional x-ray of the skull (*lateral view*) showing the electrodes in the cerebellopontine angle (*CPA*)

cerebellopontine angle (CPA) (Fig. 1). The group of Meyerson and Hakanson preferred the epidural bipolar stimulation by suturing an electrode directly to the dura overlying the trigeminal ganglion [3]. However, this procedure had many disadvantages; test-stimulation and exact positioning of the electrode in the affected trigeminal division were not possible, and moreover, this approach was associated with all the risks of a craniotomy. However, following the development of an electrode with a diameter of only 0.7 mm (Medtronic Inc., MN, USA) it was possible to place it percutaneously into the trigeminal ganglion using the same equipment and approach established for the selective percutaneous thermocoagulation [7]. Thus, it became possible to test-stimulate and position the electrode directly in the branch involved for optimal effectiveness while being minimally invasive at the same time. After a successful test-stimulation, the implantation of a pulse generator (IPG) system follows. Over the last 20 years, only small changes have been made in this technique that still can be considered as the ''gold standard'' of neuromodulation in trigeminal neuropathy. We consider this approach to be indicated in all patients with true trigeminopathic pain due to a lesion of the trigeminal nerve, iatrogenic or of other cause; however, it is often difficult to distinguish this pain syndrome and the correct diagnosis is crucial for the success of the technique. For more than 25 years, the trigeminal ganglion electrostimulation (TGES) has been the primary neurosurgical treatment for these patients in our institution.

Material and methods

In the period 1980–2005, a percutaneous test-stimulation at the post-ganglionic trigeminal divisions was performed in 321 patients with intractable trigeminopathic pain. The cause of neuropathy was iatrogenic in most patients (75%). Of the total patient population, the cause of neuropathy was maxillary sinus, orthodontic, and dental procedures in 60%, whereas 13% of the patients had undergone a previous ablative neurosurgical procedure in the area of the Gasserian Ganglion for idiopathic trigeminal neuralgia. In 12% of the patients, persisting neuropathic pain occurred after a facial injury, 6% were suffering from postherpetic neuralgia and in the remaining patients the cause of neuropathy was unknown. In the first 14 years, i.e. until 1994, the initially developed custom-made electrode (SP, Medtronic Inc., Minneapolis, MN, USA) with a diameter of 0.7 mm was used. For technical reasons, production of this electrode was then discontinued and other electrodes were developed and tested. These included the ''anchor-electrode'' (quinta trigeminal electrode, Mod. 3981, Medtronic) which is also used by other groups [1, 12] and the ''sigma-electrode'' (3483 S, Medtronic). However, neither of these electrodes led to a completely satisfactory clinical result. One of the reasons is the rather large diameter ranging from 1.2 to 1.4 mm. It became clear that the diameter of the electrodes for this procedure should not exceed the 1.0 mm in order to prevent uncomfortable or painful dysaethesias. Finally, in 1997, a new electrode with a diameter of 0.9 m was introduced (3483 SNS, Medtronic), which, since then, it has been used by us until the present time.

Surgical technique

The technique for the percutaneous insertion of the electrode for testing and permanent implantation has been described in detail by Steude *et al.* [7, 9].

Implantation for percutaneous test-stimulation

The operation is performed under local anaesthesia combined with short-lasting barbiturates. The standard needle, used for selective percutaneous thermocoagulation, is inserted 2.5 cm lateral to the labial commisure

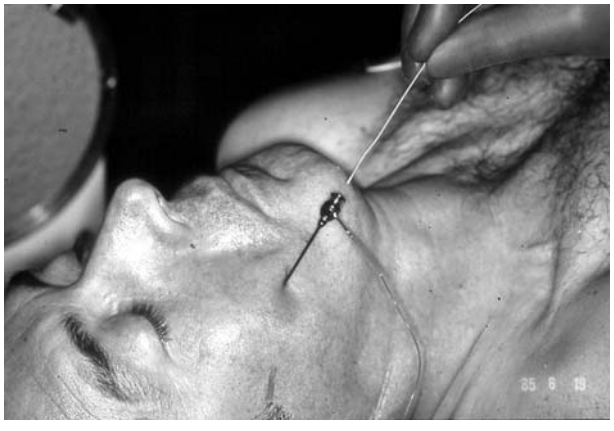

Fig. 2. Intraoperative picture taken after percutaneous puncture of the oval foramen with the needle in situ and the surgeon inserting the electrode

after putting a subcutaneous pouch of local anaesthetic. The needle is then guided under fluoroscopic control into the oval foramen. After passing through the foramen it is advanced further until the tip of the needle has reached the level of the clivus on fluoroscopy. After a brief test-stimulation, the electrode is inserted (Fig. 2) under continuous fluoroscopic monitoring until the tip has also reached at least at the level of the clivus. Test stimulation is then repeated with the patient awake. The electrode is advanced under continuous stimulation along the medial and dorsal trajectory until it evokes paraesthesias in the area innervated by the trigeminal division involved in the neuropathy. Once a satisfactory stimulation has been achieved, the needle is withdrawn under fluoroscopic control and the electrode is secured with steri-strips. Test-stimulation can than be continued for 3–5 days using an external pulse-generator (Medtronic Inc.) with the patient being able to adjust the intensity as well as the frequency of the stimulus at his own comfort. After 5 days, the electrode is easily removed.

Permanent implantation of the electrode and pulse generator system

The initial steps of the implantation procedure for the permanent system are very similar to those of the test-stimulation. The operation is performed under local anaesthesia in combination with short-lasting barbiturates. After a local subcutaneous pouch is created by a local anaesthetic drug, the puncture canula is inserted via a small (app. 5 mm) skin incision, 2.5 cm lateral to the labial commissure. It is then guided through the oval foramen under fluoroscopic control and placed in the postganglionic part of the trigeminal nerve. Thereafter, the optimal localization within the affected branch of the nerve is achieved under continuous stimulation with the help of the cooperating patient (see above). Before removing the canula under x-ray control, a subcutaneous suture is prepared at the site of the skin incision. Once the canula has been removed, the electrode is fixed by the suture; this is crucial because it is virtually the only fixation of the electrode in order to maintain its correct position within the nerve. After placement of the electrode in the correct trigeminal location, under local anaesthesia, the next steps of the implantation are performed under short-lasting barbiturates; this is more comfortable for the patient who, from now on, is not necessary to be conscious and cooperative.

Using the puncture canula, the electrode is tunnelled between maxilla and mandibula to a second small skin incision in the mandibular angle in order to prevent displacement of the electrode due to jaw movements. A transverse skin incision with a length of approximately 6 cm is made 1 cm caudal and parallel to the clavicle and a subcutaneous pouch is created. The electrode is then passed through from the incision at the mandibular angle to the infraclavicular pouch using a tunnelling device. After connection of the electrode to the IPG (Itrel III®, Medtronic), the IPG is placed in the pouch. Standard skin closure is performed thereafter. The system is telemetrically programmed 5–6 hours after implantation, aiming to produce paraesthesias in the area affected by the neuropathic pain without causing side effects by either stimulating non-painful regions or inducing motor reactions (contraction of the masseter muscle). The patient is provided with a telemetrically operating hand-programmer (Itrel-EZ®, Medtronic) allowing not only for turning ''on'' and ''off'' the stimulation but also for increasing and decreasing the amplitude for his individual comfort within the limits set by the physician. Other parameters like pulse width and frequency can only be changed by a programming device operated by the physician. Figure 3 shows the complete system currently in use (electrode model 3483 SNS, IPG Itrel III®, hand-programmer ItrelEZ®, Medtronic). Post-operative radiographic controls including skull-base x-rays and skull-base CT-scan confirm and document the final position of the electrode (Fig. 4).

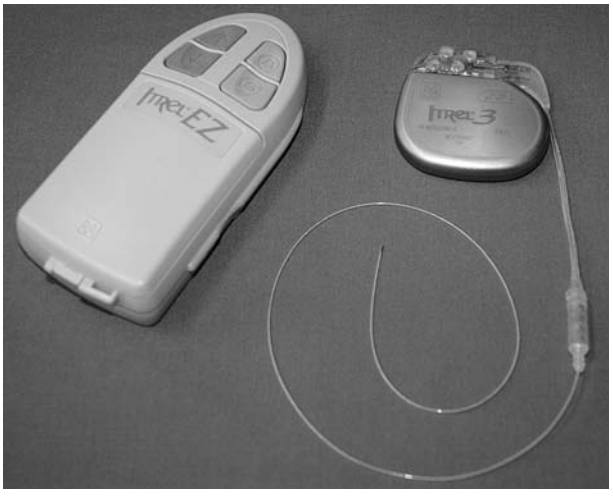

Fig. 3. System for permanent implantation (Medtronic inc.); Monopolar electrode (model 3483 SNS, diameter 0.9 mm, custom-made), implantable pulse generator (*IPG*) Itrel III® (*right*), and patient hand-programmer ITREL EZ® (*left*)

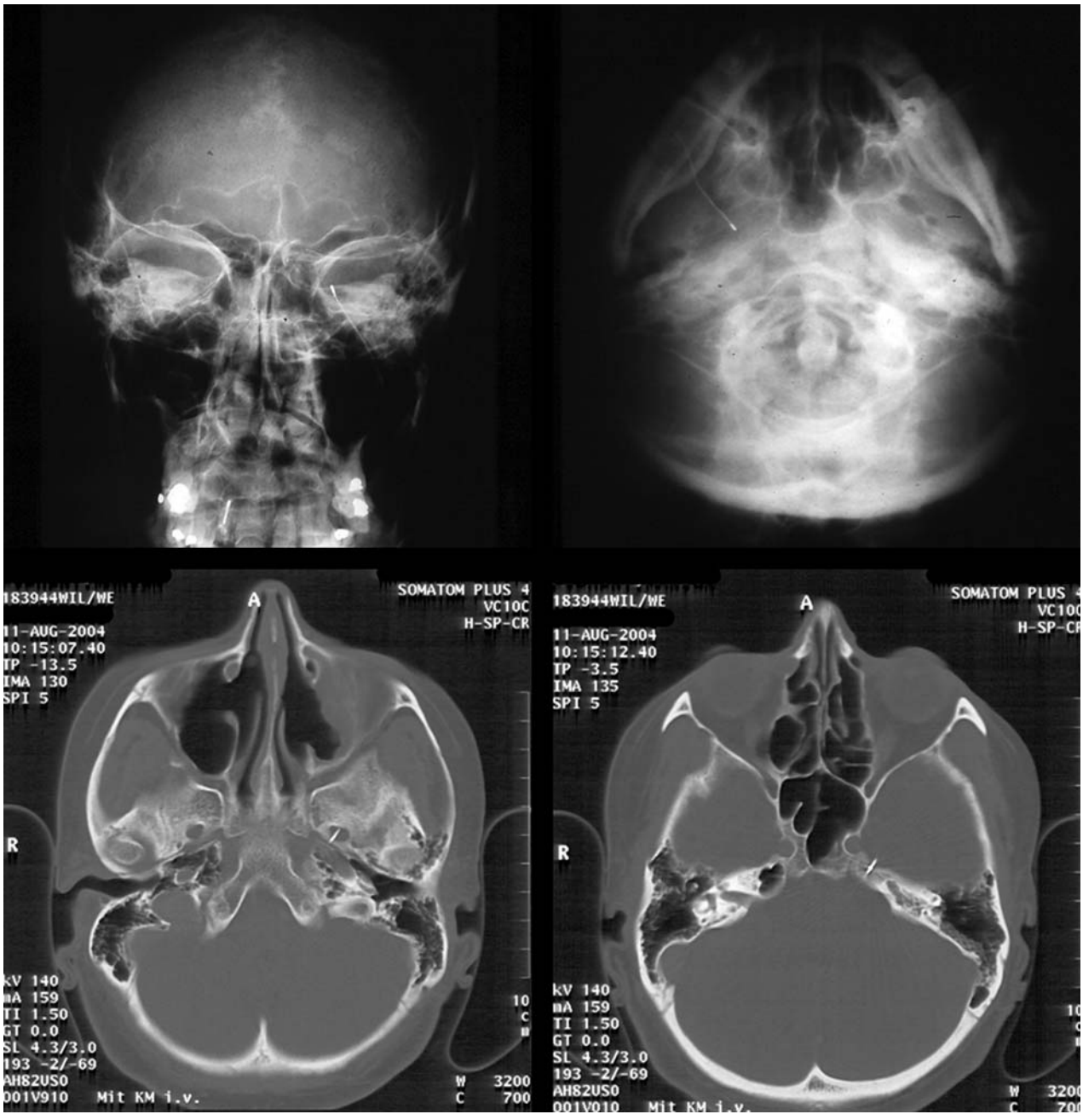

Fig. 4. Radiographic control showing the electrode passing through the oval foramen with its tip in the Cavum Meckeli on conventional x-ray (*upper row*) and CT (*lower row*) of the skull base

Clinical results

The experience and results of 182 patients treated between 1980 and 1995 [9] have now been extended to a total of 321 patients affected by intractable trigeminal neuropathy who underwent percutaneous test-stimulation from 1980 until 2005 in our institution; long-term follow data (of a minimum of five years) are available in 235 patients. This is by far the largest series reported compared to other groups using similar techniques [1, 12].

Of all patients whose long-term follow-up data are available in the series, 122 (52%) reported a pain reduction of 50% or more with the best results being observed in the posttraumatic patients (success rate: 60%) and the worst results in patients with neuropathy of unknown origin (success rate: 20%). Of the 122 patients who had a successful test, 119 patients had the system implanted for chronic TGES. The follow-up ranges between 5 and 25 years. In 82% of the implanted patients, there was an

either good or excellent analgesic effect. In the group with an iatrogenic lesion of the nerve, the percentage of significant improvement ranged from 87% in patients with a history of maxillofacial, orthodontic or dental procedures to 100% in patients with a destructive neurosurgical procedure in the area of the trigeminal ganglion. There was no levelling off of the analgesic effect in the long-term follow up. It is important to point out that there was not a single patient, in these subgroups, whose pain got worse because of the stimulation. The patients with postherpetic neuralgia showed a completely different clinical course; only 33% experienced a satisfactory pain relief, but more importantly, 67% got worse. As a consequence, post-herpetic neuralgia is no longer seen as an indication for TGES. Stimulation parameters do not vary widely; most patients preferred a pulse rate from 85 to 130 pps and amplitude of 0.2–1.2 V with 0.5 V usually being sufficient for an adequate analgesic effect (thus allowing for long battery-life).

Neuromodulation effects of TGES

Despite its proven efficacy and minimally invasive and reversible nature, TGES is applied to only a limited extent in trigeminal neuropathy. A paucity of clinical documentation and insufficient understanding of the mechanisms underlying the induced analgesia probably contribute to the limited wider implementation [11]. In recent years, several studies have been done to address the issue of whether TGES induces a ''real'' analgesia effect and not a placebo or ''psychotherapy''-related effect and, furthermore, prove the effect of TGES on pain modulation pathways.

Electrophysiology

By applying pain-related evoked potentials before, during, and after stimulation along with objective and subjective pain measurements it became possible for the first time to demonstrate the analgesic effect of TGES in trigeminal neuropathy [4, 8]. Pain-evoked potentials from painful stimulation (either dental pulp stimulation or stimulation of the nasal mucosa with painful CO_2 inflation) may be completely suppressed by TGES of the corresponding trigeminal division (Fig. 5). This benefit persists after the stimulation has stopped. Moreover, a highly significant elevation of pain threshold was observed. After 30 min of stimulation, the threshold in the directly stimulated division had increased from 20 to 200 μA. This increase outlasted the end of stimulation by more than 2 hours (Fig. 5). Notably, the full effect was observed only in the trigeminal branch stimulated directly, which underscores the necessity of exact placement of the electrode tip into the involved branch with the patient being conscious and cooperating.

PET

In a recent PET study, the cerebral mechanisms of analgesia induced by TGES were analyzed [11]; ten pa-

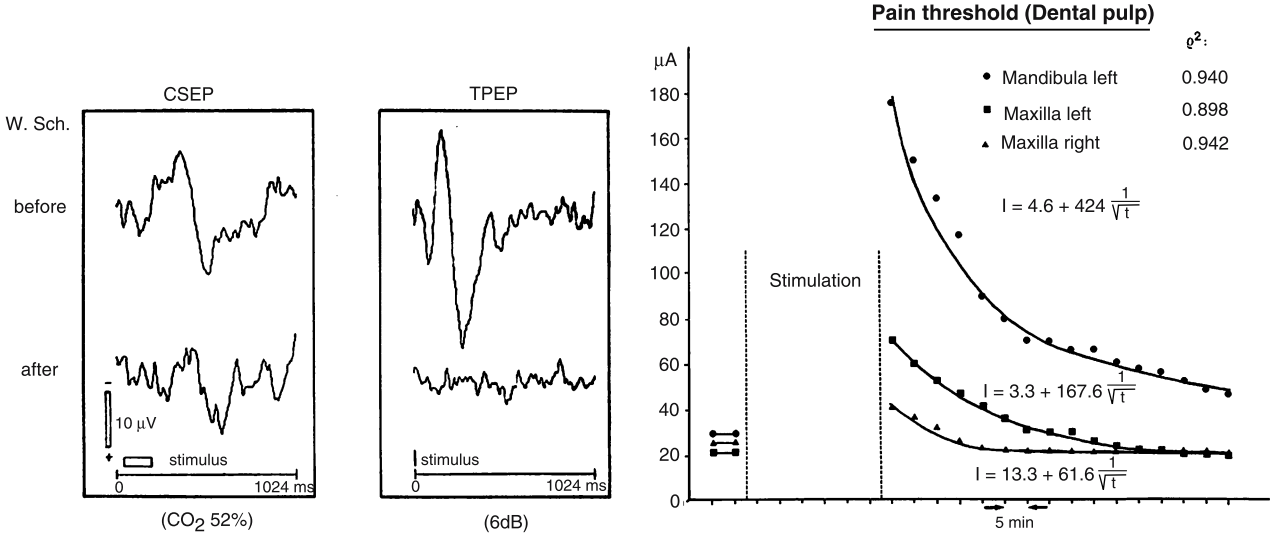

Fig. 5. Electrophysiological proof of pain modulation; (*1*) Complete suppression of pain-evoked potentials after painful CO_2-insufflation and painful pulpal stimulus (*left diagram*). (*2*) Increase of pain threshold from 20 to 200 μA in the trigeminal branch (V_3 *left*) stimulated directly (*right diagram*)

tients with one-sided trigeminopathic pain were studied after implantation of a stimulation electrode at the ipsilateral Gasserian ganglion had been performed at least 3 months earlier. Patients were scanned before stimulation (habitual pain), after short-term stimulation (1 minute st-TGES) and after long-term stimulation (lt-TGES). The patients reported significant pain relief after lt-TGES ($p = 0.006$). After st-TGES, changes in regional cerebral blood flow (rCBF) without significant pain relief were observed. Furthermore, comparison of lt-TGES and st-TGES increases in rCBF, which, after lt-TGES, were significant in perigenual parts of the anterior cingulate cortex (ACC) and neighbouring orbitofrontal and medial frontal cortices ($p < 0.001$). Regression analysis of rCBF changes and subjective ratings of pain revealed that the rCBF increase in the posterior part of the contralateral ACC was consistent with the encoding of pain [11]. Thus, in trigeminal neuropathy, a definite impact of TGES on cerebral pain modulationing pathways was demonstrated.

Complications

No severe surgery- or therapy-related complications were observed in our series over the last 25 years. There were, however, ''common'' expected complications of the technique. In the first 14 years (1980–1994) an electrode with diameter of 0.7 mm was used. There was no discomforting dysesthesia with this small electrode. Electrode dislocation occured in 10% of these first 70 patients with the frequency of this complication being proportionally related to the electrode's diameter. No dislocations of the 0.9 mm diameter, used today occurred, but the rate of dysesthesia increased to 18%; the ''anchor-electrode'' (3981, Medtronic) with a diameter of 1.2 m was associated with dysesthesia in about 30% of the patients and the anchor failed to prevent the electrode from being dislodged in about 30% of the cases. No severe infections such as meningitis or sepsis were encountered. The rate of uncomplicated local infections (treated conservatively without removal of the stimulation device) at the site of the IPG or connectors was 3% (similar to spinal cord stimulation procedures). In one patient, however, the electrode was dislodged and perforated the overlying skin at the cheek and, thus, it was removed.

Future perspectives

TGES using a monopolar electrode (Medtronic Inc.) implanted percutaneously via the oval foramen was introduced over two decades ago by Steude *et al.* and, for the time being, remains the gold standard of neuromodulation in trigeminal neuropathy. It is minimally invasive, reversible (non-destructive) and has a success rate of approximately 50%, which is higher compared to the success rate of any other medical or surgical therapeutic approach. There are potential developments that may improve the present technique. A bipolar or multipolar electrode would allow a wider variety and range of stimulation. However, the limitation that diameter should not exceed 0.9 mm (in order to prevent unpleasant or painful dysesthesia) has been a manufacturing problem. Another improvement may be the use of a rechargable IPG (e.g. Restore® Medtronic Inc., Eon™ ANS, Inc.), which can prolong battery life and reduce the number of IPG replacements. However, the voltage used in most patients is very low (mean 0.5 V), and in this special type of neuromodulation, the IPGs usually last very long, i.e. up to 9 years.

Conclusions

Chronic therapeutic electrostimulation of the trigeminal ganglion (TGES) is an effective, minimally invasive and reversible treatment option in selected patients with trigeminopathic pain. TGES should always be seriously considered in patients with persistent trigeminopathic pain. There is proof for the direct effect of TGES on known cerebral pathways of pain modulation. New electrodes with two or more leads and a diameter not exceeding 0.9 mm would allow for bipolar stimulation and an extension of the area stimulated, and thus would enhance and optimize this neuromodulatory treatment.

References

1. Meglio M (1984) Percutaneously implantable chronic electrode for radiofrequency stimulation for the Gasserian ganglion: a new perspective in the management of trigeminal pain. Acta Neurochir Suppl 33: 521–525
2. Melzack R, Wall PD (1965) Pain mechanisms: a new theory. Science 150: 971–978
3. Meyerson BA, Hakanson S (1980) Alleviation of atypical trigeminal pain by stimulation of the Gasserian ganglion ivia an implanted elctrode. Acta Neurochir Suppl 30: 303–309
4. Raab WHM, Kobal G, Steude U, *et al* (1987) Die elektrische Stimulation des Ganglion Gasseri bei Patienten mit atypischem Gesichtsschmerz: Klinische Erfahrung und experimentelle Kontrolle durch elektrische Pulpareizung. Dtsch Zahn Mund Kieferheilk Zentralsl 42: 793–797
5. Siegfried J (1976) Neurochirurgische Behandlung der symptomatischen und atypischen Gesichtsschmerzen. Munch Med Wochenschr 120: 675

6. Steude U (1978) Percutaneous electro-stimulation of the trigeminal nerve in patients with atypical trigeminal neuralgia. Acta Neurochir 21: 66
7. Steude U (1984) Radiofrequency electrical stimulation of the Gasserian ganglion in patients with atypical trigeminal neuralgia. Acta Neurochir Suppl 33: 481
8. Steude U, Fritsch H, Kobald G (1989) Therapeutic electrostimulation of the trigeminal ganglion in patients with atypical trigeminal neuralgia and the response on real pain evoked potentials. Mod Neurosurg 2: 305–310
9. Steude U (1998) Chronic trigeminal nerve stimulation for the relief of persistent pain. In: Gildenberg PL, Tasker RR (eds) Textbook of stereotactic and functional neurosurgery, McGraw-Hill, New York, pp 1557–1564
10. Sweet WH (1976) Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibres: facial pain other than trigeminal neuralgia. Clin Neurosurg 237: 96
11. Willoch F, Gamringer U, Medele R, Steude U, Toelle TR (2003) Analgesia by electrostimulation of the trigeminal ganglion in patients with trigeminopathic pain: a PET activation study. Pain 103: 119–130
12. Young RF (1995) Electrical stimulation of the trigeminal nerve root for the treatment of chronic facial pain. J Neurosurg 83: 72–78

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Neuromodulatory approaches to the treatment of trigeminal autonomic cephalalgias

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Summary

The trigeminal autonomic cephalalgias (TACs) are a group of primary headache syndromes characterised by intense pain and associated activation of cranial parasympathetic autonomic outflow pathways out of proportion to the pain. The TACs include cluster headache, paroxysmal hemicrania and SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing). The pathophysiology of these syndromes involves activation of the trigeminal-autonomic reflex, whose afferent limb projects into the trigeminocervical complex in the caudal brainstem and upper cervical spinal cord. Functional brain imaging has shown activations in the posterior hypothalamic grey matter in TACs. This paper reviews the anatomy and physiology of these conditions and the brain imaging findings. Current treatments are summarised and the role of neuromodulation procedures, such as occipital nerve stimulation and deep brain stimulation in the posterior hypothalamus are reviewed. Neuromodulatory procedures are a promising avenue for these highly disabled patients with treatment refractory TACs.

Keywords: Cluster headache; SUNCT; TAC; paroxysmal hemicrania.

Introduction

Not even considered five years ago, neuromodulatory approaches to the treatment of primary headache are now being examined in clinical studies, and may offer some patients with intractable, disabling headaches a hitherto unthinkable improvement in quality of life. The arrival of neuromodulatory approaches to primary headache has been spear-headed by functional brain imaging which provided insights into the pathophysiology of these disorders. Here, I will discuss neuromodulatory approaches to the treatment of cluster headache and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), two Trigeminal Autonomic Cephalalgias (TACs). The TACs is a grouping of headache syndromes recognised in the second edition of the International Headache Society classification [59]. The term was coined to reflect the underlying pathophysiology of a prominent part of the phenotype of the acute attacks and the excessive cranial parasympathetic autonomic reflex activation in response to nociceptive input in the ophthalmic division of the trigeminal nerve [45]. The TACs are cluster headache [40], paroxysmal hemicrania and SUNCT (Table 1) [92]. Neuromodulatory approaches will be set in the context of the pathophysiology of the conditions, and contrasted with other available treatment options, both medical and surgical. Neuromodulation has the potential to cause a revolution in the management of these patients. Our experience thus far is that the revolution will only happen if a careful clinical approach is combined with the best of neurosurgical methods: a physician/surgeon team has much to offer to these highly disabled patients.

Pathophysiology of TACs

Any explanation of the pathophysiology of TACs must account for the two major shared clinical features characteristic of the conditions: trigeminal distribution pain and ipsilateral cranial autonomic features [45], and then provide an explanation for the distinct phenotypes, when compared to other primary headache syndromes. The trigeminal-autonomic reflex provides an understanding of the shared phenotype [101], while the results of human brain imaging distinguish these conditions from other primary headaches [16]. I will review both the peripheral and central aspects since both peripheral and

Table 1. *Differential diagnosis of trigeminal autonomic cephalalgias (TACs)*

Primary TACs	Similar secondary headaches	Secondary TACs
Cluster headache	Tolosa-Hunt syndrome	cranial artery dissection [19, 78, 86] or aneurysm [140]
Paroxysmal hemicrania	maxillary sinusitis	pseudoaneurysm of intracavernous carotid artery [69]
SUNCT syndrome†	temporal arteritis	aneurysm anterior communicating artery [55]
	Raeder's paratrigeminal neuralgia [41]	basilar artery aneurysm [36]
	trigeminal neuralgia	carotid aneurysm [55]
		occipital lobe AVM [88]
		AVM middle cerebral territory [109]
		high cervical meningioma [72]
		unilateral cervical cord infarction [22]
		lateral medullary infarction [14]
		pituitary adenoma [136]
		prolactinoma [55, 121]
		meningioma of the lesser wing of sphenoid [57]
		maxillary sinus foreign body [125]
		facial trauma [75]
		orbito-sphenoidal aspergillosis [60]
		orbital myositis [77]
		head or neck injury [62]

† *SUNCT* Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

central neuromodulatory procedures are now being tested in these syndromes.

The pain-producing innervation of the cranium projects through branches of the trigeminal and upper cervical nerves [31, 108] to the trigeminocervical complex [43] from where nociceptive pathways project to higher centres [101]. A reflex activation of the cranial parasympathetic outflow provides the efferent loop.

Experimental studies

Stimulation of the trigeminal ganglion in the cat produces cranial vasodilation and neuropeptide release, notably calcitonin gene-related peptide (CGRP) and substance P [49]. The dilation is mediated by antidromic activation of the trigeminal nerve, 20% of the effect, and orthodromic activation through the cranial parasympathetic outflow via the facial (VIIth) cranial nerve, for the other 80% [74]. The afferent arm of the trigeminal-parasympathetic reflex traverses the trigeminal root [74], synapses in the trigeminal nucleus and then projects to neurons of the superior salivatory nucleus in the pons [134]. There is a glutamatergic excitatory receptor in the pontine synapse [110] and projection via the facial nerve [47] without synapse in the geniculate ganglion. The greater superficial petrosal nerve supplies classical autonomic pre-ganglionic fibres to the sphenopalatine (pterygopalatine in humans) and otic ganglia [48]. The sphenopalatine synapse involves a hexamethonium-sensitive nicotinic ganglion [48]. VIIth cranial nerve activation is associated with release of vasoactive intestinal polypeptide (VIP) [46] and blocked by VIP antibodies [44]. Brain blood flow changes depend on the frequency of stimulation [39, 126] and are independent of cerebral metabolism [38]. There is VIP in the sphenopalatine ganglion [137], as well as nitric oxide synthase, which is also involved in the vasodilator mechanism [52] (Fig. 1).

Human studies

The basic science implies an integral role for the ipsilateral trigeminal nociceptive pathways in TACs, and predicts some degree of cranial parasympathetic autonomic activation. The ipsilateral autonomic features seen clinically, such as lacrimation, rhinorrhoea, nasal congestion and eyelid oedema, are consistent with cranial parasympathetic activation, and sympathetic hypofunction (ptosis and miosis). The latter is likely to be a neurapraxic effect of carotid wall swelling [27, 104] with cranial parasympathetic activation. Some degree of cranial autonomic symptomatology is, therefore, a normal physiologic response to cranial nociceptive input [25, 26, 35, 107]. Indeed, other primary headaches, notably migraine [7], or secondary headache, such as trigem-

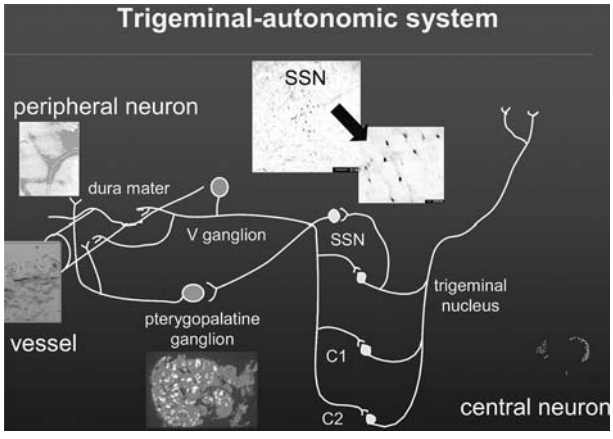

Fig. 1. The trigeminal-autonomic system: *SSN* superior salivatory nucleus

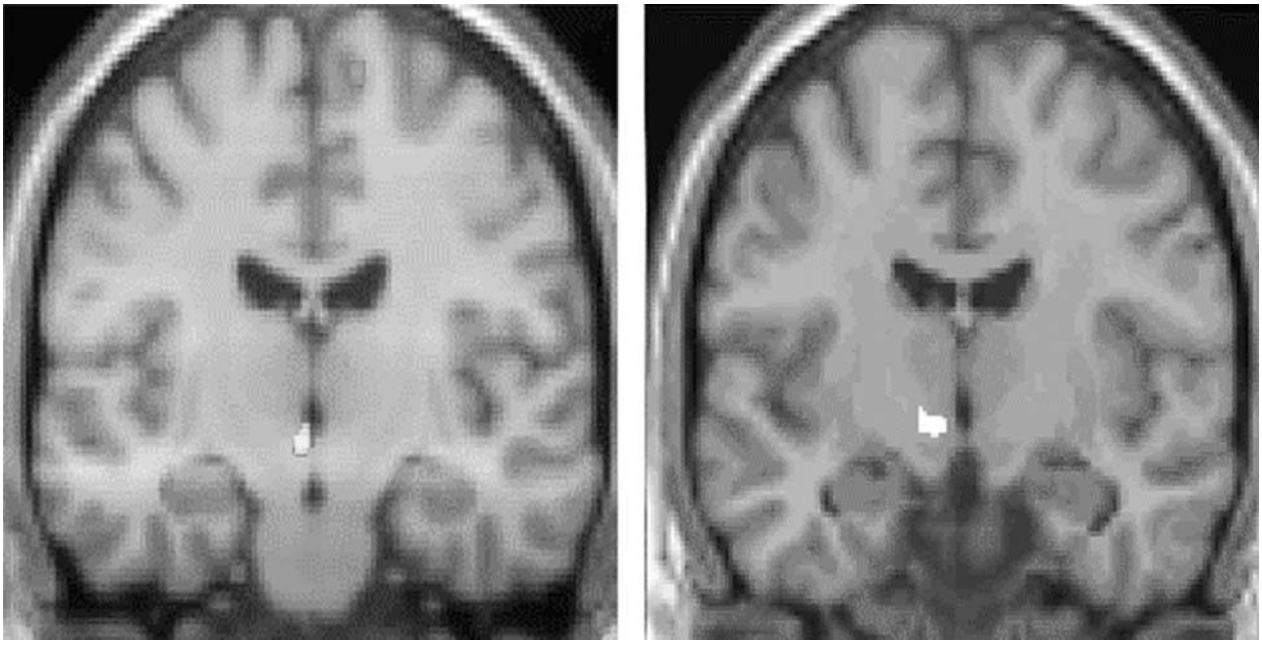

Fig. 2. Brain imaging of cluster headache and SUNCT: changes in the posterior hypothalamic grey are revealed with positron emission tomography in patients with chronic cluster headache (a) [102] imaged during an acute attack triggered by nitroglycerin, while changes in the posterior hypothalamic grey are seen with BOLD fMRI in a patient with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (*SUNCT*) (b) [106]. This region has been the direct target of neuromodulatory approaches that have been successful [34, 81]

inal neuralgia [10], or trigeminal dysaethesias [51], would be expected to have cranial autonomic activation, and they do. The distinction between the TACs and other headache syndromes is the degree of cranial autonomic activation not its presence alone [53]. This is why some patients with migraine have minor cranial autonomic activation that leads to the term cluster-migraine, when most such patients have migraine with cranial autonomic activation. This reflex also explains the curious report of a sense of aural fullness that patients with these syndromes may report if asked specifically, and that has been reported clearly in paroxysmal hemicrania [12].

Permitting trigeminal-parasympathetic activation

What is the basis for the cranial autonomic symptoms being so prominent in the TACs? Is it due to a central disinhibition of the trigeminal-autonomic reflex [12]? Evidence from functional imaging studies: positron emission tomography (PET) studies in cluster headache [102, 106, 135] (Fig. 2), PET studies in paroxysmal hemicrania [98], and functional MRI studies in SUNCT [105, 17] (Fig. 2), have demonstrated posterior hypothalamic activation. Posterior hypothalamic activation seems specific to these syndromes and is not seen in episodic [1, 5, 138] or chronic [94] migraine, or in experimental ophthalmic trigeminal distribution head pain [103]. Interestingly there is contralateral posterior hypothalamic activation in hemicrania continua (HC), in contrast to substantial ipsilateral activation in cluster headache, and additional pontine and midbrain activation in HC [96]. There are direct hypothalamic-trigeminal connections [87]. The hypothalamus is known to have a modulatory role on the nociceptive and autonomic pathways, specifically trigeminovascular nociceptive pathways [8], and is in turn activated by trigeminovascular nociceptive activation [9]. Hence, the TACs involve abnormal activation in the region of the hypothalamus with subsequent trigeminovascular and cranial autonomic activation. Cranial autonomic features are not invariably linked with trigeminal pain and may persist after lesions of the trigeminal nerve [90].

Differential diagnosis of TACs

The primary TACs need to be differentiated from secondary TAC-producing lesions, from other primary headaches, and from each other (Table 1); this illustrates the importance of careful neurological evaluation of patients contemplated for neuromodulatory approaches. An MRI of the brain with attention to the pituitary fossa and cavernous sinus will detect most secondary causes.

It is easy to make an argument, given the rarity of paroxysmal hemicrania and SUNCT, that MRI would be a reasonable part of the initial review of such patients. It is more complex for cluster headache. There are no clear studies. Our impression from a cohort that now exceeds 900 patients (The National Hospital for Neurology and Neurosurgery, Queen Square, London) is that MRI would detect no more than 1 in 100 cases of lesions in episodic cluster headache, so we cannot recommend its routine use in isolation from the history. For chronic cluster headache, an MRI seems reasonable given the very difficult nature of the long-term management and prospects for neuromodulation, which then make brain imaging more complex.

For other primary headaches, migraine is the single biggest problem in the differential diagnosis of cluster headache. Migraine can *cluster* and despite the best intentions of The IHS Classification Committee, short attacks of migraine do occur. Cranial autonomic symptoms are well reported [7], and the neuropeptide changes are the same [50] as in cluster headache [42]. The occurrence of attacks together does not seem to have the seasonal preponderance that is so typical of cluster headache [71, 130], and this can be a useful differential diagnostic feature. This author regards the term *cluster-migraine* as unhelpful and is yet to see a convincing case of a distinct biological entity usefully described by this name. One might expect by chance that migraine could occur in up to one-third of CH sufferers given the peak prevalence of migraine in females and the generally accepted dominant inheritance pattern. The criterion for the effect of movement was added to cluster headache to sharpen the difference with migraine. The Committee hoped this would draw attention to the fact that most cluster headache patients feel restless or agitated [6], while most migraine patients are quiescent, as IHS-I recognised [58]. In clinical practice this symptom, and the periodicity, are extremely helpful in differential diagnosis. The other feature of cluster headache, and this is a feature of TACs when compared to migraine, is that patients with TACs more often complain of unilateral, homolateral photophobia [64]. In addition triggering of headache quickly with alcohol, within 30 min is more typical of cluster headache, whereas alterations to sleep patterns, eating, stress or menses do not generally affect cluster headache. Warm environments seem to be a trigger in cluster headache whereas barometric pressure change is a trigger of migraine [18].

The TACs themselves (Table 2) can often be differentiated by their attack length. This is certainly true when comparing cluster headache to SUNCT. The IHS

Table 2. *Clinical features of trigeminal autonomic cephalalgias (TACs)*

	Cluster headache	Paroxysmal hemicrania	SUNCT syndrome
Sex F:M	1:4	2:1	1:2
Pain			
– Type	stabbing, boring	throbbing, boring, stabbing	burning, stabbing, sharp
– Severity	severe to excruciating	excruciating	moderate to severe
Site	orbit, temple, face	orbit, temple	periorbital
Attack frequency	1/alternate day–8 daily	1–40/day	1/day–30/hour
Duration of attack	15–180 min	2–30 min	5–240 sec
Autonomic features	yes	yes	yes (prominent conjunctival injection *and* lacrimation)
*Migrainous features**	yes	yes	yes
Alcohol trigger	yes	occasional	no
Indomethacin effect	–	++	–

* Nausea, photophobia or phonophobia (often ipsilateral to the pain).

Table 3. *Cluster headache*

1. *Diagnostic criteria*
A. At least 5 attacks fulfilling B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min if untreated
C. Headache is accompanied by at least one of the following:
  – ipsilateral conjunctival injection and/or lacrimation
  – ipsilateral nasal congestion and/or rhinorrhoea
  – forehead and facial sweating
  – ipsilateral eyelid oedema
  – ipsilateral forehead and facial sweating
  – ipsilateral miosis and/or ptosis
  – a sense of restlessness or agitation
D. Attacks have a frequency from 1 every other day to 8 per day.
E. Not attributed to another disorder

1.1. *Episodic cluster headache*
Description: Occurs in periods lasting 7 days–1 year separated by pain free periods lasting one month or more
Diagnostic criteria:
A. All fulfilling criteria A–E of 3.1
B. At least 2 cluster periods lasting from 7 to 365 days and separated by pain-free remissions of $\leq$1 month.

1.2. *Chronic cluster headache*
Description: Attacks occur for more than one year without remission or with remissions lasting less than one month
Diagnostic criteria:
A. All alphabetical headings of 3.1
B. Attacks recur over >1 year without remission periods or with remission periods <1 month

Table 4. *Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)*

Diagnostic criteria
A. At least 20 attacks fulfilling criteria B–E
B. Attacks of unilateral, orbital, supraorbital or temporal stabbing or pulsating pain last 5–240 sec
C. Pain is accompanied by ipsilateral conjunctival injection and lacrimation
D. Attacks occur with a frequency from 3 to 200 per day
E. Not attributed to another disorder

Table 5. *Short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)*

1. *Diagnostic criteria*
A. At least 20 attacks fulfilling criteria B–E
B. Attacks of unilateral orbital, supraorbital or temporal stabbing pain lasting from 2 sec to 10 min
C. Pain is accompanied by one of:
– conjunctival injection and/or tearing
– nasal congestion and or rhinorrhoea
– eyelid oedema
D. Attacks occur with a frequency of ≥ 1 per day for more than half the time
E. Not attributed to another disorder
1.1. *Episodic SUNA*
Description: SUNA attacks occurring for 7 days–1 year with pain free intervals longer than 1 month
1.2. *Chronic SUNA*
Description: At least 2 attack periods last 7 days–1 year separated by remission periods of less than one month (untreated)

criteria for TACs does betray an uncomfortable biological naivety with regard to the timing. The A, C, D, E/F criteria are rather similar for each TAC (Tables 3–5). It seems neat in some way to have SUNCT be up to 4 min long, paroxysmal hemicrania from 2 to 30 min and cluster headache from 15 min onwards. The overlap seems minimal. It almost goes without saying that this must be wrong in absolute terms, biology rarely provides such neat rules, but it does provide a useful way to identify cases of sufficiently similarity to make meaningful biological studies.

Cluster headache

Cluster headache (CH) is a form of primary headache that is almost always unilateral and occurs in association with cranial autonomic features. In most patients, it has a striking circannual and circadian periodicity. It is an excruciating syndrome and is probably one of the most painful conditions known to humans with female patients describing each attack as being worse than childbirth.

Clinical features

A *cluster headache* or *attack* is an individual episode of pain that can last from a few minutes to some hours. A *cluster bout* or *period* refers to the duration over which recurrent cluster attacks are occurring; it usually lasts some weeks or months. A *remission* is the pain-free period between two cluster bouts.

The cluster attack

The attacks are strictly unilateral, with very few exceptions, although the headache may alternate sides. The pain is excruciatingly severe. It is located mainly around the orbital and temporal regions though any part of the head can be affected. The headache usually lasts 45–90 min but can range from 15 min to 3 h. It has an abrupt onset and cessation. Interictal pain or discomfort is present in some patients [76].

The signature feature of CH is the association of pain with cranial autonomic symptoms, and it is extremely unusual for these not to be reported. The International Headache Society diagnostic criteria [59] require the attacks to be accompanied by at least one of the following, which have to be present on the pain side: conjunctival injection, lacrimation, miosis, ptosis, eyelid oedema, rhinorrhoea, nasal blockage, forehead or facial sweating or a sense of restlessness of aggravation (Table 3). The autonomic features are transient, lasting only for the duration of the attack, with the exception of partial Horner's syndrome; ptosis or miosis may rarely persist, especially after frequent attacks.

The full range of typical migrainous symptoms are reported in a significant proportion of cluster patients [6, 128, 129]. Premonitory symptoms (tiredness, yawning), associated features (nausea, vomiting, photophobia, phonophobia) and aura symptoms have all been described in relationship to cluster attacks. *However, in contrast to migraine, CH sufferers are usually restless and irritable, preferring to move about, looking for a movement or posture that may relieve the pain* [6].

The cluster attack frequency varies between one every alternate day to three daily, although some have up to eight daily, and clinical experience suggests even more are possible. The condition can have a striking circadian rhythmicity, with some patients reporting that the attacks occur at the same time each day. Alcohol, nitroglycerin, exercise, and elevated environmental temperature are recognised precipitants of acute cluster attacks. Alcohol induces acute attacks, usually within an hour of intake, in the vast majority of sufferers, contrasting with migraine sufferers who

generally have headache some hours after alcohol intake. Alcohol triggers attacks during a cluster bout but not in a remission. Allergies, food sensitivities, reproductive hormonal changes [6] and stress do not appear to have any significant role in precipitating attacks.

The cluster bout

CH is classified according to the duration of the bout. About 80–90% of patients have e*pisodic cluster headache* (ECH), which is diagnosed when they experience recurrent bouts, each with a duration of more than a week and separated by remissions lasting more than one month. The remaining 10–20% of patients have c*hronic cluster headache* (CCH) in which either no remission occurs within one year or the remissions last less than one month. In practice, the therapeutic issue is whether the breaks are short enough in any individual patient to warrant preventive treatment.

Most patients with ECH have one or two annual cluster periods, each lasting between one and three months. Often, a striking circannual periodicity is seen with the cluster periods, with the bouts occurring in the same month of the year. In others, the cluster periods tend to recur at regular intervals that are consistently different than 12 months. Although the duration of the cluster and remission periods varies between individuals, these periods remain relatively consistent within the same individual.

Natural history

Although there is a paucity of literature on the long-term prognosis of CH, the available evidence suggests that it is a lifelong disorder in the majority of patients. In one study, about one-tenth of patients with ECH evolved into CCH whereas one-third of patients with CCH transformed into ECH [89]. An encouraging piece of information for CH sufferers is that a substantial proportion of them can expect to develop longer remission periods as they age [63].

Treatment

The management of CH includes offering advice on general measures to patients, treatment with abortive and preventive agents, and surgery, now including neuromodulatory procedures.

General measures and patient education

Patients should be advised to abstain from taking alcohol during the cluster bout. Otherwise, dietary factors seem to have little importance in CH. Anecdotal evidence suggests that patients should be cautioned against prolonged exposure to volatile substances, such as solvents and oil based paints. It can be suggested that afternoon naps be avoided as sleeping can precipitate attacks in some patients.

Abortive agents

The pain of CH builds up very rapidly to such an excruciating intensity that most oral agents are too slowly absorbed to control the pain within a reasonable period of time. The most efficacious abortive agents are those that involve parenteral or nasal administration [92]. Sumatriptan 6 mg by injection [29], or nasal spray 20 mg, and zolmitriptan 5 mg by nasal spray [15], each been shown to be effective within 30 min in placebo-controlled trials. Oxygen inhalation is effective compared to air [32]. Topical local anaesthetic has been used with some useful effect, although the evidence is less robust [68]. When available, intranasal dihydroergotamine may be useful [3]. Subcutaneous octreotide can be effective, as demonstrated by a placebo-controlled trial [97], and somatostatin receptor targets may be an avenue for future drug development.

Preventive treatments

The aim of preventive therapy is to produce a rapid suppression of attacks and to maintain the remission with minimal side effects until the cluster bout is over, or for a longer period in patients with chronic cluster headache. The mainstay treatments are high dose verapamil, typically from 160 to 960 mg daily [76, 70], lithium [28], methysergide [20], melatonin [79] and prednisolone [65]. There are several promising open-label reports of topiramate being effective [33, 73, 82, 100, 123, 141] and a controlled trial seems warranted.

Nerve blocks

Anthony [4] described the use of local anaesthetic and corticosteriod injections around the greater occipital nerve (GON) homolateral to the pain. This procedure recently has been studied in a controlled fashion and it has been suggested that the corticosteroid component is important for the useful effect [2]. In another study, of fourteen patients treated with GON injection, four had a good response, five had a moderate response and five no response [118]. We find it a variable but sometimes-effective strategy that in experienced hands has almost

no morbidity save about 1% incidence of localised alopecia due to fat atrophy at the injection site [127]. While its use seems largely that of short-term prophylaxis some clinicians use it for acute attack treatment.

Surgery

This is a last-resort measure in treatment-resistant patients and should only be considered when the pharmacological options have been exploited to the fullest. Patients must be carefully selected. There is an emerging distinction between destructive procedures, which have historically been the only option, and neuromodulatory procedures. For the moment, we have abandoned destructive procedures, since they are irreversible, in favour of studies of neuromodulatory approaches.

Destructive procedures

Only patients whose headaches are exclusively unilateral should be considered for destructive surgery, as patients whose attacks have alternated sides are at risk of a contralateral recurrence after surgery. A number of procedures that interrupt either the trigeminal sensory or autonomic (cranial parasympathetic) pathways can be performed though few are associated with long-lasting results while the side effects can be devastating. The procedures that have been reported to show some success include trigeminal sensory rhizotomy via a posterior fossa approach [66, 67], radiofrequency trigeminal gangliorhizolysis [99] and microvascular decompression of the trigeminal nerve with or without microvascular decompression of the nervus intermedius [85]. Gamma knife treatment seems ineffective when compared to its morbidity [24]. Complete trigeminal analgesia may be required for the best results. Complications include diplopia, hyperacusis, jaw deviation, corneal anaesthesia and anaesthesia dolorosa. Aggressive long-term ophthalmic follow-up is essential.

Neuromodulatory procedures

Leone *et al*. [81] reported the use posterior hypothalamic neurostimulation in one patient and subsequently in a cohort of patients with chronic CH treated with deep brain stimulation (DBS) [34]. The target was derived from brain imaging work in CH [102], and has proved effective in those patients. Unfortunately there is a mortality associated with this procedure [124], which has led to some caution in its adoption. Based on a promising report of greater occipital nerve stimulation [139] in other headache forms, and effects particularly in migraine [94], suboccipital nerve stimulation is also being trialled in CH. These non-destructive procedures need careful evaluation so the best candidates are selected for their application in practice [83]. Initial experience with both DBS and occipital nerve stimulation [23] are extremely promising, and controlled trials are certainly warranted.

Short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)

SUNCT syndrome, like the other trigeminal autonomic cephalalgias (TACs), manifests as a unilateral headache that occurs in association with cranial autonomic features. The features that distinguish it from the other TACs are: very brief duration of attacks that can occur very frequently and the presence of *prominent* conjunctival injection and lacrimation, both of which are present in the vast majority of patients (Table 4). For the reason that in some patients with the same clinical problem, one of conjunctival injection or tearing is absent, we feel the syndrome should be renamed *SUNA*: short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (Table 5). SUNCT syndrome was described relatively recently [131] and more fully characterized in 1989 [132].

Epidemiology

The prevalence of SUNCT syndrome is not known although the extremely low number of reported cases suggests that it is a rare syndrome. The disorder has a male predominance (36 males, 16 females) with a sex ratio of 2.1:1. The typical age of onset is between 40 and 70 years, though ranges from 10 to 77 years [93].

Clinical features

The pain is usually maximal in the ophthalmic distribution of the trigeminal nerve, especially the orbital or periorbital regions, forehead and temple, although it may radiate to the other ipsilateral trigeminal divisions. Attacks are typically unilateral; however, in three patients the pain was simultaneously experienced on the opposite side [111]. The pain is generally moderate to severe and described as stabbing, burning, pricking or electric shock-like in character. The individual attacks

are very brief, lasting between 5 and 250 sec [114], although attacks lasting up to 2 h each have been described [91, 113, 122]. The paroxysms begin abruptly, reaching the maximum intensity within 2–3 sec; the pain is maintained at the maximum intensity before abating rapidly [111]. Most patients are completely pain-free between attacks, although some report a persistent dull interictal discomfort [113].

Acute headache episodes in SUNCT syndrome are accompanied by a variety of associated symptoms. The attacks are virtually always accompanied by both ipsilateral conjunctival injection and lacrimation. Ipsilateral nasal congestion, rhinorrhoea, eyelid oedema, ptosis, meiosis and facial redness or sweating are less commonly reported. These cranial autonomic symptoms, particularly conjunctival injection and lacrimation, are typically very prominent in SUNCT syndrome. The associated conjunctival injection and tearing usually begin 1–2 sec after onset of the pain and may outlast the pain by a few seconds. Nausea, vomiting, photophobia and phonophobia are not normally associated with SUNCT syndrome but may be present and when present the photophobia is highly likely to be ipsilateral to the pain [64]. Unlike in cluster headache, restlessness is not as clear a feature of SUNCT syndrome [111].

The majority of patients can precipitate attacks by touching certain trigger zones within trigeminal innervated distribution and, occasionally, even from an extra-trigeminal territory. Precipitants include touching the face or scalp, washing, shaving, eating, chewing, brushing teeth, talking and coughing [111]. Unlike in trigeminal neuralgia, most patients have no refractory period to triggering.

Differential diagnosis

The differential diagnosis of very brief headaches includes: SUNCT (primary and secondary forms); trigeminal neuralgia; primary stabbing headache and paroxysmal hemicrania.

Differentiating SUNCT from trigeminal neuralgia can be challenging in some cases, as there is a considerable overlap in the clinical phenotypes of the two syndromes. Both headaches are short-lasting, can have a high frequency of attacks and display clustering of attacks. Both are principally unilateral headaches and the trigger zones behave similarly. The usual onset is during middle or old age in both. However, there are a number of striking differences between these two syndromes (see Table 6), awareness of which can aid in their differentiation [53, 133].

Table 6. *Differentiating features of typical SUNCT and trigeminal neuralgia*

Feature	SUNCT	Trigeminal neuralgia
Gender ratio (male:female)	2.1:1	1:2
Site of pain	V1	V2/3
Severity of pain	moderate to severe	very severe
Duration (sec)	5–250	<5
Autonomic features	prominent	sparse or none
Refractory period	absent	present
Response to carbamazepine	partial	complete

Primary idiopathic stabbing headache refers to brief, sharp or jabbing pain in the head that occurs either as a single episode or in brief repeated volleys. The pain is usually over the ophthalmic trigeminal distribution while the face is generally spared. The pain usually lasts a fraction of a second but can persist for up to 1 min, thereby overlapping with the phenotype of SUNCT, and recurs at irregular intervals (hours to days). These headaches are generally easily distinguishable clinically as they differ in several respects: in primary stabbing headache there is a female preponderance; the site and radiation of pain often varies between attacks; the majority of the attacks tend to be spontaneous; cranial autonomic features are absent; and the attacks commonly subside with the administration of indomethacin [115, 116].

SUNCT syndrome also has to be differentiated from short-lasting paroxysmal hemicrania. Paroxysmal hemicrania prevails in females; the attacks have a uniform distribution through day and night; the triggers differ from those in SUNCT; and the attacks are exquisitely responsive to indomethacin. If there is any diagnostic uncertainty then a trial of indomethacin is warranted.

Treatment

Until recently, SUNCT was thought to be highly refractory to treatment [112]. Several categories of drugs used in other headache syndromes i.e. non-steroidal anti-inflammatory drugs (including indomethacin), Paracetamol (Acetaminophen), 5-hydroxytryptamine agonists (triptans, ergotamine and dihydroergotamine), β-blockers, tricyclic antidepressants, calcium channel antagonists (verapamil and nifedipine), methysergide, lithium, prednisolone (prednisone), phenytoin, baclofen and intravenous lignocaine have proved to be ineffective [112].

Acute

We have found intravenous lidocaine very effective in the acute suppression of SUNCT [95], although we are

cautious of neuropsychiatric side effects that are very common in these patients [37].

Preventive

Partial improvement with carbamazepine has been observed in several patients [30, 91, 112, 117, 122]. Recently, lamotrigine has been reported to be highly efficacious in a number of patients [13, 21, 56, 80, 119]. There are a number of reported cases of SUNCT patients who responded completely to Gabapentin [54, 61, 120], typically 900–2700 mg [101] daily. We have recently reported a patient who responded completely to topiramate 50 mg daily [91]. These observations clearly need to be confirmed in other cases. Nonetheless, given the debilitating nature of this headache, gabapentin and topiramate are reasonable second line agents in patients who fail a trial of lamotrigine.

Surgery

Several surgical approaches have been tried in SUNCT syndrome. Anaesthetic blockades of pericranial nerves have been reported to be ineffective [112]. Black and Dodick reported on two SUNCT cases refractory to various surgical procedures [11]. The first patient underwent a glycerol rhizotomy, gamma-knife radiosurgery and microvascular decompression of the trigeminal nerve while the second patient underwent gamma-knife radiosurgery of the trigeminal root exit zone and two microvascular decompressions of the trigeminal nerve. Neither patient benefited from these procedures. In addition, the first patient suffered from anaesthesia dolorosa and the second patient from unilateral deafness, chronic vertigo and disequilibrium as a result of surgery. We have seen two patients who had failed to demonstrate a persistent response following trigeminal thermocoagulation and microvascular decompression (unpublished observations). Although there are some reports of successful procedures none has greater than eighteen months follow-up and we do not recommend destructive procedures at all at the moment.

Neuromodulation

The most exciting developments in the treatment of SUNCT has been a recent report that deep brain stimulation in the region of the posterior hypothalamus is useful in SUNCT [84]. It is likely that occipital nerve stimulation will also be used, since some patients with SUNCT benefit from greater occipital nerve injection as cluster headache patients do (Afridi, Shields, Bhola and Goadsby, unpublished data).

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References

1. Afridi S, Giffin NJ, Kaube H, Friston KJ, Ward NS, Frackowiak RS, Goadsby PJ (2005) A PET study in spontaneous migraine. Arch Neurol 62: 1270–1275
2. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F, Schoenen J (2005) Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain 118: 92–96
3. Andersson PG, Jespersen LT (1986) Dihydroergotamine nasal spray in the treatment of attacks of cluster headache. Cephalalgia 6: 51–54
4. Anthony M (1985) Arrest of attacks of cluster headache by local steroid injection of the occipital nerve. In: Rose FC (ed) Migraine: clinical and research advances. Karger, London, pp 169–173
5. Bahra A, Matharu MS, Buchel C, Frackowiak RSJ, Goadsby PJ (2001) Brainstem activation specific to migraine headache. Lancet 357: 1016–1017
6. Bahra A, May A, Goadsby PJ (2002) Cluster headache: a prospective clinical study in 230 patients with diagnostic implications. Neurology 58: 354–361
7. Barbanti P, Fabbrini G, Pesare M, Vanacore N, Cerbo R (2002) Unilateral cranial autonomic symptoms in migraine. Cephalalgia 22: 256–259
8. Bartsch T, Levy MJ, Knight YE, Goadsby PJ (2004) Differential modulation of nociceptive dural input to [hypocretin] Orexin A and B receptor activation in the posterior hypothalamic area. Pain 109: 367–378
9. Benjamin L, Levy MJ, Lasalandra MP, Knight YE, Akerman S, Classey JD, Goadsby PJ (2004) Hypothalamic activation after stimulation of the superior sagittal sinus in the cat: a Fos study. Neurobiol Dis 16: 500–505
10. Benoliel R, Sharav Y (1998) Trigeminal neuralgia with lacrimation or SUNCT syndrome? Cephalalgia 18: 85–90
11. Black DF, Dodick DW (2002) Two cases of medically and surgically intractable SUNCT: a reason for caution and an argument for a central mechanism. Cephalalgia 22: 201–204
12. Boes CJ, Swanson JW, Dodick DW (1998) Chronic paroxysmal hemicrania presenting as otalgia with a sensation of external acoustic meatus obstruction: two cases and a pathophysiologic hypothesis. Headache 38: 787–791
13. Chakravarty A, Mukherjee A (2003) SUNCT syndrome responsive to lamotrigine: documentation of the first Indian case. Cephalalgia 23: 474–475
14. Cid C, Berciano J, Pascual J (2000) Retro-ocular headache with autonomic features resembling ‘‘continuous’’ cluster headache in a lateral medullary infarction. J Neurol Neurosurg Psychiatry 69: 134–141
15. Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ (2006) Effectiveness of intranasal zolmitriptan in acute cluster headache. A randomized, placebo-controlled, double-blind crossover study. Arch Neurol 63: 1537–1542

16. Cohen AS, Goadsby PJ (2004) Functional neuroimaging of primary headache disorders. Curr Neurol Neurosci Rep 4: 105–110
17. Cohen AS, Matharu MS, Kalisch R, Friston K, Goadsby PJ (2004) Functional MRI in SUNCT shows differential hypothalamic activation with increasing pain. Cephalalgia 24: 1098–1099
18. Cooke LJ, Rose MS, Becker WJ (2000) Chinook winds and migraine headache. Neurology 54: 302–307
19. Cremer P, Halmagyi GM, Goadsby PJ (1995) Secondary cluster headache responsive to sumatriptan. J Neurol Neurosurg Psychiatry 59: 633–634
20. Curran DA, Hinterberger H, Lance JW (1967) Methysergide. Res Clin Studies Headache 1: 74–122
21. D'Andrea G, Granella F, Ghiotto N, Nappi G (2001) Lamotrigine in the treatment of SUNCT syndrome. Neurology 57: 1723–1725
22. de la Sayette V, Schaeffer S, Coskun O, Leproux F, Defer G (1999) Cluster headache-like attack as an opening symptom of a unilateral infarction of the cervical cord: persistent anaesthesia and dysaesthesia to cold stimuli. J Neurol Neurosurg Psychiatry 66: 397–400
23. Dodick DW, Trentman T, Zimmerman R, Eross EJ (2003) Occipital nerve stimulation for intractable chronic primary headache disorders. Cephalalgia 23: 701
24. Donnet A, Valade D, Regis J (2005) Gamma knife treatment for refractory cluster headache: prospective open trial. J Neurol Neurosurg Psychiatry 76: 218–221
25. Drummond PD (1988) Autonomic disturbance in cluster headache. Brain 111: 1199–1209
26. Drummond PD, Lance JW (1992) Pathological sweating and flushing accompanying the trigeminal lacrimation reflex in patients with cluster headache and in patients with a confirmed site of cervical sympathetic deficit. Evidence for parasympathetic cross-innervation. Brain 115: 1429–1445
27. Ekbom K, Greitz T (1970) Carotid angiography in cluster headache. Acta Radiol 10: 177–186
28. Ekbom K, Solomon S (2000) Management of cluster headache. In: Olesen J, Tfelt-Hansen P, Welch KMA (eds) The headaches, 2nd edn. Lippincott, Williams & Wilkins, Philadelphia, pp 731–740
29. Ekbom K, The Sumatriptan Cluster Headache Study Group (1991) Treatment of acute cluster headache with sumatriptan. N Engl J Med 325: 322–326
30. Ertsey C, Bozsik G, Afra J, Jelencsik I (2000) A case of SUNCT syndrome with neurovascular compression. Cephalalgia 20: 325
31. Feindel W, Penfield W, McNaughton F (1960) The tentorial nerves and localization of intracranial pain in man. Neurology 10: 555–563
32. Fogan L (1985) Treatment of cluster headache: a double blind comparison of oxygen vs air inhalation. Arch Neurol 42: 362–363
33. Forderreuther S, Mayer M, Straube A (2002) Treatment of cluster headache with topiramate: effects and side-effects in five patients. Cepahalalgia 22: 186–189
34. Franzini A, Ferroli P, Leone M, Broggi G (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches. The first reported series. Neurosurgery 52: 1095–1101
35. Frese A, Evers S, May A (2003) Autonomic activation in experimental trigeminal pain. Cephalalgia 23: 67–68
36. Giffin N, Goadsby PJ (2001) Basilar artery aneurysm with autonomic features: an interesting pathophysiological problem. J Neurol Neurosurg Psychiatry 71: 805–808
37. Gil-Gouveia R, Goadsby PJ (2005) Neuropsychiatric side effects of lidocaine: examples from the treatment of headache and a review. Cephalalgia 25 (in press)
38. Goadsby PJ (1989) Effect of stimulation of the facial nerve on regional cerebral blood flow and glucose utilization in cats. Am J Physiol 257: R517–R521
39. Goadsby PJ (1991) Characteristics of facial nerve elicited cerebral vasodilatation determined with laser Doppler flowmetry. Am J Physiol 260: R255–R262
40. Goadsby PJ (2002) Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. Lancet Neurol 1: 37–43
41. Goadsby PJ (2002) Raeders Syndrome: ''Paratrigeminal'' paralysis of oculo-pupillary sympathetic. J Neurol Neurosurg Psychiatry 72: 297–299
42. Goadsby PJ, Edvinsson L (1994) Human in vivo evidence for trigeminovascular activation in cluster headache. Brain 117: 427–434
43. Goadsby PJ, Hoskin KL (1997) The distribution of trigeminovascular afferents in the nonhuman primate brain Macaca nemestrina: a c-fos immunocytochemical study. J Anat 190: 367–375
44. Goadsby PJ, Macdonald GJ (1985) Extracranial vasodilatation mediated by VIP (Vasoactive Intestinal Polypeptide). Brain Res 329: 285–288
45. Goadsby PJ, Lipton RB (1997) A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic features, including new cases. Brain 120: 193–209
46. Goadsby PJ, Shelley S (1990) High frequency stimulation of the facial nerve results in local cortical release of vasoactive intestinal polypeptide in the anesthetised cat. Neurosci Lett 112: 282–289
47. Goadsby PJ, Lambert GA, Lance JW (1983) Effects of locus coeruleus stimulation on carotid vascular resistance in the cat. Brain Res 278: 175–183
48. Goadsby PJ, Lambert GA, Lance JW (1984) The peripheral pathway for extracranial vasodilatation in the cat. J Auton Nerv Syst 10: 145–155
49. Goadsby PJ, Edvinsson L, Ekman R (1988) Release of vasoactive peptides in the extracerebral circulation of man and the cat during activation of the trigeminovascular system. Ann Neurol 23: 193–196
50. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann Neurol 28: 183–187
51. Goadsby PJ, Edvinsson L, Ekman R (1992) Cutaneous stimulation leading to facial flushing and release of calcitonin gene-related peptide. Cephalalgia 12: 53–56
52. Goadsby PJ, Uddman R, Edvinsson L (1996) Cerebral vasodilatation in the cat involves nitric oxide from parasympathetic nerves. Brain Res 707: 110–118
53. Goadsby PJ, Matharu MS, Boes CJ (2001) SUNCT syndrome or trigeminal neuralgia with lacrimation. Cephalalgia 21: 82–83
54. Graff-Radford SB (2000) SUNCT syndrome responsive to gabapentin. Cephalalgia 20: 515–517
55. Greve E, Mai J (1988) Cluster headache-like headaches: a symptomatic feature? A report of three patients with intracranial pathologic findings. Cephalalgia 8: 79–82
56. Gutierrez-Garcia JM (2002) SUNCT syndrome responsive to lamotrigine. Headache 42: 823–825
57. Hannerz J (1989) A case of parasellar meningioma mimicking cluster headache. Cephalalgia 9: 265–269
58. Headache Classification Committee of The International Headache Society (1988) Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8 Suppl 7: 1–96
59. Headache Classification Committee of The International Headache Society (2004) The international classification of headache disorders, 2nd edn. Cephalalgia 24 Suppl 1: 1–160
60. Heidegger S, Mattfeldt T, Rieber A, Wikstroem M, Kern P, Kern W, Schreiber H (1997) Orbito-sphenoidal aspergillus infection mimicking cluster headache: a case report. Cephalalgia 17: 676–679
61. Hunt CH, Dodick DW, Bosch P (2002) SUNCT responsive to gabapentin. Headache 42: 525–526

62. Hunter CR, Mayfield FH (1949) Role of the upper cervical roots in the production of pain in the head. Am J Surg 78: 743–749
63. Igarashi H, Sakai F (1996) Natural history of cluster headache. Cephalalgia 390–391
64. Irimia P, Cittadini E, Paemeliere K, Cohen A, Kaube H, Goadsby PJ (2006) Unilateral phonophobia and photophobia: a helpful symptom for the diagnosis of trigeminal autonomic cephalalgias (TACs) and hemicrania continua (HC). Cephalalgia (in press)
65. Jammes JL (1975) The treatment of cluster headaches with prednisone. Dis Nerv Syst 36: 375–376
66. Jarrar RG, Black DF, Dodick DW, Davis DH (2003) Outcome of trigeminal nerve section in the treatment of chronic cluster headache. Neurology 60: 1360–1362
67. Kirkpatrick PJ, O'Brien M, MacCabe JJ (1993) Trigeminal nerve section for chronic migrainous neuralgia. Br J Neurosurg 7: 483–490
68. Kitrelle JP, Grouse DS, Seybold ME (1985) Cluster headache: local anesthetic abortive agents. Arch Neurol 42: 496–498
69. Koenigsberg AD, Solomon GD, Kosmorsky DO (1994) Pseudoaneurysm within the cavernous sinus presenting as cluster headache. Headache 34: 111–113
70. Krabbe A, Steiner TJ (2000) Prophylactic treatment of cluster headache. In: Sjaastad O, Nappi G (eds) Cluster headache syndrome in general practice: basic concepts. Smith-Gordon, London, pp 91–96
71. Kudrow L (1980) Cluster headache: mechanisms and management. Oxford University Press, Oxford
72. Kuritzky A (1984) Cluster headache-like pain caused by an upper cervical meningioma. Cephalalgia 4: 185–186
73. Lainez MJ, Pascual J, Pascual AM, Santonja JM, Ponz A, Salvador A (2003) Topiramate in the prophylactic treatment of cluster headache. Headache 43: 784–749
74. Lambert GA, Bogduk N, Goadsby PJ, Duckworth JW, Lance JW (1984) Decreased carotid arterial resistance in cats in response to trigeminal stimulation. J Neurosurg 61: 307–315
75. Lance JW (1993) Mechanism and management of headache, 5th edn. Butterworth Scientific, London
76. Lance JW, Goadsby PJ (2005) Mechanism and management of headache, 7th edn. Elsevier, New York
77. Lee MS, Lessell S (2002) Orbital myositis posing as cluster headache. Arch Neurol 59: 635–636
78. Leira EC, Cruz-Flores S, Leacock RO, Abdulrauf SI (2001) Sumatriptan can alleviate headaches due to carotid artery dissection. Headache 41: 590–591
79. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G (1996) Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia 16: 494–496
80. Leone M, Rigamonti A, Usai S, D'Amico D, Grazzi L, Bussone G (2000) Two new SUNCT cases responsive to lamotrigine. Cephalalgia 20: 845–847
81. Leone M, Franzini A, Bussone G (2001) Stereotatic stimulation of the posterior hypothalamic gray matter in a patient with intractable cluster headache. New Engl J Med 345: 1428–1429
82. Leone M, Dodick D, Rigamonti A, D'Amico D, Grazzi L, Mea E, Bussone G (2003) Topiramate in cluster headache prophylaxis: an open trial. Cephalalgia 23: 1001–1002
83. Leone M, Franzini A, Broggi G, Dodick D, Rapoport A, Goadsby PJ, Schoenen J, Bonavita V, Bussone G (2004) Deep brain stimulation for intractable chronic cluster headache: proposals for patient selection. Cephalalgia 24: 934–937
84. Leone M, Franzini A, D'Andrea G, Broggi G, Casucci G, Bussone G (2005) Deep brain stimulation to relieve drug-resistant SUNCT. Ann Neurol 57: 924–927
85. Lovely TJ, Kotsiakis X, Jannetta PJ (1998) The surgical management of chronic cluster headache. Headache 38: 590–594
86. Mainardi F, Maggioni F, Dainese F, Amista P, Zanchin G (2002) Spontaneous carotid artery dissection with cluster-like headache. Cephalalgia 22: 557–559
87. Malick A, Burstein R (1998) Cells of origin of the trigeminohypothalamic tract in the rat. J Comparative Neurol 400: 125–144
88. Mani S, Deeter J (1982) Arteriovenous malformation of the brain presenting as a cluster headache – a case report. Headache 22: 184–185
89. Manzoni GC, Micieli G, Granella F, Tassorelli C, Zanferrari C, Cavallini A (1991) Cluster headache-course over ten years in 189 patients. Cephalalgia 11: 169–174
90. Matharu MS, Goadsby PJ (2002) Persistence of attacks of cluster headache after trigeminal nerve root section. Brain 175: 976–984
91. Matharu MS, Boes CJ, Goadsby PJ (2002) SUNCT syndrome: prolonged attacks, refractoriness and response to topiramate. Neurology 58: 1307
92. Matharu MS, Boes CJ, Goadsby PJ (2003) Management of trigeminal autonomic cephalalgias and hemicrania continua. Drugs 63: 1637–1677
93. Matharu MS, Cohen AS, Boes CJ, Goadsby PJ (2003) SUNCT syndrome: a review. Curr Pain Headache Rep 7: 308–318
94. Matharu MS, Bartsch T, Ward N, Frackowiak RSJ, Weiner RL, Goadsby PJ (2004) Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain 127: 220–230
95. Matharu MS, Cohen AS, Goadsby PJ (2004) SUNCT syndrome responsive to intravenous lidocaine. Cephalalgia 24: 985–992
96. Matharu MS, Cohen AS, McGonigle DJ, Ward N, Frackowiak RSJ, Goadsby PJ (2004) Posterior hypothalamic and brainstem activation in hemicrania continua. Headache 44: 747–761
97. Matharu MS, Levy MJ, Meeran K, Goadsby PJ (2004) Subcutaneous octreotide in cluster headache- randomized placebo-controlled double-blind cross-over study. Ann Neurol 56: 488–494
98. Matharu MS, Cohen AS, Frackowiak RSJ, Goadsby PJ (2006) Posterior hypothalamic activation in paroxysmal hemicrania using PET. Cephalalgia 59: 535–545
99. Mathew NT, Hurt W (1998) Percutaneous radiofrequency trigeminal gangliorhizolysis in intractable cluster headache. Headache 28: 328–331
100. Mathew NT, Kailasam J, Meadors L (2002) Prophylaxis of migraine, transformed migraine, and cluster headache with topiramate. Headache 42: 796–803
101. May A, Goadsby PJ (1999) The trigeminovascular system in humans: pathophysiological implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cereb Blood Flow Metabo 19: 115–127
102. May A, Bahra A, Buchel C, Frackowiak RSJ, Goadsby PJ (1998) Hypothalamic activation in cluster headache attacks. Lancet 352: 275–278
103. May A, Kaube H, Buchel C, Eichten C, Rijntjes M, Juptner M, Weiller C, Diener HC (1998) Experimental cranial pain elicited by capsaicin: a PET-study. Pain 74: 61–66
104. May A, Buchel C, Bahra A, Goadsby PJ, Frackowiak RSJ (1999) Intra-cranial vessels in trigeminal transmitted pain: a PET Study. NeuroImage 9: 453–460
105. May A, Bahra A, Buchel C, Turner R, Goadsby PJ (1999) Functional MRI in spontaneous attacks of SUNCT: short-lasting neuralgiform headache with conjunctival injection and tearing. Ann Neurol 46: 791–793
106. May A, Bahra A, Buchel C, Frackowiak RSJ, Goadsby PJ (2000) PET and MRA findings in cluster headache and MRA in experimental pain. Neurology 55: 1328–1335
107. May A, Buchel C, Turner R, Goadsby PJ (2001) MR-angiography in facial and other pain: neurovascular mechanisms of trigeminal sensation. J Cereb Blood Flow Metabol 21: 1171–1176

108. McNaughton FL, Feindel WH (1977) Innervation of intracranial structures: a reappraisal. In: Rose FC (ed) Physiological aspects of clinical neurology. Blackwell Scientific Publications, Oxford, pp 279–293
109. Munoz C, Diez-Tejedor E, Frank A, Barreiro P (1996) Cluster headache syndrome associated with middle cerebral artery arteriovenous malformation. Cephalalgia 16: 202–205
110. Nakai M, Tamaki K, Ogata J, Maeda M (1993) Parasympathetic cerebrovascular center of the facial nerve. Circ Res 72: 470–475
111. Pareja JA, Sjaastad O (1997) SUNCT syndrome. A clinical review. Headache 37: 195–202
112. Pareja JA, Kruszewski P, Sjaastad O (1995) SUNCT syndrome: trials of drugs and anesthetic blockades. Headache 35: 138–142
113. Pareja JA, Joubert J, Sjaastad O (1996) SUNCT syndrome. Atypical temporal patterns. Headache 36: 108–110
114. Pareja JA, Ming JM, Kruszewski P, Caballero V, Pamo M, Sjaastad O (1996) SUNCT syndrome: duration, frequency and temporal distribution of attacks. Headache 36: 161–165
115. Pareja JA, Ruiz J, Deisla C, Alsabbah H, Espejo J (1996) Idiopathic stabbing headache (jabs and jolts syndrome). Cephalalgia 16: 93–96
116. Pareja JA, Kruszewski P, Caminero AB (1999) SUNCT syndrome versus idiopathic stabbing headache (jabs and jolts syndrome). Cephalalgia 19 Suppl 25: 46–48
117. Peatfield R, Bahra A, Goadsby PJ (1998) Trigeminal-autonomic cephalgias (TACs). Cephalalgia 18: 358–361
118. Peres MFP, Stiles MA, Siow HC, Rozen TD, Young WB, Silberstein SD (2002) Greater occipital nerve blockade for cluster headache. Cephalalgia 22: 520–522
119. Piovesan EJ, Siow C, Kowacs PA, Werneck LC (2003) Influence of lamotrigine over the SUNCT syndrome: one patient follow-up for two years. Arq Neuropsiquiatr 61: 691–694
120. Porta-Etessam J, Martinez-Salio A, Berbel A, Benito-Leon J (2002) Gabapentin (neurontin) in the treatment of SUNCT syndrome. Cephalalgia 22: 249
121. Porta-Etessam J, Ramos-Carrasco A, Berbel-Garcia A, Martinez-Salio A, Benito-Leon J (2001) Clusterlike headache as first manifestation of a prolactinoma. Headache 41: 723–725
122. Raimondi E, Gardella L (1998) SUNCT syndrome. Two cases in Argentina. Headache 38: 369–371
123. Rapoport AM, Bigal ME, Tepper SJ, Sheftell FD (2003) Treatment of cluster headache with topiramate: effects and side-effects in five patients. Cephalalgia 23: 69–70
124. Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M, Remacle JM, de Noordhout AM (2005) Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 128: 940–947
125. Scorticati MC, Raina G, Federico M (2002) Cluster-like headache associated to a foreign body in the maxillary sinus. Neurology 59: 643–644
126. Seylaz J, Hara H, Pinard E, Mraovitch S, MacKenzie ET, Edvinsson L (1988) Effect of stimulation of the sphenopalatine ganglion on cortical blood flow in the rat. J Cereb Blood Flow Metabol 8: 875–878
127. Shields KG, Levy MJ, Goadsby PJ (2004) Alopecia and cutaneous atrophy following greater occipital nerve infiltration. Neurology 63: 2193–2194
128. Silberstein SD, Niknam R, Rozen TD, Young WB (2000) Cluster headache with aura. Neurology 54: 219–221
129. Siow HC, Young WB, Peres MF, Rozen TD, Silberstein SD (2002) Hemiplegic cluster. Headache 42: 136–139
130. Sjaastad O (1992) Cluster Headache Syndrome. Saunders WB, London
131. Sjaastad O, Russell D, Horven I, Bunnaes U (1978) Multiple neuralgiform unilateral headache attacks associated with conjunctival injection and appearing in clusters. A nosological problem. Proceedings of the Scandinavian Migraine Society, Arhus, 31
132. Sjaastad O, Saunte C, Salvesen R, Fredriksen TA, Seim A, Roe OD, Fostad K, Lobben OP, Zhao JM (1989) Shortlasting unilateral neuralgiform headache attacks with conjunctival injection, tearing, sweating, and rhinorrhea. Cephalalgia 9: 147–156
133. Sjaastad O, Kruszewski P (1992) Trigeminal neuralgia and ''SUNCT'' syndrome: similarities and differences in the clinical picture. An overview. Functional Neurology 7: 103–107
134. Spencer SE, Sawyer WB, Wada H, Platt KB, Loewy AD (1990) CNS projections to the pterygopalatine parasympathetic preganglionic neurons in the rat: a retrograde transneuronal viral cell body labeling study. Brain Res 534: 149–169
135. Sprenger T, Boecker H, Tolle TR, Bussone G, May A, Leone M (2004) Specific hypothalamic activation during a spontaneous cluster headache attack. Neurology 62: 516–517
136. Tfelt-Hansen P, Paulson OB, Krabbe AE (1982) Invasive adenoma of the pituitary gland and chronic migrainous neuralgia. A rare coincidence or a causal relationship? Cephalalgia 2: 25–28
137. Uddman R, Tajti J, Moller S, Sundler F, Edvinsson L (1999) Neuronal messengers and peptide receptors in the human sphenopalatine and otic ganglia. Brain Res 826: 193–199
138. Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, Coenen HH, Diener HC (1995) Brainstem activation in spontaneous human migraine attacks. Nat Med 1: 658–660
139. Weiner RL, Reed KL (1999) Peripheral neurostimulation for control of intractable occipital neuralgia. Neuromodulation 2: 217–222
140. West P, Todman D (1991) Chronic cluster headache associated with a vertebral artery aneurysm. Headache 31: 210–212
141. Wheeler SD, Carrazana EJ (1999) Topiramate-treated cluster headache. Neurology 53: 234–236

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Deep brain stimulation for neuropathic pain

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Summary

Deep brain stimulation (DBS) for pain was one of the earliest indications for the therapy. This study reports the outcome of DBS of the sensory thalamus and the periventricular and peri-aqueductal grey area (PVG/PAG) complex for different intractable neuropathic pain syndromes. Forty-seven patients (30 males and 17 females) were selected for surgery; they were suffering from any of the following types of pain: post-stroke neuropathic pain, phantom limb pain, post-herpetic neuralgia, anaesthesia dolorosa, brachial plexus injury and neuropathic pain secondary to neural damage from a variety of causes. Of the 47 patients selected for trial stimulation, 38 patients proceeded to permanent implantation. Patients suffering from post-stroke pain were the most likely to fail trial stimulation (33%), in contrast to individuals with phantom limb/post-brachial plexus injury pain and anaesthesia dolorosa, all of whom underwent permanent implantation. PVG stimulation alone was optimal in 17 patients (53%), whilst a combination of PVG and thalamic stimulation produced the greatest degree of analgesia in 11 patients (34%). Thalamic stimulation alone was optimal in 4 patients (13%). DBS of the PVG alone was associated with the highest degree of pain alleviation, with a mean improvement of 59% ($p < 0.001$) and a $\geq$50% improvement in 66% of patients. Post-stroke pain responds in 70% of patients. We conclude that the outcomes of surgery appear to vary according to aetiology, but it would appear that the effects are best for phantom limb syndromes, head pain and anaesthesia dolorosa.

Keywords: Deep brain stimulation; DBS; neuropathic pain; phantom limb pain; anaesthesia dolorosa; brachial plexus; periventricular and periaquaductal grey area.

Introduction

Deep brain stimulation for pain was one of the earliest indications for the therapy. Many targets were tried with some reported success such as the caudate nucleus and septal area [5]. Later, more success was reported targeting the sensory thalamus (VPL and VPM) and the periventricular and peri-aqueductal grey area (PVG/PAG) [7]. The indications were largely of nociceptive pain; failed back surgery was the largest indication numerically. Despite the apparent successes, the technique was abandoned for reasons unrelated to the effects obtained by such workers as Young and Kumar [11, 16].

In the late 1980s, a USA FDA ruling required clinical trials to evaluate the safety and efficacy of DBS for the treatment of pain. Two electrode models were evaluated in multi-centre trials. Both trials were prematurely concluded, due to discontinuation of the manufacture of the lead used in one, and problems with slow enrolment, high attrition and low efficacy in the other [1]. Results collected from the two trials failed to show an acceptable success rate; therefore DBS for the treatment of pain was not given FDA approval. Whilst this has meant that use of DBS in treating pain has remained on an 'experimental' basis in the USA, its use continues in North America, Europe and Asia.

Neuropathic pain remains an enormous clinical problem and very commonly resists all medical therapy. Given the early promising reports, in Oxford we began to offer motor cortex stimulation (MCS) in attempts to alleviate central pain. Although MCS emerged as a technique for the alleviation of central pain [2, 3, 9, 13–15], with reported success rates of up to 75%, this was not our experience. We, therefore, re-explored the use of deep brain stimulation for neuropathic pain syndromes and our experience, reported here, has led to its continued use. We report our experience in patient selection, surgical technique, clinical results and subsequent management.

Methods

Forty-seven patients (30 males and 17 females) with intractable neuropathic pain were selected for surgery, on the basis of their clinical evaluation. In all patients the pain had a definable organic origin (Table 1). All reasonable conventional pain management techniques had failed or were poorly tolerated. Patients with psychiatric disturbances, such as

Table 1. *Etiology in 34 patients undergoing DBS for intractable neuropathic pain*

Aetiology	Total
Post-stroke	18
Phantom limb/brachial plexus injury	12
Anaesthesia dolorosa	3
Spinal cord injury	3
Multiple sclerosis	1
Malignancy	1
Post-herpetic	1
Other	8
Overall	47

psychotic illness and severe depression, were excluded. This pain was refractory to multiple pharmacological and non-pharmacological therapies, including epidural morphine, TENS and ultrasonic therapy, as well as oral amitriptylline, carbamazepine, and opioids. They were referred to our service from specialist pain clinics nationally in the UK. The mean age at surgery was 50 years (range 24–76 years).

Pre- and post-operative evaluation was carried out using the McGill Pain Questionnaire (MPQ) (to assess pain) [12]. Each patient kept a pain diary to assess pain intensity on a self-rated visual analogue scale (VAS). VAS pain scores were taken after a rest period, to avoid distortion by exercise or activity. Patients were asked to give two scores per day over a two-week period. All scores over the fortnight period were averaged. The preoperative and postoperative evaluations were compared, in order to assess the effect of DBS on the patient's pain. These procedures were approved by the Local Ethics Committee.

The pain syndromes taken on were post-stroke neuropathic pain, phantom limb pain, post-herpetic neuralgia, anaesthesia dolorosa, brachial plexus injury and neuropathic pain secondary to neural damage from a variety of causes. The patients with phantom limb pain commonly described severe unremitting painful posturing of the absent limb and the other groups commonly described a severe burning hyperaesthesia as the most agonising component of their pain.

Surgical technique

A magnetic resonance imaging (MRI) scan of each patient's brain had been performed several weeks before surgery. T1-Weighted sequences were acquired. For surgery, a CRW base ring was applied to the patients' head under local anaesthesia. A stereotactic CT scan was then performed and using the Radionics Image Fusion® and Stereoplan® programme the co-ordinates for the PVG and VPL were calculated. A double oblique

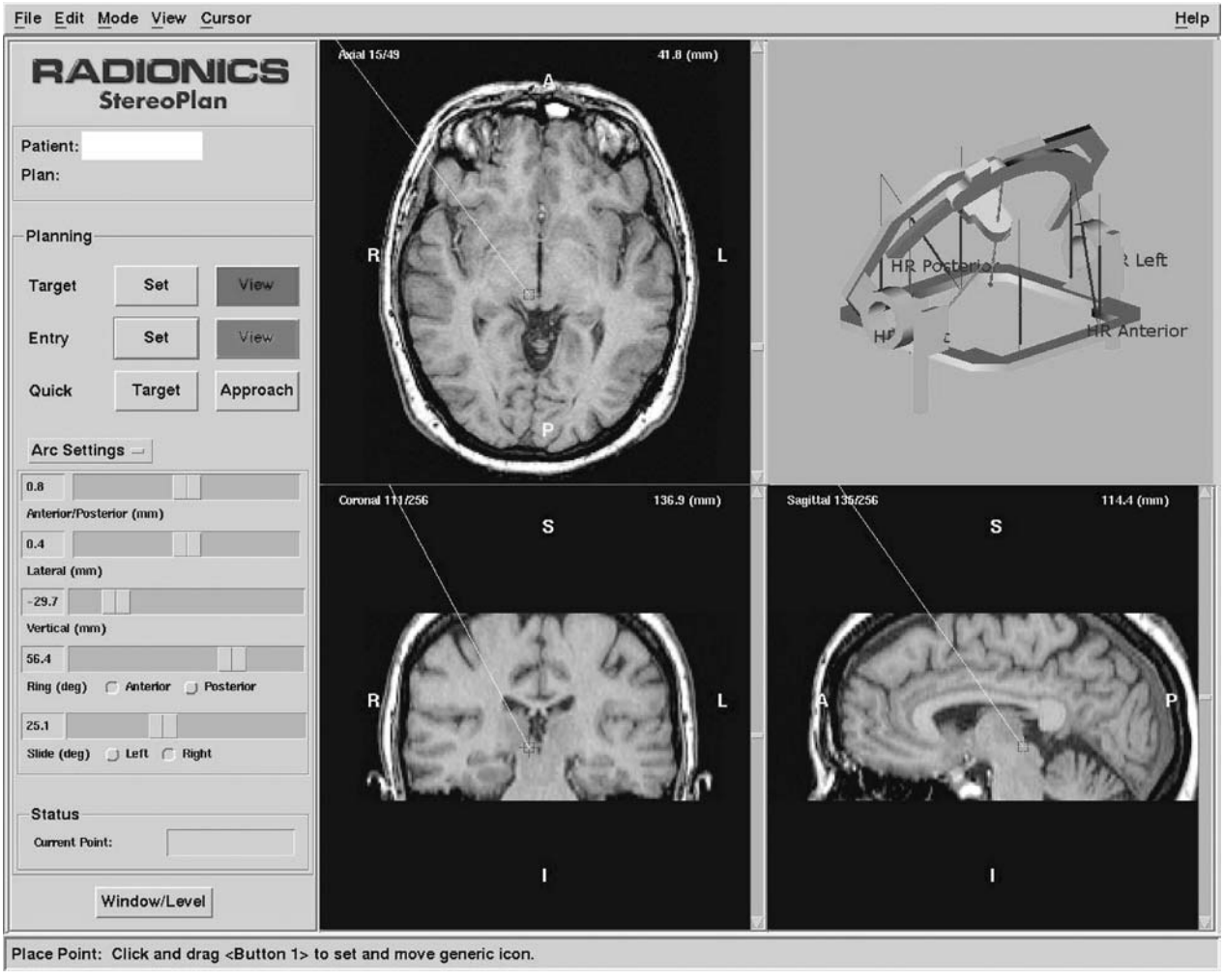

Fig. 1. Targeting of the right periventricular/periaqueductal grey (*PVG/PAG*) region

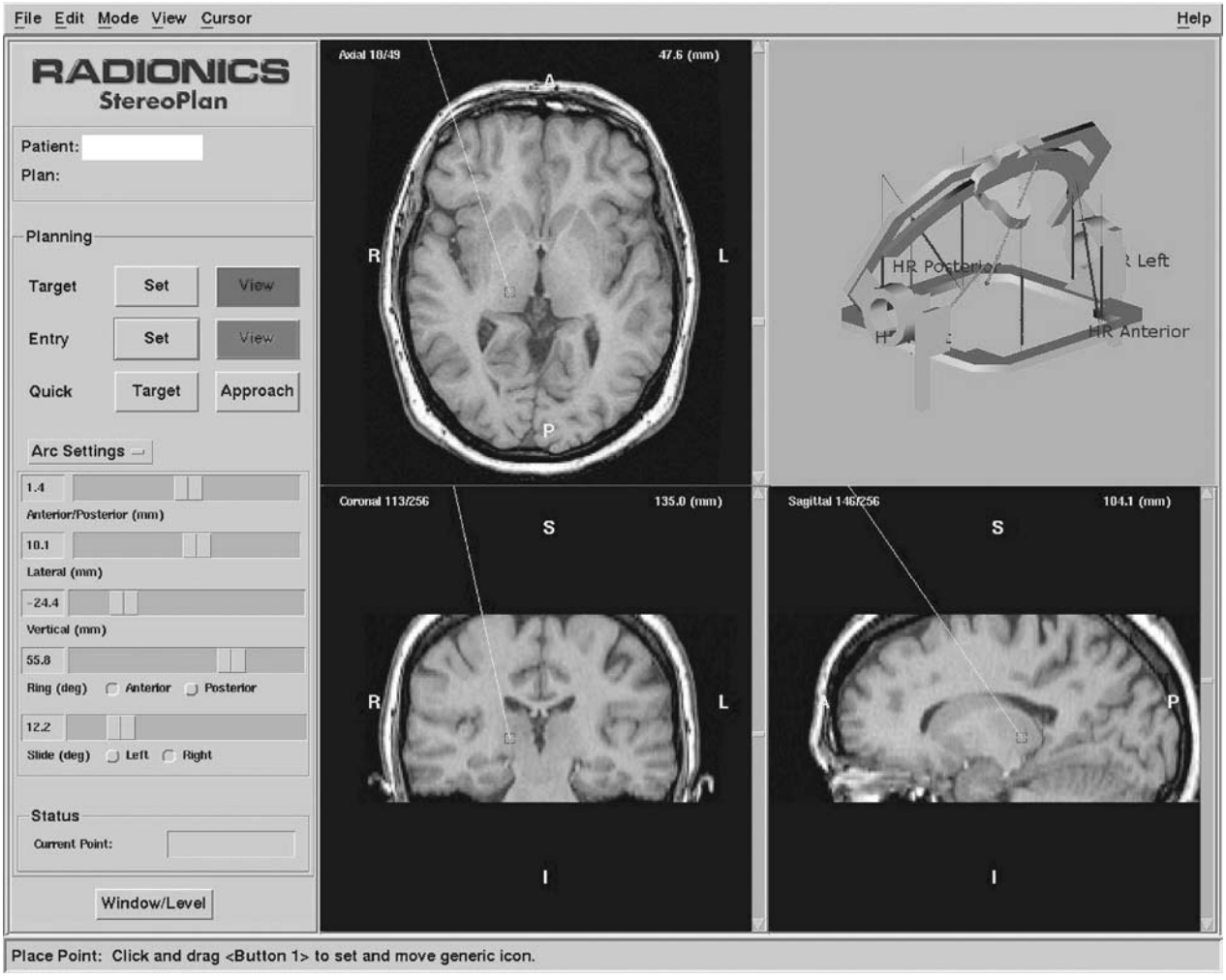

Fig. 2. Targeting of the right ventroposterolateral (*VPL*) nucleus of the thalamus

trajectory (Fig. 1) was used with an entry point just anterior to the coronal suture and laterality of approach dictated by ventricular width. The PVG/PAG was proximally located 2–3 mm lateral to the wall of the third ventricle and 2 mm anterior to the level of the posterior commissure and distally the deepest electrode lay in the superior colliculus. The VPL was located 12 mm lateral and 5–8 mm posterior to the mid commissural point (Fig. 2). Patients with strokes in the sensory thalamus were only implanted in the PVG/PAG. After washing the patient's scalp with alcoholic chlorhexidine, a parasaggital posterior frontal scalp incision 3.0 cm from the midline was made contra-lateral to the side of pain. The VPL was implanted with a Medtronic 3387 electrode where stimulation induced paraesthesiae in the area of pain and the PVG with a Medtronic 3387 electrode where stimulation induced relief of pain or a sensation of warmth in the area of pain. The deepest electrode was noted to be in a satisfactory position if eye bobbing was induced at intensity of stimulation at least twice that required for sensory effects. It has been our experience that there exists a somatotopy to the PVG/PAG area in that the contralateral foot lies upper at the level of the posterior commissure and the face lies at the level of the superior colliculus The electrodes were then fixed to the skull with a miniplate prior to externalisation.

In all patients the electrodes were externalised for a week of trial stimulation. If the patients were satisfied with the degree of pain relief, full implantation of a Medtronic pulse generator was performed in the following week under general anaesthesia.

Following surgery, the patients were assessed at 1–2 months, and subsequently at 3 monthly intervals. Assessment was equivalent to that used preoperatively. These measures enabled comparisons of the pre- and postoperative data to be made to assess the clinical outcome of DBS. Pain relief was quantified using three methods: mean % pain relief, proportion of patients experiencing $\geq$50% pain relief, and a four-tiered categorization of pain outcome. This four-tiered system is as follows: poor (<40% improvement in pain intensity), fair (40–59% improvement), good (60–79%), excellent (80–100%).

Of the 47 patients, 38 felt pain relief was good enough during the trial period to proceed to full implantation. Of these 6 were lost to follow up (3 unrelated deaths) leaving 32 with data.

Results

Overall results

Results of trial stimulation

Of the 47 patients selected for trial stimulation, 38 patients proceeded to permanent implantation. This is summarized in Table 2. The mean age of patients proceeding

Table 2. *Successful and failed trial stimulation*

Aetiology	Total	Failed trial	Implantation
Post-stroke	18	6 (33%)	12 (67%)
Phantom limb/brachial plexus injury	12	0	12 (100%)
Anaesthesia dolorosa	3	0	3 (100%)
Spinal cord injury	3	2 (67%)	1 (33%)
Other	11	1 (9%)	10 (91%)
Overall	47	9 (19%)	38 (81%)

to permanent implantation was 50 years. Patients suffering from post-stroke pain were the most likely to fail trial stimulation (33%), in contrast to individuals with phantom limb/post-brachial plexus injury pain and anaesthesia dolorosa, all of whom underwent permanent implantation.

Pain alleviation

The outcome data is presented in Table 3. Six patients (12%) were lost to follow-up. At a mean follow-up of 44.5 months (range 1–76 months) the intensity of pain was reduced by an average of $52 \pm 27\%$ (range 14–100%). The mean VAS score was 8.13 (SD 1.23) preoperatively, and 3.93 (SD 2.15) postoperatively ($p < 0.001$). Pain relief $\geq$50% was obtained in 50% of patients (16/32). Excellent pain relief was achieved in 19% (6/32), good relief in 13% (4/32), fair relief in 31% (10/32), and poor relief in 38% (12/32).

Table 3. *Results of DBS for neuropathic pain*

Patient	Pre-op pain score	Post-op pain score	Improvement %	Stimulation site(s)
1	9.7	6.8	30	PVG
2	8.5	6.8	20	thalamus
3	7.2	3.6	50	PVG/thalamus
4	9.2	5.3	42	PVG
5	8.2	1.9	77	PVG
6	9.1	2	88	PVG
7	6.7	5.1	24	PVG/thalamus
8	10	7.4	26	PVG
9	8.1	1	88	PVG
10	8.2	5	39	PVG
11	8.5	6.75	21	PVG/thalamus
12	8.9	5.1	43	PVG/thalamus
13	6.9	0	100	thalamus
14	8.5	0	100	PVG
15	8.9	6.1	31	PVG/thalamus
16	8.1	3.7	54	PVG
17	6.4	5.5	14	thalamus
18	7.4	3.3	55	PVG
19	7.2	3.6	50	PVG
20	6.3	4.8	24	PVG/thalamus
21	9.8	3.2	77	thalamus
22	8.2	3.4	58	PVG/thalamus
23	6.8	2.5	63	PVG
24	9.3	7.9	15	PVG/thalamus
25	5.8	3.1	47	PVG
26	8.2	1.5	82	PVG/thalamus
27	9	4.7	48	PVG
28	10	0	100	hypothalamus
29	8.2	3.5	57	PVG
30	10	2.5	75	PVG
31	6.3	4.8	24	PVG
32	6.6	5	24	PVG

Ninety-four percent of patients (30/32) complained of 'burning pain' preoperatively, and the severity of this component was diminished at follow-up in 78% (23/30). In 57% of these patients (17/30), this component of the pain was completely alleviated.

Patients with post-stroke pain had a mean improvement in pain severity of $49 \pm 28\%$, with 44% (4/9) describing a $\geq$50% improvement in severity of pain following surgery. Twenty-two percent (2/9) of these patients had a fair outcome, 11% (1/9) had a good outcome, and two patients (22%) had and excellent outcome. Poor outcome was seen in 44% (4/9) of these patients.

Phantom limb and brachial plexus injury

Phantom limb patients had a mean improvement of $51 \pm 14\%$ (6 of 7 patients) with a wide range (18–74%). Improvement $\geq$50% had a 67% (4/6). Similarly, brachial plexus injury patients had a mean improvement of 50% (21–72%) with 60% improving $\geq$50%. Overall in these two categories, 40% (2/5) had a fair outcome and 40% (2/5) had a good outcome.

Cranial pain syndromes

Of eight patients with craniofacial pain syndromes (including one cluster headache), overall improvement was 68% (11–100%). Analgesia 100% was achieved in one patient with post-herpetic neuralgia and in one with cluster headache. Excellent pain relief occurred in 38% (3/8), good relief in 38% (3/8), fair in 13% (1/8) and poor in 13%.

Spinal cord injury

We have not been particularly successful at treating spinal cord injury. Two out of three patients failed trial stimulation and were therefore not implanted. The remaining patient has not achieved significant pain relief although this may be related to a very high level of opiates.

Others

This group comprises a miscellany of conditions including perineal pain and neck pain (post-surgical). Overall improvement in pain scores was 69%.

Site of stimulation

The likelihood of success was also determined according to the site of stimulation. PVG stimulation alone was optimal in 17 patients (53%), whilst a combination of PVG and thalamic stimulation produced the greatest degree of analgesia in 11 patients (34%). Thalamic stimulation alone was optimal in 4 patients (13%). DBS of the PVG alone was associated with the highest degree of pain alleviation, with a mean improvement of 59% ($p < 0.001$) and a $\geq$50% improvement in 66% of patients. Patients requiring thalamic stimulation alone obtained a mean improvement in pain severity of 53% ($p = 0.084$). Those patients who required both PVG and VPL/VPM stimulation had the lowest magnitude of pain amelioration (mean improvement 36%; $p = 0.001$). Figures 1 and 2 show typical targeting sites and trajectories for the PVG and VPL respectively, when using the Radionics® Stereoplan(TM) software. Figure 3 shows a typical post-operative magnetic resonance scan in a patient with both PVG and VPL electrodes.

Stimulation parameters

The amplitude, pulse width, and frequency of stimulation are displayed in Table 4. Mean values for each electrode site, together with the range of values, are given. There was no difference in mean amplitude between the two sites, however the required amplitude varied considerably between patients. A higher mean pulse width was observed for stimulation of the PVG when compared with the sensory thalamus (257 vs. 182 ms), however the range of values was extensive but similar for the two stimulation locations. The frequency of stimulation required to produce and maintain analgesia was much lower than that found in DBS for movement disorders. The mean stimulation frequencies were 22 Hz for the PVG and 26 Hz for the sensory thalamus. The range of stimulation frequencies was 5–30 Hz for PVG stimulation and 10–50 Hz for VPL/VPM stimulation. The precise frequency at which maximal analgesic effect was produced varied from patient to patient and was determined by careful titration during the trial period, followed by further adjustments after pulse generator implantation.

Table 4. *Mean stimulation parameters*

	PVG	Sensory thalamus
Amplitude (V)	2.4 (0.8–4.5)	2.4 (0.7–4.4)
Pulse width (ms)	257 (120–450)	182 (60–400)
Frequency (Hz)	22 (5–30)	26 (10–50)

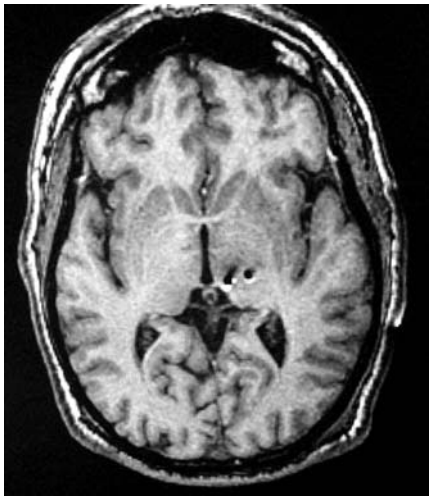

Fig. 3. Axial MRI scan of implanted electrodes in the PVG and VPL in a patient with pain secondary to a brachial plexus injury

Health-related quality of life

To assess the overall improvement or otherwise in this group of patients, pre- and post-operative EUROQOL data was recorded for the last 15 consecutive patients undergoing surgery. These health-related quality of life measures revealed a mean improvement following surgery of 38%, using a paired sample *t*-test (mean pre-operative value 46.5 ± 18.6, mean post-operative value 64.1 ± 19.9; $p = 0.014$).

Complications

Wound infection occurred in two patients, requiring a prolonged course of antibiotic therapy. Fracture of the electrode lead occurred in one patient, requiring revision of the electrode. There was no incidence of intracranial haemorrhage, post-operative neurological deficit, or mortality.

Discussion

This study reports the outcome of deep brain stimulation of the sensory thalamus and the PVG/PAG complex for different neuropathic pain syndromes. We believe that this single-centre prospective study shows a beneficial effect of such therapy for neuropathic pain syndromes.

However, the outcomes of surgery appear to vary according to aetiology. Our conclusions must be taken in the light of the fact that certain aetiologies are of a smaller number than others. It would appear that the effects are best for phantom limb syndromes, head pain (including one patient with cluster headaches) and anaesthesia dolorosa. Post-stroke pain responds in 70% of patients.

Given the difficulties inherent with assessing pain outcomes with VAS scores we have now taken to collecting pre and post-operative EUROQOL scores which have shown that there is significant benefit. We have found that it appears to be a somewhat better pain alleviation when the PVG/PAG target site is used. It would appear on reviewing published images of recent groups [4, 10] that there is a correspondence in what we have reported as PVG/PAG and CM-pf. With further experience from ours and other groups this may be well clarified. The target coordinates are very similar to those used historically [8] for both sites and we have used this nomenclature.

Historically, loss of effect with time has been quoted as a major problem with this therapy. In our experience, the possible cause of this is patient perception. Since pain is rarely totally abolished, with time any residual pain becomes more intrusive and patients score the pain higher. However, in an N of 1 study, turning off the stimulation causes exacerbation of pain that had been scored as maximum. Hence if only VAS scores were rated this would lead to apparent loss of effect. We have tried to address this problem. We assessed patients after a stable pattern of stimulation was achieved in an N of 1 trial in which they are randomly switched "on" or "off" in 10 trials and the pain scores were charted [6]. This was limited by the fact that in some patients pain relief lasted for up to 24 hours after cessation of stimulation and was not practical. Nevertheless, we believe that deep brain stimulation for neuropathic pain is an effective therapy and further studies are required to improve outcome.

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References

1. Burchiel KJ (2001) Deep brain stimulation for chronic pain: the results of two multi-center trials and a structured review. Pain Med 2: 177
2. Canavero S, Bonicalzi V (2001) Motor cortex stimulation. J Neurosurg 94: 688–689
3. Carroll D, Joint C, Maartens N, Shlugman D, Stein J, Aziz TZ (2000) Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. Pain 84: 431–437
4. Franzini A, Ferroli P, Leone M, Broggi G (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52: 1095–1099; discussion 1099–1101
5. Gol A (1967) Relief of pain by electrical stimulation of the septal area. J Neurol Sci 5: 115–120
6. Green AL, Shad A, Watson R, Nandi D, Yianni J, Aziz TZ (2004) N-of-1 Trials for assessing the efficacy of deep brain stimulation neuropathic pain. Neuromodulation 7(2): 76–81
7. Gybels J, Kupers R (1990) Deep brain stimulation in the treatment of chronic pain in man: where and why? Neurophysiol Clin 20: 389–398
8. Jones AK, Kulkarni B, Derbyshire SW (2002) Functional imaging of pain perception. Curr Rheumatol Rep 4: 329–333
9. Katayama Y, Fukaya C, Yamamoto T (1998) Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. J Neurosurg 89: 585–591
10. Krauss JK, Pohle T, Weigel R, Burgunder JM (2002) Deep brain stimulation of the centre median-parafascicular complex in patients with movement disorders. J Neurol Neurosurg Psychiatry 72: 546–548
11. Kumar K, Toth C, Nath RK (1997) Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery 40: 736–746; discussion 746–747
12. Melzack R (1975) The McGill pain questionnaire: major properties and scoring methods. Pain 1(3): 277–299
13. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
14. Smith H, Joint C, Schlugman D, Nandi D, Stein J, Aziz T (2001) Motor cortex stimulation for neuropathic pain. Neurosurgical Focus 3: 1–9
15. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir [Suppl 52]: 137–139
16. Young RF, Tronnier V, Rinaldi PC (1992) Chronic stimulation of the Kolliker-Fuse nucleus region for relief of intractable pain in humans. J Neurosurg 76: 979–985

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Movement disorders

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Surgical considerations in movement disorders: deep brain stimulation, ablation and transplantation

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Summary

Surgical therapy for movement disorders has been practiced since the early 20th century, mostly for Parkinson's disease. At its onset, large destructive procedures like open resection of cortex, parts of the basal ganglia or its fibre connections produced variable, ill-documented results. With the introduction of the stereotactic operating technique in the second half of the century, ablative surgery became more refined, and more selective interventions became possible to alleviate the suffering of those patients for whom no other treatment modalities were yet available. However, the introduction of levodopa-based pharmacological therapy pushed surgical therapy almost completely to the background.

In the past two decades, there has been a resurgence of interest in surgery for movement disorders, due to both limitations of long-term pharmacological therapy and the advent of the treatment modality of deep brain stimulation. The subject has now grown into a large field of clinical and scientific interest. Parkinson's disease is the most widespread surgical indication, but in other movement disorders considerable improvement can be achieved by surgery as well, most notably in dystonia. A short review of the surgical therapy for these disorders is presented.

Keywords: Neuromodulation; ablation; deep brain stimulation; transplantation; movement disorder; review.

Parkinson's disease

Patients most suitable for surgery are those with advanced idiopathic Parkinson's disease, whose symptoms are responsive to dopamine treatment [75], and who have no significant cognitive impairment [56]. Accompanying mood disorders should be adequately controlled, and a history of psychosis that was not levodopa-induced is a relative contra-indication. Isolated tremor-dominant Parkinson's disease that is unresponsive to levodopa, with minimal hypokinesia or rigidity, can be considered for treatment as well. Patients with parkinsonism that is unresponsive to levodopa, as part of some form of multiple system degeneration or due to ischemia or other brain injury, are not good surgical candidates [34, 63].

Ablative procedures

Thalamotomy

Neurosurgical thalamotomy in the nucleus ventrointermedius is effective in 85–93% of patients with incapacitating tremor that is refractory to drug therapy [29, 30, 47]. Rigidity can improve to some extent as well [48], but hypokinesia is generally unaffected by thalamotomy.

Permanent complications are reported in a wide range from 9 to 47% of patients [21, 26, 29, 47, 57, 76], and mainly consist of deterioration of gait and dysarthria. Bilateral thalamotomy carries a high risk of cognitive, speech and balance problems [46, 58, 61] and is no longer performed [31]. In the era of deep brain stimulation, thalamotomy is now reserved for those patients who have long-term unilateral tremor-dominant disease, in whom deep brain stimulation cannot be performed.

Pallidotomy

Pallidotomy produces a marked improvement in contralateral rigidity and hypokinesia, and can virtually abolish levodopa induced dyskinesias. Tremor improves as well, although to a lesser degree than after thalamotomy. In two single-blind clinical trials comparing unilateral pallidotomy to pharmacological treatment alone [14, 72], it was shown that pallidotomy produces an overall improvement of 31% in the motor score of the Unified Parkinson's Disease Rating Scale (UPDRS)

after six months. Gait disturbances and the freezing in ''off''-periods decrease as well after unilateral pallidotomy, but most studies show this effect to be lost after several years [38]. Bilateral pallidotomy has been applied until recently, but is accompanied by a higher complication rate, mainly dysarthria and neuropsychological deterioration [15, 18], and is generally not recommended. The long-term outcome of pallidotomy is somewhat controversial, but there are a number of reports of sustained benefit after long periods of follow-up [19, 20, 37]. Nowadays, pallidotomy is still a viable treatment modality for patients with advanced Parkinson's disease with motor-fluctuations and severe ''off''-state hypokinesia and rigidity along with tremor, in whom deep brain stimulation cannot be performed.

Subthalamotomy

Lesioning in the subthalamic nucleus has generally been avoided for fear of inducing hemiballism. Based on the effectiveness of improving parksinsonian symptoms by deep brain stimulation in the subthalamic nucleus, and economic restraints to apply this technique, a limited number of studies of subthalamotomy have been published. Unilateral subthalamotomy produced a 30–37% improvement in ''off''-state motor score [53, 62], that was sustained after two years in one series [53]. After bilateral subthalamotomy, 50% reduction of the ''off''-state motor score was reported [1]. Postoperative hemiballism did indeed occur in up to one third of the patients, but generally resolved spontaneously, and other side-effects seemed to be limited. The role of subthalamotomy in the surgical treatment of Parkinson's disease will have to be determined by further studies.

Deep brain stimulation

Thalamic stimulation

Continuous deep brain stimulation in the thalamus has consistently been shown to produce excellent control of tremor in Parkinson's disease [5, 31, 51], comparable to that after thalamotomy, with a sustained benefit after more than 10 years [6]. Bilateral stimulation can be performed, and is often necessary to abolish midline tremors [52]. However, thalamic stimulation has only limited effect on the other cardinal symptoms of Parkinson's disease, comparable to the findings after thalamotomy. The main advantage of thalamic stimulation over thalamotomy is the lower rate of side-effects, occurring in around 15% of patients, which are usually mild and can sometimes be lessened by adjusting the stimulation parameters. Due to this difference in complications, thalamic stimulation was shown to produce more functional improvement for the patients than thalamotomy [57]. In Parkinson's disease, thalamic stimulation has largely lost its role in favour of subthalamic stimulation, due to the lack of improvement in the other cardinal features of the disease besides tremor. In long-term stable tremor-dominant disease, it can however still be considered, and thalamic stimulation is the treatment of choice in other forms of medication-resistant tremor, most notably essential tremor [44].

Pallidal stimulation

Deep brain stimulation of the globus pallidus is usually performed bilaterally, and can produce a 39–55% improvement in total ''off''-phase motor score [9, 23, 73], which effect can be sustained for up to two years after surgery [16, 23]. The larger symptom reduction of pallidal stimulation in comparison to pallidotomy is due to the fact that pallidotomy was usually applied unilaterally. In a small study, however, efficacy of pallidal stimulation was gradually lost after five years of follow-up [74]. The improvements after pallidal stimulation concern all motor symptoms of Parkinson's disease. Besides decreasing hypokinesia, rigidity, tremor, gait disturbances and dyskinesias, there is also a significant reduction of ''off''-period dystonia and an increase in total ''on'' time [65]. Complications after pallidal stimulation are rare and can often be reduced by stimulation parameter adjustments. Especially neuropsychological deterioration is rarely seen. This may well prove to be the key factor giving pallidal stimulation a continuing role in the future, as subthalamic stimulation seems to bear a higher risk of neuropsychological side-effects [2]. Further research is therefore necessary to firmly establish if the long-term efficacy of pallidal stimulation is indeed less stable than that of subthalamic stimulation.

Subthalamic nucleus stimulation

Stimulation in the subthalamic nucleus is generally the preferred surgical therapy for advanced Parkinson's disease. There is a marked reduction of all motor symptoms of the disease, just as in stimulation of the globus pallidus. Besides the reduction of tremor, hypokinesia and rigidity of the extremities, the improvement in midline symptoms such as gait and balance is often remarkable [33]. Subthalamic stimulation can improve total

motor scores by 44–66% [9, 35], and this effect has been shown to last up until five years after surgery [35]. Subthalamic stimulation attenuates motor fluctuations, and the sudden ''on–off'' fluctuations become milder or disappear completely. Compared to pallidal stimulation, subthalamic stimulation may lead to a larger percentage of ''on''-time during the day without involuntary movements [65]. In contrast to pallidal stimulation, dopaminergic drugs are reduced substantially after subthalamic stimulation, for the combination of stimulation and baseline drug dosages can lead to increased dyskinesias [39]. In some cases, dopaminergic drugs can be stopped completely, whereby the stimulation produces the same effect as medication did preoperatively [70]. As a general rule, patients can expect to improve to the level of their best baseline ''on''-state more continuously after subthalamic stimulation.

Complications are generally mild and well-tolerated, and are mainly experienced during the fine-tuning of the stimulation: dysarthria, paresthesias or dystonia. There is, however, growing concern about the occurrence of cognitive [60] or mood [7] disturbances and behavioural changes [28] after subthalamic stimulation, which might be caused by current spread into associative and limbic regions of this small nucleus. A contributing factor might be imbalance of stimulation settings and medication adjustments early after surgery.

Continuing research into the comparison of subthalamic and pallidal stimulation for Parkinson's disease will elucidate their respective roles in the treatment of Parkinson's disease. It is conceivable that selection of the best target site of stimulation will be determined individually for each patient depending on symptom profile and neuropsychological factors [2, 49].

Transplantation

The idea of replacing the degenerated dopaminergic input into the striatum directly by transplanting dopaminergic neurons is perhaps the most logical and direct approach towards fighting Parkinson's disease. In the initial attempts, autologous adrenal medullary cells were used. Although the first case-reports were optimistic [4, 45], larger series demonstrated no significant improvement in motor performance and a high morbidity and mortality [25]. Thereafter, the use of adrenal medullary cells was abandoned in favour of transplantation of human fetal mesencephalic dopaminergic cells. The initial reports showed proof of principle with evidence of graft survival, functional dopaminergic release, and improved motor function in the patients [32, 41, 54, 55]. Two clinical trials were then performed, and although PET-scans showed increased dopamine uptake demonstrating graft survival, no significant clinical improvement was achieved. Furthermore, a significant proportion of the treated patients developed increased dyskinesias that did not resolve after discontinuation of dopaminergic drugs [22, 50]. A number of aspects of this therapy are not yet standardized, most notably the transplantation procedure, tissue handling, patient selection, and immunosuppressive treatment. The number of graft sites and their positioning may need to be tailored to the individual patient. The use of fetal tissue causes obvious problems and alternative sources of dopaminergic neurons will have to come from stem cell technology. Transplantation of dopaminergic neurons might still prove a viable approach in the future, but these issues have yet to be resolved [77].

Dystonia

Dystonia is a syndrome characterized by sustained muscle contractions, causing twisting and repetitive movements or abnormal postures. Surgical therapy can offer improvement in various types of dystonia that are refractory to drug therapy or injection of botulinum toxin: primary generalized dystonia, secondary generalized dystonia due to an insult to the brain, and some forms of cervical dystonia.

Ablative procedures

Thalamotomy in generalized dystonia

Application of thalamotomy for dystonia followed the observations of improvement of dystonic symptoms in Parkinson's disease after thalamotomy. The largest series of unilateral thalamotomy in generalized dystonia showed good improvement in 25% and moderate improvement in 45% of patients [12], which results were confirmed in a smaller more recent series [64]. It appeared that the complication rate of pallidotomy was lower than that of thalamotomy [27], and the focus of research shifted to the globus pallidus for the treatment of dystonia, even more so after the development of deep brain stimulation. Special mention for the future, however, is deserved by the observation that thalamotomy was more effective in secondary hemidystonia than in primary dystonia [3, 10], whereas secondary dystonia does not respond as well to the currently favoured pallidal stimulation.

Pallidotomy in generalized dystonia

Soon after the renewed interest for pallidotomy in Parkinson's disease, this procedure was applied to dystonia patients as well, with remarkable results, although the total number of patients reported is small [17, 40, 71, 79]. Most patients were treated with bilateral pallidotomy and a consistent finding has been that patients with primary dystonia respond remarkably well, whereas patients with secondary dystonia do not improve much.

One group compared their successive results with thalamotomy and pallidotomy for dystonia, and they found that pallidotomy resulted in much better outcome than thalamotomy in primary dystonia [79]. In their patients with secondary dystonia, both treatments produced moderate to marked improvement in about half of the patients, and although disappointing when compared to primary dystonia, either treatment can still produce benefit for some secondary dystonia patients.

Although severe complications have been reported after bilateral pallidotomy, present-day localisation techniques probably allow for safer application of this technique. Even though stimulation is safer than lesioning, and has several other advantages, the results thus far with modern bilateral pallidotomy in primary dystonia definitely suggest that this is a viable approach in cases where stimulation cannot be performed.

Ablative surgery in cervical dystonia

Cervical dystonia, formerly named spasmodic torticollis, is the most frequent dystonic disorder, and presently the treatment of choice is repeated injections with botulinum toxin in the muscles involved. For the 10–25% of patients who are primary or secondary non-responders, selective peripheral denervation tailored to the individual dystonic pattern [8, 11] is the ablative surgical treatment of choice.

Both thalamotomy and pallidotomy have been applied in cervical dystonia, but experience dates from before the introduction of botulinum toxin, and both procedures were abandoned due to higher success-rates and lower morbidity of peripheral denervation. From a recent review on this subject we have learnt mainly that bilateral stereotactic surgery has better outcome than unilateral surgery [43], which has relevance for therapeutic strategies in the era of stimulation.

Deep brain stimulation

Thalamic stimulation

One recent series of 12 patients was published applying high-frequency thalamic stimulation for both primary and secondary dystonia, and only five patients had mild to moderate improvement of limb dystonia without resolving axial symptoms [67]. As in ablative surgery the pallidal target appeared to be superior to the thalamus for treating dystonia; hence, the globus pallidus became the target of choice for these patients. Four case-reports describe thalamic stimulation in secondary dystonia: one had temporary good effect of intermittent stimulation, probably simulating a sensory "geste antagoniste" [59]; one had good effect of pallidal stimulation but no effect of simultaneously implanted thalamic stimulation [66]; one had no effect of pallidal stimulation that was applied for only six weeks and had good effect of subsequent thalamic stimulation [24]; one had good effect on paroxysmal nonkinesogenic arm-dystonia [42]. There is insufficient data to decide if there is a role for thalamic stimulation in secondary dystonia in the future.

Pallidal stimulation

Bilateral pallidal stimulation produces marked and sustained improvement in primary generalized dystonia, with a mean symptomatic improvement of 51% and one third of patients improving more than 75%, as was recently shown in a clinical trial [69], confirming the results of earlier studies [13, 17, 78]. At present, this is considered the surgical treatment of choice in these patients. Although no direct comparison with bilateral pallidotomy is available, the main reason for assuming a preference for stimulation is its postulated lower incidence of adverse effects. However, with present-day image-based and electrophysiological localization methods this is definitely undecided. Another advantage of stimulation is the adjustability of stimulation parameters, which allows for a dynamic approach over time. In secondary dystonia, the results are less favourable and more variable [17], and treatment is probably more complex due to the heterogeneous population, many patients harbouring other neurological symptoms due to the underlying disorder [68]. Future research will determine if and how these patients can be treated best by functional neurosurgery.

Patients with cervical dystonia that have inadequate response to botulinum toxin and who are not candidates for selective peripheral denervation, often have complex forms of cervical dystonia, with head tremor, phasic dystonic movements, anterocollis or combinations thereof. In these cases, bilateral pallidal stimulation has been shown to produce 60% improvement in both disease severity and disability scores, with an accompanying reduction of more than 50% in associated pain scores [36, 78].

Future research

A substantial body of evidence has been produced in the past two decades, providing new insights into the treatment of movement disorders such as Parkinson's disease and dystonia. The now widespread application of deep brain stimulation has not only enabled us to alleviate the symptoms of many patients, but has also given us a valuable tool to study their diseases.

General recommendations about the best treatment and the alternatives for the individual patients at present can be made, but it is definitely too early to decide that subthalamic and pallidal stimulation are the definitive treatments of choice for Parkinson's disease and dystonia. Additional controlled studies in homogeneous groups of patients are essential to determine the optimal treatment for these patients in the long term.

References

1. Alvarez L, Macias R, Lopez G, Alvarez E, Pavon N, Rodriguez-Oroz MC, Juncos JL, Maragoto C, Guridi J, Litvan I, Tolosa ES, Koller W, Vitek J, DeLong MR, Obeso JA (2005) Bilateral subthalamotomy in Parkinson's disease: initial and long-term response. Brain 128: 570–583
2. Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP (2005) Pallidal vs. subthalamic nucleus deep brain stimulation in Parkinson disease. Arch Neurol 62: 554–560
3. Andrew J, Fowler CJ, Harrison MJ (1983) Stereotaxic thalamotomy in 55 cases of dystonia. Brain 106: 981–1000
4. Backlund EO, Granberg PO, Hamberger B, Knutsson E, Martensson A, Sedvall G, Seiger A, Olson L (1985) Transplantation of adrenal medullary tissue to striatum in parkinsonism. First clinical trials. J Neurosurg 62: 169–173
5. Benabid AL, Pollak P, Gervason C, Hoffmann D, Gao DM, Hommel M, de Rougemont J (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 337: 403–406
6. Benabid AL, Benazzouz A, Hoffmann D, Limousin P, Krack P, Pollak P (1998) Long-term electrical inhibition of deep brain targets in movement disorders. Mov Disord [Suppl 3] 13: 119–125
7. Berney A, Vingerhoets F, Perrin A, Guex P, Villemure JG, Burkhard PR, Benkelfat C, Ghika J (2002) Effect on mood of subthalamic DBS for Parkinson's disease: a consecutive series of 24 patients. Neurology 59: 1427–1429
8. Bertrand CM (1993) Selective peripheral denervation for spasmodic torticollis: surgical technique, results, and observations in 260 cases. Surg Neurol 40: 96–103
9. Burchiel KJ, Anderson VC, Favre J, Hammerstad JP (1999) Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. Neurosurg 45: 1375–1382
10. Cardoso F, Jankovic J, Grossman RG, Hamilton WJ (1995) Outcome after stereotactic thalamotomy for dystonia and hemiballismus. Neurosurg 36: 501–507
11. Cohen-Gadol AA, Ahlskog JE, Matsumoto JY, Swenson MA, McClelland RL, Davis DH (2003) Selective peripheral denervation for the treatment of intractable spasmodic torticollis: experience with 168 patients at the Mayo Clinic. J Neurosurg 98: 1247–1254
12. Cooper IS (1976) 20 year follow-up study on the neurosurgical treatment of dystonia musculorum deformans. In: Elridge R, Fahn S (eds) Advances in neurology, vol 14. Raven Press, New York
13. Coubes P, Cif L, El Fertit H, Hemm S, Vayssiere N, Serrat S, Picot MC, Tuffery S, Claustres M, Echenne B, Frerebeau P (2004) Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. J Neurosurg 101: 189–194
14. de Bie RMA, de Haan PS, Nijssen PCG, Rutgers AWF, Beute GN, Bosch DA, Haaxma R, Schmand B, Schuurman PR, Staal MJ, Speelman JD (1999) Unilateral pallidotomy in Parkinson's disease: a randomised, singleblind, multicentre trial. Lancet 354: 1665–1669
15. de Bie RMA, Schuurman PR, Esselink RA, Bosch DA, Speelman JD (2002) Bilateral pallidotomy in Parkinson's disease: a retrospective study. Mov Disord 17: 533–538
16. Durif F, Lemaire JJ, Debilly B, Dordain G (2002) Long-term follow-up of globus pallidus chronic stimulation in advanced Parkinson's disease. Mov Disord 17: 803–807
17. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM (2004) Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. Neurosurg 54: 613–619
18. Favre J, Burchiel KJ, Taha JM, Hammerstad J (2000) Outcome of unilateral and bilateral pallidotomy for Parkinson's disease: patient assessment. Neurosurg 46: 344–353
19. Fazzini E, Dogali M, Sterio D, Eidelberg D, Beric A (1997) Stereotactic pallidotomy for Parkinson's disease – a long-term follow-up of unilateral pallidotomy. Neurology 48: 1273–1277
20. Fine J, Duff J, Chen R, Hutchinson W, Lozano AM, Lang AE (2000) Long-term follow-up of unilateral pallidotomy in advanced parkinson's disease. New Engl J Med 342: 1708–1714
21. Fox MW, Ahlskog JE, Kelly PJ (1991) Stereotactic ventrolateralis thalamotomy for medically refractory tremor in post-levodopa era Parkinson's disease patients. J Neurosurg 75: 723–730
22. Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, Dillon S, Winfield H, Culver S, Trojanowski JQ, Eidelberg D, Fahn S (2001) Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 344: 710–719
23. Ghika J, Villemure JG, Fankhauser H, Favre J, Assal G, Ghika-Schmid F (1998) Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year follow-up review. J Neurosurg 89: 713–718
24. Ghika J, Villemure JG, Miklossy J, Temperli P, Pralong E, Christen-Zaech S, Pollo C, Maeder P, Bogousslavsky J, Vingerhoets F (2002) Postanoxic generalized dystonia improved by bilateral Voa thalamic deep brain stimulation. Neurology 58: 311–313
25. Goetz CG, Stebbins GT, Klawans HL, Koller WC, Grossman RG, Bakay RA, Penn RD (1991) United Parkinson foundation neurotransplantation registry on adrenal medullary transplants: presurgical, and 1- and 2-year follow-up. Neurology 41: 1719–1722
26. Goldman MS, Ahlskog JE, Kelly PJ (1992) The symptomatic and functional outcome of stereotactic thalamotomy for medically intractable essential tremor. J Neurosurg 76: 924–928
27. Hariz MI, De Salles AA (1997) The side-effects and complications of posteroventral pallidotomy. Acta Neurochir [Suppl] 68: 42–48
28. Houeto JL, Mesnage V, Mallet L, Pillon B, Gargiulo M, du Moncel ST, Bonnet AM, Pidoux B, Dormont D, Cornu P, Agid Y (2002) Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 72: 701–707
29. Jankovic J, Cardoso F, Grossman RG, Hamilton WJ (1995) Outcome after stereotactic thalamotomy for parkinsonian, essential, and other types of tremor. Neurosurg 37: 680–686
30. Kelly PJ, Gillingham FJ (1980) The long-term results of stereotaxic surgery and L-dopa therapy in patients with Parkinson's disease. A 10-year follow-up study. J Neurosurg 53: 332–337

31. Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, Tuite P, Sime E, Lazano A, Hauser R, Malapira T, Smith D, Tarsy D, Miyawaki E, Norregaard T, Kormos T, Olanow CW (1997) High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 42: 292–299
32. Kordower JH, Freeman TB, Snow BJ, Vingerhoets FJ, Mufson EJ, Sanberg PR, Hauser RA, Smith DA, Nauert GM, Perl DP, Olanow CW (1995) Neuropathological evidence of graft survival and striatal reinnervation after the transplantation of fetal mesencephalic tissue in a patient with Parkinson's disease. N Engl J Med 332: 1118–1124
33. Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, Benabid AL (1998) Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 121: 451–457
34. Krack P, Dowsey PL, Benabid AL, Acarin N, Benazzouz A, Kunig G, Leenders KL, Obeso JA, Pollak P (2000) Ineffective subthalamic nucleus stimulation in levodopa-resistant postischemic parkinsonism. Neurology 54: 2182–2184
35. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 349: 1925–1934
36. Krauss JK, Loher TJ, Pohle T, Weber S, Taub E, Barlocher CB, Burgunder JM (2002) Pallidal deep brain stimulation in patients with cervical dystonia and severe cervical dyskinesias with cervical myelopathy. J Neurol Neurosurg Psychiatry 72: 249–256
37. Laitinen LV, Bergenheim AT, Hariz MI (1992) Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg 76: 53–61
38. Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchinson W (1997) Posteroventral medial pallidotomy in advanced Parkinson's disease. New Engl J Med 337: 1036–1042
39. Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, Benabid AL (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. New Engl J Med 339: 1105–1111
40. Lin JJ, Lin GY, Shih C, Lin SZ, Chang DC, Lee CC (1999) Benefit of bilateral pallidotomy in the treatment of generalized dystonia. Case report. J Neurosurg 90: 974–976
41. Lindvall O, Widner H, Rehncrona S, Brundin P, Odin P, Gustavii B, Frackowiak R, Leenders KL, Sawle G, Rothwell JC, Ourklund AB, Marsden CD (1992) Transplantation of fetal dopamine neurons in Parkinson's disease: one-year clinical and neurophysiological observations in two patients with putaminal implants. Ann Neurol 31: 155–165
42. Loher TJ, Krauss JK, Burgunder JM, Taub E, Siegfried J (2001) Chronic thalamic stimulation for treatment of dystonic paroxysmal nonkinesigenic dyskinesia. Neurology 56: 268–270
43. Loher TJ, Pohle T, Krauss JK (2004) Functional stereotactic surgery for treatment of cervical dystonia: review of the experience from the lesional era. Stereotact Funct Neurosurg 82: 1–13
44. Lyons KE, Pahwa R (2004) Deep brain stimulation and essential tremor. J Clin Neurophysiol 21: 2–5
45. Madrazo I, Drucker-Colin R, Diaz V, Martinez-Mata J, Torres C, Becerril JJ (1987) Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease. N Engl J Med 316: 831–834
46. Matsumoto K, Asano T, Baba T, Miyamoto T, Ohmoto T (1976) Long-term follow-up results of bilateral thalamotomy for parkinsonism. Appl Neurophysiol 39: 257–260
47. Nagaseki Y, Shibazaki T, Hirai T, Kawashima Y, Hirato M, Wada H, Miyazaki M, Ohye C (1986) Long-term follow-up results of selective VIM-thalamotomy. J Neurosurg 65: 296–302
48. Narabayashi H, Yokochi F, Nakajima Y (1984) Levodopa-induced dyskinesia and thalamotomy. J Neurol Neurosurg Psychiatry 47: 831–839
49. Okun MS, Foote KD (2005) Subthalamic nucleus vs. globus pallidus interna deep brain stimulation, the rematch: will pallidal deep brain stimulation make a triumphant return? Arch Neurol 62: 533–536
50. Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, Shannon KM, Nauert GM, Perl DP, Godbold J, Freeman TB (2003) A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 54: 403–414
51. Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK (1998) Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. Neurology 51: 1063–1069
52. Ondo W, Almaguer M, Jankovic J, Simpson RK (2001) Thalamic deep brain stimulation: comparison between unilateral and bilateral placement. Arch Neurol 58: 218–222
53. Patel NK, Heywood P, O'Sullivan K, McCarter R, Love S, Gill SS (2003) Unilateral subthalamotomy in the treatment of Parkinson's disease. Brain 126: 1136–1145
54. Peschanski M, Defer G, N'Guyen JP, Ricolfi F, Monfort JC, Remy P, Geny C, Samson Y, Hantraye P, Jeny R (1994) Bilateral motor improvement and alteration of L-dopa effect in two patients with Parkinson's disease following intrastriatal transplantation of foetal ventral mesencephalon. Brain 117: 487–499
55. Piccini P, Brooks DJ, Bjorklund A, Gunn RN, Grasby PM, Rimoldi O, Brundin P, Hagell P, Rehncrona S, Widner H, Lindvall O (1999) Dopamine release from nigral transplants visualized in vivo in a Parkinson's patient. Nat Neurosci 2: 1137–1140
56. Saint-Cyr JA, Trepanier LL (2000) Neuropsychologic assessment of patients for movement disorder surgery. Mov Disord 15: 771–783
57. Schuurman PR, Bosch DA, Bossuyt PMM, Bonsel GJ, van Someren EJW, de Bie RMA, Merkus MP, Speelman JD (2000) A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. New Engl J Med 342: 461–468
58. Selby G (1967) Stereotactic surgery for the relief of Parkinson's disease. 2. An analysis of the results in a series of 303 patients (413 operations). J Neurol Sci 5: 343–375
59. Sellal F, Hirsch E, Barth P, Blond S, Marescaux C (1993) A case of symptomatic hemidystonia improved by ventroposterolateral thalamic electrostimulation. Mov Disord 8: 515–518
60. Smeding HM, Esselink RA, Schmand B, Koning-Haanstra M, Nijhuis I, Wijnalda EM, Speelman JD (2005) Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD – a comparison of neuropsychological effects. J Neurol 252: 176–182
61. Speelman JD (1991) Parkinson's disease and stereotaxic neurosurgery (thesis). Rodopi, Amsterdam
62. Su PC, Tseng HM, Liu HM, Yen RF, Liou HH (2003) Treatment of advanced Parkinson's disease by subthalamotomy: one-year results. Mov Disord 18: 531–538
63. Tarsy D, Apetauerova D, Ryan P, Norregaard T (2003) Adverse effects of subthalamic nucleus DBS in a patient with multiple system atrophy. Neurology 61: 247–249
64. Tasker RR, Doorly T, Yamashiro K (1988) Thalamotomy in generalized dystonia. Adv Neurol 50: 615–631
65. The Deep-Brain Stimulation for Parkinson's Disease Study Group (2001) Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 345: 956–963
66. Trottenberg T, Paul G, Meissner W, Maier-Hauff K, Taschner C, Kupsch A (2001) Pallidal and thalamic neurostimulation in severe tardive dystonia. J Neurol Neurosurg Psychiatry 70: 557–559
67. Vercueil L, Pollak P, Fraix V, Caputo E, Moro E, Benazzouz A, Xie J, Koudsie A, Benabid AL (2001) Deep brain stimulation in the treatment of severe dystonia. J Neurol 248: 695–700

68. Vercueil L, Krack P, Pollak P (2002) Results of deep brain stimulation for dystonia: a critical reappraisal. Mov Disord [Suppl 3] 17: S89–S93
69. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, Lagrange C, Tezenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P (2005) Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 352: 459–467
70. Vingerhoets FJ, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J (2002) Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology 58: 396–401
71. Vitek JL, Chockkan V, Zhang JY, Kaneoke Y, Evatt M, DeLong MR, Triche S, Mewes K, Hashimoto T, Bakay RA (1999) Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 46: 22–35
72. Vitek JL, Bakay RA, Freeman A, Evatt M, Green J, McDonald W, Haber M, Barnhart H, Wahlay N, Triche S, Mewes K, Chockkan V, Zhang JY, DeLong MR (2003) Randomized trial of pallidotomy versus medical therapy for Parkinson's disease. Ann Neurol 53: 558–569
73. Volkmann J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V (2001) Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 56: 548–551
74. Volkmann J, Allert N, Voges J, Sturm V, Schnitzler A, Freund HJ (2004) Long-term results of bilateral pallidal stimulation in Parkinson's disease. Ann Neurol 55: 871–875
75. Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, Arnulf I, Pidoux B, Dormont D, Cornu P, Agid Y (2002) Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 125: 575–583
76. Wester K, Hauglie-Hanssen E (1990) Stereotaxic thalamotomy – experiences from the levodopa era. J Neurol Neurosurg Psychiatry 53: 427–430
77. Winkler C, Kirik D, Bjorklund A (2005) Cell transplantation in Parkinson's disease: how can we make it work? Trends Neurosci 28: 86–92
78. Yianni J, Bain P, Giladi N, Auca M, Gregory R, Joint C, Nandi D, Stein J, Scott R, Aziz T (2003) Globus pallidus internus deep brain stimulation for dystonic conditions: a prospective audit. Mov Disord 18: 436–442
79. Yoshor D, Hamilton WJ, Ondo W, Jankovic J, Grossman RG (2001) Comparison of thalamotomy and pallidotomy for the treatment of dystonia. Neurosurg 48: 818–824

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Deep brain stimulation and chemical neuromodulation: current use and perspectives for the future

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Summary

During the last decade there has been a marked increase in the applications of deep brain stimulation for the treatment of neurological and psychiatric disorders. In addition, the last years were marked by the first studies using the intraparenchymal administration of drugs into the brain. There have been improvements in outcome and an increase in the number of surgical candidates and conditions to be treated. This will act as a driving force to improve the technology applied to design and manufacture new devices.

Keywords: Deep brain stimulation; movement disorders; pain; epilepsy; Tourette's syndrome; obsessive-compulsive disorder; depression; vagus nerve stimulation.

Introduction

In the last decade deep brain stimulation (DBS) has become established as an accepted and important therapy in the field of Functional Neurosurgery. The knowledge gained with the application of DBS for movement disorders and pain has already been leveraged towards the treatment of other disorders, including epilepsy and psychiatric conditions. In addition to stimulation, the last years were marked by the first trials using the intraparenchymal administration of drugs, namely glial cell line-derived neurotrophic factor (GDNF) for the treatment of Parkinson's disease (PD) [22].

In the years to come, we expect to see a considerable expansion of the indications for DBS and the establishment of new techniques of chemical neuromodulation. This review will focus on the areas of current and future engagement and investigation in these rapidly growing fields.

Deep brain stimulation

Movement disorders

The treatment of movement disorders has been revolutionized by the therapy of deep brain stimulation (DBS). The ability to reversibly and adjustably inhibit selected targets has enabled bilateral treatment and obviated the need for tissue destruction. It has thus seen a far increased application in disease treatment.

Parkinson's disease

Most centers to date are currently favoring the use of subthalamic nucleus (STN) DBS over other targets for the treatment of Parkinson's disease (PD) [23]. Studies using double blind assessment have demonstrated that bilateral STN stimulation provides lasting improvements in tremor, rigidity, the involuntary movements induced by levodopa, and to a lesser extent bradykinesia, gait and postural instability [34].

To be considered a good candidate for STN DBS, patients have to be diagnosed with PD, present disabling motor fluctuations, a prolonged ''off'' state, significant dyskinesias, and a good clinical response to levodopa [14, 27, 58, 66, 68, 83]. The last item is particularly important as the response to levodopa seems to predict clinical outcome [12]. The main exclusion criteria for STN DBS in most centers are the presence of significant cognitive and psychiatric symptoms, medical problems that might pose a risk for the patient during the procedure (i.e. coagulopathies), a poor response to levodopa, and old age (more than 70 years) [14, 27, 58, 66, 68, 78, 83].

To overcome some of these problems, the use of different surgical targets has been advocated. Motor cortex stimulation (MCS) is being examined as an alternative for patients at high risk for DBS [10]. Even though results with this technique are still preliminary, the clinical benefit does not seem to match that achieved with STN DBS. Anecdotal reports have shown that stimulation of the pedunculopontine nucleus (PPN) can be safely performed in surgical candidates [49]. As PPN DBS ameliorates akinesia in non-human parkinsonian primates [30] and is involved in mechanisms of gait [56], results from this preliminary trial are much awaited. Despite of these few innovative approaches, it is worth mentioning that most non-dopaminergic parkinsonian symptoms, including speech problems, cognitive and psychological difficulties, bladder, bowel and sexual dysfunction, among others, as they are resistant to both levodopa and surgery and still pose a major disability to patients with advanced PD. This should be taken into account in the development of future alternative therapies to treat patients with PD.

Another major challenge in the future will be to devise therapies that not only treat the symptomatology of PD but that are also capable of arresting the progression of the illness. While it has been hypothesized that early surgical interventions could reduce nigral degeneration due to a decrease in glutamatergic release by the STN [61], this has not been clearly demonstrated so far. In the clinical scenario, one of the trials addressing this issue is using gene therapy with the premise that one could reduce STN glutamatergic overdrive by altering the phenotype of its cells into GABAergic neurons [16]. This phase I clinical trial has been designed mainly to assess the safety of the procedure and the escalation of doses of the viral injections [32]. Yet, as a similar approach was protective in animal models of PD [46], the outcome of this series of patients is highly awaited.

There has been much interest on the administration of GDNF to treat PD. In parkinsonian non-human primates and rodents, studies have shown that the intraventricular or intraparenchymal administration of GDNF was neuroprotective and able to induce regeneration of tyrosine hydroxylase-positive terminals in the substantia nigra and striatum [3, 69]. As a result, clinical trials have been set and initially attempted the intraventricular administration of the drug with no significant improvement [52]. It has been hypothesized that the relative size of the human brain made the transependymal diffusion of GDNF insufficient to create the necessary concentrations of the drug to produce an effect. Clinical trials were then designed to deliver GDNF directly into the brain parenchyma. Gill *et al.* demonstrated a 39% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores at 1 year and no significant adverse effects with the intraputaminal administration of the drug [22]. In addition, they observed a significant increase in striatal dopamine levels as assessed by positron emission tomography (PET) [22]. These promising results were the basis for a phase II multicenter study with a randomized blinded crossover design. Unfortunately, this study showed no significant differences in UPDRS motor scores between patients that received GDNF or placebo at 6 months (Amgen press release June 28, 2004). The reasons for the discrepancies between the open label and the blinded trials are still unclear but may be due to the dose of medication injected, the tip diameter of the catheters, issues related to the delivery/diffusion of the GDNF, or a placebo effect in the open label study. Animal studies with other neurotrophins are under way but new clinical studies using these agents are likely not to occur so soon.

Dystonia and tremor disorders

Bilateral globus pallidus internus (GPi) stimulation has become an important therapeutic alternative for the treatment of dystonia [7, 15, 35, 38, 45, 77]. The clinical response to surgery seems to be dependent on etiology, with primary generalized and cervical dystonia responding better than secondary dystonia [18, 37, 44, 76]. In addition, patients with the DYT1 mutation seem to be good candidates for pallidal DBS, with reports demonstrating a 50–80% decrease in Burke-Fahn-Marsden severity scores (BFMDS) 12 months after the procedure [13, 15, 18, 35]. Improvement in patients with non-DYT1 primary generalized dystonia is on the order of 40–60% [15, 18, 35, 36]. Patients with secondary dystonia have an overall reduction of 10–35% in BFM scores after GPi DBS [18, 35].

The improvement in cervical dystonia as assessed by the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is in the order of 60–80% [19, 35, 37]. It has been noted by several authors that the time course of response for pain is quicker than for motor symptoms and disability. Long-term follow-up studies are still needed to assess whether the improvements observed with surgery are long lasting.

In addition to the GPi, stimulation of the subthalamic nucleus is currently being explored for the treatment of generalized dystonias with anedoctal reports showing promising results [67].

Beyond the treatment of PD and dystonia, DBS is finding increased application to other movement disorders. As DBS can be performed bilaterally, it has been favored over lesions for the treatment of essential tremor [55, 57, 59]. In addition, thalamic DBS has also been used to treat patients with tremor due to multiple sclerosis and other disorders [6, 29].

Pain

Treatment of chronic pain syndromes has employed an impressive array of electrical stimulation procedures. These include stimulation of peripheral nerves, spinal cord, deep brain targets (including the thalamus and peri-aquiductal grey), and the motor cortex [8, 9, 17, 25, 39–43, 50, 51, 70, 82]. Hypothalamic and occipital nerve stimulation have been proposed for the treatment of cluster and other forms of headache [20, 47].

Despite of the vast utilization of many of these treatments and the extensive publication of case series, there remains a good deal of disagreement and controversy in the field. Two of the main reasons for this are the heterogeneous nature of the disorders treated, and the lack of randomized placebo-controlled clinical trials comparing the various stimulation techniques with the best medical treatment options available, or comparing one surgical option to another. Given the extensive imaging and physiologic data now available, the idea in the future is to increase the number of such studies and assess predictors of outcome, to choose of the most appropriate targets for each condition.

Epilepsy

Epilepsy is a natural candidate among the neurological disorders that may lend themselves to electrical stimulation therapy. The possibility of recognizing aberrant firing activity and arresting it through the delivery of electrical current is an old one. Cardiac implantable defibrillators essentially operate on the same principles and have been very successful. A recent trial employing this ''closed loop'' system in epilepsy is currently under way with the premise that epileptiform events detected in the hippocampus or cortex could be used to trigger the delivery of current, in order to block or decrease seizure activity [65].

The most established neuromodulation therapy for epilepsy is vagal nerve stimulation (VNS). This has been an accepted treatment for intractable seizures for more than a decade, with trials indicating a mean decline in the frequency of seizures on the order of 25–30% [5, 24]. In addition to VNS, deep brain stimulation for the treatment of epilepsy has shown a good outcome when electrodes are implanted in the centromedian thalamic nucleus [72, 73], the anterior thalamic nucleus [28, 33], the subthalamus [4, 11] and hippocampus [74, 75, 80, 81]. However, most of these procedures have yet to be carried over to controlled trials.

Psychiatric disorders

The success of neural stimulation in other arenas has generated great expectations of its potential use in psychiatric disease. The reversibility of deep brain stimulation has instilled a new wave of optimism in both the psychiatric and neurosurgical communities. Three diseases have thus far been subjected to DBS trials: Tourette's syndrome (TS), obsessive-compulsive disorder (OCD), and depression.

Tourette's syndrome can be considered a disease that lies on the interface between movement and psychiatric disorders. The first study using DBS for TS targeted the medial thalamus [71], a region in which ablative procedures have been previously successful [26]. Results with DBS in the medial thalamus have shown a tic reduction in the order of 72–90% [79].

Most studies using DBS to treat patients with OCD have targeted the anterior capsule. Overall, it seems that 1/2–2/3 of the patients have an adequate response to surgery (more than 35–40% reduction in Yale-Brown Obsessive Compulsive Scale – YBOCS scores) [1, 53, 54]. One of the difficulties during the programming of stimulators in the anterior capsule seems to be the high amount of current needed to control the patients' symptoms, which translates into a high number of battery changes [54]. This raises a question regarding the specificity of the target. In fact, recent reports have stated that rather than stimulating the whole capsule, stimulation in the transition of the capsular white matter and the nucleus accumbens [60] or in the region of the ventral caudate [2] seem to lead to a similar outcome with a smaller energy expenditure.

So far, the targets used to treat refractory depression with DBS are the subgenual cingulate region (Brodmann area 25 – BA 25) [48] and the inferior thalamic peduncle [31]. Surgical candidates are patients with severely disabling depression who failed various treatment options, including medications, psychotherapy, and often electroconvulsive therapy. The study by Mayberg *et al.* using the BA25 as a target was very elegant, as it comprised a

hypothesis-driven investigation. Preliminary imaging reports from the same author have shown that BA25 is metabolically overactive in treatment-resistant depression [48]. DBS was then used to reduce this elevated activity. Four out of the 6 patients treated with BA25 stimulation had a striking and sustained remission in their depression scores [48]. In addition, antidepressant effects were associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites, measured with positron emission tomography. The study by Jimenez *et al.* targeting the inferior thalamic peduncle comprised a single case but the results were certainly encouraging and demand further investigation [31].

In addition to DBS, VNS has also been proposed as a treatment for major depression [21, 62–64]. Rush *et al.* have recently published the results of a multicenter trial in which patients treated with VNS were initially randomized to receive either active stimulation or no stimulation for 8 weeks [63]. After this phase, both VNS and sham treated patients received active therapy until they completed 1 year of stimulation [64]. At short term, no significant differences were seen in Hamilton Rating Scale for Depression (HRSD24) scores, the primary outcome measurement of the study [63]. Yet, VNS was well tolerated and improved Inventory of Depressive Symptomatology – Self-Report (IDS-SR30) scores, one of the secondary measurements of outcome in that study [63]. The conclusion of that report was that there was not enough evidence of short-term efficacy for adjuvant VNS in the treatment of resistant depression [63]. After 12 months of stimulation, the patients' HRSD24 scores were significantly improved compared to baseline (rate of improvement of 0.45 points per month in average) [64]. At the end of the trial, 27.2% of the participants were considered to be responders (a reduction $\leq$50% in HRSD24 scores compared to baseline), and 15.8% were considered to be in remission (defined as HRSD24 scores $\leq$9) [64].

The future of stimulation systems

As is currently practiced, stimulation of the nervous system requires intensive resources. The interactions between the drugs and the adjustments in stimulation parameters require several visits to determine not only the optimal contact and settings but also the correct drug dosage. It will be necessary to develop ways of reducing the time required for the programming. In this respect, the development of electrophysiological or imaging indicators will be useful in arriving at the optimal combination of parameter settings and drugs in a shorter time. In addition, new developments in the ability to program pulse generators through remote access, telephone lines or the Internet will likely become useful.

Another area of advance relates to the power source for stimulation. In disorders that require high-energy delivery, the necessity to replace batteries is a major concern. This could be partially solved with the development of rechargeable batteries. Of similar interest is the possibility of miniaturizing pulse generators and DBS systems, so they will be able to fit within the confines of a burr hole or be as thin as a flat panel overlaid on the skull. Adding recharging capability would reduce the requirement for large batteries. As a better understanding of the mechanisms of action develops, it will be possible to optimize stimulation parameters and perhaps reduce the size of DBS systems and the necessity for having such powerful batteries. In addition, newer designs in the electrode arrays may also optimize the therapeutic efficacy and minimize the adverse effect associated with deep brain stimulation.

Most of the considerations described above for stimulation devices and generators are also valid for drug delivery systems (i.e. pumps). Yet, two additional comments deserve attention. First the mechanisms of drug diffusion for the compounds to be used and the design of specific catheters have to be taken into account. As previously mentioned, this was one of the factors that might have contributed to the differences between the pilot and phase II studies with GDNF for PD. Second, safety studies need to be conducted on drugs with a potential modulatory role in neural circuits (i.e. GABAergic agonists) so they may start being employed in clinical practice.

Conclusions

During the last years there has been an escalation in the applications of neural stimulation for the treatment of several neurological disorders. With a better understanding of the pathogenesis of neurological disorders and the mechanisms of action of stimulation and drug delivery techniques, we will likely be able to improve the outcomes and increase the indications for these procedures. The number of patients with movement disorders, pain, epilepsy, and psychiatric disorders that may benefit from surgery is enormous. This will act as a driving force to increase the efforts to improve the technology applied to design and manufacture new devices.

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References

1. Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, Martis B, Giordani B (2005) Deep brain stimulation for refractory obsessive-compulsive disorder. Biol Psychiatry 57: 510–516
2. Aouizerate B, Cuny E, Martin-Guehl C, Guehl D, Amieva H, Benazzouz A, Fabrigoule C, Allard M, Rougier A, Bioulac B, Tignol J, Burbaud P (2004) Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. Case report. J Neurosurg 101: 682–686
3. Beck KD, Valverde J, Alexi T, Poulsen K, Moffat B, Vandlen RA, Rosenthal A, Hefti F (1995) Mesencephalic dopaminergic neurons protected by GDNF from axotomy-induced degeneration in the adult brain. Nature 373: 339–341
4. Benabid AL, Koudsie A, Benazzouz A, Vercueil L, Fraix V, Chabardes S, Lebas JF, Pollak P (2001) Deep brain stimulation of the corpus luysi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. J Neurol 248: III37–47
5. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, Tarver WB, Wernicke JF (1994) Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia 35: 616–626
6. Berk C, Carr J, Sinden M, Martzke J, Honey CR (2002) Thalamic deep brain stimulation for the treatment of tremor due to multiple sclerosis: a prospective study of tremor and quality of life. J Neurosurg 97: 815–820
7. Bittar RG, Yianni J, Wang S, Liu X, Nandi D, Joint C, Scott R, Bain PG, Gregory R, Stein J, Aziz TZ (2005) Deep brain stimulation for generalised dystonia and spasmodic torticollis. J Clin Neurosci 12: 12–16
8. Burchiel KJ, Anderson VC, Brown FD, Fessler RG, Friedman WA, Pelofsky S, Weiner RL, Oakley J, Shatin D (1996) Prospective, multicenter study of spinal cord stimulation for relief of chronic back and extremity pain. Spine 21: 2786–2794
9. Canavero S, Bonicalzi V (1995) Cortical stimulation for central pain. J Neurosurg 83: 1117
10. Canavero S, Paolotti R, Bonicalzi V, Castellano G, Greco-Crasto S, Rizzo L, Davini O, Zenga F, Ragazzi P (2002) Extradural motor cortex stimulation for advanced Parkinson disease. Report of two cases. J Neurosurg 97: 1208–1211
11. Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 4 Suppl 3: S83–S93
12. Charles PD, Van Blercom N, Krack P, Lee SL, Xie J, Besson G, Benabid AL, Pollak P (2002) Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 59: 932–934
13. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B (2000) Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 355: 2220–2221
14. Daniele A, Albanese A, Contarino MF, Zinzi P, Barbier A, Gasparini F, Romito LM, Bentivoglio AR, Scerrati M (2003) Cognitive and behavioural effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 74: 175–182
15. Detante O, Vercueil L, Thobois S, Broussolle E, Costes N, Lavenne F, Chabardes S, Lebars D, Vidailhet M, Benabid AL, Pollak P (2004) Globus pallidus internus stimulation in primary generalized dystonia: a H215O PET study. Brain 127: 1899–1908
16. During MJ, Kaplitt MG, Stern MB, Eidelberg D (2001) Subthalamic GAD gene transfer in Parkinson disease patients who are candidates for deep brain stimulation. Hum Gene Ther 12: 1589–1591
17. Eliasson T, Augustinsson LE, Mannheimer C (1996) Spinal cord stimulation in severe angina pectoris – presentation of current studies, indications and clinical experience. Pain 65: 169–179
18. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM (2004) Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. Neurosurgery 54: 613–619; discussion 619–621
19. Eltahawy HA, Saint-Cyr J, Poon YY, Moro E, Lang AE, Lozano AM (2004) Pallidal deep brain stimulation in cervical dystonia: clinical outcome in four cases. Can J Neurol Sci 31: 328–332
20. Franzini A, Ferroli P, Leone M, Broggi G (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52: 1095–1099; discussion 1099–1101
21. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, Howland R, Kling MA, Moreno F, Rittberg B, Dunner D, Schwartz T, Carpenter L, Burke M, Ninan P, Goodnick P (2005) A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 58: 364–373
22. Gill SS, Patel NK, Hotton GR, O'Sullivan K, McCarter R, Bunnage M, Brooks DJ, Svendsen CN, Heywood P (2003) Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat Med 9: 589–595
23. Hamani C, Richter E, Schwalb JM, Lozano AM (2005) Bilateral subthalamic nucleus stimulation for Parkinson's disease: a systematic review of the clinical literature. Neurosurgery 56: 1313–1321; discussion 1321–1324
24. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51: 48–55
25. Hassenbusch SJ, Stanton-Hicks M, Schoppa D, Walsh JG, Covington EC (1996) Long-term results of peripheral nerve stimulation for reflex sympathetic dystrophy. J Neurosurg 84: 415–423
26. Hassler R, Dieckmann G (1970) Stereotaxic treatment of tics and inarticulate cries or coprolalia considered as motor obsessional phenomena in Gilles de la Tourette's disease. Rev Neurol (Paris) 123: 89–100
27. Herzog J, Volkmann J, Krack P, Kopper F, Potter M, Lorenz D, Steinbach M, Klebe S, Hamel W, Schrader B, Weinert D, Muller D, Mehdorn HM, Deuschl G (2003) Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. Mov Disord 18: 1332–1337
28. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
29. Hooper J, Taylor R, Pentland B, Whittle IR (2002) A prospective study of thalamic deep brain stimulation for the treatment of movement disorders in multiple sclerosis. Br J Neurosurg 16: 102–109
30. Jenkinson N, Nandi D, Miall RC, Stein JF, Aziz TZ (2004) Pedunculopontine nucleus stimulation improves akinesia in a Parkinsonian monkey. Neuroreport 15: 2621–2624
31. Jimenez F, Velasco F, Salin-Pascual R, Hernandez JA, Velasco M, Criales JL, Nicolini H (2005) A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. Neurosurgery 57: 585–593; discussion 585–593

32. Kaplitt MG (2005) Gene therapy for neurological disorders. 14th World Federation of Stereotactic and Functional Neurosurgery Meeting
33. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45: 346–354
34. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 349: 1925–1934
35. Krause M, Fogel W, Kloss M, Rasche D, Volkmann J, Tronnier V (2004) Pallidal stimulation for dystonia. Neurosurgery 55: 1361–1368; discussion 1368–1370
36. Krauss JK (2002) Deep brain stimulation for dystonia in adults. Overview and developments. Stereotact Funct Neurosurg 78: 168–182
37. Krauss JK, Loher TJ, Pohle T, Weber S, Taub E, Barlocher CB, Burgunder JM (2002) Pallidal deep brain stimulation in patients with cervical dystonia and severe cervical dyskinesias with cervical myelopathy. J Neurol Neurosurg Psychiatry 72: 249–256
38. Krauss JK, Yianni J, Loher TJ, Aziz TZ (2004) Deep brain stimulation for dystonia. J Clin Neurophysiol 21: 18–30
39. Kumar K, Nath R, Wyant GM (1991) Treatment of chronic pain by epidural spinal cord stimulation: a 10-year experience. J Neurosurg 75: 402–407
40. Kumar K, Toth C, Nath RK (1997) Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery 40: 736–746; discussion 746–747
41. Kumar K, Wyant GM, Nath R (1990) Deep brain stimulation for control of intractable pain in humans, present and future: a ten-year follow-up. Neurosurgery 26: 774–781; discussion 781–782
42. Law JD, Swett J, Kirsch WM (1980) Retrospective analysis of 22 patients with chronic pain treated by peripheral nerve stimulation. J Neurosurg 52: 482–485
43. Levy RM, Lamb S, Adams JE (1987) Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. Neurosurgery 21: 885–893
44. Loher TJ, Hasdemir MG, Burgunder JM, Krauss JK (2000) Long-term follow-up study of chronic globus pallidus internus stimulation for posttraumatic hemidystonia. J Neurosurg 92: 457–460
45. Lozano AM, Abosch A (2004) Pallidal stimulation for dystonia. Adv Neurol 94: 301–308
46. Luo J, Kaplitt MG, Fitzsimons HL, Zuzga DS, Liu Y, Oshinsky ML, During MJ (2002) Subthalamic GAD gene therapy in a Parkinson's disease rat model. Science 298: 425–429
47. Matharu MS, Bartsch T, Ward N, Frackowiak RS, Weiner R, Goadsby PJ (2003) Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. Brain
48. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. Neuron 45: 651–660
49. Mazzone P (2005) DBS for movement disorders: where are we going? 14th World Federation of Stereotactic and Functional Neurosurgery Meeting
50. Nashold BS (1980) Peripheral nerve stimulation for pain. J Neurosurg 53: 132–133
51. Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y (eds) (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
52. Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws ER Jr, Lozano AM, Penn RD, Simpson RK Jr, Stacy M, Wooten GF (2003) Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. Neurology 60: 69–73
53. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B (1999) Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet 354: 1526
54. Nuttin BJ, Gabriels LA, Cosyns PR, Meyerson BA, Andreewitch S, Sunaert SG, Maes AF, Dupont PJ, Gybels JM, Gielen F, Demeulemeester HG (2003) Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 52: 1263–1272; discussion 1272–1274
55. Ondo W, Almaguer M, Jankovic J, Simpson RK (2001) Thalamic deep brain stimulation: comparison between unilateral and bilateral placement. Arch Neurol 58: 218–222
56. Pahapill PA, Lozano AM (2000) The pedunculopontine nucleus and Parkinson's disease. Brain 123 (Pt 9): 1767–1783
57. Pahwa R, Lyons KL, Wilkinson SB, Carpenter MA, Troster AI, Searl JP, Overman J, Pickering S, Koller WC (1999) Bilateral thalamic stimulation for the treatment of essential tremor. Neurology 53: 1447–1450
58. Pahwa R, Wilkinson SB, Overman J, Lyons KE (2003) Bilateral subthalamic stimulation in patients with Parkinson disease: long-term follow up. J Neurosurg 99: 71–77
59. Rehncrona S, Johnels B, Widner H, Tornqvist AL, Hariz M, Sydow O (2003) Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. Mov Disord 18: 163–170
60. Rezai A (2005) DBS for psychiatric disorders. 14th World Federation of Stereotactic and Functional Neurosurgery Meeting
61. Rodriguez MC, Obeso JA, Olanow CW (1998) Subthalamic nucleus-mediated excitotoxicity in Parkinson's disease: a target for neuroprotection. Ann Neurol 44: S175–S188
62. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, Nahas Z, Haines S, Simpson RK Jr, Goodman R (2000) Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry 47: 276–286
63. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, Rapaport MH, Zajecka J, Nierenberg AA, Husain MM, Ginsberg D, Cooke RG (2005) Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 58: 347–354
64. Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, Lavori P, Howland R, Kling MA, Rittberg B, Carpenter L, Ninan P, Moreno F, Schwartz T, Conway C, Burke M, Barry JJ (2005) Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry 58: 355–363
65. Simth JR, Murro AM, Politsky J, Park YD, Fountas KN, Jenkins PD, Greene D (2004) Closed loop stimulation in the control of focal epilepsy. ASSFN Biennial Meeting. Cleveland, OH
66. Simuni T, Jaggi JL, Mulholland H, Hurtig HI, Colcher A, Siderowf AD, Ravina B, Skolnick BE, Goldstein R, Stern MB, Baltuch GH (2002) Bilateral stimulation of the subthalamic nucleus in patients with Parkinson disease: a study of efficacy and safety. J Neurosurg 96: 666–672
67. Sun B (2005) Subthalamic nucleus stimulation for primary dystonia and tardive dyskinesia. 14th World Federation of Stereotactic and Functional Neurosurgery Meeting
68. Thobois S, Mertens P, Guenot M, Hermier M, Mollion H, Bouvard M, Chazot G, Broussolle E, Sindou M (2002) Subthalamic nucleus stimulation in Parkinson's disease: clinical evaluation of 18 patients. J Neurol 249: 529–534

69. Tomac A, Lindqvist E, Lin LF, Ogren SO, Young D, Hoffer BJ, Olson L (1995) Protection and repair of the nigrostriatal dopaminergic system by GDNF in vivo. Nature 373: 335–339
70. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1991) Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl 52: 137–139
71. Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J (1999) Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. Lancet 353: 724
72. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28: 421–430
73. Velasco F, Velasco M, Velasco AL, Jimenez F (1993) Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity. Epilepsia 34: 1052–1064
74. Velasco M, Velasco F, Velasco AL (2001) Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. J Clin Neurophysiol 18: 495–513
75. Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, Marquez I (2000) Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41: 158–169
76. Vercueil L, Pollak P, Fraix V, Caputo E, Moro E, Benazzouz A, Xie J, Koudsie A, Benabid AL (2001) Deep brain stimulation in the treatment of severe dystonia. J Neurol 248: 695–700
77. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, Lagrange C, Tezenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P (2005) Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 352: 459–467
78. Vingerhoets FJ, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J (2002) Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology 58: 396–401
79. Visser-Vandewalle V, Temel Y, van der Linden C, Ackermans L, Beuls E (2004) Deep brain stimulation in movement disorders. The applications reconsidered. Acta Neurol Belg 104: 33–36
80. Vonck K, Boon P, Achten E, De Reuck J, Caemaert J (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 52: 556–565
81. Vonck K, Boon P, Goossens L, Dedeurwaerdere S, Claeys P, Gossiaux F, Van Hese P, De Smedt T, Raedt R, Achten E, Deblaere K, Thieleman A, Vandemaele P, Thiery E, Vingerhoets G, Miatton M, Caemaert J, Van Roost D, Baert E, Michielsen G, Dewaele F, Van Laere K, Thadani V, Robertson D, Williamson P (2003) Neurostimulation for refractory epilepsy. Acta Neurol Belg 103: 213–217
82. Weiner RL (2003) Peripheral nerve neurostimulation. Neurosurg Clin N Am 14: 401–408
83. Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, Arnulf I, Pidoux B, Dormont D, Cornu P, Agid Y (2002) Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 125: 575–583

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GDNF delivery for Parkinson's disease

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Summary

The mainstays of Parkinson's disease (PD) treatment remain symptomatic, including initial dopamine replacement and subsequent deep brain stimulation, however, neither of these approaches is neuroprotective. Neurotrophic factors – proteins that activate cell signalling pathways regulating neuronal survival, differentiation, growth and regeneration – represent an alternative for treating dopaminergic neurons in PD but are difficult to administer clinically because they do not pass through the blood–brain barrier. Glial cell line-derived neurotrophic factor (GDNF) has potent neurotrophic effects particularly but not exclusively on dopaminergic neurons; in animal models of PD, it has consistently demonstrated both neuroprotective and neuroregenerative effects when provided continuously, either by means of a viral vector or through continuous infusion either into the cerebral ventricles (ICV) or directly into the denervated putamen. This led to a human PD study in which GDNF was administered by monthly bolus intracerebroventricular injections, however, no clinical benefit resulted, probably because of the limited penetration to the target brain areas, and instead significant side effects occurred. In an open-label study of continuous intraputamenal GDNF infusion in five patients (one unilaterally and four bilaterally), we reported excellent tolerance, few side effects and clinical benefit evident within three months of the commencement of treatment. The clinical improvement was sustained and progressive, and by 24-months patients demonstrated a 57 and 63% improvement in their off-medication motor and activities of daily living UPDRS subscores, respectively, with clear benefit in dyskinesias. The benefit was associated with a significant increase in putamenal ^{18}F-dopa uptake on positron emission tomography (PET), and in one patient coming to autopsy after 43 months of unilateral infusion there was evident increased tyrosine hydroxylase immunopositive nerve fibres in the infused putamen. A second open trial in 10 patients using unilateral intraputamenal GDNF infusions has also demonstrated a greater than 30% bilateral benefit in both on- and off-medication scores at 24 weeks. Based on our 6-month results, a randomized controlled clinical trial was conducted to confirm the open-label results, however, GDNF infusion over 6-months did not confer the predetermined level of clinical benefit to patients with PD despite increased ^{18}F-dopa uptake surrounding the catheter tip. It is possible that technical differences between this trial and the positive open label studies contributed to this negative outcome.

Keywords: Neuromodulation; drug delivery; PD; convection-enhanced delivery; GDNF.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterised by impairment of motor and cognitive functions due to the progressive death of selected populations of neurons, predominantly dopaminergic neurons within the pars compacta of the substantia nigra. PD is the second most common progressive neurodegenerative disorder and occurs at a rate of approximately 1 in 1000 people over the age of 55 in North America with more than 1 million affected individuals currently affected [87], and an estimated overall prevalence in Europe of 1.6 per 100 in the population 65 years of age and older [38]. There is no gender preference. Mortality among affected individuals is 2–5 times greater than for their age-matched unaffected peers [18, 97, 109], and life expectancy is markedly reduced [109].

Although symptomatic therapies are efficacious in the early stages of the disease, the goal would be to identify neuroprotective therapies, i.e. find factors that could arrest or slow down the degenerative process. While there are multiple causes of neurodegenerative diseases including environmental, genetic and age-associated factors, the treatments may be directed at similar underlying mechanisms via neuroprotective or reparative interventions. In a theoretical framework, one working model of neuronal damage and the prevention of cell death is the concept of ''neuronal resilience''. Depending on the status of the cell with respect to pretraumatic events and gene-expression relevant to neuronal preservation, the neuron will exist far from or close to the threshold for irreversible neuronal damage. The neuron can thus be thought of as oscillating between protected and vulnerable conditions. This model of neuronal homeostasis suggests that a number of separate thera-

peutic measures, including delivery of neurotrophic factors, may be required to reduce the overall probability of degeneration in those neuronal populations that approach their specific threshold for degeneration [68].

Neurotrophic factors as candidates for cell protection

Neurotrophic factors are naturally occurring proteins that have an impact on cell survival and proliferation, differentiation, biochemical function and morphological plasticity [6]. They not only promote the differentiation and growth of developing neurons and phenotypic maintenance and survival of adult mature neurons but also represent a potential means of modifying neuronal dysfunction, astrocytic activation and inflammatory reactions under pathological conditions. A large body of evidence suggests that some neurotrophic factors under certain conditions also modulate neuronal plasticity during aging and under traumatic or degenerative conditions [21]. Previously, it was thought that different neuronal populations were each responsive to only a single neurotrophic factor. However, evidence indicates that there is overlap and redundancy, whereby a single neurotrophic factor may affect more than one cell type, and a specific cell type may respond to several neurotrophic factors [83]. Classically, a neurotrophic factor is produced and secreted by target cells, be they nerve cells or other cells, and then taken up by the innervating nerve terminals to exert local effects and, via retrograde axonal transport, trophic effects on the nerve cell body [119, 122]. However, the actions of neurotrophic factors are associated not only with retrograde transport from the target tissue but also autocrine and paracrine mechanisms [77, 106].

Neurotrophic factors are expressed in different regions of the nervous system during different phases of development [100, 131]. It has been proposed that growing axons compete for limited amounts of neurotrophic factors, which are produced by target tissues [53, 156]. Neurons which fail to obtain a sufficient quantity of the necessary neurotrophic factors die by a process called programmed cell-death [35, 138]. Further, in adulthood, neurotrophic factors are required to maintain neuronal functions and specific neuronal phenotype [21]; however, it is unclear to what degree the mature neurons remain dependent upon target-derived support. The site-specific neurotrophic factor expression in the adult brain suggests various mechanisms of action in relation to the observed selective neuronal trophism. In response to injury, trophic factors and their receptors increase in concentration, suggesting an endogenous regenerative response of these molecules [64], and insufficiency of such trophic support due to decreased neurotrophic factor supply or impaired target cell response may account for some of the cell death in neurodegenerative diseases [10, 60]. Recent evidence suggests that alterations in the neurotrophic levels either due to age, genetic background or other factors might contribute to neurodegeneration. It has been proposed that the loss of endogenous target-derived trophic support for selective neuronal populations may lead to the neuronal degeneration characteristic of Alzheimer's, Parkinson's and other neurodegenerative diseases but direct support for this hypothesis is currently lacking [35].

Neurotrophic factors serve the function of neuroprotectant molecules against cytotoxic cell damage. They can act as antiexcitotoxins and antioxidants and, as such, they have the capacity to enhance mitochondrial function. They have been shown to upregulate calcium buffering proteins, antioxidant enzymes and antiapoptotic factors [104]. Taken together with the widespread expression of the receptors for neurotrophic factors and the pleiotropic effects on different neuronal and glial cell types, these lines of evidence make it necessary to target trophic molecules to either a specific subpopulation of neurons or to the injury site itself and its immediate vicinity in order to provide neuronal protection, administered either prior to or following a neurotoxic insult. Based on their specificities, neurotrophic factors have become attractive drug candidates for the treatment of neurodegenerative diseases that affect specific populations of neurons. Since the discovery of nerve growth factor (NGF) in the 1950s [33, 54] the prospect of applying neurotrophic factors to the treatment of neurological disorders has motivated investigators and excited clinicians. Over the past 2 decades in particular, great advances have been made in discovering new factors, characterizing and cloning them, and demonstrating their therapeutic potential in animal models of neurological disease [9]. There are currently more than 20 trophic factors that have been identified, showing potential for use in a variety of neurodegenerative diseases, including PD [34, 139].

Neurotrophic factors and Parkinson's disease

The slower progressive nature of dopaminergic neuronal loss in PD coupled to the relatively long run-in period for the condition (approximately 5 years; [44,

101, 110]) makes this disorder an attractive candidate for neurotrophic factor ''rescue''. In other words, the delivery of a neurotrophic factor at the time of clinical presentation could arrest and even reverse the parkinsonian symptoms and by doing so cure the patient. Of course, this assumes that solely rescuing the dopaminergic neurons in the nigrostriatal pathway will achieve a cure, even though there is pathology outside this system. Nevertheless, as a starting point, rescuing the dopaminergic neurons and their striatal projections is useful, and in this respect several factors have been shown to produce significant beneficial effects on dopamine (DA) neurons in culture and in animal models [34]. Those producing effects on dopaminergic neurons in vitro include, but are not limited to, brain derived neurotrophic factor (BDNF) [65, 66]; neurotrophin-3 (NT-3) [66]; NT-4/5 [66]; insulin-like growth factor -1 (IGF-1) [76]; both α-fibroblastic growth factor (αFGF) and βFGF [37, 41]; epidermal growth factor (EGF) [27]; GDNF [42, 93]; ciliary neurotrophic factor (CNTF); platelet derived neurotrophic factor (PDGF) and transforming growth factor-α (TGF-α) [34, 84, 139]. All these factors have been shown to support survival of embryonic dopaminergic neurons with varying degrees of potency and specificity.

In MPTP- and 6-OHDA-lesioned animal models of Parkinson's disease, BDNF [47] and GDNF [48, 140] have been shown to promote the survival of mesencephalic dopaminergic neurons. In the initial rodent studies, low doses of BDNF failed to attenuate nigral dopamine loss following medial forebrain bundle transection [89]. However, later studies with higher doses showed ameliorative effects. Supranigral implants of fibroblasts engineered to secrete human BDNF are shown to protect dopaminergic neurons from MPTP toxicity [47]. Studies on BDNF and NT-3 in a 6-OHDA striatal perfusion neurodegeneration model show evidence of increased dopamine metabolism and turnover as determined by homovanillic acid (HVA) and dopamine ratios, and improvement in amphetamine-induced rotation despite no obvious effect on neuron survival or sprouting [7]. The transplantation of BDNF-transduced astrocytes into the striatum of 6-OHDA lesioned animals did not enhance dopamine neuron survival, although it significantly reduced amphetamine-induced rotation indicating behavioral recovery in one study [155]. Studies with the MPTP-primate model have shown potent and long-lasting effects on the substantia nigra, preservation of dopaminergic neurons and a significant amelioration of behavioral symptoms after the administration of GDNF [50].

Where there are comparative data, GDNF has been found to be among the most potent and specific neurotrophic factors for the nigrostriatal pathway [24], and has consistently been shown to dramatically protect and enhance the function of dopamine neurons in animal models [49, 55]. GDNF is as potent as CNTF and NT-4 and five to ten times more potent than BDNF in promoting survival of all axotomized nigrostriatal neurons in lesioned rats [99]. Not only is GDNF found in the substantia nigra [39, 74] and the striatum [74, 116], but there is some evidence that PD patients may have reduced levels of GDNF in the substantia nigra [28]. This suggests that loss of GDNF may contribute to the process of degeneration of dopamine cells in the substantia nigra, making it a front-runner for therapeutic trials for PD.

Neurotrophic factor delivery

The major difficulties encountered in the use of neurotrophic factors for the treatment of neurodegenerative diseases are the impossibility for these molecules to cross the blood–brain-barrier, their instability in a fluid environment, and their side-effects associated with systemic administration and from binding to extra-target receptors with intracerebroventricular (ICV) infusion or injection [1, 3, 57, 128]. Local administration is therefore required to achieve therapeutic concentrations in the tissue. The efficiency of local distribution, and hence effectiveness of local therapy, depends on the rate of protein migration through tissue. Intranasal administration offers a method for bypassing the blood–brain barrier and contributes to better central nervous system penetration of neurotrophic factors [139]. However, the nasal route does not allow for the focal delivery of these potent molecules and high doses of trophic factors may be necessary to elicit therapeutic effects. Within the extracellular space of the brain, fluids move either by diffusion or by bulk flow (convection). Diffusive flux results from a concentration gradient and depends heavily on molecular weight. Unfortunately, the effective and toxic concentrations of many compounds are not sufficiently different to permit extensive distribution based on diffusion alone. In contrast to diffusion, bulk flow results from a pressure gradient; its flux is largely independent of MW and solutions are distributed in relatively homogeneous concentrations.

Different strategies for delivery of GDNF in animal models of PD have been explored: ICV infusion [61]; intraparenchymal injection [129]; continuous intraparen-

chymal infusion [4]; the grafting of genetically engineered cells [115]; in vivo gene transfer [79]; fibrin glue preparation [30]; and the use of biodegradable microspheres [72] and non-biodegradable polymeric devices [141].

Matrix-based, injection, and cellular delivery systems provide protein to the brain via dramatically different mechanisms: diffusion from a polymer or protein matrix, flow through a synthetic channel, and secretion after synthesis by cellular machinery. These approaches are similar in at least one important regard: after release from the matrix, cannula, or cell, protein molecules move to their cellular sites of action by migrating through the interstitial space of tissue. With some notable exceptions (high-flow infusion where migration relies on convection [111]), diffusion is the principal mechanism of protein distribution through brain tissue. Diffusion through the tissue interstitium is a slow process [32]; substantial metabolism or clearance can occur during the period of migration. As a result, the volume of tissue exposed to protein can be relatively small. Penetrability of a neurotrophic factor administered by interstitial drug delivery is dependant on the rate of dispersion versus elimination. If diffusion is the primary mechanism for dispersion, the extent of dispersion is dependant on the concentration gradient between the point of delivery and the surrounding brain, infusate diffusivity and molecular weight of the protein. Elimination is dependant on the stability of the protein within the interstitial space; for proteins eliminated by receptor-mediated internalization and degradation elimination is dependant on the number of receptors and the affinity to the receptor. Thus, despite the effectiveness of techniques relying on diffusion in preclinical studies their application may potentially be limited in the clinic.

To date, in response to the preclinical studies, attempts to apply neurotrophic factors clinically have so far been disappointing because of their poor efficacy and induction of troublesome side effects. In these clinical trials, the recombinant protein was delivered into the cerebrospinal fluid (intraventricularly or intrathecally) in patients suffering from amyotrophic lateral sclerosis (ALS), peripheral neuropathy, PD or Alzheimer disease (AD) [3, 147]. Results from these studies indicate that the neurotrophic factors, whose receptors are widely distributed, are prone to inducing pronounced side effects when delivered by these routes. Excruciating pain was indeed described with the ICV administration of NGF in AD patients [43, 120]; weight loss, nausea and abnormal sexual behaviour was reported with the ICV administration of GDNF in PD patients [82]. The poor penetration across the blood–brain barrier, as well as the limited passage of proteins from the cerebrospinal fluid into the brain tissue, has made it necessary to administer the factors at doses that are likely to induce side effects. These effects may not be so evident in small-sized experimental animals. For this reason, they may have gone unnoticed in the preclinical studies and may have become apparent in some cases only at the phase II/III stage of the clinical trails when larger numbers of patients were included. The therapeutic value of neurotrophic-factor delivery, therefore, may not be possible to achieve unless the factors are specifically targeted and regionally restricted to the area of interest within the central nervous system to achieve significant results without widespread, unwanted adverse effects. Animal experiments have shown that direct parenchymal administration dramatically reduces the occurrence of side-effects reported with ICV application [8, 112].

In order to achieve homogenous distributions of these high MW proteins to a region of interest within the CNS, in vivo gene therapy and convection-enhanced delivery (from high-flow continuous infusion) techniques are required. Previous studies have demonstrated that convection-enhanced delivery to the brain can be used to distribute small- or large-MW infusate in a homogenous, targeted and safe manner with a clinically effective volume of distribution that is linearly proportional to the volume of infusion [22, 92, 111, 114]. Studies have shown that convective distribution is significantly affected by volume of infusion, rate of infusion, cannula size and target location (gray as opposed to white matter) [22, 29, 92, 111]. By understanding these parameters that influence convective-delivery within the CNS, delivery of these potentially therapeutic agents can be optimised in the clinical setting.

Glial cell line-derived neurotrophic factor

GDNF was first isolated from the conditioned medium of cultured rat glial cells from the B49 cell line [93] as a potent neurotrophic factor described as having relative specificity for dopaminergic neurons within dissociated rat embryonic midbrain cultures [85, 91, 93, 94]. GDNF and related factors, neuturin, artemin and persephin, constitute a family of neurotrophic factors distantly related to the transforming growth factor-β (TGF-β) superfamily [5, 13]. Although there is only limited amino acid-sequence homology between GDNF and prototypic members of the TGF-β family, they do share marked conformational similarity [40].

After intracellular processing, GDNF is secreted as a glycosylated mature protein of 134 amino-acid residues. In its active form, GDNF is a disulphide-bonded homodimer of MW 32–42 kDa [93, 94]. The first 37 N-terminal amino acids constitute a high-affinity, heparin-binding domain that may limit diffusion of the molecule in vivo through its interactions with extracellular matrix heparin sulphate proteoglycans, thereby allowing local concentrations to increase. GDNF undergoes N-terminal cleavage both in vitro, in mammalian cell cultures, and in vivo, in rhesus monkeys, but the truncated form, des37-GDNF, retains full biologic activity in promoting dopaminergic neuronal survival despite lacking the heparin-binding domain. Monoclonal antibody inhibition data also indicate that the N-terminal region of GDNF is not critical for activity [153]. The human GDNF gene has been cloned, and recombinant human GDNF displaying full biological activity has been expressed in *E. coli* [93].

GDNF signals through a unique multicomponent receptor complex comprising the specific GFRα1 receptor, which is anchored to lipid rafts within the plasma membrane by glycosylphosphatidylinositol, and the transmembrane Ret receptor that incorporates an intracellular tyrosine kinase domain [5, 136]. The process involves the binding of GDNF to GFRα1 and subsequent recruitment of Ret to the lipid raft, thereby triggering its association with Src, which is required for downstream signalling. The binding of GDNF-GFRα1 to the extracellular domain of Ret leads to activation of the intracellular tyrosine kinase domain and the subsequent activation of intracellular signalling pathways that lead to neuronal differentiation and survival [137].

GDNF-GFRα1 has also been shown capable of signalling in a Ret-independent manner via direct activation of an Src-like kinase in an immortalized neuronal precursor cell line not expressing Ret [146], although the physiologic significance of this alternative mechanism remains to be clarified [5].

Analyses of tissue distribution of GDNF mRNA have provided insight into the potential roles of this neurotrophic factor and indicate that GDNF acts as a target-derived neurotrophic factor for both dopaminergic and motor neurons. GDNF mRNA was expressed in the striatum and skeletal muscle, the target fields for dopaminergic substantia nigra neurons and motor neurons, respectively. In situ hybridization and reverse transcription polymerase chain reaction studies have demonstrated GDNF mRNA expression in many regions of the developing and adult brain, as well as in peripheral tissues (e.g. kidney, gut), indicating that GDNF may have multiple actions [31, 126, 144]. Indeed, GDNF has potent survival promoting actions on other CNS and PNS neurons, including sensory and autonomic ganglia [25, 145, 157], Purkinje cells of the cerebellum [113], locus coeruleus neurons [12], thalamic and hippocampal neurons [103], as well as neurons in the cingulate cortex and olfactory bulb [144], with effects on noradrenergic, serotoninergic, and cholinergic cell populations [12, 15, 89, 93, 102, 151, 152]. Analysis of GDNFR-α mRNA demonstrated its presence from embryonic day 15 and distribution in the adult rat ventral midbrain, spinal cord, subpopulations of the dorsal root ganglia, developing kidneys (nephrons), and smooth and striated muscle associated with the enteric nervous system. It was also found in the retina, thalamus, pons, medulla oblongata, pituitary gland, urogenital tract and pancreatic primordium [142]. Similarly, elevated c-*ret* mRNA expression was observed in the adult rat spinal cord, pons, medulla, hypothalamus, thalamus and cerebellum. Levels of c-*ret* mRNA increased progressively during the postnatal development in the ventral midbrain containing the SN, with a peak of expression between postnatal day 6 and 8, the period during which axons of DA neurons of the SN make functional contact with the striatum [143]. Jing *et al.* [71] showed that GDNFR-α was expressed by cultured rat spinal cord motoneurons and that addition of GDNF to these cultures led to autophosphorylation of Ret. Similarly, Trupp *et al.* [143] reported that GDNF bound to Ret induced Ret autophosphorylation in a GDNF-responsive motoneuron cell line derived from embryonic mouse spinal cord motoneurons. High levels of Ret were reported in adult rat spinal cord, pons, medulla, hypothalamus, thalamus and cerebellum, but Ret was barely detectable in the striatum, hippocampus and cortex. Interestingly, a progressive increase in Ret level was observed postnatally in rat ventral mesencephalon, and a high level of Ret was detected in the adult rat SN suggesting dopaminergic neuronal soma expression of Ret.

Knockout mice lacking GDNF [108, 125, 130], GFRαl [26], or Ret [132] die shortly after birth and share a phenotype of kidney agenesis and an absence of many parasympathetic and enteric neurons. The similar phenotypes of ligand and receptor knockouts indicate a specific pairing of GDNF with GFRal and Ret in vivo. In all 3 knockouts, there is a significant loss of spinal and cranial motor neurons and a corresponding increase in dying cells [5]. In contrast, motor neuron survival is promoted by the muscle specific overexpression of

GDNF or by GDNF treatment in utero [123]. This finding may have therapeutic relevance: In a transgenic ALS model, virus mediated intramuscular GDNF expression led to enhanced motor neuron survival, resulting in delayed disease onset and increased survival of the mice [2, 150]. GDNF promotes survival of a subgroup of developing sensory neurons [25], which show reduced soma size in knockout mice lacking GDNF or GFRαl [14]. GDNF has potent and selective effects on a subset of dorsal root ganglia cells involved in nociception [19], and it has been reported as a therapeutic treatment in rat models of neuropathic pain states [23]. Finally, analysis of adult GDNF hemizygous mice has shown another function of GDNF outside the brain: GDNF regulates spermatogonal differentiation, and low GDNF levels lead to disturbed spermatogenesis [105]. The ability of GDNF to stimulate nigrostriatal function in intact and lesioned animals may, at least in part, reflect a direct action of GDNF on the function of dopaminergic neurons. These effects, as observed in in vitro studies, include increases in the spontaneous firing rate and the quantal size of terminal dopamine release [127], as well as an increased excitability of the dopaminergic neurons that is mediated by A-type K^+ channels and high voltage-activated Ca^{2+} channels [150]. Furthermore, in addition to its in vitro effects on neuronal survival, results from multiple studies on the effects of r-metHuGDNF in chemically lesioned rodents and rhesus monkeys, reveal both neuroprotective and neurorestorative properties, supporting the scientific rationale for its therapeutic use as a neurotrophic factor in the treatment of PD, and ALS [16, 48, 140, 154, 157].

Ventricular delivery of recombinant GDNF in human Parkinson's disease

Based on the promising studies of the effects of GDNF in animal models of PD, an initial clinical trial testing GDNF by ventricular delivery using an indwelling reservoir was carried out in 50 parkinsonian patients for 8 months in a randomized, double-blind placebo-controlled trial [117]. While the doses of GDNF (25–4000 μg/month) were in excess of those employed for nonhuman primate studies, little therapeutic efficacy was observed in these parkinsonian patients and in fact was associated with multiple side effects including nausea, vomiting, anorexia, weight loss, paraesthesias and hyponatraemia. Furthermore, a postmortem report on one 65-year-old patient, with a 23-year history of PD, that had received monthly injections of GDNF with no symptomatic improvement had no apparent DA regeneration or GDNF diffusion from the ventricle into appropriate brain regions at postmortem [82]. The problem may have been with the site and method of delivery;

Table 1. *Patient data and overall effects of GDNF*

	P1	P2	P3	P4	P5
Patient data					
– Age	62	46	56	56	51
– Duration of PD	6	13	30	27	19
– Unilateral/bilateral pump (U/B)	U	B	B	B	B
– L-DOPA equivalents at 0 months	667	615	2154	680	762
– Change in L-DOPA at 1 year	+10%	+6%	−51%	+10%	−44%
Side effects					
– Hypersalivation			*		*
– Taste abnormalities	*		*	*	*
– Lhermittes	*	*	*	*	*
– Headaches				*	*
– Vivid dreams	*	*			
– MRI changes	*	*	*	*	*
– Nausea/vomiting					
– Weight loss					
– Pump-related discomfort					*
Procedural adverse events					
– Repositioning of catheter	*				
– Pump infection				*	
Other clinical effects					
– Recovery taste/smell	*			*	*
– Revival sexual function			*	*	*
– Improved bladder function					*
– Reduction in tinnitus					*

i.e. monthly injections of the trophic factor into the lateral ventricle. Sufficient titres of GDNF may not have diffused through the ventricular wall and brain parenchyma to the targeted DA neurons in the SN and their afferent projections to the putamen.

Chronic intraputamenal GDNF delivery using programmable pumps

In our phase I safety study, five advanced PD patients (Table 1) with a previous history of good responses to L-dopa underwent stereotactic unilateral (P1) or bilateral insertion (P2–5) of in-house drug infusion catheters (Figs. 1 and 2) into the postero-dorsal putamen (Fig. 3). Infusion into the postero-dorsal putamen (i.e. its sensorimotor component) was chosen because in PD this is the most severely dopamine depleted region. We anticipated that if clinical benefits were shown, this would be due to local dopamine terminal sprouting in the putamen along with retrograde transport of GDNF down the surviving nigro-striatal axons, as previously reported in primate models (Fig. 4) [56]. Human recombinant GDNF was chronically infused *via* indwelling SynchroMed™ pumps implanted in the abdominal region (Fig. 5).

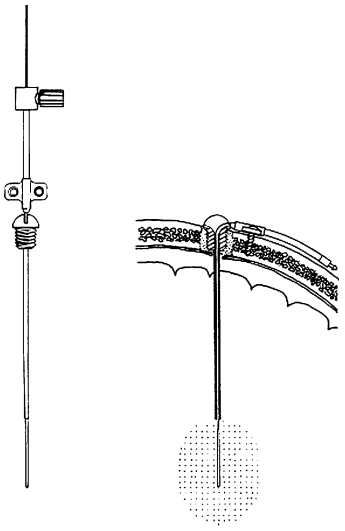

Fig. 2. Intraparenchymal catheter inserted to target down through a guide tube implanted to a point above the target. Guide tube hub secured in skull burr-hole with acrylic cement. Intraparenchymal catheter secured to skull with screws and connected to pump catheter

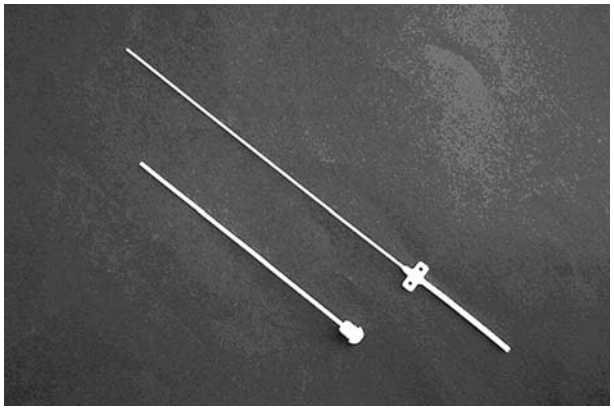

Fig. 1. Guide tube and intraparenchymal catheter (in-house investigational device)

After implantation, the SynchroMed pumps were primed with recombinant-methionyl human GDNF (r-metHuGDNF) (Amgen Inc., Thousand Oaks, California)

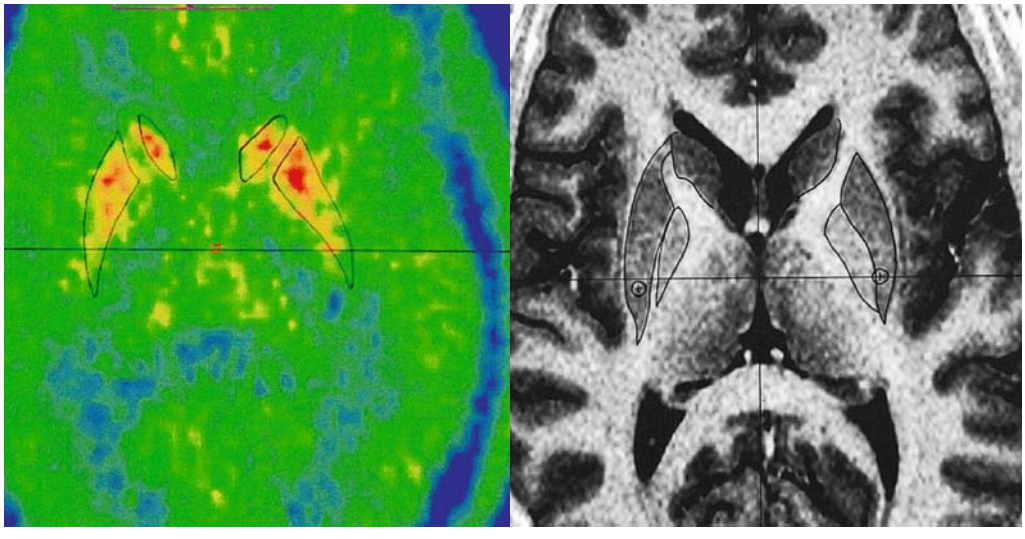

Fig. 3. Stereotactic MRI-directed targeting of postero-dorsal putamen for catheter implantation. Baseline ^{18}F-dopa PET scan used for co-localization within the posterior putamen dopamine deficient areas

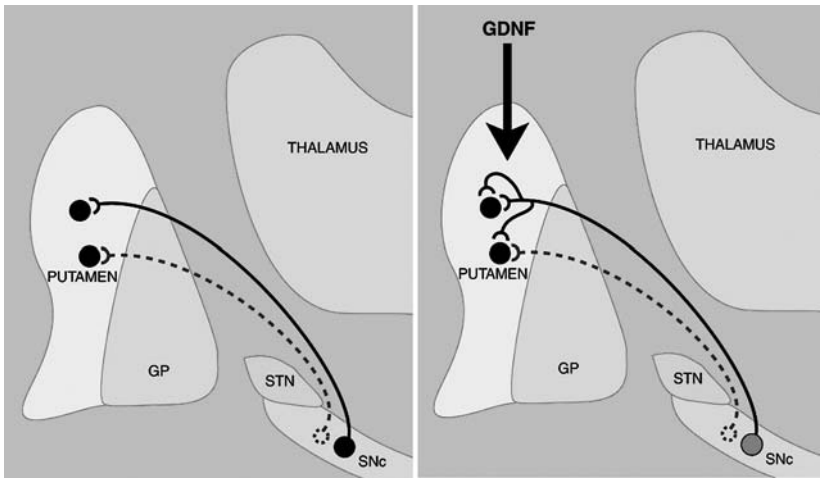

Fig. 4. Hypothesis: GDNF infusion into the postero-dorsal (sensorimotor) putamen is retrogradely transported to the substantia nigra down surviving dopaminergic neurons leading to up-regulation, neuroprotection and neurorestoration through neurite branching

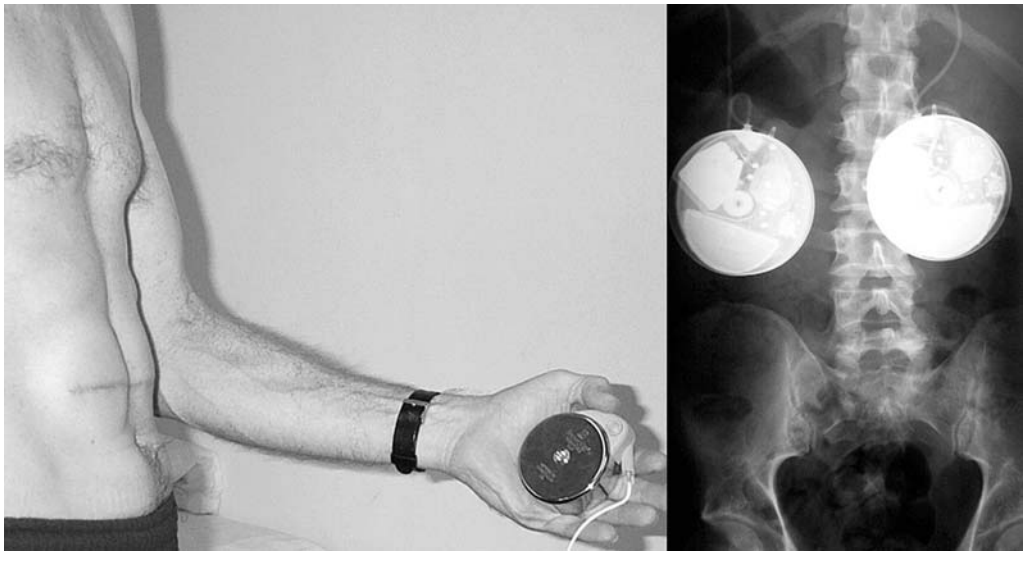

Fig. 5. Intraparenchymal catheters connected to SynchroMed pumps implanted in the abdominal wall for GDNF infusion

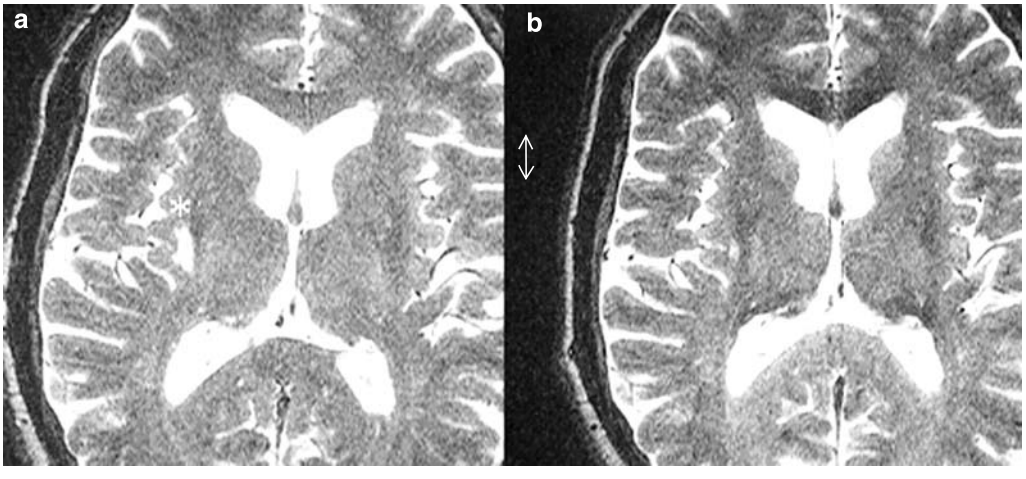

Fig. 6. Peri-catheter high-signal changes at high – 43.2 μg/putamen/day (a), and after reduction to the low dose – 14.4 μg/putamen/day (b) in P1 (* with unilateral administration)

and programmed to deliver a continuous infusion of 14.4 µg of r-metHuGDNF per putamen per day at rate of 6 µl per hour. The pumps were refilled monthly with fresh solution. The low concentration of r-metHuGDNF was maintained for a period of 8 weeks. At 2 months the pumps were refilled with fresh solution of higher concentration and programmed to deliver 43.2 µg of r-metHuGDNF per putamen per day at a rate of 6 µl per hour. Providing good tolerance and no side effects, this dose was to be maintained for the duration of the trial (12 months). However, due to the development of local reversible high-signal MRI changes of uncertain significance (Fig. 6), the infusion parameters were altered to deliver lower doses (10.8–14.4 µg of r-metHuGDNF) at lower rates (2–6 µl per hour), in attempt to establish safe and clinically effective parameters, with repeat MRI monitoring at regular intervals up to 12 months. Between 12 and 18 months, all patients received a continuous

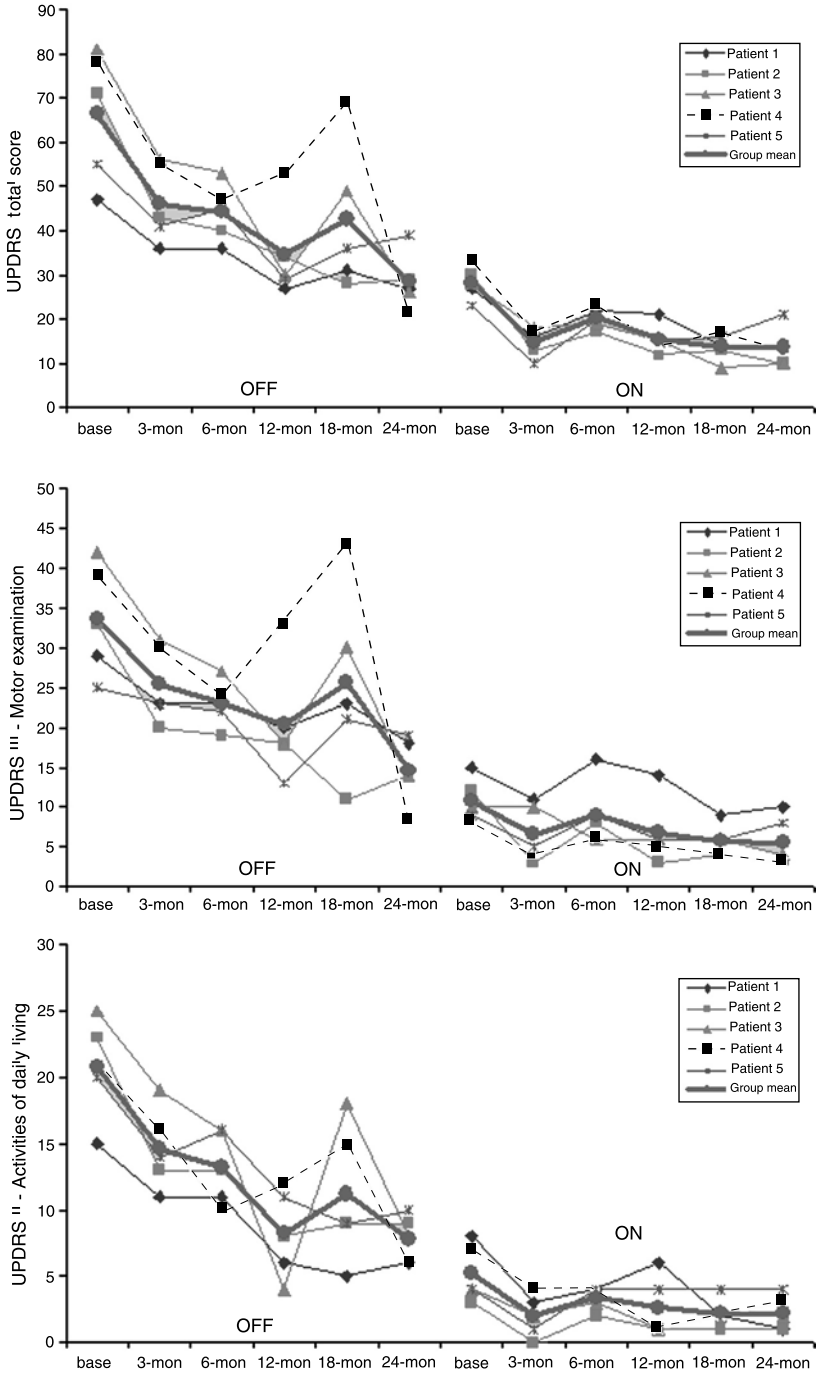

Fig. 7. UPDRS total scores (Fig. 7a), activities of daily living subscores (UPDRS II – Fig. 7b), and motor subscores (UPDRS III – Fig. 7c) for patients at baseline, 3, 6, 12, 18 and 24 months of GDNF infusion in both off and on medication states

infusion of 14.4 µg of r-metHuGDNF per putamen per day at rate of 6 µl per hour. At 18 months the dose of GDNF was increased to 28.8 µg per putamen per day at rate of 6 µl per hour, and remained so until 24 months except in P4 who reverted back to 14.4 µg at 20 months.

In this predominantly safety trial, drug-infusion was tolerated well and side effects were limited (Table 1) and included consistently Lhermitte's phenomenon, which occurred in all patients and remained mild, non-distressing, and intermittent. Other side effects, which were inconsistent and intermittent, included non-specific headaches, vivid dreams, taste and smell abnormalities, apthous ulceration and hypersalivation. There was no nausea, anorexia, vomiting, weight loss or hyponatraemia reported as in the previous intraventricular trial [82, 117]. In all patients, T2 MR images showed a region of high-signal intensity around the tips of the catheters with drug infusion. This response varied between patients, and even between the two hemispheres in bilaterally implanted cases. The signal change was most evident following the dose escalation of GDNF. The explanation for this signal change remains unclear as documented previously [51], however, with consistency and stability of findings, we are inclined to believe that these areas of high signal represent areas of drug delivery (Fig. 6).

Chronic GDNF infusion resulted in improved motor function in all patients, reduction in ''off''-time duration and severity, reduction in dyskinesias duration and severity, and a corresponding increase in good ''on''-time duration. After 24 months, there was a 57% improvement in the off-medication motor sub-score of the Unified Parkinson's Disease Rating Scale (UPDRS) and 63% improvement in the activities of daily living (ADL) sub-score (Fig. 7) [124]. In all patients, the rate of symptomatic improvement was maximal in the first 3 months of GDNF infusion and, thereafter, there was slower but sustained improvement up to 24 months. Medication induced dyskinesias were reduced by about 70%. This was accompanied by a 23% increase in whole putamen ^{18}F-dopa uptake ($p<0.05$) at 24-months; with uptake in the anterior half of the putamen increased by 6.8% ($p>0.05$), in the posterior half increased by 60% ($p<0.01$), and maximally (83%) in a region immediately surrounding the cannula tip [63] (Figs. 8 and 9 show changes evident at 6- and 12-months). Health-related quality of life (QOL) measures (PDQ-39 and SF-36)

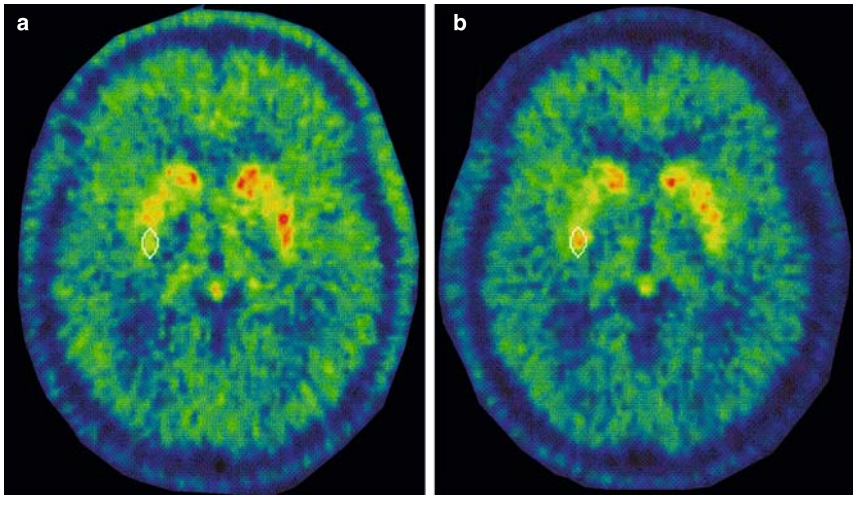

Fig. 8. GDNF increases ^{18}F-dopa influx. (a) PET image of P1 before GDNF infusion. (b) Same patient 12 months after unilateral GDNF infusion to the putamen. Circle represents region of interest around the catheter tip used in the analysis

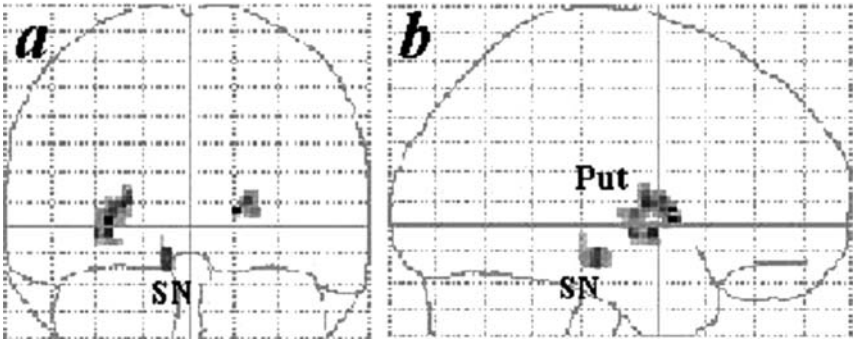

Fig. 9. Statistical Parametric Maps demonstrating the spatial distribution of regions of increases in ^{18}F-dopa uptake in the total patient group following 6 months of GDNF delivery (darker boxes indicate siginificantly increased regions: $P<0.05$, uncorrected at cluster level). (a) Coronal section and (b) sagittal section. *Put* putamen; *SN* substantia nigra

showed general improvement over time, with the overall scores tending towards levels expected in a control population. Neuropsychological assessment results indicated no significant detrimental effects of GDNF infusion on cognition. Three patients had long-standing loss of sensation of smell and taste, as is often the case in PD. These symptoms greatly improved or resolved completely between 3 and 6 weeks of GDNF infusion (Table 1).

We concluded that GDNF delivered by intraparenchymal infusion is safe, causes significant symptomatic improvement, and represents a potential neuroprotective and restorative therapy for PD. The early changes in sense of smell and motor function suggest an initial pharmacological action of GDNF within the putamen, likely, in part, to involve a direct stimulatory effect on dopamine release as shown in rodent models [62]. The reduction in dyskinesia duration and severity was not related to levodopa equivalent medication reduction in these patients, suggesting that GDNF might regulate dopamine production, release and metabolism in the striatum, thus improving the processing of motor output; and this may explain why our patients experienced better quality of life when on medication, and as seen in primates [107]. This exciting initial trial has been followed up in the United States, at the University of Kentucky, with an FDA-approved phase-I safety trial on the use of unilateral chronically administered GDNF in ten patients with advanced PD; and an FDA-approved phase-II multicenter randomized placebo-controlled trial sponsored by Amgen Inc. using bilateral chronic administration in patients with advanced PD.

University of Kentucky chronic unilateral intraputamenal GDNF phase-I safety trial

The phase-I University of Kentucky study reported safety and improvement in bilateral motor functions in 10 patients with advanced PD through the unilateral intraputaminal infusion of GDNF [133]. Each patient was placed on a dose-escalation regimen of GDNF: 3, 10, and 30 μg/day at successive 8-week intervals, followed by a 1-month wash-out period. The Unified Parkinson's Disease Rating Scale (UPDRS) total scores in the on and off states significantly improved by 34 and 33%, respectively, at 24 weeks compared with baseline scores (95% confidence interval [CI] 18–47% for off scores and 16–51% for on scores). In addition, UPDRS motor scores in both the on and off states significantly improved by 30% at 24 weeks compared with baseline scores (95% CI 15–48% for off scores and 5–61% for on scores). Improvements occurred bilaterally, as measured by balance and gait and increased speed of hand movements and all significant improvements of motor function continued through the wash-out period. The only observed side effects were transient Lhermitte symptoms in two patients.

Randomized controlled bilateral intraputamenal GDNF infusion study

The phase-II randomized controlled clinical trial sponsored by Amgen Inc. was designed to confirm initial clinical benefits observed in our Bristol phase-I study, however, concluded that GDNF did not confer the predetermined level of clinical benefit to patients despite an increased 18F-dopa [86]. In this study, thirty-four PD patients were randomized 1:1 to receive bilateral continuous intraputaminal infusion of GDNF 15 μg/putamen/day or placebo. The primary endpoint was the change in Unified Parkinson Disease Rating Scale (UPDRS) motor score in the practically-defined off condition at 6 months. Secondary endpoints included other UPDRS scores, motor tests, dyskinesia ratings, patient diaries, and ^{18}F-dopa uptake. At 6 months, mean % changes in ''off'' UPDRS motor score were −10.0 and −4.5% in the GDNF and placebo groups, respectively. This treatment difference was not significant (95% confidence interval: −23.0, 12.0, $p = 0.53$). Secondary endpoint results were similar between the groups. A 32.5% treatment difference favoring GDNF in mean ^{18}F-dopa influx constant ($p = 0.019$) was observed. GDNF infusion was well tolerated, with the most frequent adverse events, in comparison to the placebo group, included paraesthesias (65 vs. 18%), headache (29 vs. 6%) and upper respiratory tract infections (24 vs. 6%). Since the completion of the phase-II clinical trial, two safety issues arose. First, three patients from this study have developed neutralizing anti-GDNF antibodies, which could potentially cross-react with endogenous GDNF. The long-term potential implications of these findings remain unknown; however, all of these patients remain asymptomatic. One patient in the Bristol open study, who had also developed neutralizing antibodies at some unknown timepoint, had shown sustained improvement after 3 years of GDNF treatment. Secondly, an unusual segmental cerebellar injury, characterized by variable Purkinje and granule cell loss, was found in four of 15 monkeys in a 6-month toxicology study with 100 μg liatermin per day into one putamen. Due to these uncertain and

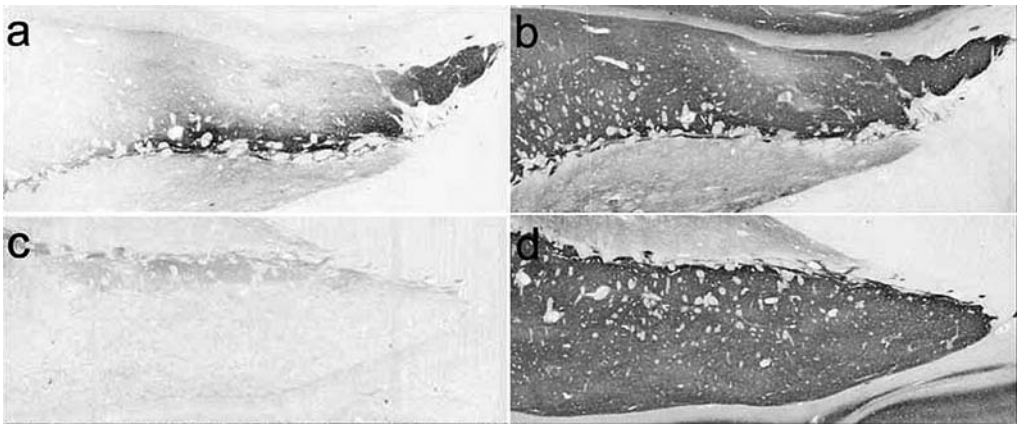

Fig. 10. Post-mortem immunohistochemical findings in axial sections through posterior part of right (a, b) and left (c, d) putamen viewed from above with posterior putamen to the right of the figure. Note the increased density of GFAP-immunopositive astrocytes around the end of the catheter track in the posterior third of the right (a) compared with the left (c) putamen. TH-immunopositive structures occupy a much greater part of the right (b) than the left (d) putamen

unquantifiable safety concerns Amgen has halted further clinical studies of GDNF.

GDNF infusion induces neuronal sprouting in the human brain

Three months following withdrawal of the drug by Amgen, patient 1 in the Bristol phase-I trial, having received 43-months of continous unilateral GDNF infusion, died of a myocardial infarct [98]. Post-mortem examination revealed severe coronary atheroma. Gross examination of the brain showed a fine catheter track passing through the right parasagittal frontal cortex and white matter into the posterior third of the right putamen. Dopaminergic fibres and neurons were identified with antibody to tyrosine hydroxylase (TH). There was a more-than-five-fold greater area occupied by TH-immunopositive structures in the posterior third of the right than the left putamen (area fraction 13.8 vs. 2.6%) (Fig. 10). The findings indicated for the first time that infusion of GDNF into the posterior putamen causes a marked local increase in TH-immunopositive nerve fibres. Labelling for the sprout-associated protein, growth associated protein 43 (GAP43) showed a one-third more sprouting of fibres in the posterior putamen on the side of infusion, and a probable increase in the substantia nigra, as suggested by the relatively strong expression of GAP43 on the side of infusion. These observations parallel those in experimental models of PD [36, 75, 121, 140]. It remains unclear how much of the increase in TH-immunopositive nerve fibres is due to axonal sprouting and how much to upregulation of TH in spared but dysfunctional fibres [75]. In either case, however, the findings provide a possible substrate for the sustained clinical improvement and enhanced ^{18}F-dopa uptake in human patients receiving intraputaminal infusion of GDNF [51, 124].

Discussion

The three clinical trials demonstrated that continuous intraputaminal delivery of GDNF is safe. Although caution must be exercised in interpreting results of the two open-label trials, the sustained improvements in all 15 patients are consistent with extensive preclinical data indicating the efficacy of GDNF in treating PD. The potential of GDNF as a therapeutic agent in PD, stems from its ability not only to provide symptomatic relief, but also to modify the disease state, distinct from other current therapeutic strategies for PD, such as deep brain stimulation and dopamine replacement therapy. Yet, it is possible that a combined approach using, for example, fetal dopamine cell grafts and GDNF may prove to be even more potent in reversing the parkinsonian symptoms in patients. Experimentally, GDNF is both neuroprotective and able to induce a prominent functional upregulation in intact and lesioned nigral dopamine neurons; and in some cases, it can also induce a pronounced regenerative response. The viral vector experiments, in particular, indicate that the most pronounced functional effects may result from a combined action involving all three mechanisms. The extent of these effects in our human pilot study remains to be fully elucidated. The early onset of symptomatic improvement, accompanied by an increase in ^{18}F-dopa uptake limited to the area immediately surrounding the cannula tip, seems compat-

ible with a functional upregulation in residual dopamine neurons. The progressive and sustained improvement in symptomology, and the increased ^{18}F-dopa uptake throughout the whole putamen at 24-months, and the post mortem findings confirm reduced progression of disease (neuroprotection) and a regenerative response beyond the functional upregulation. However, while the data from the open-label clinical trials in humans look encouraging, the results from the phase-II multicentre, randomised, placebo-controlled study did not confer the predetermined level of clinical benefit. The phase-II trial was designed to replicate the Bristol open-label study in 5 patients with PD. In open-label studies the expectations of patients can be profound and probably very different from those involved in a randomized placebo-controlled trial of symptomatic drug therapy, nevertheless the outcome of the placebo group in the phase-II study was not significantly different in comparison to baseline. Furthermore, placebo effects are known to occur in drug treatments for PD, but patients generally improve 30% at most and this is rarely sustained on repeated testing over 6 months [52]. Although the magnitude of a placebo response in this setting is difficult to quantify, it is important to note that our overall 57% reductions in ''off'' UPDRS scores are higher than might be expected from placebo, with these improvements being progressive and sustained up to 24 months.

Other potential explanations for the differences in outcome between the trials include differences in patient selection and treatment methodologies. The patients participating in the open trials, particularly the Bristol study had generally milder disease than those participating in the double blind study, and conversely some patients in the double blind study had severe burnt out disease. It remains possible that more mildly affected patients have a greater potential to respond to the influence of GDNF on sprouting of remaining nigrostriatal neurons.

Methodological differences between the open studies and the double blind study included drug dosage and method of delivery. Patients in the open studies eventually received higher doses than in the double-blind trial. Perhaps, a more important difference between the studies was in the method of drug delivery. The open label studies exploited GDNF delivery using a convection-enhanced method, rather than the method used in the phase II study, which depended primarily on diffusion to deliver the GDNF. Convection-enhanced delivery can increase the volume of distribution of the drug over that achievable by diffusion by up to 155-fold [92].

Convection-enhanced delivery exploits bulk flow in the extracellular space that results from a pressure gradient: its flux is largely independent of molecular weight and solutions are distributed in relatively homogenous concentrations. This is in contrast to diffusion that is dependent on establishing a concentration gradient. Catheter and fluid delivery parameters are important factors in the application of convection-enhanced delivery. Drug emerging from a single port in the distal end will tend to travel up the path of least resistance, i.e. up the catheter/tissue interface [29]. Because the flow up this space is proportional to the radius squared, small changes in catheter size, i.e. from the 0.6 mm diameter used in the Bristol study versus the 1.2 mm (1.0 mm plus radio-opaque markings on catheter = 1.2 mm) used in the phase II study, will reduce the resistance outside the catheter by 4-fold, therefore reducing the pressure gradient and bulk flow into the tissue substantially. If the 1.2 mm catheter also traumatises the tissue causing local necrosis, which is likely, then the resistance to flow outside it will be very low. In these circumstances and at the flow rate used in the phase II study a pressure gradient sufficient to drive the fluid into the tissues may never be achieved. The drug will then simply flows back along the catheter tissue interface to the cortex and enter the CSF space to produce wide-spread side-effects. Penetration into the tissues is now dependent upon diffusion down a concentration gradient, which due to the size of the GDNF molecule will be very limited. In this study, increasing the infusion rate beyond about 6 µl per hour, increased leak back and loss of infusate and infusate concentration had no effect on the volume of distribution. In contrast in the Kentucky study, despite the use of a 1.0 mm diameter catheter, GDNF was delivered using a continuous basal rate of 2 µl/hour with 6-hourly pulsed boluses of 21.3 µl to supplement the basal rate and to promote convection-enhanced delivery increasing the spread into the surrounding striatum. The 1.0 mm catheter used in the Kentucky study had a 5 mm tip length with 40-ports, in comparison to the phase-II study, where the catheter had a single terminal port. In a recent study, in nonhuman primates (Gash *et al.*, unpublished data) [133], GDNF had a mean distribution area of $31 \pm 8\,mm^2$ when delivered through a 1 mm diameter single-port catheter and $119 \pm 16\,mm^2$ via a multiport catheter–even by using the same pump delivery parameters, suggesting that catheter design with multiple terminal ports may be an important factor.

Although in the Kentucky study GDNF was administered contralaterally to the most affected side, motor

improvement occurred bilaterally, with results comparable to those for bilateral intraputaminal GDNF infusion. Although these bilateral effects indicate that GDNF administration may be at least temporarily successful in treating only one hemisphere of the brain, there is a strong theoretical argument together with some supporting evidence from fetal transplant studies for the treatment of both hemispheres [95, 96, 118]. Infusion of GDNF into both sides of the brain may be needed to provide optimal bilateral neuroprotection of the dopaminergic nerve terminals in the basal ganglia and cell bodies in the substantia nigra [51, 124].

Due to the progressive nature of PD, sustained or continuous delivery of trophic factors may be necessary for optimal, long-term neuronal effects. However, the post-mortem findings following 3-months of GDNF cessation in our study and the persistence of clinical effect after a 1-month washout in the Kentucky study are consistent with data from previous studies involving animal models of PD [54, 56, 59], although these persistent gains may be lower in magnitude compared with the maximal benefit observed during active GDNF infusion. Both human and preclinical studies to date are unable to fully determine the dose-response effect, and additional studies are needed to analyze variable dose and fluid delivery parameters against time effects of GDNF. It is clear from animal studies that functional upregulation in intact or lesioned nigral dopaminergic neurons can be obtained by ICV, intranigral or intrastriatal routes, although the ICV route effects do not translate to humans. Only intrastriatal GDNF is capable of protecting degenerating or damaged nigrostriatal axons and terminals and inducing any substantial regenerative growth response. However, it is effective in cases only when a significant portion of the nigrostiatal projection remains intact, and thus efficacy is diminished in animals with advanced parkinsonism. In advanced cases, as suggested by primate data, intranigral delivery, acting through increased transmission in downstream targets may provide symptomatic relief. Conversely, direct infusion into the substantia nigra (SN) in early disease may be protective to prevent disease progression. In PD patients, the optimal site of GDNF delivery may also depend on the site of the primary insult. Degeneration involving the lateral part of SNc (also called lateral area A9 of Dahlstrom and Fuxe), which projects to the posterior dorsal motor striatum and globus pallidus externus, is associated with rigidity and bradykinesia whereas degeneration involving the medial SNc (medial area A9), parts of area A8 and A10 which innervate the subthalamic nucleus/ zona incerta and globus pallidus internus has been reported to be associated with tremor predominant PD and ''on/off'' fluctuations [45, 46, 58, 69, 70, 78, 134], and may explain the limited effect on tremor in the tremor predominant PD cases. Therefore, whether the optimal choice involves GDNF acting on axon terminals in the striatum or the subthalamic region, or on cell bodies in the SN or a combination of targets remains to be elucidated.

With convection-enhanced striatal delivery, it is possible that more rostral portions of the putamen will continue to degenerate if the GDNF does not penetrate this far. By understanding the parameters that influence convective-delivery within the CNS, including volume and rate of infusion, delivery of GDNF can be optimised in the clinical setting. With the appropriate modifications, it could be realistic that GDNF migration could be predicted and appropriately customized to treat a pre-specified volume of tissue based on the extent of degeneration, or customised to the size of the appropriate target chosen on the basis of predominant symptomology. Future studies delivering the GDNF through multiple sites within the putamen may be necessary to optimise the therapeutic effect. Alternatively, penetration of GDNF may be increased using modified equally active forms of the drug with a lower molecular weight and with reduced affinity to the heparin-binding sites, increasing its transport through the interstitial spaces.

Convection-enhanced delivery of recombinant GDNF protein has potential problems, including complications associated with a chronically implanted infusion device. It would clearly be advantageous for PD patients to receive a single ''on–off'' injection of GDNF, through cell or viral vector delivery strategies [20, 80]. Nevertheless these alternate approaches do generate issues of safety, in that if problems arise, one cannot simply switch off the supply of a cell or virally delivered trophic factor. Clearly, more experiments in nonhuman primate models will be necessary to prove that these techniques lead to long-term GDNF expression, as well as proving that the procedure is completely safe. In this respect, the use of a regulatable promoter to provide a means of controlling expression of the transgene may prove necessary. Along these lines, inducible lentiviral vector systems containing the entire tetracycline-regulated system have been tested in vitro and in vivo in rats [73] and Kordower *et al.* are now investigating the tetracycline regulatable system [148] as a way of driving GDNF expression through oral administration of doxycycline [79]. A strategy implanting stem cells engineered to

deliver GDNF may be more advantageous in that the host brain is not genetically manipulated, preventing insertional mutagenesis and preserving the function of neurons in the host [11]. The neural stem cells can be fully characterised and the degree of differentiation of the cell and/or the levels of production of growth factor can be standardized. In addition, extra safety features such as the incorporation of a regulatable promoter to provide a means of controlling expression of the transgene may prove necessary as described above, or the incorporation of a ''suicide cassette'' in the cells would allow for the elimination of the cells, should it be necessary. Stem cells may not be immunologically compatible with most patients, and they could cause teratomas if tight control over differentiation and cell proliferation is not achieved, and may require the need to immunosuppress the hosts in order to prevent the rejection of grafts in certain transplantation conditions. In the future, it would be important to develop strategies to decrease the risk of graft rejection, by either identifying and matching antigens in host and donors, or by performing grafts of multipotent stem cells isolated from the same individual, including bone marrow stem cells. Our understanding of the rules and limits to integration of differentiated cells into neural circuits is also in its infancy. A complete understanding will be necessary if we are to realize fully the potential of stem cells. Nonetheless, the active interest and substantial recent progress in this area sustains the enthusiastic hope that this approach could eventually achieve the ultimate goal of repairing the damaged brain, and may prove to be a more safe and amenable strategy than the direct genetic manipulation of the host brain.

Safe and effective approaches for site-specific delivery of neurotrophic factors may be essential for realizing their potential in treating brain injuries and diseases. The open-label intraparenchymal studies make an important first step towards demonstrating both safety and efficacy of growth factors delivered directly into the brain parenchyma; and could not only help design better treatment for PD, but could also lay the foundation for further related studies in other neurodegenerative diseases such as AD, ALS and Huntington's disease where various neurotrophic factors have also been shown to have beneficial effects in animal models [17, 81, 135].

Conclusions

In summary, intraparenchymal neurotrophic factor infusion represents a new approach in treating neurodegenerative disease, with trophic actions having the potential of promoting protection, repair, and restoration of specific neurons and thus moderating disease progression. Preclinical studies and the open-label trials suggest that GDNF's effects in the treatment of Parkinson's disease are mediated through a combination of improved functioning of remaining normal dopaminergic neurons, reduction in disease progression and by stimulating inherent regenerative capabilities in injured dopaminergic neurons. Despite the failure of significant GDNF effect in the phase-II controlled study, possibly secondary to technical differences between this trial and the positive open label studies, the benefits seen in the open-label studies should compel further investigation into optimized methods of GDNF delivery in a larger population of patients with PD.

References

1. ALS CNTF Treatment Study Group (1996) A double-blind placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rHCNTF) in amyotrophic lateral sclerosis. Neurology 46: 1244–1249
2. Acsadi G, Anguelov RA, Yang H, Toth G, Thomas R, Jani A, Wang Y, Ianakova E, Mohammad S, Lewis RA, Shy ME (2002) Increased survival and function of SOD1 mice after glial cell-derived neurotrophic factor gene therapy. Hum Gene Ther 13: 1047–1059
3. Aebischer P, Ridet J (2001) Recombinant proteins for neurodegenerative diseases: the delivery issue. Trends Neurosci 24: 533–540
4. Ai Y, Markesbery W, Zhang Z, Grondin R, Elseberry D, Gerhardt GA, Gash DM (2003) Intraputamenal infusion of GDNF in aged rhesus monkeys: distribution and dopaminergic effects. J Comp Neurol 461: 250–261
5. Airaksinen MS, Saarma M (2002) The GDNF family: signalling, biological functions and therapeutic value. Nat Rev Neurosci 3: 383–394
6. Alexi T, Borlongan CV, Faull RL, Williams CE, Clark RG, Gluckman PD, Hughes PE (2000) Neuroprotective strategies for basal ganglia degeneration: Parkinson's and Huntington's diseases. Prog Neurobiol 60: 409–470
7. Altar CA, Boylan CB, Fritsche M, Jackson C, Hyman C, Lindsay RM (1994) The neurotrophins NT-4/5 and BDNF augment serotonin, dopamine, and GABAergic systems during behaviorally effective infusions to the substantia nigra. Exp Neurol 130: 31–40
8. Anderson KD, Alderson RF, Altar CA, DiStefano PS, Corcoran TL, Lindsay RM, Wiegand SJ (1995) Differential distribution of exogenous BDNF, NGF, and NT-3 in the brain corresponds to the relative abundance and distribution of high-affinity and low-affinity neurotrophin receptors. J Comp Neurol 357: 296–317
9. Apfel SC (2001) Neurotrophic factor therapy – prospects and problems. Clin Chem Lab Med 39: 351–355
10. Appel SH (1981) A unifying hypothesis for the cause of amyotrophic lateral sclerosis, parkinsonism, and Alzheimer disease. Ann Neurol 10: 499–505
11. Arenas E (2002) Stem cells in the treatment of Parkinson's disease. Brain Res Bull 57: 795–808
12. Arenas E, Trupp M, Akerud P, Ibanez CF (1995) GDNF prevents degeneration and promotes the phenotype of brain noradrenergic neurons in vivo. Neuron 15: 1465–1473

13. Baloh RH, Tansey MG, Johnson EM Jr, Milbrandt J (2000) Functional mapping of receptor specificity domains of glial cell line-derived neurotrophic factor (GDNF) family ligands and production of GFRalpha1 RET-specific agonists. J Biol Chem 275: 3412–3420
14. Baudet C, Mikaels A, Westphal H, Johansen J, Johansen TE, Ernfors P (2000) Positive and negative interactions of GDNF, NTN and ART in developing sensory neuron subpopulations, and their collaboration with neurotrophins. Development 127: 4335–4344
15. Beck KD, Irwin I, Valverde J, Brennan TJ, Langston JW, Hefti F (1996) GDNF induces a dystonia-like state in neonatal rats and stimulates dopamine and serotonin synthesis. Neuron 16: 665–673
16. Beck KD, Valverde J, Alexi T, Poulsen K, Moffat B, Vandlen RA, Rosenthal A, Hefti F (1995) Mesencephalic dopaminergic neurons protected by GDNF from axotomy-induced degeneration in the adult brain. Nature 373: 339–341
17. Beck M, Karch C, Wiese S, Sendtner M (2001) Motoneuron cell death and neurotrophic factors: basic models for development of new therapeutic strategies in ALS. Amyotroph Lateral Scler Other Motor Neuron Disord 2 Suppl 1: S55–S68
18. Bennett DA, Beckett LA, Murray AM, Shannon KM, Goetz CG, Pilgrim DM, Evans DA (1996) Prevalence of parkinsonian signs and associated mortality in a community population of older people. N Engl J Med 334: 71–76
19. Bennett DL, Michael GJ, Ramachandran N, Munson JB, Averill S, Yan Q, McMahon SB, Priestley JV (1998) A distinct subgroup of small DRG cells express GDNF receptor components and GDNF is protective for these neurons after nerve injury. J Neurosci 18: 3059–3072
20. Bjorklund A, Kirik D, Rosenblad C, Georgievska B, Lundberg C, Mandel RJ (2000) Towards a neuroprotective gene therapy for Parkinson's disease: use of adenovirus, AAV and lentivirus vectors for gene transfer of GDNF to the nigrostriatal system in the rat Parkinson model. Brain Res 886: 82–98
21. Blesch A, Grill RJ, Tuszynski MH (1998) Neurotrophin gene therapy in CNS models of trauma and degeneration. In: Van Leeuwen FW, Salchi A, Giger RJ, Holtmaat AJGD, Verhaagen J (eds) Progress in brain research. Elsevier Science BV, Amsterdam, pp 473–484
22. Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH (1994) Convection-enhanced delivery of macromolecules in the brain. Proc Natl Acad Sci USA 91: 2076–2080
23. Boucher TJ, Okuse K, Bennett DL, Munson JB, Wood JN, McMahon SB (2000) Potent analgesic effects of GDNF in neuropathic pain states. Science 290: 124–127
24. Bowers WJ, Howard DF, Federoff HJ (1997) Gene therapeutic strategies for neuroprotection: implications for Parkinson's disease. Exp Neurol 144: 58–68
25. Buj-Bello A, Buchman VL, Horton A, Rosenthal A, Davies AM (1995) GDNF is an age-specific survival factor for sensory and autonomic neurons. Neuron 15: 821–828
26. Cacalano G, Farinas I, Wang LC, Hagler K, Forgie, A, Moore M, Armanini M, Phillips H, Ryan AM, Reichardt LF, Hynes M, Davies A, Rosenthal A (1998) GFRalpha1 is an essential receptor component for GDNF in the developing nervous system and kidney. Neuron 21: 53–62
27. Casper D, Mytilineou C, Blum M (1991) EGF enhances the survival of dopamine neurons in rat embryonic mesencephalon primary cell culture. J Neurosci Res 30: 372–381
28. Chauhan NB, Siegel GJ, Lee JM (2001) Depletion of glial cell line-derived neurotrophic factor in substantia nigra neurons of Parkinson's disease brain. J Chem Neuroanat 21: 277–288
29. Chen MY, Lonser RR, Morrison PF, Governale LS, Oldfield EH (1999) Variables affecting convection-enhanced delivery to the striatum: a systematic examination of rate of infusion, cannula size, infusate concentration, and tissue-cannula sealing time. J Neurosurg 90: 315–320
30. Cheng H, Fraidakis M, Blomback B, Lapchak P, Hoffer B, Olson L (1998) Characterization of a fibrin glue-GDNF slow-release preparation. Cell Transplant 7: 53–61
31. Choi-Lundberg DL, Bohn MC (1995) Ontogeny and distribution of glial cell line-derived neurotrophic factor (GDNF) mRNA in rat. Brain Res Dev Brain Res 85: 80–88
32. Clauss MA, Jai RK (1990) Interstitial transport of rabbit and sheep antibodies in normal and neoplastic tissues. Cancer Res 50: 3487–3492
33. Cohen S, Levi-Montalcini R, Hamburger V (1954) A nerve growth stimulating factor isolated from sarcomas 37 and 180. Proc Natl Acad Sci USA 40: 1014–1018
34. Collier TJ, Sortwell CE (1999) Therapeutic potential of nerve growth factors in Parkinson's disease. Drugs Aging 14: 261–287
35. Connor B, Dragunow M (1998) The role of neuronal growth factors in neurodegenerative disorders of the human brain. Brain Res Rev 27: 1–39
36. Date I, Aoi M, Tomita S, Collins F, Ohmoto T (1998) GDNF administration induces recovery of the nigrostriatal dopaminergic system both in young and aged parkinsonian mice. Neuroreport 9: 2365–2369
37. Date I, Notter MF, Felten SY, Felten DL (1990) MPTP-treated young mice but not aging mice show partial recovery of the nigrostriatal dopaminergic system by stereotaxic injection of acidic fibroblast growth factor (aFGF). Brain Res 526: 156–160
38. de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, Manubens-Bertran JM, Alperovitch A, Rocca WA (1997) Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON collaborative study. European community concerted action on the epidemiology of Parkinson's disease. J Neurol Neurosurg Psychiatry 62: 10–15
39. Del Fiacco M, Quartu M, Serra MP, Follesa P, Lai ML, Bachis A (2002) Topographical localization of glial cell line-derived neurotrophic factor in the human brain stem: an immunohistochemical study of prenatal, neonatal and adult brains. J Chem Neuroanat 23: 29–48
40. Eigenbrot C, Gerber N (1997) X-ray structure of glial cell-derived neurotrophic factor at 1.9 A resolution and implications for receptor binding. Nat Struct Biol 4: 435–438
41. Engele J, Bohn MC (1991) The neurotrophic effects of fibroblast growth factors on dopaminergic neurons in vitro are mediated by mesencephalic glia. J Neurosci 11: 3070–3078
42. Engele J, Franke B (1996) Effects of glial cell line-derived neurotrophic factor (GDNF) on dopaminergic neurons require concurrent activation of cAMP-dependent signaling pathways. Cell Tissue Res 286: 235–240
43. Eriksdotter Jonhagen M, Nordberg A, Amberla K, Backman L, Ebendal T, Meyerson B, Olson L, Seiger Shigeta M, Theodorsson E, Viitanen M, Winblad B, Wahlund LO (1998) Intracerebroventricular infusion of nerve growth factor in three patients with Alzheimer's disease. Dement Geriatr Cogn Disord 9: 246–257
44. Fearnley JM, Lees AJ (1991) Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 114 (Pt 5): 2283–2301
45. Francois C, Savy C, Jan C, Tande D, Hirsch EC, Yelnik J (2000) Dopaminergic innervation of the subthalamic nucleus in the normal state, in MPTP-treated monkeys, and in Parkinson's disease patients. J Comp Neurol 425: 121–129
46. Francois C, Yelnik J, Tande D, Agid Y, Hirsch EC (1999) Dopaminergic cell group A8 in the monkey: anatomical organization and projections to the striatum. J Comp Neurol 414: 334–347
47. Frim DM, Uhler TA, Galpern WR, Beal MF, Breakefield XO, Isacson O (1994) Implanted fibroblasts genetically engineered to

produce brain-derived neurotrophic factor prevent 1-methyl-4-phenylpyridinium toxicity to dopaminergic neurons in the rat. Proc Natl Acad Sci USA 91: 5104–5108
48. Gash DM, Gerhardt GA, Hoffer BJ (1998a) Effects of glial cell line-derived neurotrophic factor on the nigrostriatal dopamine system in rodents and nonhuman primates. Adv Pharmacol 42: 911–915
49. Gash DM, Zhang Z, Gerhardt G (1998b) Neuroprotective and neurorestorative properties of GDNF. Ann Neurol 44: S121–S125
50. Gash DM, Zhang Z, Ovadia A, Cass WA, Yi A, Simmerman L, Russell D, Martin D, Lapchak PA, Collins F, Hoffer BJ, Gerhardt GA (1996) Functional recovery in parkinsonian monkeys treated with GDNF. Nature 380: 252–255
51. Gill SS, Patel NK, Hotton GR, O'Sullivan K, McCarter R, Bunnage M, Brooks DJ, Svendsen CN, Heywood P (2003) Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat Med 9: 589–595
52. Goetz CG, Leurgans S, Raman R, Stebbins GT (2000) Objective changes in motor function during placebo treatment in PD. Neurology 54: 710–714
53. Grimes ML, Zhou J, Beattie EC, Yuen EC, Hall DE, Valletta JS, Topp KS, LaVail JH, Bunnett NW, Mobley WC (1996) Endocytosis of activated TrkA: evidence that nerve growth factor induces formation of signaling endosomes. J Neurosci 16: 7950–7964
54. Grondin R, Cass WA, Zhang Z, Stanford JA, Gash DM, Gerhardt GA (2003) Glial cell line-derived neurotrophic factor increases stimulus-evoked dopamine release and motor speed in aged rhesus monkeys. J Neurosci 23: 1974–1980
55. Grondin R, Gash DM (1998) Glial cell line-derived neurotrophic factor (GDNF): a drug candidate for the treatment of Parkinson's disease. J Neurol 245: P35–P42
56. Grondin R, Zhang Z, Yi A, Cass WA, Maswood N, Andersen AH, Elsberry DD, Klein MC, Gerhardt GA, Gash DM (2002) Chronic, controlled GDNF infusion promotes structural and functional recovery in advanced parkinsonian monkeys. Brain 125: 2191–2201
57. Haller MF, Saltzman WM (1998) Localized delivery of proteins in the brain: can transport be customized? Pharm Res 15: 377–385
58. Hassani OK, Francois C, Yelnik J, Feger J (1997) Evidence for a dopaminergic innervation of the subthalamic nucleus in the rat. Brain Res 749: 88–94
59. Hebert MA, Gerhardt GA (1997) Behavioral and neurochemical effects of intranigral administration of glial cell line-derived neurotrophic factor on aged Fischer 344 rats. J Pharmacol Exp Ther 282: 760–768
60. Hefti F (1983) Is Alzheimer disease caused by lack of nerve growth factor? Ann Neurol 13: 109–110
61. Hoane MR, Gulwadi AG, Morrison S, Hovanesian G, Lindner MD, Tao W (1999) Differential in vivo effects of neurturin and glial cell-line-derived neurotrophic factor. Exp Neurol 160: 235–243
62. Hoffman AF, van Horne CG, Eken S, Hoffer BJ, Gerhardt GA (1997) In vivo microdialysis studies on somatodendritic dopamine release in the rat substantia nigra: effects of unilateral 6-OHDA lesions and GDNF. Exp Neurol 147: 130–141
63. Hotton GR, Patel NK, Gill SS, Heywood P, Svendson SN, Brooks DJ (2004) The long term effect of glial derived neurotrophic factor infusions and 18F-dopa uptake in Parkinson's disease. Neurology 62: S38.001, A345
64. Hughes PE, Alexi T, Walton M, Williams CE, Druganow M, Clark RG, Gluckman PD (1999) Activity and injury-dependant expression of inducible trophic factors, growth factors, and apoptosis-related genes within the central nervous system. Progr Neurobiol 57: 421–450
65. Hyman C, Hofer M, Barde YA, Juhasz M, Yancopoulos GD, Squinto SP, Lindsay RM (1991) BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. Nature 350: 230–232
66. Hyman C, Juhasz M, Jackson C, Wright P, Ip NY, Lindsay RM (1994) Overlapping and distinct actions of the neurotrophins BDNF, NT-3, and NT-4/5 on cultured dopaminergic and GABAergic neurons of the ventral mesencephalon. J Neurosci 14: 335–347
67. Hynes MA, Poulsen K, Armanini M, Berkemeier L, Phillips H, Rosenthal A (1994) Neurotrophin-4/5 is a survival factor for embryonic midbrain dopaminergic neurons in enriched cultures. J Neurosci Res 37: 144–154
68. Isacson O, Deacon T (1997) Neural transplantation studies reveal the brain's capacity for continuous reconstruction. Trends Neurosci 20: 477–482
69. Jellinger K, Riederer P, Tomonaga M (1980) Progressive supranuclear palsy: clinico-pathological and biochemical studies. J Neural Transm Suppl: 111–128
70. Jellinger KA (2002) Recent developments in the pathology of Parkinson's disease. J Neural Transm Suppl: 347–376
71. Jing S, Wen D, Yu Y, Holst PL, Luo Y, Fang M, Tamir R, Antonio L, Hu Z, Cupples R, Louis JC, Hu S, Altrock BW, Fox GM (1996) GDNF-induced activation of the ret protein tyrosine kinase is mediated by GDNFR-alpha, a novel receptor for GDNF. Cell 85: 1113–1124
72. Jollivet C, Aubert-Pouessel A, Clavreul A, Venier-Julienne MC, Remy S, Montero-Menei CN, Benoit JP, Menei P (2004) Striatal implantation of GDNF releasing biodegradable microspheres promotes recovery of motor function in a partial model of Parkinson's disease. Biomaterials 25: 933–942
73. Kafri T, van Praag H, Gage FH, Verma IM (2000) Lentiviral vectors: regulated gene expression. Mol Ther 1: 516–521
74. Kawamoto Y, Nakamura S, Matsuo A, Akiguchi I, Shibasaki H (2000) Immunohistochemical localization of glial cell line-derived neurotrophic factor in the human central nervous system. Neuroscience 100: 701–712
75. Kirik D, Georgievska B, Bjorklund A (2004) Localized striatal delivery of GDNF as a treatment for Parkinson disease. Nat Neurosci 7: 105–110
76. Knusel B, Hefti F (1991) Trophic actions of IGF-I, IGF-II and insulin on cholinergic and dopaminergic brain neurons. Adv Exp Med Biol 293: 351–360
77. Kokaia Z, Bengzon J, Metsis M, Kokaia M, Persson H, Lindvall O (1993) Coexpression of neurotrophins and their receptors in neurons of the central nervous system. Proc Natl Acad Sci USA 90: 6711–6715
78. Kolmac C, Mitrofanis J (1998) Distribution of various neurochemicals within the zona incerta: an immunocytochemical and histochemical study. Anat Embryol (Berl) 199: 265–280
79. Kordower JH (2003) In vivo gene delivery of glial cell line–derived neurotrophic factor for Parkinson's disease. Ann Neurol 53: S120–S134
80. Kordower JH, Emborg ME, Bloch J, Ma SY, Chu Y, Leventhal L, McBride J, Chen EY, Palfi S, Roitberg BZ, Brown WD, Holden JE, Pyzalski R, Taylor MD, Carvey P, Ling Z, Trono D, Hantraye P, Deglon N, Aebischer P (2000) Neurodegeneration prevented by lentiviral vector delivery of GDNF in primate models of Parkinson's disease. Science 290: 767–773
81. Kordower JH, Isacson O, Emerich DF (1999a) Cellular delivery of trophic factors for the treatment of Huntington's disease: is neuroprotection possible? Exp Neurol 159: 4–20
82. Kordower JH, Palfi S, Chen EY, Ma SY, Sendera T, Cochran EJ, Mufson EJ, Penn R, Goetz CG, Comella CD (1999b) Clinicopathological findings following intraventricular glial-derived neurotrophic factor treatment in a patient with Parkinson's disease. Ann Neurol 46: 419–424

83. Korsching S (1993) The neurotrophic factor concept: a reexamination. J Neurosci 13: 2739–2748
84. Krieglstein K, Unsicker K (1994) Transforming growth factor-beta promotes survival of midbrain dopaminergic neurons and protects them against N-methyl-4-phenylpyridinium ion toxicity. Neuroscience 63: 1189–1196
85. Lachyankar MB, Condon PJ, Quesenberry PJ, Litofsky NS, Recht LD, Ross AH (1997) Embryonic precursor cells that express Trk receptors: induction of different cell fates by NGF, BDNF, NT-3, and CNTF. Exp Neurol 144: 350–360
86. Lang AE, Gill SS, Patel NK, Lozano AM, Nutt JG, Penn R (2006) Randomized controlled trial of intraputamenal GDNF infusion in Parkinson disease. Ann Neurol 59: 459–466
87. Lang AE, Lozano AM (1998) Parkinson's disease. First of two parts. N Engl J Med 339: 1044–1053
88. Lapchak PA (1996) Therapeutic potentials for glial cell line-derived neurotrophic factor (GDNF) based upon pharmacological activities in the CNS. Rev Neurosci 7: 165–176
89. Lapchak PA, Beck KD, Araujo DM, Irwin I, Langston JW, Hefti F (1993) Chronic intranigral administration of brain-derived neurotrophic factor produces striatal dopaminergic hypofunction in unlesioned adult rats and fails to attenuate the decline of striatal dopaminergic function following medial forebrain bundle transection. Neuroscience 53: 639–650
90. Levi-Montalcini R (1987) The nerve growth factor: thirty-five years later. Embo J 6: 1145–1154
91. Li Duan M, Bordet T, Mezzina M, Kahn A, Ulfendahl M (2002) Adenoviral and adeno-associated viral vector mediated gene transfer in the guinea pig cochlea. Neuroreport 13: 1295–1299
92. Lieberman DM, Laske DW, Morrison PF, Bankiewicz KS, Oldfield EH (1995) Convection-enhanced distribution of large molecules in gray matter during interstitial drug infusion. J Neurosurg 82: 1021–1029
93. Lin LF, Doherty DH, Lile JD, Bektesh S, Collins F (1993) GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. Science 260: 1130–1132
94. Lin LF, Zhang TJ, Collins F, Armes LG (1994) Purification and initial characterization of rat B49 glial cell line-derived neurotrophic factor. J Neurochem 63: 758–768
95. Lindvall O, Hagell P (2000) Clinical observations after neural transplantation in Parkinson's disease. Prog Brain Res 127: 299–320
96. Lindvall O, Rehncrona S, Brundin P, Gustavii B, Astedt B, Widner H, Lindholm T, Bjorklund A, Leenders KL, Rothwell JC *et al* (1989) Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. A detailed account of methodology and a 6-month follow-up. Arch Neurol 46: 615–631
97. Louis ED, Marder K, Cote L, Tang M, Mayeux R (1997) Mortality from Parkinson disease. Arch Neurol 54: 260–264
98. Love S, Plaha P, Patel NK, Hotton GR, Brooks DJ, Gill SS (2005) Glial cell line-derived neurotrophic factor induces neuronal sprouting in human brain. Nat Med 11: 703–704
99. Lu X, Hagg T (1997) Glial cell line-derived neurotrophic factor prevents death, but not reductions in tyrosine hydroxylase, of injured nigrostriatal neurons in adult rats. J Comp Neurol 388: 484–494
100. Maisonpierre PC, Belluscio L, Friedman B, Alderson RF, Wiegand SJ, Furth ME, Lindsay RM, Yancopoulos GD (1990) NT-3, BDNF, and NGF in the developing rat nervous system: parallel as well as reciprocal patterns of expression. Neuron 5: 501–509
101. Marek K, Innis R, van Dyck C, Fussell B, Early M, Eberly S, Oakes D, Seibyl J (2001) [123I]beta-CIT SPECT imaging assessment of the rate of Parkinson's disease progression. Neurology 57: 2089–2094
102. Martin D, Miller G, Cullen T, Fischer N, Dix D, Russell D (1996) Intranigral or intrastriatal injections of GDNF: effects on monoamine levels and behavior in rats. Eur J Pharmacol 317: 247–256
103. Martin D, Miller G, Rosendahl M, Russell DA (1995) Potent inhibitory effects of glial derived neurotrophic factor against kainic acid mediated seizures in the rat. Brain Res 683: 172–178
104. Mattson MP (1998) Neuroprotective strategies based on targeting of postreceptor signalling events. Neuroprotective signal transduction, Humana Press, Totown, pp 301–335
105. Meng X, Lindahl M, Hyvonen ME, Parvinen M, de Rooij DG, Hess M, Raatikainen-Ahokas A, Sainio K, Rauvala H, Lakso M, Pichel JG, Westphal H, Saarma M, Sariola H (2000) Regulation of cell fate decision of undifferentiated spermatogonia by GDNF. Science 287: 1489–1493
106. Miranda RC, Sohrabji F, Toran-Allerand CD (1993) Neuronal colocalization of mRNAs for neurotrophins and their receptors in the developing central nervous system suggests a potential for autocrine interactions. Proc Natl Acad Sci USA 90: 6439–6443
107. Miyoshi Y, Zhang Z, Ovadia A, Lapchak PA, Collins F, Hilt D, Lebel C, Kryscio R, Gash DM (1997) Glial cell line-derived neurotrophic factor-levodopa interactions and reduction of side effects in parkinsonian monkeys. Ann Neurol 42: 208–214
108. Moore MW, Klein RD, Farinas I, Sauer H, Armanini M, Phillips H, Reichardt LF, Ryan AM, Carver-Moore K, Rosenthal A (1996) Renal and neuronal abnormalities in mice lacking GDNF. Nature 382: 76–79
109. Morens DM, Davis JW, Grandinetti A, Ross GW, Popper JS, White LR (1996) Epidemiologic observations on Parkinson's disease: incidence and mortality in a prospective study of middle-aged men. Neurology 46: 1044–1050
110. Morrish PK, Sawle GV, Brooks DJ (1996) An [18F]dopa-PET and clinical study of the rate of progression in Parkinson's disease. Brain 119(Pt 2): 585–591
111. Morrison PF, Laske DW, Bobo H, Oldfield EH, Dedrick RL (1994) High-flow microinfusion: tissue penetration and pharmacodynamics. Am J Physiol 266: R292–R305
112. Morse JK, Wiegand SJ, Anderson K, You Y, Cai N, Carnahan J, Miller J, DiStefano PS, Altar CA, Lindsay RM *et al* (1993) Brain-derived neurotrophic factor (BDNF) prevents the degeneration of medial septal cholinergic neurons following fimbria transection. J Neurosci 13: 4146–4156
113. Mount HT, Dean DO, Alberch J, Dreyfus CF, Black IB (1995) Glial cell line-derived neurotrophic factor promotes the survival and morphologic differentiation of Purkinje cells. Proc Natl Acad Sci USA 92: 9092–9096
114. Muldoon LL, Nilaver G, Kroll RA, Pagel MA, Breakefield XO, Chiocca EA, Davidson BL, Weissleder R, Neuwelt EA (1995) Comparison of intracerebral inoculation and osmotic blood–brain barrier disruption for delivery of adenovirus, herpesvirus, and iron oxide particles to normal rat brain. Am J Pathol 147: 1840–1851
115. Nakao N, Yokote H, Nakai K, Itakura T (2000) Promotion of survival and regeneration of nigral dopamine neurons in a rat model of Parkinson's disease after implantation of embryonal carcinoma-derived neurons genetically engineered to produce glial cell line-derived neurotrophic factor. J Neurosurg 92: 659–670
116. Nosrat CA, Tomac A, Lindqvist E, Lindskog S, Humpel C, Stromberg I, Ebendal T, Hoffer BJ, Olson L (1996) Cellular expression of GDNF mRNA suggests multiple functions inside and outside the nervous system. Cell Tissue Res 286: 191–207
117. Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws ER Jr, Lozano AM, Penn RD, Simpson RK Jr, Stacy M, Wooten GF

(2003) Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. Neurology 60: 69–73
118. Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, Shannon KM, Nauert GM, Perl DP, Godbold J, Freeman TB (2003) A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 54: 403–414
119. Olson L (1996) Toward trophic treatment in parkinsonism: a primate step. Nat Med 2: 400–401
120. Olson L, Nordberg A, von Holst H, Backman L, Ebendal T, Alafuzoff I, Amberla K, Hartvig P, Herlitz A, Lilja A *et al* (1992) Nerve growth factor affects 11C-nicotine binding, blood flow, EEG, and verbal episodic memory in an Alzheimer patient (case report). J Neural Transm Park Dis Dement Sect 4: 79–95
121. Opacka-Juffry J, Ashworth S, Hume SP, Martin D, Brooks DJ, Blunt SB (1995) GDNF protects against 6-OHDA nigrostriatal lesion: in vivo study with microdialysis and PET. Neuroreport 7: 348–352
122. Oppenheim RW (1989) The neurotrophic theory and naturally occurring motoneuron death. Trends Neurosci 12: 252–255
123. Oppenheim RW, Houenou LJ, Parsadanian AS, Prevette D, Snider WD, Shen L (2000) Glial cell line-derived neurotrophic factor and developing mammalian motoneurons: regulation of programmed cell death among motoneuron subtypes. J Neurosci 20: 5001–5011
124. Patel NK, Bunnage M, Plaha P, Svendsen CN, Heywood P, Gill SS (2005) Intraputamenal infusion of glial cell line-derived neurotrophic factor in PD: a two-year outcome study. Ann Neurol 57: 298–302
125. Pichel JG, Shen L, Sheng HZ, Granholm AC, Drago J, Grinberg A, Lee EJ, Huang SP, Saarma M, Hoffer BJ, Sariola H, Westphal H (1996) Defects in enteric innervation and kidney development in mice lacking GDNF. Nature 382: 73–76
126. Pochon NA, Menoud A, Tseng JL, Zurn AD, Aebischer P (1997) Neuronal GDNF expression in the adult rat nervous system identified by in situ hybridization. Eur J Neurosci 9: 463–471
127. Pothos EN, Davila V, Sulzer D (1998) Presynaptic recording of quanta from midbrain dopamine neurons and modulation of the quantal size. J Neurosci 18: 4106–4118
128. Ridet JL, Deglon N, Aebischer P (2000) Gene transfer techniques for the delivery of GDNF in Parkinson's disease. Novartis Found Symp 231: 202–215; discussion 215–219, 302–306
129. Rosenblad C, Martinez-Serrano A, Bjorklund A (1998) Intrastriatal glial cell line-derived neurotrophic factor promotes sprouting of spared nigrostriatal dopaminergic afferents and induces recovery of function in a rat model of Parkinson's disease. Neuroscience 82: 129–137
130. Sanchez MP, Silos-Santiago I, Frisen J, He B, Lira SA, Barbacid M (1996) Renal agenesis and the absence of enteric neurons in mice lacking GDNF. Nature 382: 70–73
131. Schecterson LC, Bothwell M (1992) Novel roles for neurotrophins are suggested by BDNF and NT-3 mRNA expression in developing neurons. Neuron 9: 449–463
132. Schuchardt A, D'Agati V, Larsson-Blomberg L, Costantini F, Pachnis V (1994) Defects in the kidney and enteric nervous system of mice lacking the tyrosine kinase receptor ret. Nature 367: 380–383
133. Slevin JT, Gerhardt GA, Smith CD, Gash DM, Kryscio R, Young B (2005) Improvement of bilateral motor functions in patients with Parkinson disease through the unilateral intraputaminal infusion of glial cell line-derived neurotrophic factor. J Neurosurg 102: 216–222
134. Smith Y, Kieval JZ (2000) Anatomy of the dopamine system in the basal ganglia. Trends Neurosci 23: S28–S33
135. Sofroniew MV, Howe CL, Mobley WC (2001) Nerve growth factor signaling, neuroprotection, and neural repair. Annu Rev Neurosci 24: 1217–1281
136. Takahashi M (2001) The GDNF/RET signaling pathway and human diseases. Cytokine Growth Factor Rev 12: 361–373
137. Tansey MG, Baloh RH, Milbrandt J, Johnson EM Jr (2000) GFRalpha-mediated localization of RET to lipid rafts is required for effective downstream signaling, differentiation, and neuronal survival. Neuron 25: 611–623
138. Thoenen H, Barde YA, Davies AM, Johnson JE (1987) Neurotrophic factors and neuronal death. Ciba Found Symp 126: 82–95
139. Thorne RG, Frey WH 2nd (2001) Delivery of neurotrophic factors to the central nervous system: pharmacokinetic considerations. Clin Pharmacokinet 40: 907–946
140. Tomac A, Lindqvist E, Lin LF, Ogren SO, Young D, Hoffer BJ, Olson L (1995) Protection and repair of the nigrostriatal dopaminergic system by GDNF in vivo. Nature 373: 335–339
141. Tornqvist N, Bjorklund L, Almqvist P, Wahlberg L, Stromberg I (2000) Implantation of bioactive growth factor-secreting rods enhances fetal dopaminergic graft survival, outgrowth density, and functional recovery in a rat model of Parkinson's disease. Exp Neurol 164: 130–138
142. Treanor JJ, Goodman L, de Sauvage F, Stone DM, Poulsen KT, Beck CD, Gray C, Armanini MP, Pollock RA, Hefti F, Phillips HS, Goddard A, Moore MW, Buj-Bello A, Davies AM, Asai N, Takahashi M, Vandlen R, Henderson CE, Rosenthal A (1996) Characterization of a multicomponent receptor for GDNF. Nature 382: 80–83
143. Trupp M, Arenas E, Fainzilber M, Nilsson AS, Sieber BA, Grigoriou M, Kilkenny C, Salazar-Grueso E, Pachnis V, Arumae U (1996) Functional receptor for GDNF encoded by the c-ret proto-oncogene. Nature 381: 785–789
144. Trupp M, Belluardo N, Funakoshi H, Ibanez CF (1997) Complementary and overlapping expression of glial cell line-derived neurotrophic factor (GDNF), c-ret proto-oncogene, and GDNF receptor-alpha indicates multiple mechanisms of trophic actions in the adult rat CNS. J Neurosci 17: 3554–3567
145. Trupp M, Ryden M, Jornvall H, Funakoshi H, Timmusk T, Arenas E, Ibanez CF (1995) Peripheral expression and biological activities of GDNF, a new neurotrophic factor for avian and mammalian peripheral neurons. J Cell Biol 130: 137–148
146. Trupp M, Scott R, Whittemore SR, Ibanez CF (1999) Ret-dependent and -independent mechanisms of glial cell line-derived neurotrophic factor signaling in neuronal cells. J Biol Chem 274: 20885–20894
147. Tuszynski MH (2002) Growth-factor gene therapy for neurodegenerative disorders. Lancet Neurol 1: 51–57
148. Vigna E, Cavalieri S, Ailles L, Geuna M, Loew R, Bujard H, Naldini L (2002) Robust and efficient regulation of transgene expression in vivo by improved tetracycline-dependent lentiviral vectors. Mol Ther 5: 252–261
149. Wang J, Chen G, Lu B, Wu CP (2003) GDNF acutely potentiates Ca^{2+} channels and excitatory synaptic transmission in midbrain dopaminergic neurons. Neurosignals 12: 78–88
150. Wang LJ, Lu YY, Muramatsu S, Ikeguchi K, Fujimoto K, Okada T, Mizukami H, Matsushita T, Hanazono Y, Kume A, Nagatsu T, Ozawa K, Nakano I (2002) Neuroprotective effects of glial cell line-derived neurotrophic factor mediated by an adeno-associated virus vector in a transgenic animal model of amyotrophic lateral sclerosis. J Neurosci 22: 6920–6928
151. Weis C, Marksteiner J, Humpel C (2001) Nerve growth factor and glial cell line-derived neurotrophic factor restore the cholinergic neuronal phenotype in organotypic brain slices of the basal nucleus of Meynert. Neuroscience 102: 29–38
152. Williams LR, Inouye G, Cummins V, Pelleymounter MA (1996) Glial cell line-derived neurotrophic factor sustains axotomized

basal forebrain cholinergic neurons in vivo: dose-response comparison to nerve growth factor and brain-derived neurotrophic factor. J Pharmacol Exp Ther 277: 1140–1151

153. Xu RY, Pong K, Yu Y, Chang D, Liu S, Lile JD, Treanor J, Beck KD, Louis JC (1998) Characterization of two distinct monoclonal antibodies specific for glial cell line-derived neurotrophic factor. J Neurochem 70: 1383–1393
154. Yan Q, Matheson C, Lopez OT (1995) In vivo neurotrophic effects of GDNF on neonatal and adult facial motor neurons. Nature 373: 341–344
155. Yoshimoto Y, Lin Q, Collier TJ, Frim DM, Breakefield XO, Bohn MC (1995) Astrocytes retrovirally transduced with BDNF elicit behavioral improvement in a rat model of Parkinson's disease. Brain Res 691: 25–36
156. Yuen EC, Howe CL, Li Y, Holtzman DM, Mobley WC (1996) Nerve growth factor and the neurotrophic factor hypothesis. Brain Dev 18: 362–368
157. Zurn AD, Baetge EE, Hammang JP, Tan SA, Aebischer P (1994) Glial cell line-derived neurotrophic factor (GDNF), a new neurotrophic factor for motoneurones. Neuroreport 6: 113–118

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Neuronal networks of the basal ganglia and the value of recording field potentials from them

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Summary

The basal ganglia constitute parts of highly sophisticated and complex neuronal networks, which represent essential elements of functional circuits, actively involved in the control of movement. The physiologic properties of these networks and their interchange with different brain areas could serve as a model for the pathophysiologic explanation of various movement disorders, particularly Parkinson's disease. Stimulation of these networks and subsequent recording of the evoked Local Field Potentials is currently used not only for understanding the pathophysiology of movement disorders but also for the physiologic localization of the anatomical target during deep brain stimulation procedures. An overview of the currently available research and clinical data from the recording of Local Field Potentials as well as the advantages, the disadvantages and the limitations of this methodology are presented in this chapter.

Keywords: Neuromodulation; basal ganglia; field potential; macrostimulation; neuronal network.

Introduction

The vast majority of the currently performed intracranial neuromodulating procedures target the basal ganglia. These large, deep-sited nuclei are connected to each other and also to other brain areas, formatting complex functional neuronal networks with characteristic electrical activity. Recording and analysis of this electrical activity in the form of local field potentials (LFPs) can provide additional information to the specialists in operative neuromodulation in regards to the physiologic properties of these neuronal networks in pathophysiological states. In this chapter, the reader can find a brief description of the anatomical structure of the basal ganglia neuronal circuits, a few important physiologic aspects of them and finally an overview of the role of LFP recordings in targeting specific anatomical targets such as the subthalamic nucleus, the thalamus and the globus pallidus.

Description of basal ganglia neuronal networks

Basal ganglia is a term widely used for describing a highly complex group of subcortical nuclei, consisting of striatum (caudate nucleus and putamen), globus pallidus, substantia nigra and subthalamic nucleus, which are connected to each other and have input and output to different brain areas [39]. These functional connections of the basal ganglia represent highly sophisticated and complex neuronal networks, intimately involved in the control of movement as well as in various cognitive and behavioral functions: these connections form circuits with characteristic patterns of electrophysiologic activity [39]. This electrical activity can be detected during field potential recording. The brief description of these neuronal circuits is necessary for better understanding of the field potential recordings obtained and their clinical and research importance in operative neuromodulation.

The striatum, which includes the caudate nucleus and the putamen and along with the subthalamic nucleus (STN) represent the input nuclei of the basal ganglia, receives excitatory input from the cerebral cortex, practically from the entire cortical mantle (motor, pre-motor, somatosensory, associative and limbic cortex) [39]. More specifically, projective fibers from the motor, pre-motor and somatosensory cortex terminate to the post-commissural putamen [39], fibers from the associative cortex project to the caudate nucleus and the rostral putamen [39] while the limbic cortex projects to the ventral striatum [39]. These glutamatergic cortico-striatal projections

are characterized by a strict topographic organization [39]. In addition, the striatal excitatory input circuitry is completed by the thalamo-striatal projection circuit, originating mainly from the intra-laminar thalamic nuclei (the nuclei centralis and para-fascicularis) [34, 39]; this functional projection is also glutamatergic, highly specific and topographically organized [34, 39]. The nucleus centralis projects mainly to the post-commissural sensory motor part of the putamen while the nucleus para-fascicularis' projected fibers terminate mostly to the limbic-associative striatum [34]. Another glutamatergic cortico-subthalamic projection, exclusively ipsilateral [21, 39], has also been demonstrated [39]. This cortico-subthalamic input circuit, contrary to the previously described ones, originates from the pre-motor, motor and pre-frontal cortex [21, 30, 39]. Similarly to all other cortical and thalamic input projections, the cortico-subthalamic one is somatotopically organized [21, 30]. In addition to the cortex, the thalamic intra-laminar nuclei, the dorsal raphe nucleus, the mesopontine tegmentum and the dopaminergic Substantia Nigra pars compacta (SNc) represent sources of direct subthalamic nucleus input [31].

The striatal output can be divided for simplification purposes into two discrete pathways: a direct and an indirect one [39]. In the direct striato-fugal pathway, which is a GABAergic projection, the striatum is directly connected to the internal Globus Pallidus (GPi) and the Substantia Nigra pars reticulata (SNr) [31, 39]. Contrariwise, in the indirect pathway the striatum sends fibers firstly to the external Globus Pallidus (GPe), then to the STN and subsequently to the GPi and SNr [31, 39]. This indirect pathway is topographically organized [31, 39]. Immunohistochemical and electron microscopy studies have demonstrated the existence of local, collateral dendritic networks connecting these two striato-fugal pathways [39, 41, 46]. Along with this ''classic'', indirect pathway [39], another less typical indirect output pathway exists: it originates from the GPe and terminates to the GPi and SNr without passing through the STN [39]. Furthermore, the existence of a GPe projection to the thalamic reticularis nucleus has been described and experimentally confirmed [3–5, 10, 13, 23]. Finally, a reciprocal inter-connective circuitry between the STN and GPe has been identified and described in detail [9, 28, 35, 36, 40].

The output nuclei of the basal ganglia (GPi and SNr) send projective fibers to the different target nuclei. More specifically, the GPi sends projective fibers to the pars principalis anterior thalamic nucleus, to the pars oralis (VL_o), to the lateral part of the pars medialis (VL_m), to the intralaminar thalamic nuclei (mainly to the nucleus centralis), to the lateral habenular nucleus and to the pedunculopontine nucleus (PPN) [39]. The SNr projects to the medial part of the ventro-lateral nucleus (VL_m) and to the magno-cellular part of the ventral-anterior nucleus (VA_{mc}) as well as to the para-central (PCN), to the dorso-medial para-laminar nucleus (DM_{pe}), to the nucleus centralis/nucleus para-fascicularis complex, to the PPN, to the superior colliculus and to the medullary reticular formation [39]. Furthermore, less massive projections originating from the STN to the SNc [39], to the PPN [39], to the spinal cord [39] and to the striatum [39] have been described in previous studies.

This brief overview describes the highly complex neuronal network of the basal ganglia nuclei and also outlines a model of their functional organization, which currently serves as a basis for understanding the pathophysiology of movement disorders and particularly Parkinson's disease [39].

Physiologic consideration of basal ganglia neuronal networks

It is apparent from the brief description of the above described neuronal circuits, that basal ganglia represent parts of a multi-synaptic loop, which transforms higher order cognitive activity into action [29]. In the cerebral cortex, where neurons are arranged in layers, afferent fibers terminate, more or less, in a laminated fashion: activation of certain afferent systems often results in potential changes that show a characteristic laminar arrangement in the depths of the cortex [27]. Experimental studies have shown, that multi-second oscillations in firing rate with periods in the range of 2–60 s, and averaging 2–35 s, are present in 50–90% of spike trains from neurons in basal ganglia nuclei [1, 2, 33]. This oscillatory firing activity has been shown to organize the propagation and synchronization of faster oscillatory activity in the distributed neuronal circuits [2]. Synchronous neuronal discharge oscillations in the cerebral cortex play an important role in normal motor processing and it has been demonstrated, that this oscillatory activity is associated with such functions as binding of neuronal activity in disparate motor areas, recruitment of motor-unit discharge, reduction of computational effort or processing load and modification of motor states [25]. In addition, the existence of similar oscillatory activity in the STN-GPe network has been demonstrated; this activity is intimately related to the observed rhythmic cortical activity

[25]. It is also widely accepted that STN neurons in patients with Parkinson's disease (PD) show high-frequency oscillations at 15–30 Hz as this has been demonstrated in animals and humans by several investigators [7, 25, 32] by using mostly coherence analysis of depth LFP recordings. The most satisfactory pathophysiologic explanation of this phenomenon is the observed degeneration of the SNc and the subsequent depletion of striatal dopamine, which leads to the emergence of STN neurons with increased spontaneous activity and periodic oscillatory activity [7, 25]. Furthermore, analysis of pallidal LFP recordings in awake, cooperative patients with established diagnosis of PD, have demonstrated that there is a decreased tendency to synchronization at 4–10 Hz [38]. Contrariwise, the observed firing rates in cases of dystonia show that there is usually a decrease in the 11–30 Hz oscillatory activity and an increase in the 4–10 Hz range [38]. LFP recordings nicely demonstrate that each movement disorder is associated with discrete abnormal spatio-temporal pattern of activity [25, 38].

The existence of multiple, discrete functional loops between the cerebral cortex and the STN has been recently postulated [18]. This theory, proposed by Fogelson *et al*. states that the utilization of distinct frequencies by the same anatomical cortico-subthalamic network, may provide a means of marking and segregating related processing, over and above any anatomical segregation of processing systems [18]. In their well-designed, prospective, clinical study examining nine patients with established diagnosis of PD, they showed that significant coherence existed between the obtained Electro-EncephaloGraphy (EEG) and LFPs recordings from the subthalamic nucleus area [18]; this coherence was apparent in the theta (3–7 Hz), alpha (8–13 Hz), lower beta (14–20 Hz) and upper beta (21–32 Hz) bands, although activity in the alpha and upper beta bands dominated [18]. More specifically, theta coherence predominately involved lateral and mesial cortical areas, alpha and lower beta coherence mesial and ipsilateral motor areas while upper beta coherence involved the midline cortex [18]. Subthalamic nucleus area LFPs led EEG in the theta band [18]. Contrariwise, EEG led the depth LFPs in the lower and upper beta bands [18]. Interestingly, subthalamic LFP activity in the alpha band could either lag or lead EEG [18]. Similarly, Foffani *et al*. arrived in the same conclusion, when in a patient with PD they concomitantly recorded movement-related EEG signals and LFPs from sensori-motor cerebral cortex, GPi and STN [17]. These findings lead to a novel model that could lend itself to an effective approach of movement-related brain activity and movement disorders.

The previously described functional loops and their oscillatory firing in physiological as well as in pathological states and the potential of recording all this electrical activity by using depth LFP recordings gives the functional neurosurgeon the opportunity to use all this information as a feedback signal, in order to improve the therapeutic effect of the current neuromodulating surgical interventions.

Basal ganglia field potential recordings during neuromodulating surgical procedures

The most efficient way for accurate localization of the selected anatomical target in deep brain stimulation (DBS) cases, which represent nowadays the vast majority of intracranial neuromodulating procedures, still remains controversial [20, 37]. One school favors the use of anatomical localization by utilizing neuro-imaging techniques and field potential recordings while the other one believes that micro-electrode recording during such procedures is essential and significantly increases the accuracy while minimizes the chance of suboptimal implantation [20, 37]. Although both sides can present a series of strong arguments supporting their beliefs, it is widely accepted that field potential recording is simpler than single cell recordings and less time consuming; on the other hand, it does not allow the identification of the exact limits and the somatotopic organization of the anatomical target while its overall accuracy is inferior to the one obtained by microelectrode recording. This controversy might be resolved in the near future as our experience with neuromodulation procedures will be exponentially increasing and the follow-up of these patients will become longer.

In this section, the authors would like to present an overview of the current practice and the practical significance of field potential recordings in the most commonly utilized anatomical targets, starting from LFP recordings from the STN. Even though the usage of subthalamic nucleus FPs has not been routinely employed in the identification of the STN in deep brain stimulation (DBS) cases, Liu *et al*. [26] have reported intraoperative LFP recordings from patients with PD. In their series, they used adjacent pairs of the four electrode contacts of the implanted DBS electrode [26]. The FP recordings were filtered between 0.5 Hz and 1 kHz, amplified with a gain of $\times$1000 (Cambridge Electronic Design 1902, Cambridge, UK), digitized at a sampling rate of

250 Hz and displayed online with an adjustable time scale of seconds to minutes [26]. Recordings were repeatedly made during rest, resting tremor as well as passive and active movement of the patient's wrist [26]. Coherence methodology was used in the statistical analysis of the obtained electrophysiologic data [26]. They demonstrated that the recorded oscillatory activity in the LFPs of the STN contralateral to the arm with tremor was increased in the resting tremor state compared to the rest state [26]. No significant increase in STN activity was recorded in response to passive movements of either the contralateral or the ipsilateral wrist [26]. Their findings suggest that the STN primarily projects contralaterally and the increased STN oscillation likely contributes to generation of resting tremor, rather than responding to the proprioceptive feedback from the tremulous arm [26]. Furthermore, high frequency (100 Hz) stimulation of the STN induced 4 Hz tremor in both forearms, gradually increasing in magnitude, and also oscillation of the contralateral (non-stimulated) STN at the same frequency [26]. Contrariwise, higher frequency stimulation (130 Hz) completely suppressed tremor in both arms, and oscillatory activity in the contralateral STN completely disappeared [26].

Similarly, Foffani *et al*. in their clinical series, consisting of nine patients with idiopathic PD, recorded post-operative (2–3 days post-operatively) LFPs from the STN using two pairs of contacts of the implanted DBS electrode: closely spaced (1–2 contacts) and widely spaced (0–3 contacts) [16]. The field potential recordings were obtained during rest, voluntary movements, 8–12 hours after withdrawal of dopaminergic medication, before and after administration of 100–200 mg of oral fast-acting levodopa or 6 mg of subcutaneous apomorphine or 40 mg of intra-muscular orphenadrine [16]. At rest state, and in the absence of dopaminergic medication, in most cases the 100–1000 Hz band showed no consistent rhythm [16]. Levodopa administration elicited a 300 Hz rhythm at rest [16]. This 300 Hz rhythm was also increased by apomorphine but not by orphenadrine [16]. The recorded 300 Hz rhythm was modulated by voluntary movement [16]. The dopamine-dependent 300 Hz rhythm probably reflects a bistable compound nuclear activity and supports high-resolution information processing in the basal ganglia neuronal network [16]. An absent 300 Hz subthalamic rhythm could be a patho-physiological characteristic of PD [16]. This high-frequency rhythm also provides the rationale for an excitatory – and not only inhibitory – interpretation of DBS mechanism of action [16].

Likewise, Priori *et al*. in a similar clinical study including 20 subthalamic nuclei of thirteen patients with PD, recorded post-operative LFPs through DBS electrodes implanted in the STN [32]. The obtained signals were pre-amplified, differentially amplified and filtered (2–1000 Hz, Cambridge 1902, Cambridge Electronic Design, Cambridge, UK) [32]. Signals were appropriately digitized (sampling rate 2500 Hz, Cambridge 1401, Cambridge Electronic Design, Cambridge, UK) [32]. LFPs were recorded at rest both before (off-state) and after (on-state) acute administration of different anti-parkinsonian medications such as levodopa, apomorphine or orphenadrine [32]. Power spectral analysis of the recorded LFPs, was performed [32]. In the off-state, STN LFPs showed clearly defined peaks of oscillatory activity below 50 Hz: at low frequencies (2–7 Hz), in the alpha (7–13 Hz), low beta (13–20 Hz) and high beta (20–30 Hz) range [32]. In the on-state after levodopa and apomorphine administration, low-beta activity significantly decreased and low-frequency activity increased [32]. Contrariwise, orphenadrine increased beta activity [32]. Power changes elicited by levodopa and apomorphine at low frequencies and in the beta range were not correlated while changes in the alpha band correlated well with the low beta rhythm [32]. They concluded that in the STN there are at least two rhythms below 50 Hz that are separately modulated by anti-parkinsonian medications [32].

Stimulation test via the implanted DBS has been used for intra-operative physiological verification of the electrode accurate placement. Especially in cases that micro-electrode recording is not employed, macro-stimulation test is the only method for confirming proper placement of the implanted electrode. Proximity of the active contact of the implanted lead electrode to the medial or inferior borders of STN is indicated by activation of lenniscal fibers while proximity to the lateral border is indicated by activation of the adjacent cortico-spinal tract [43]. Starr *et al*. in their study, used frequency of 185 Hz, pulse width of 60 msec and amplitude ranging from 0 to 10 V for macro-stimulation in bipolar mode [42, 45]. They claimed that stimulation-induced tremor was the only motor sign for accurate localization of their target [42, 45]. They also noted the fact that some adverse effects were associated with the used stimulated parameters [42, 45]. The most common ones were dysarthria or facial contraction associated with cortico-bulbar activation or contralateral paresthesias associated with lemniscal activation [42, 45]. They also reported that stimulation-induced bulbar effects with low-threshold

(<3 V) stimulation indicated lateral position of the implanted lead [42, 45].

The clinical value of LFP recordings and the role of macro-stimulation in subthalamic DBS implantation cases remain very controversial. In cases that the placement of the implanted DBS electrode produces an immediate temporary therapeutic effect, this effect might well be the result of a micro-subthalamotomy due to local trauma caused by the implanted macro-electrode [6]. It could be argued that this ''micro''-effect represents an indication of optimal trajectory [6]. However, the possibility that the macro-electrode or the implanted DBS electrode passed through the optimal target on its way to its current location cannot be ruled out [6]. Additionally, intra-operative macro-stimulation in judging clinical efficacy is significantly compromised by parameters such as patient's fatigue, confusion, lack of cooperation as well as certain limitations on the range of macro-stimulation parameters that can be tested. These limitations significantly complicate intra-operative macro-stimulation for targeting purposes as this has been nicely pointed out by Baker *et al*. [6]. Furthermore, the same limiting factors are applicable in routinely utilizing post-operative macro-stimulation for setting and fine adjustment of a previously implanted DBS.

In regards to the routine usage of LFPs in physiological localization of thalamic nuclei as anatomical targets, it is well known that different thalamic nuclei have discrete recording patterns. Macro-stimulation of thalamic targets (V_{im}) causing suppression of tremor predicts a good response to subsequent chronic stimulation [8, 22, 24, 44]. Stimulation of the active lead contacts in the proximity of the posterior and lateral borders of the motor thalamus are indicated by activation of the sensory thalamus and cortico-spinal tract, respectively [43]. Likewise, V_c nucleus can be safely identified by a high level of neuronal activity; responses are usually evoked from stimulation of fingers and lips with a medio-lateral somatotopy [19]. It has been demonstrated that stimulation of the posterior parts of V_{im} generally will give rise to paresthesia [14]. Paresthesia usually but not always is felt in the general region where the stimulated neurons have their receptive fields [14]. In addition, V_{im} and perhaps V_{op} nuclei can be identified by the presence of responses to stimulation of tendons or movement of joints. Furthermore, phasic tremor frequency activity can also be recorded mainly from V_{im} nucleus and to a lesser extent from V_{op} thalamic nucleus. The recording of spindles, an EEG pattern characterized by a 7–10/sec rhythm may also be characteristic for V_{op} nucleus.

The recording of field potentials from the GPi can easily identify the adjacent anatomical structures of internal capsule and optic tract [19]. Macro-stimulation via the implanted electrode in the inferior and postero-medial borders of the GPi activates the optic and the cortico-spinal tracts, respectively [12]. Intra-operative flash visual evoked potentials recording from the visual cortex has been reported during the GPi localization process with macro-stimulation and field potential recording [19]. The importance of any significant changes in the obtained visually evoked potentials can be depicted by the fact that Bonaroti *et al*. [11], in their series, had to modify their initially selected anatomical target based on the obtained potential recording changes [19]. Macro-stimulation of the GPi evokes in the vast majority of cases contra-lateral hand contractions and visual phosphenes, although various motor responses, ranging from hand to tongue contractions, have been documented and reported [15, 19]. It is apparent that the combination of LFP recordings in combination with macro-stimulation can provide valuable information to the performing neurosurgeon in regards to the physiologic confirmation of the selected anatomical target [19]. The importance of macro-stimulation in these procedures is indicated by the fact that among 28 centers in North America involved in practice of pallidotomy all but one routinely employed the technique of macro-stimulation for physiologic localization of the anatomical target [15, 19].

In summary, the usage of LFP recordings from basal ganglia neuronal networks is characterized by certain limitations. In comparison to micro-electrode recordings, LFP recording is characterized by significantly lower spatial resolution and accuracy. However, LFP recording is significantly simpler and faster than micro-electrode recording. These two physiologic localization methodologies could be complementary to each other in complicated cases. The wide utilization of advanced neuro-imaging techniques in the future (3T MRI units) might increase the accuracy of anatomical localization and favor the utilization of the simpler and faster LFP recording and macro-stimulation methodology.

References

1. Allers KA, Kreiss DS, Walters JR (2000) Multisecond oscillations in the subthalamic nucleus: effects of apomorphine and dopamine cell lesion. Synapse 38: 38–50
2. Allers KA, Ruskin DN, Bergstrom DA, Freeman LE, Ghazi LJ, Tierney PL, Walters JR (2002) Multisecond periodicities in basal ganglia firing rates correlate with theta bursts in transcortical and hippocampal EEG. J Neurophysiol 87: 1118–1122

3. Asanuma C (1989) Axonal arborizations of a magnocellular basal nucleus input and their relation to the neurones in the thalamic reticular nucleus of rats. Proc Natl Acad Sci USA 86(12): 4746–4750
4. Asanuma C (1994) GABAergic and pallidal terminals in the thalamic reticular nucleus of squirrel monkeys. Exp Brain Res 101: 439–451
5. Asanuma C, Porter LL (1990) Light and electron microscopic evidence for GABAergic projection from the caudal basal forebrain to the thalamic reticular nucleus in rats. J Comp Neurol 302: 159–172
6. Baker KB, Boulis NM, Rezai AR, Montgomery EB (2004) Target selection using microelectrode recording. In: Israel Z, Burchiel K (eds) Microelecrode recording in movement disorder surgery. Thieme Medical Publishers, New York, pp 138–151
7. Belluscio MA, Kasanetz F, Riquelme LA, Murer MG (2003) Spreading of slow cortical rhythms to the basal ganglia output nuclei in rats with nigrostriatal lesions. Eur J Neurosci 17: 1046–1052
8. Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, Payen I, Benazzouz A (1996) Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 84: 203–214
9. Bevan MD, Francis CM, Bolam JP (1995) The glutamate-enriched cortical and thalamic input to neurones in the subthalamic nucleus of the rat: convergence with GABA-positive terminals. J Comp Neurol 361: 491–511
10. Bickford ME, Gunluk AE, Van Horn SC, Sherman SM (1994) GABAergic projection from the basal forebrain to the visual sector of the thalamic reticular nucleus in the cat. J Comp Neurol 348: 481–510
11. Bonaroti EA, Rose RD, Kondziolka D, Baser S, Lunsford LD (1997) Flash visual evoked potential monitoring of optic tract function during macroelectrode-based pallidotomy. Neurosurg Foc 2(3):E4
12. Caparros-Lefebvre D, Ruchoux MM, Blond S, Petit H, Percheron G (1994) Long-term thalamic stimulation in Parkinson's disease: Postmortem anatomoclinical study. Neurology 44: 1856–1860
13. Cornwall J, Cooper JD, Phillipson OT (1990) Projections to the rostral reticular thalamic nucleus in the rat. Exp Brain Res 80: 157–171
14. El-Tahawy H, Lozano AM, Dostrovsky JO (2004) Electrophysiological findings in V_{im} and V_c. In: Israel Z, Burchiel K (eds) Microelecrode recording in movement disorder surgery. Thieme Medical Publishers, New York, pp 63–71
15. Favre J, Taha JM, Nguyen TT, Gildenberg PL, Burchiel KJ (1996) Pallidotomy: a survey of current practice in North America. Neurosurg 39: 883–892
16. Foffani G, Priori A, Egidi M, Rampini P, Tamma F, Caputo E, Moxon KA, Cerutti S, Barbieri S (2003) 300-Hz subthalamic oscillations in Parkinson's disease. Brain 126: 2153–2163
17. Foffani G, Bianchi AM, Priori A, Baselli G (2004) Adaptive autoregressive identification with spectral power decomposition for studying movement-related activity in scalp EEG signals and basal ganglia local field potentials. J Neural Eng 1: 165–173
18. Fogelson N, Williams D, Tijssen M, van Bruggen G, Speelman H, Brown P (2006) Different functional loops between cerebral cortex and the subthalmic area in Parkinson's disease. Cereb Cortex 16: 64–75
19. Garonzik IM, Ohara S, Hua SE, Lenz FA (2004) Microelectrode techniques: single-cell and field potential recordings. In: Israel Z, Burchiel K (eds) Microelecrode recording in movement disorder surgery. Thieme Medical Publishers, New York, pp 28–37
20. Hariz MI (2004) Is MER necessary in movement disorder surgery? The case against. In: Israel Z, Burchiel K (eds) Microelecrode recording in movement disorder surgery. Thieme Medical Publishers, New York, pp 197–207
21. Hartmann-von Monakow K, Akert K, Kunzle H (1978) Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. Exp Brain Res 33: 395–403
22. Hassler R, Riechert T, Mundinger F, Umbach W, Gangleberger JA (1960) Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. Brain 83: 337–350
23. Hazrati L-N, Parent A (1991) Projection from the external pallidum to the reticular thalamic nucleus in the squirrel monkey. Brain Res 550: 142–146
24. Hirai T, Miyazaki M, Nakajima H, Shibazaki T, Ohye C (1983) The correlation between tremor characteristics and the predicted volume of effective lesions in stereotaxic nucleus ventralis intermedius thalamotomy. Brain 106: 1001–1018
25. Levy R, Ashby P, Hutchison WD, Lang AE, Lozano AM, Dostrovsky JO (2002) Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease. Brain 125: 1196–1209
26. Liu X, Ford-Dunn HL, Hayward GN, Nandi D, Miall RC, Aziz TZ, Stein JF (2002) The oscillatory activity in the Parkinsonian subthalamic nucleus investigated using the macro-electrodes for deep brain stimulation. Clin Neurophysiol 113: 1667–1672
27. Matsuda Y, Fujimura K (1995) Responses of the medial prefrontal cortex to stimulation of the amygdale in the rat: a study with laminar field potential recording. Neurosc Res 23: 281–288
28. Moriizumi T, Nakamura Y, Kitao Y, Kudo M (1987) Ultrastructural analyses of afferent terminals in the subthalamic nucleus of the cat with a combined degeneration and horseradish peroxidase tracing method. J Compu Neurol 265: 159–174
29. Murer MG, Tseng KY, Kasanetz F, Belluscio M, Riquelme LA (2002) Brain oscillations, Medium spiny neurons, and Dopamine. Cell Mol Neurobiol 22: 611–632
30. Nambu A, Takada M, Inase M, *et al* (1996) Dual somatotopical representations of the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. J Neurosci 16: 2671–2683
31. Parent A, Hazrati L-N (1995) Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Rev 20: 128–154
32. Priori A, Foffani G, Pessenti A (2004) Rhythm specific pharmacologic modulation of subthalamic activity in Parkinson's disease. Exp Neurol 189: 369–379
33. Ruskin DN, Bergstrom DA, Baek D, Freeman LE, Walters JR (2001) Cocaine or selective block of dopamine transporters influences multisecond oscillations in firing rate in the globus pallidus. Neuropsychopharmacology 25: 25–40
34. Sadikot AF, Parent A, Francois C (1992) Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections. J Comp Neurol 315: 137–159
35. Shink E, Smith Y (1995) Differential synaptic innervation of neurones in the internal and the external segments of the globus pallidus by the GABA- and glutamate-containing terminals in the squirrel monkey. J Comp Neurol 358: 119–141
36. Shink E, Bevan MD, Bolam JP, Smith Y (1996) The subthalamic nucleus and the external pallidum: Two tightly interconnected structures that control the output of the basal ganglia in the monkey. Neuroscience 73: 335–357
37. Sierens DK, Bakay RAE (2004) Is MER Necessary in movement disorder surgery? The case in favor. In: Israel Z, Burchiel K (eds) Microelecrode recording in movement disorder surgery. Thieme Medical Publishers, New York, pp 186–196

38. Silberstein P, Kuhn AA, Kupsch A, Trottenberg T, Krauss JK, Wohrle JC, Mazzone P, Insola A, Di Lazzaro V, Oliviero A, Aziz T, Brown P (2003) Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. Brain 126: 2597–2608
39. Smith Y, Shink E, Sidibe M (1998) Neuronal circuitry and synaptic connectivity of the basal ganglia. Neurosurg Clin N Am 9: 203–222
40. Smith Y, Bolam JP, Von Krosigk M (1990) Topographical and synaptic organization of the GABA-containing pallidosubthalamic projection in the rat. Eur J Neurosci 2: 500–511
41. Somogyi P, Bolam JP, Smith AD (1981) Monosynaptic cortical input and local axon collaterals of identified striatonigral neurones. A light and electron microscopic study using the Golgi-peroxidase transport-degeneration procedure. J Comp Neurol 195: 567–584
42. Starr PA, Christine C, Lindsey N, Byrd D, Marks WJ (2002) Implantation of deep brain stimulators into the subthalamic nucleus: technical approach and MRI-verified lead locations. J Neurosurg 97: 370–387
43. Starr PA, Vitek JL, Bakay RA (1998) Deep brain stimulation for movement disorders. Neurosurg Clin N Am 9: 381–402
44. Tasker RR, Organ LW, Hawrylyshyn P (1982) Investigation of the surgical target for alleviation of involuntary movement disorders. App Neurophysiol 45: 261–274
45. Theodosopoulos PV, Turner RS, Starr PA (2004) Electrophysiological findings in STN and SNr. In: Israel Z, Burchiel K (eds) Microelecrode recording in movement disorder surgery. Thieme Medical Publishers, New York, pp 28–37
46. Yung KKL, Smith AD, Levey AI, Bolam JP (1996) Synaptic connections between spiny neurons of the direct and indirect pathways in the neostriatum of the rat: evidence from dopamine receptor and neuropeptide immunostaining. Eur J Neurosci 8: 861–869

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Technical aspects and considerations of deep brain stimulation surgery for movement disorders

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Summary

Deep brain stimulation (DBS) represents one of the more recent advancements in Neurosurgery. Even though its most successful applications evolved in movement disorders (MDs), indications now include pain, psychiatric disorders, epilepsy, cluster headaches and Tourette syndrome. As this type of surgery gains popularity and the indications for DBS surgery increase, so it will certainly increase the number of neurosurgeons who will use this neuromodulatory technique. A detailed description of the technical aspects of the DBS procedure, as it is performed in our department, is presented. In our opinion, our method is a good combination of all the well-established necessary techniques in a cost-effective way. This technical article may be helpful to neurosurgeons considering to start performing this type of surgery. It could also prompt others who perform DBS regularly to express their views, and hence, lead to further refinement of this demanding procedure.

Keywords: Deep brain stimulation (DBS); movement disorders (MD); stereotactic neurosurgery; surgical techniques.

Introduction

Surgical therapies have made a rapid re-entry into the therapy of movement disorders (MDs) since the early 1990s and have nowadays become far more effective and safe because of the scientific rationale for targets selection, the definition of better clinical criteria for patient selection, the progress in stereotactic techniques, and the availability of superior imaging modalities and intraoperative electrophysiology. DBS is currently the most promising of these interventions and has proven to be a safe and effective procedure for the treatment of MDs.

The optimal methods and techniques for the implantation the DBS lead have not yet been standardized. In this article we present the main technical aspects and considerations of DBS surgery and outline the procedure in a step-wise manner, based on the experience of the Movement Disorders Surgery Unit at the Department of Neurosurgery of the University of Athens in Athens. This is currently the leading multidisciplinary movement disorder surgery service in Greece. The technique described here is based on the experience obtained on fifty [50] surgically treated patients.

Patient selection and indications for surgery

The results of DBS for MDs are dependent on careful patient selection and the experience of the surgical team. For PD, indications include: 1) patients who have been adequately tried on optimal doses of antiparkinsonian medication but continue to be disabled because of motor fluctuations and levodopa induced dyskinesias, 2) patients who have intolerance to the psychological effects of L-Dopa and dopaminergic agonists, 3) patients with mood changes due to medications (DBS STN permits a reduction in the L-Dopa dose), 4) responsiveness to L-Dopa challenge test. Other indications include essential tremor, multiple sclerosis tremor and dystonia.

Contraindications for surgery

The definite exclusion criteria include: 1) secondary Parkinsonism and other Parkinsonian syndromes, 2) uncorrectable coagulopathy, 3) significant cognitive impairment and 4) severe depression or psychopathology.

Relative contraindications include: 1) ventriculomegaly (may require extreme angles to reach the target), 2) poorly controlled serious medical illnesses that may jeopardize the lifespan of the patient, 3) magnetic resonance imaging (MRI) abnormalities such as severe cerebral atrophy or multiple infarcts (because they predict poor

outcome), 4) patients not capable to co-operate during surgery, 5) patients not willing or are unable to attend repeated follow up, and 6) age >75 years.

Preoperative investigations

Before a patient is considered suitable for surgery, he/she undergoes a detailed clinical examination by a neurologist specialised in movement disorders. The neurologist confirms the diagnosis, selects candidates suitable for surgery, performs the L-Dopa challenge test to identify L-Dopa responsiveness and to reliably predict the likely benefits of surgery in individual cases. When a patient is selected as a surgical candidate, preoperative investigations include: 1) standard blood tests, 2) coagulation status, 3) electrocardiogram, 4) chest X-ray, 5) neuropsychological assessment, 6) clinical status assessment scales (UPDRS, PDQ-39, Fahn-Tolosa, EDSS), 7) video recording and gait assessment, and 8) brain MRI.

Preoperative medication

Antiplatelet agents are stopped approximately 2 weeks prior to surgery. Warfarin is also stopped and the patient's coagulation status monitored. Surgery is undertaken only when coagulation studies normalise. Anti-hypertension medications are continued and are administered on the morning of surgery, either intravenously or orally with a sip of water. All anti-parkinsonian medications are seized 18 hours prior to the procedure in order to avoid medication-induced dyskinesias during surgery and to allow the patient to be in an ''off'' state thus maximizing the clinical information gained by intraoperative examination.

Informed consent

Patients and their families are given a full description of the procedure and its rationale. We have found this to help patients co-operate better with the team during surgery. This ensures that they understand that the procedure aims in improving clinical symptoms and is not a definitive cure for their disease. This helps patients having realistic expectations. Potential complications are also discussed including infection, seizures, haemorrhage, stroke and death [2].

Preoperative MRI

Two days prior to surgery, a brain MRI (1.5 Tesla, Philips) without a stereotactic frame is obtained, with the patient in his best ''on'' medical condition; this helps reduce frame and movement related artefacts. Contiguous 2 mm axial slices with 0 mm gap are acquired in the AC-PC plane (axial) and perpendicular to it (coronal). The sequences include T1 weighted axial images, coronal and axial T2-weighted fast spin echo images and axial inversion recovery fast spin echo images, according to the targeted nucleus. For the past 2 years we have also been using a specially designed sequence (T1 Wref/fMRI) [13]. This is a multi-slice turbo sequence with inversion recovery and a maximum water-fat shift that provides an excellent anatomical definition of the targeted nuclei boundaries and the presence of infracted areas (lacunae), thus allowing a more accurate direct targeting and a better interpretation of intra-patient variations in micro-electrode recordings (MERs). The MR images are recorded onto a compact disc and transferred to our workstation (Stereoplan – Radionics Inc., Burlington, MA, USA).

Stereotactic frame placement

The stereotactic frame (Cosman–Roberts–Wells – Radionics Inc., Burlington, MA, USA) is placed under local anaesthesia (10 ml xylocaine 2%) on the morning of the procedure in the operating theatre. Proper frame alignment is important as it ensures that the patient images as well as maps made from intraoperative physiological exploration are interpretable in terms of familiar anatomy corresponding to standard brain atlases [14]. In case of frame misalignment, we use the surgical planning software to correct this. The frame is assembled and placed over the patient's head so that the base ring is parallel to a line extending between the inferior orbital rim and the external auditory meatus; this is approximately parallel to the AC-PC line [3]. Straight placement is facilitated by the earplugs provided, which align the frame to the external auditory meatus, thus avoiding any lateral shift (roll) and rotation (yaw). We try to keep the mouth and eyes uncovered, to allow both airway access in case of emergency and also the visual examination during the procedure. We place the short pins in front and the long ones at the back. The localizer is then attached and the patient is transferred to the CT scanner for a stereotactic brain CT.

Stereotactic brain CT

Once in the CT room, the patient's head is affixed to the scanner bed, trying to keep it straight in the gantry.

Even though the CRW frame is CT independent, affixing it allows avoidance of patient movements that may be excessive on the day of operation since the patient is off medication. CT allows for geometrically accurate images with no distortion even in the presence of a stereotactic frame and thus permits placement of the patient's brain into a Cartesian stereotactic space. We use continuous 2 mm slices, with 0° gantry, extending from the vault of the skull to its base. If the frame placement is ideal, obtained images will be parallel to the AC-PC line and in the same plane as the preoperative MRI; this will permit fusion of the 2 imaging modalities with minimum error. Obtained images are again recorded onto a compact disc and transferred to the workstation. The patient is then returned to the operating theatre and all anaesthetic preparations are made (IV line, oxygen mask, invasive arterial pressure monitoring, EEG and heart rate monitoring) while the surgical team proceeds with surgical planning.

Image fusion

After the MRI and stereotactic CT images are transferred to the workstation, they are checked for slice uniformity and duplicate slices removed, if present. The 2 imaging modalities (geometrically accurate CT and high definition 3D MRI) are then fused digitally in the workstation (Radionics Image Fusion, Radionics Inc., Burlington, MA, USA). This is done by manual selection of 3 identical anatomical landmarks on the 2 imaging modalities, usually the two optic nerves and the pineal gland. This co-registration volumetrically correlates the stereotactic CT to the preoperative MRI, thus independently scaling and rotating in all 3 planes (x–z) [2]. The MRI, having been spatially corrected and volumetrically correlated to the CT, is projected in all 3 dimensions (axial, coronal, and sagittal) and used for localisation of the anatomical target [2]. All image sets are reformatted using our surgical planning software so as to be parallel to the AC-PC line and orthogonal to the midsagittal plane.

Targets and surgical planning

The geometric coordinates of the targets we use for DBS can be seen in Table 1. For the STN, the intended target is the centre of its motor territory. For the GPi, the intended target is the anterolateral part of the motor territory, 2–4 mm from the internal capsule in order to avoid current spread to the later with subsequent side effects. For the thalamus, intended target is the Vim.

Table 1. *Coordinates of DBS targets in movement disorders*

Anatomical target	Stereotactic co-ordinates
STN	12 mm lateral to the midline 2–4 mm posterior to midcommissural point 3 mm inferior to the AC-PC line
GPi	20–22 mm lateral to the midline 2–3 mm anterior to midcommissural point 3–6 mm inferior to the AC-PC line
Thalamus (Vim)	14–15 mm lateral to the midline 3–5 mm posterior to midcommissural plane 0–1 mm superior to the AC-PC plane

Even though direct visualisation of even small targets as the STN ($9 \times 7 \times 5$ mm), [9, 12] using T2 weighted fast spin echo sequences has been widely reported in the literature [1, 17] we have often noticed that the borders of the targeted nucleus are usually not defined precisely. We have therefore been hesitant to rely solely on direct visual targeting [15]. On the other hand, AC and PC are always clearly identified and the target coordinates readily available in the literature; however, there is individual variation in the anatomical location of the targeted nuclei, and again relying solely on these fixed values cannot be recommended [4]. Finally, the use of standard stereotaxy atlases of the human brain again do not take into account individual variations. The variation noticed in several studies between final target selection, the classic geometrical coordinates and stereotactic atlases [8, 14, 15] clearly depict these differences in individual anatomy.

We therefore use a combination of 3 methods for targeting. This technique utilizes all available targeting methods and aims in maximizing the accuracy of the targeting procedure. After identification of the AC and PC, we start with direct visualisation and selection of the target on the fused CT/MRI. We then proceed to indirect targeting using the standard geometric coordinates of the targeted nuclei (Table 1) with respect to the AC-PC line to make small adjustments in the indirect coordinates. The final target is then correlated to the electronic version of the Schaltenbrand and Wahren "Atlas for Stereotaxy of the human brain" which is available on the workstation's software [12]. The high degree of accuracy of this targeting method was demonstrated during MERs, since the anatomical target was within the boundaries of the electrophysiologically defined nucleus in most cases.

Once the target has been established, the entry point and approach angles are determined using the planning

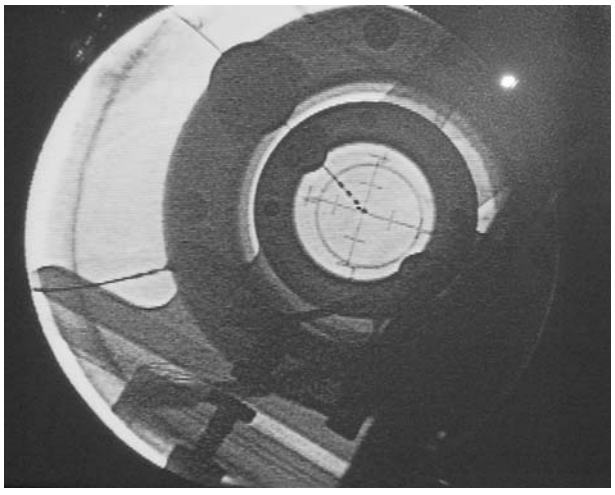

Fig. 1 Fluoroscopic guidance of DBS lead placement

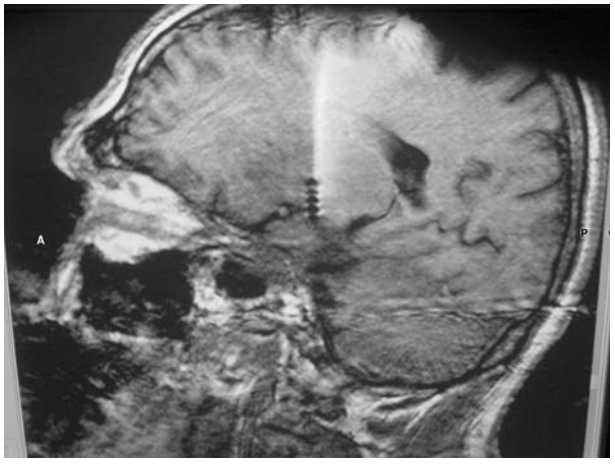

Fig. 2 Post-operative MRI showing the DBS lead in the STN

software. A typical entry point is usually just anterior to the coronal suture, 2–3,5 cm from the midline for both the GPi and STN and the angle varies between 20–45° from the midline in a coronal plane. We use the ''probe's eye view'', in order to examine in a ''virtual operation'' the exact trajectory of the electrode through the parenchyma. Based on this visualization of the trajectory, small adjustments in the slide and ring settings are made to avoid traversing sulci, cortical veins, dural venous lakes and the lateral ventricles. After completion of the surgical planning, all stereotactic coordinates are recorded, the stereotactic frame assembled accordingly and the coordinates double checked. The phantom localiser is used to ensure that the frame is in good working order, assembled correctly and that coordinates have been accurately set.

Surgical procedure

Step 1 – patient positioning – surgical exposure

The patient is placed in a semi-sitting position and the head-ring clamped to a Mayfield head-holder in neutral position. The hair is shaved and the scalp disinfected with aqueous povidone-iodine. The head is draped in a way that the eyes and mouth are not covered. Systolic arterial pressure is maintained below 130 mmHg to reduce the risk of intraparenchymal haemorrhage. A first dose of anti-staphylococcal antibiotics is administered prior to skin incision. We perform one small semi-linear skin incision on each side with their center being approximately located just anteriorly to the coronal suture, making sure not to compromise vascularisation of the scalp located between them.

Since it is usually easier to define the nuclei electrical activity on the side operated first (possibly due to brain shifts occurring after CSF leak from the initial trajectory), we start the procedure on that side. With the use of an electrical drill, a 14 mm burr hole is drilled, making sure that it is placed in the middle of the skin flap to reduce the risk for wound breakdown and infection. The Navigus Cranial Base Ring (Image-guided Neurologics, Melbourne, FL) is mounted over the burr hole, using the 2 screws provided, aligning its exit groove with the direction that the subcutaneous portion of the lead will have when it is tunnelled. We coagulate the dura and open it sharply using a blade. We expand the dural incision so that it is big enough to accommodate the five [5] microrecording electrodes to be inserted simultaneously. Immediately after the dural opening, we use DuraSeal (Confluent Surgical Inc., Waltham, MA) to avoid CSF leak that could lead to brain shift and postoperative headaches and to minimize the risk of air emboli. This also dampens the pulsation artefact during MERs [14].

A micropositioner system (Microtargeting Drive – Medtronic Inc., Minneapolis, MN) is used to advance the electrodes in a controlled fashion, while measuring the exact depths. This system allows the use of a 5-hole array which can accommodate 5 discrete channels at 2 mm distances, through which the recording electrodes and later the DBS lead can be inserted. In either case, multiple parallel trajectories may be explored simultaneously, without making any changes in the stereotactic frame coordinates. We simultaneously advance 5 guide cannules, withdraw the stylets and then, introduce the micro-targeting electrodes (Medtronic Inc., Minneapolis, MN). MERs start at 5 mm above the intended target.

Step 2 – MERs

MERs are used for intraoperative electrophysiological localisation of the targeted nucleus and to define as precisely as possible the final location of the DBS lead within the target. In MERs, a fine tipped electrode is introduced into the brain in a computationally controlled fashion. This microelectrode is connected to an amplifier and a recording-analysis system which detects and analyzes the neuronal activity which is encountered by the electrode as it traverses through the parenchyma towards the target. This electrical activity is displayed on a computer screen and also sent to an audio monitor so that it can be simultaneously seen and heard.

The role of MERs in providing added accuracy or clinical benefits in comparison to the use of macrostimulation alone has been an issue of debate for the past few years, with some groups reporting excellent outcomes without their use [2, 5, 20]. It is a fact though that targeting based upon imaging, geometric coordinates or atlases alone has a limited accuracy due to intra-patient variations, the mechanical properties of the frame used (regardless of the imaging modality) and by the slice thickness of the CT/MRI. There are additional factors that may further decrease the targeting accuracy and the application accuracy of any stereotactic system; these include: 1) image distortion, 2) poor visualisation of the targeted structure that precludes the ability to compensate for anatomic variability, 3) brain shifts that occur mainly after dural opening, and 4) physiological function not occurring in the predicted anatomic location [6, 14, 18]. Thus, imaging guided stereotaxy alone may often prove inadequate for placing a DBS lead within or several millimeters of the target [14]. This discrepancy between stereotactic imaging and electrophysiologically determined targets has been observed by several studies where the use of intraoperative electrophysiology resulted in a significant deviation (>2 mm) from the initial anatomic target in 25–50% of cases [1, 3, 8, 11, 21].

According to Starr [14], the value of MERs for target localisation rests on their ability to identify: 1) grey and white matter transition, because extracellularly recorded action potentials are recorded from neural cell bodies but infrequently from axons, 2) characteristic spontaneous discharge patterns of the different basal ganglion nuclei, and 3) motor subterritories within a target, by identifying movement related neurons. Furthermore, microelectrode mapping allows real time identification of structural boundaries with submilimetric precision, thus offering a higher spatial resolution than image based stereotaxy alone, while microstimulation can evoke motor and sensory phenomena thus localising microexcitable fibber pathways near the target. MERs therefore may prove beneficial, especially in cases where the initial anatomical target is outside the nucleus, near its borders and in proximity with nearby structures or within non-motor regions of the nucleus.

We have found this real time physiological confirmation of the target to be a very useful adjunct to our imaging guided localisation. Using 5 discrete trajectories, microelectrodes are advanced towards the target in 0.5 mm increments with the Microtargeting Drive. Neuronal activity is monitored with the Leadpoint Neural Activity Monitoring System (Medtronic Inc., Minneapolis, MN). Sedative agents are not given or discontinued during MERs. While advancing the electrode, entry into the nucleus is usually identified by a sudden increase in the density of cellular discharge with the characteristic pattern of the particular nucleus [4]. We also try to identify the location of movement related cells within the targeted nucleus; that is cells exhibiting an alteration in their discharge frequency during passive movement of the contralateral extremities, which is synchronous to the limb movement [15]. The identification of such cells seems to be a good predictor of surgical outcome.

The MERs data are compared to a standard anatomical atlas of stereotaxy, to determine the exact location of the nuclei; they are also used to estimate the maximum length of nucleus traversed by the electrode, since the final DBS location will be in the trajectory that gives the longest run through the centre of the targeted nucleus's activity and contains movement related cells, provided that side-effects will not occur during macrostimulation. We usually continue descending the electrodes until the optic tract and the substantia nigra reticulate (SNr) are identified when performing DBS in GPi and STN, respectively. This will help us to define the lower borders of these structures, which again may prove useful in both implanting the final electrode and during postoperative stimulation. We test for the presence of the optic tract with the aid of a flashlight after reducing the light in the operating theatre. The patient is instructed to look into the flashlight as it is moved towards to and away from his eyes, while we record the presence of light evoked action potential discharges on the neuronal activity monitor. Even though it has been suggested that microelectrodes should not penetrate more than 2 mm deep to the pallidal base for MERs purposes because of the potential risk for damaging vessels in the choroidal fissure [4], we have never had this complication in

our practice. SNr is identified by its characteristic discharge pattern.

Step 3 – macrostimulation

In the absence of MERs, electrophysiological localisation can be done by intraoperative test stimulation, but the exact role of this technique in guiding DBS lead placement has not been established. This is because improvement in rigidity and bradykinesia may correlate with the impact's effect while stimulation induced improvement may take a few minutes. Furthermore, even though tremor is usually suppressed with stimulation intraoperatively [10, 11, 19], the degree of intraoperative tremor supression does not seem to predict long term control; it is known that, even those patients who display modest or absence tremor relief intraoperatively, will usually experience more substantial relief with chronic stimulation [15]. Therefore, we do not usually rely on the macrostimulation-induced relief from symptoms as the primary criterion for the correct lead placement and prefer to rely on MERs. Macrostimulation is mainly used to establish voltage thresholds for various adverse effects.

After withdrawing the microrecording electrode, which had the longest run of satisfactory recordings through the targeted nucleus as these were evaluated by the MERs, we use the probe to perform intraoperative test stimulation at its trajectory. During this procedure, we monitor the patient for the development of side effects, such as facial contractions including tongue and lips, contractions of contralateral limbs, dyskinesias, dysarthria, paresthesias, tonic eye deviation or blurred vision. Even though absence of side effects does not necessarily imply safe distance from clinically important white matter tracts, the side effects can guide us in selecting another trajectory, usually the one that provided the second-best recordings [14]. Generally, we consider selecting a different trajectory only if motor or visual side effects occur at 2 Volts or less. The optic tract is identified by producing stimulation induced visual phenomena, typically reported as ''flashes'' [7].

Step 4 – lead implantation and verification

Once the best location for the permanent DBS electrode placement is determined, the probe and the electrode are withdrawn from the brain parenchyma and replaced by the permanent quadripolar DBS macroelectrode (Medtronic electrodes 3389 and 3387). The implantable DBS multi-contact electrode which has been measured accordingly in order for its tip to rest in the desired position is then advanced through the appropriate holes of the Microdrive in the pathway of the withdrawn probe. In STN, the DBS electrode is placed in a way that its tip lays at the ventral border of the nucleus, at least 2 contacts lie within it and 1 above it, in the Zona Incerta. We try to avoid deep placement close to the SNr, since this has been associated with midbrain oedema and postoperative mental status changes. In GPi, the main concern is to avoid the placement of the DBS electrode near to the internal capsule and optic tract, because this may lead to significant side effects from these structures. Final test stimulation is given with the DBS electrode in place to assure that it is working properly and it is in the correct position. Following this, the guide wire inside the DBS lead is retracted and the lead secured. Using fluoroscopy, lateral skull X-rays are obtained to verify that the lead is in the intended position and has not moved while securing it (Fig. 1). The same procedure is then repeated on the opposite side.

Step 5 – lead anchoring

We have initially used the Medtronic cap provided within the set to secure the DBS electrode in place. With this technique, we have noticed a 1–2 mm downward displacement of the DBS electrode on several occasions, when verifying its position with fluoroscopy as previously described. For the past 2 years we have therefore been using the Navigus cap. After the DBS electrode has been placed in its final position, the Navigus support clip is placed around the lead and snapped into the base ring. Then, the lead is guided through the Navigus cranial base groove and finally secured by the application of the Navigus cap over it. A small amount of DuraSeal is added to prevent CSF leak and subsequently formation of fluid collection (''seroma'') anywhere along the subcutaneous space, where the electrode and the internal pulse generator (IPG) device will be implanted. The electrodes are then tunnelled and placed in the subcutaneous tissue of the scalp, on the side that the IPG will be placed, which is usually the left. The two surgical wounds are sutured, the right in two layers using vicryl 2.0 for the subcutaneous tissue and nylon 3.0 for the skin, while the left temporarily in one layer using nylon; the left wound will be reopened a bit later during the electrodes internalization procedure. Extreme caution is required to make sure that the subcutaneous knots stay in the deep wound layers and that careful apposition of

skin edges is achieved. Failure to do so may prolong time required for wound healing thus increasing the possibility for hardware infection.

Step 6 – IPG internalisation

After removal of the stereotactic arc and head-ring, the patient is sedated and intubated. He is placed into the supine position with the ipsilateral shoulder slightly elevated and the head rotated away from the side of implantation. The surgical team will at this time scrub again and the patient is administered a second dose of anti-staphylococcal antibiotics. A 5–6 cm incision is made under the clavicle and a subcutaneous pocket dissected bluntly over the pectoralis fascia, to hold the IPG (Kinetra, Medtronic). The electrodes are externalized by reopening the wound on the left side, the side of the subcutaneous pocket. The lead extender is then tunnelled under the scalp and behind the ear between the 2 incisions and attached to the DBS leads proximally and to the pulse generator distally. If an intermediate incision is required, this is placed behind the ear. The silastic sheaths are placed over the connections and secured with silk sutures. The transparent sheath is always used for the right DBS lead and the white sheath for the left lead, so it is easy to identify the leads in case electrode revision will be required. The connectors are positioned 2–4 mm behind the ear, deep in the subcutaneous tissue to avoid risk of erosion and unsatisfactory cosmesis. We also avoid placing them in the neck since the constant mobility of the area may result in a lead fracture. After the electrodes have been implanted, the IPG is placed into its subcutaneous pocket with the engraved letters on the case facing superficially. The wounds are again sutured as previously described. The total procedure time, including mounting the head-ring and the stereotactic CT is approximately 7 hours.

Post-operative MRI

Postoperative documentation of the exact final location of the DBS electrode is extremely important and cannot be overemphasized. This will help to define the area being stimulated and to select the DBS lead contacts most appropriate for stimulation. Furthermore, it will offer the surgical team a method for assessing the accuracy of their approach and guide them to further refinement of the planning and overall surgical technique. In post-operative MRI, the lead is seen as a relatively discrete round signal void approximately 3 mm in diameter, which is actually larger than the actual diameter of the lead. The centre of the round signal void is considered to represent the true lead position [15, 16]. All our patients will routinely undergo post-operative MRI within 48 hours from the procedure, so in case of erroneous lead placement we may re-implant as soon as possible, even though this has not been required in any case yet. The images are fused with the preoperative ones, in order to calculate the error in electrode placement in the z, x and y axis. The presence of a persistent error on one of the three axes, would suggest that the frame needs re-calibration.

Postoperative treatment

After the procedure the patient is extubated and returned to the ward. The surgical wounds are checked and cleaned daily until the time of discharge. We usually administer postoperative antibiotics for 48 hours. Stitches are removed on the 10th postoperative day, because the presence of the subcutaneous caps may stretch the skin and delay satisfactory wound healing. The Parkinson medication is usually restarted on the afternoon following the procedure at the preoperative doses. The stimulator is turned on the second post-operative day, after the MRI has verified that the DBS electrodes are in the correct position. When the stimulator is turned on for the first time, we try to identify the best contacts for stimulation and the presence of side effects. We tend not to pursuit high amplitude stimulation at this first postoperative period, since brain oedema around the lead may result in current spread and side effects from surrounding structures. The final stimulation parameters vary according to the targeted nucleus and are usually titrated during the first month of patient follow up, in accordance to appropriate modifications of the medication.

Conclusions

Many different ways of performing DBS have been described in the literature but the best practices are far from being established. Our surgical approach aims for an optimum clinical outcome with minimal patient risk and represents a synthesis of techniques: CT and MRI fusion for stereotactic localisation, direct targeting with visualisation of the anatomic target and indirect confirmation with geometric coordinates and the aid of a stereotactic atlas, MERs for intraoperative confirmation of the motor territory of the targeted nucleus, intraoperative macrostimulation to determine voltage thresholds

for stimulation induced adverse effects from nearby structures and postoperative MRI to confirm final lead location. Even though we have standardised the main aspects of our technique, our methodology continues to evolve as our own experience increases and also according to new information from the literature and to technological, surgical and anaesthetic advances.

References

1. Bejjani BP, Dormont D, Pidoux B, Yelnik J, Damier P, Arnulf I, Bonnet AM, Marsault C, Agid Y, Philippon J, Cornu P (2000) Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance. J Neurosurg 92(4): 615–625
2. Bittar RG, Burn SC, Bain PG, Owen SL, Joint C, Shlugman D, Aziz TZ (2005) Deep brain stimulation for movement disorders and pain. J Clin Neurosci 12(4): 457–463
3. Cuny E, Guehl D, Burbaud P, Gross C, Dousset V, Rougier A (2002) Lack of agreement between direct magnetic resonance imaging and statistical determination of a subthalamic target: the role of electrophysiological guidance. J Neurosurg 97(3): 591–597
4. Hamid NA, Mitchell RD, Mocroft P, Westby GW, Milner J, Pall H (2005) Targeting the subthalamic nucleus for deep brain stimulation: technical approach and fusion of pre- and postoperative MR images to define accuracy of lead placement. J Neurol Neurosurg Psychiatry 76(3): 409–414
5. Hariz MI (2002) Safety and risk of microelectrode recording in surgery for movement disorders. Stereotact Funct Neurosurg 78(3–4): 146–157
6. Kirschman DL, Milligan B, Wilkinson S, Overman J, Wetzel L, Batnitzky S, Lyons K, Pahwah R, Koller WC, Gordon MA (2000) Pallidotomy microelectrode targeting: neurophysiology-based target refinement. Neurosurgery 46(3): 613–622; discussion 622–624
7. Lozano A, Hutchison W, Kiss Z, Tasker R, Davis K, Dostrovsky J (1996) Methods for microelectrode-guided posteroventral pallidotomy. J Neurosurg 84: 194–202
8. Merello M, Cammarota A, Cerquetti D, Leiguarda RC (2000) Mismatch between electrophysiologically defined and ventriculography based theoretical targets for posteroventral pallidotomy in Parkinson's disease. J Neurol Neurosurg Psychiatry 69(6): 787–791
9. Morel A, Magnin M, Jeanmonod D (1997) Multiarchitectonic and stereotactic atlas of the human thalamus. J Comp Neurol 387: 588–630
10. Pollak P, Krack P, Fraix V, Mendes A, Moro E, Chabardes S, Benabid AL (2002) Intraoperative micro- and macrostimulation of the subthalamic nucleus in Parkinson's disease. Mov Disord 17 Suppl 3: S155–S161
11. Rodriguez MC, Guridi OJ, Alvarez L, Mewes K, Macias R, Vitek J, DeLong MR, Obeso JA (1998) The subthalamic nucleus and tremor in Parkinson's disease. Mov Disord 13 Suppl 3: 111–118
12. Schaltenbrand G, Wahren W (1977) Atlas for stereotaxy of the human brain. Georg Thieme, New York
13. Sakas DE, Boviatsis EJ, Tagaris G, Kouyialis AT, Stathis P, Korfias S (2002) A modified CT-MRI fusion protocol increases targeting accuracy and reduces microrecordings time in pallidal surgery. Acta Neurochir (Wien) 146: 940
14. Starr PA (2002) Placement of Deep brain Stimulators in the subthalamic nucleus or Globus pallidus internus: technical approach. Sterotact Funct Neurosurg 79: 118–145
15. Starr PA, Christine CW, Theodosopoulos PV, Lindsey N, Byrd D, Mosley A, Marks WJ Jr (2002) Implantation of deep brain stimulators into the subthalamic nucleus: technical approach and magnetic resonance imaging-verified lead locations J Neurosurg 97(2): 370–387
16. Starr PA, Turner RS, Rau G, Lindsey N, Heath S, Volz M, Ostrem JL, Marks WJ Jr (2004) Microelectrode-guided implantation of deep brain stimulators into the globus pallidus internus for dystonia: techniques, electrode locations, and outcomes. Neurosurg Focus 17(1): 20–31
17. Starr PA, Vitek JL, DeLong MR, Bakey RAE (1999) MRI-based stereotactic targeting of the globus pallidus and subthalamic nucleus. Neurosurgery 44(2): 303–314
18. Sumanaweera TS, Adler JR Jr, Napel S, Glover GH (1994) Characterization of spatial distortion in magnetic resonance imaging and its implications for stereotactic surgery. Neurosurgery 35(4): 696–703; discussion 703–704
19. Taha JM, Favre J, Baumann TK, Burchiel KJ (1997) Tremor control after pallidotomy in patients with Parkinson's disease: correlation with microrecording findings. J Neurosurg 86(4): 642–647
20. Voges J, Volkmann J, Allert N, Lehrke R, Koulousakis A, Freund HJ, Sturm V (2002) Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson disease: correlation of therapeutic effect with anatomical electrode position. J Neurosurg 96(2): 269–279
21. Zonenshayn M, Rezai AR, Mogilner AY, Beric A, Sterio D, Kelly PJ (2000) Comparison of anatomic and neurophysiological methods for subthalamic nucleus targeting. Neurosurgery 47(2): 282–294

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Deep brain stimulation for Parkinson's disease

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Summary

Indications for the treatment of Parkinson's disease (PD) with deep brain stimulation (DBS) are severe, therapy refractory tremor and complications of long-term levodopa uptake. Since its first application DBS has become a standard therapy for these patients. Theoretically, the ventrolateral part of the internal pallidum (GPI) or the subthalamic nucleus (STN) are suitable targets in order to treat all cardinal symptoms of patients in an advanced stage of PD stereotactically. Although clinical efficacy of both GPI or STN stimulation is obviously comparable, it has become widely accepted to prefer STN over GPI DBS. If PD-associated, medically intractable tremor is the most disabling symptom, stimulation of the ventrolateral motor thalamus can be an alternative. Anatomical targets for DBS are small and located in critical brain areas. Furthermore, this type of surgery is highly elective. As a consequence, high resolution multiplanar imaging and adequate treatment planning software are indispensable prerequisites for DBS surgery. Currently, commercially available impulse generators deliver a permanent high frequency periodic pulse train stimulation that interacts rather unspecifically with the firing pattern of both normal and pathological neurons. Prospectively, the development of more specific stimulation paradigms may help to improve the efficacy of this treatment modality.

Keywords: Neuromodulation; deep brain stimulation; DBS; Parkinson's disease; review.

Introduction

Typical, idiopathic Parkinson's disease (PD) affects on average 100 per 100,000 population. Cardinal symptoms are bradykinesia, rigor, tremor, and postural instability. Even though at the beginning of the disease the patients respond excellently to the substitution of dopamine with oral levodopa, up to 50% of cases present with instability of medication effect on motor symptoms and develop drug induced dyskinesias 5–6 years after the onset of medication therapy [47, 80, 90]. These patients are severely disabled by on–off fluctuations which occur unpredictably and independently of medication uptake.

The basal ganglia model described by Alexander *et al.* [2] suggests that in PD the internal pallidum (GPI) and the subthalamic nucleus (STN) are overactive. Therefore, two targets are theoretically suitable to treat all cardinal symptoms of patients in an advanced stage of this disease stereotactically. Inspired by the experience gained with lesioning, Siegfried and Lippitz presented first three PD patients treated successfully with deep brain stimulation (DBS) in the GPI [94]. In the same year (1994), Benabid *et al.* reported about positive effects on PD motor symptoms and dyskinesia when stimulation electrodes were placed in the STN [8].

The DBS program of the Department of Stereotaxy and Functional Neurosurgery, University of Cologne, started in the year 1996. Until December 2005, we operated a total of 563 patients, the majority of them for PD (457 patients). In the present manuscript we mainly summarize methodological and clinical data from the literature to provide practically relevant stand-of-the-art information to the reader. When applicable we supplemented this information by remarks reflecting our own policy.

Patient selection

Indications for the treatment of PD with DBS are severe, therapy refractory tremor and complications of long-term levodopa uptake. Selection of PD patients for DBS is a multidisciplinary process combining the expert opinion of a neurologist and stereotactic neurosurgeon, in some cases also needing the opinion of a psychiatrist. The main selection criteria are [17]:

(i) Drug resistance: candidates for DBS surgery suffer from severe motor complications (fluctuations and dyskinesias) despite optimized medication. Therefore, the cooperating neurologist – ideally

an expert for movement disorders – will critically review actual and previous medication schemes. Because most patients are referred for surgery at a later stage of disease, drug resistance, however, is a weak parameter.

(ii) L-Dopa sensitivity: candidates for DBS should have an excellent response to L-Dopa preoperatively documented with a standardized L-Dopa test. This test is performed minimum 12 hours after withdrawal of all antiparkinsonian medication (off-medication) with a supra-threshold levodopa dose (e.g. 1.5-fold dose of the individual morning levodopa dose plus the morning levodopa equivalent dose of dopaminagonists) [50]. At the time of best medication effect (''best-on'') the patient is examined using standardized tests, for instance, the Unified Parkinsons Disease Rating Scale (UPDRS) [24]. Improvement should be at least 50% relative to off-medication conditions.

(iii) Disability: weighted is the surgical risk against the anticipated improvement of the quality of life in response to DSB. In other words, the severity of the patient's impairment should justify the risk associated with surgery. ''Disability'' does not only refer to the degree of motor disturbances but also to aspects which are determined by the individual situation of the patient (e.g. social impairment due to the disease, profession, patient's age, etc.).

(iv) Neurosurgical risks and contraindications: to be considered is the individual surgical risk that may be increased due to different medical conditions. Magnetic resonance imaging (MRI), documentation of patient's history, extended clinical examination, and neuropsychological tests help elucidate contraindications for DBS surgery (Table 1, modified from Ref. [118]).

Table 1. *Exclusion criteria in patient selection in deep brain stimulation for treatment of Parkinson's disease (modified from Ref. [118])*

– Severe brain atrophy
– Preexisting brain damage (e.g. infarction, trauma, tumor, vessel malformation)
– Severe cerebral micro-angiopathy
– Severe systemic disease
– Chronic immune suppressive therapy
– Chronic anticoagulant therapy
– ''Biological'' age >75 years
– Signs of dementia
– Severe frontal dysexecutive syndrome
– Established paranoid psychosis
– Severe affective disorders (depression or mania)
– Severe disorders of personality or behavior

The above mentioned criteria are strictly applied for the selection of patients theoretically being candidates for either GPI or STN stimulation. If PD-associated, medically intractable tremor is the most disabling symptom, stimulation inside the ventrolateral motor thalamus can be an alternative even when the cited objective criteria are not fulfilled. Thalamic stimulation, however, does not improve akinesia, rigor, or postural instability. Long-term evaluations documented an ongoing good tremor control, but showed that the disease progresses and that after several years other motor symptoms will mainly interfere with the patient's well being [81]. As a consequence, we prefer STN DBS in younger patients, even when tremor is the dominant symptom. Thalamic stimulation is reserved for older patients with a long history of tremor-dominant PD, in whom a quick response of the disabling symptom is desired.

Description of surgical technique

Accuracy of targeting

If all factors that may influence the accuracy of stereotactic surgery, such as mechanical properties of the stereotactic apparatus (a modified Riechert Mundinger system [99]), imaging, surgeon, and instruments have been considered, the mean spatial accuracy for the placement of e.g. a radioactive source (iodine-125 seed) is 2.0 mm [106]. In contrast, Holloway *et al.* reported a substantially higher absolute 3D-error of 3.2 ± 1.4 mm when they introduced DBS electrodes with a frameless stereotactic system [35]. Based on the above, frame-based stereotaxy seems to be for us the most precise technique at present.

Treatment planning

Magnetic resonance imaging (MRI) provides a soft tissue contrast satisfying all requirements related to target definition and control of the surgical approach. The structures which need to be visualized for targeting are: anterior commissure (AC), posterior commissure (PC), intercommissural line (AC–PC-line), STN boundaries, and boundaries and subunits of the pallidum [97]. Of importance is also the visualization of trajectories in relation to organs at risk (mostly brain vessels) in a multiplanar mode.

One limitation of MRI when used for calibration of the stereotactic coordinate system is geometric image distortion, which is largest at the periphery of the field of view, the place where the fiducials are fixed to the

Table 2. *Technical data for intraoperative stereotactic imaging*

Modality	Parameters
CT[1]	matrix size 512 × 512, slice distance 2 mm, 50–70 slices
MR-imaging	
t1-weighted[2]	sequence: gradient-echo, time of repetition 30 ms, time of echo 15 ms flip angle 40 ± bandwidth 35 Hz per pixel
t2-weighted[2]	sequence: spin-echo, time of repetition 2000 ms, time of echo 90 ms flip angle 90 ± bandwidth 120 Hz per pixel
inversion recovery[3]	sequence: TSE, time of inversion 400 ms, time of repetition 4000 ms, time of echo 13 ms, TSE-factor 7

[1] Siemens SOMATOM: field of view 290 mm, voltage 120 kV, charge 350 mAs, kernel H40s, single slice mode.
[2] Philps Gyroscan INTERA Version 7.0 (Magnetic field 1.5 T): matrix size 512 × 512, field of view 290 mm, slice distance 2 mm, 70 slices 3D-encoding.
[3] Philps Gyroscan INTERA Version 7.0 (Magnetic field 1.5 T): matrix size 256 × 256, field of view 256 mm, slice distance 2 mm.

frame. Even though it is possible to quantify these inaccuracies in phantom studies [43, 123], object-dependent distortion in MRI [41] complicates the transfer of these results to patient imaging different from computed tomography (CT).

In general, we perform both CT and MRI examinations intraoperatively with fiducials mounted to the frame. Following the direct fiducial based transformation of CT-images into the stereotactic coordinate system, MR-images are integrated using direct and landmark based image transformation [22]. Technical data are listed in Table 2.

Documentation of electrode localization

The systematic postoperative documentation of electrode localization is a prerequisite for the correlation of therapeutic and undesired effects of DBS with anatomy. Stereotactic radiography (STX-XRAY) using X-ray tubes installed in the operating room provides a precise and artifact free control. In a second step, coordinates of the electrode tip and of single contacts can be transferred into treatment planning MR-images for detailed functional and anatomic analysis [114].

In comparison to STX-XRAY, CT or MRI control, examinations with the stereotactic frame attached to the patient's head display anatomic information immediately. One disadvantage of both CT- and MR-control images are artifacts caused by the implanted electrodes. The particular problem of MRI controls are the restrictions due to the implanted ferromagnetic material. Rezai *et al.* [82] investigated in a clinically relevant phantom study the heat induction inside a 1.5 T magnetic field for different implant configurations. Using the head-coil (specific absorption rate (SAR): 0.07–0.24 W/kg) the maximum measured temperature increment was 7 °C at the tip of the electrode, while using the body coil (SAR: 098–3.9 W/kg) the temperature increase ranged from 2 to 25 °C. MRI safety recommendations limit SAR to 0.1 W/kg in investigations of DBS patients [66].

Targets

Three targets are suitable for DBS in the treatment of PD motor symptoms: (i) the ventral motor area of the thalamus together with the subthalamic region, (ii) the ventro-postero-lateral part of the GPI, and (iii) the STN. In general, for indirect definition of stereotactic targets, coordinates are taken from a stereotactic brain atlas (e.g. Schaltenbrand-atlas [88] or Talairach atlas [100]) and are transferred into the patient's brain using the AC–PC line as anatomic reference. Brain atlas derived coordinates need to be adjusted to the dimensions of the individual brain using the length of the AC–PC line, the thalamus height at the middle of the AC–PC line, and the hemispheric width or width of the third ventricle as reference [10]. Direct targeting is possible, whenever boundaries and/or subunits of a given anatomic structure are visible on MR images.

Motor thalamus

This term refers to the ventral thalamic region with cerebellar and basal ganglia (pallidal and nigral) afferent territories [39]. Hassler inaugurated the thalamic ventralis intermedius (V.im.) nucleus in ablative PD surgery [31]. Atlas coordinates for targeting of the V.im. are 7.0 mm anterior to PC and 14.5 mm lateral to the AC–PC line [88]. Mundinger recommended in addition to thalamic motor nuclei also lesioning of cerebellothalamic or pallidothalamic fibers aiming directly at the subthalamic area [69].

Two rationales suggest also stimulation therapy in this area: First, subcortical afferents particularly connections between the dentate nucleus and motor thalamus are bundled at the ventral border of the V.im. [32]. Second, the principal component of the subthalamic motor area – the zona incerta – [71] is reciprocally connected with several cortical areas, upper brainstem, cerebellum, and thalamus [72, 79]. Our clinical observations and single reports from the literature [3, 44, 70] indicate that substantial tremor improvement, particularly of proximal components can be achieved by DBS using elec-

trode contacts below the ventral base of the motor thalamus.

Globus pallidus internus (GPI)

Brain atlas coordinates in general are the same as recommended by Laitinen for lesional pallidal surgery [55]: 2–3 mm anterior to the midpoint of the AC–PC line (midcommissural point, MCP), 20–22 mm lateral and 3–6 mm ventral from this point.

Variation of the stimulation target inside the GPI seems to cause different clinical effects [6, 48, 121]. Krack *et al.* hypothesized that the inner portion of the GPI might be involved in the pathophysiology of akinesia and the outer portion in that of rigidity; he considered the central part of the GPI as the optimal site for GPI-stimulation in PD [48]. In nine consecutive PD patients treated in our series with GPI-DBS the clinical effect was correlated with electrode localization; the most effective electrode contacts were located 3.5 ± 1.9 mm anterior to the MCP, 2.0 ± 2.6 mm below, and 22.5 ± 2.1 mm lateral to the AC–PC line [116].

Subthalamic nucleus (STN)

Targeting of the STN is complex because of its lens shape, its small dimension (approximately 10 mm rostrocaudal, 10.5 mm mediolateral, and 7 mm dorsoventral), and its oblique orientation with respect to the three anatomical axes. Brain atlas derived coordinates for indirect targeting are: 2–3 mm behind the MCP, 3.7 mm below and 12 mm lateral to the AC–PC line [8, 88]. The nucleus can also be directly targeted on MR-images utilizing t2-weighted or inversion recovery (IR)-sequences.

Zonenshayn *et al.* [124] reported that atlas based and midcommissural methods provided the most accurate guidance. This conclusion, confirmed by others, [15] is in contrast to the data of Richter *et al.* [83], who demonstrated that the position of the anterior border of the STN, when defined directly on MR-images, seems to be more posterior and the medial border to be more lateral than their position in the brain atlas. Also the size of the nucleus was highly variable appearing smaller on MR-images compared to the brain atlas. These authors concluded that care must be taken when relying on coordinates relative to the commissures for targeting of STN [83].

Postoperative localization studies revealed that the optimum functional target inside the STN for the treatment of PD motor symptoms by DBS seems to be at the dorsolateral border zone of the nucleus [30, 34, 56, 86, 114, 122].

Electrophysiology

Most frequently applied techniques are macrostimulation and microelectrode or semi-microelectrode recording.

Macrostimulation

Low frequency stimulation (≤ 10 Hz) is applied to challenge side effects. High frequency stimulation (100–200 Hz) is considered to improve disease associated symptoms subsequently confirming the anatomic target.

Microelectrode recording (MER)

Arguments in favor of MER are the fine degree of localization together and research insights into individual properties and population characteristics of neurons, which in turn may provide important insights into the pathophysiology of a particular disease.

A few publications compared the accuracy of both MR imaging and MER when applied in STN targeting. According to Zonenshayn *et al.* [124] direct MRI targeting of the STN was the least accurate method if compared to targeting with physiological recordings (average distance error: 2.6 mm). Others, however, reported much smaller deviations suggesting that MER is not a "must". Comparing the indirect with semi-microrecording, targeting, the average distance between the location of the center of the STN as determined stereotactically and electrophysiologically was in the order of 0.5–0.9 (SD range: 0.5–0.7) [56]. In another study, mean absolute coordinate changes of the intraoperatively determined target, compared to the calculated target, were near 1 mm for the vertical and anterior-posterior direction and only 0.5 mm for the lateral direction [98]. Hamani *et al.* found a good correlation between MER and the borders of the STN defined directly with MRI except for the anterior–posterior axis [28].

At present, it is not possible to give a general recommendation for MER because clinical studies performed in the past did not address questions like impact of MER on targeting accuracy, clinical outcome and surgical risk on a high evidence level. With the data available, the theoretical advantages of MER need to be balanced against the potentially increased risk of infections, brain shift due to the loss of CSF, or intracerebral hemorrhage when multiple electrodes are used. It appears that MER may provide additional information about the accuracy of the individual anatomical targeting; therefore, it has value when applied within a limited time

frame and in combination with extended MRI-based 3D-treatment planning.

Clinical results

DBS of the ventrolateral motor thalamus

Thalamic (V.im.) stimulation for the treatment of tremor was first applied by Benabid *et al.* [7]. Clinical studies performed thereafter confirmed the good results of this group. By neurostimulation in the V.im. or ventralis oralis posterior (V.o.p.) nucleus complete or partial tremor suppression was achieved in 71–100% of PD patients (Table 3) [1, 9, 12, 14, 46, 60, 73, 81, 92]. One prospective comparative study randomized patients with PD either for thalamotomy (23 patients) or thalamic DBS (21 patients) [92]. Both modalities improved tremor effectively. According to the Frenchay Activity Index, however, DBS resulted in comparably better functional outcome and was associated with a lower rate of adverse events. Parkinsonian motor symptoms other than tremor did only respond sporadically [14, 60, 81, 101]. These general effects of thalamic DBS, however, are not comparable to those gained with GPI or STN DBS.

As a result of the microthalamotomy effect there is sometimes need to adjust stimulation parameters during the first weeks following surgery [9, 73, 101]. Voltage increment during the first year after surgery was significant in two studies [46, 60] but did not reach significance during the long-term (6–7 years) follow-up in another study [81].

Frequently observed side effects of thalamic DBS which could not be thoroughly ameliorated by parameter adjustment were paresthesias (7.5%) [1], disequilibrium (3.7–5.0%) [1, 12, 46], arm or foot dystonia (3.8–11%) [12, 14, 46], and dysarthria (10–22%) [1, 92].

Table 3. *Clinical studies on thalamic stimulation for the treatment of Parkinson disease*

Citation	Tremor improvement* # no. (%) implanted thalami § no. (%) treated pts.	Follow-up time
Blond [12]	§19/19 (100)	NA
Caparros-Lefebvre [14]	§8/10 (80)	22–34 months
Alesch[1] [1]	#31/33 (94)	3–48 months
Benabid [9]	#104/118 (88)	0.5–8 years
Koller[2] [46]	§17/24 (71)	12 months[6]
Ondo[3] [73]	§19/19 (100)	3 months[6]
Limousin [60]	§63/74 (85)	12 months[6]
Schuurman[4] [92]	§thalamotomy: 21/23 (91) §DBS: 21/22 (95)	6 months[6]
Rehncrona[5] [81]	§12/12 (100)	6–7 years

NA Not addressed; * sum of complete and partial (some symptoms under stress) response, [1] results pooled for PD (23 pts.) and Essential Tremor (4 pts.); [2] multicenter study, blinded evaluation; [3] prospective study, blinded motor evaluation; [4] prospective randomized study (thalamotomy vs. DBS); [5] retrospective long-term analysis, blinded re-evaluation; [6] median time.

DBS of the Globus pallidus internus or Subthalamic nucleus

Studies with a maximum follow-up of 2 years

Motor symptoms. Within the first years after surgery, GPI stimulation in the off-medication state improved motor symptoms (UPDRS part III) at an average of $37.3 \pm 14.3\%$ if compared to baseline (range: 31–55%, Table 4) [4, 16, 27, 48, 52, 53, 61, 75, 93, 94, 108, 118] and STN stimulation at an average of $50.5 \pm 10.7\%$ (range: 28–64%, Table 6) [13, 16, 25, 33, 37, 40, 45, 52, 59, 62, 67, 74, 76, 95, 105, 111, 112, 117]. Weaver *et al.* calculated in a meta-analysis a significant mean improvement of 40.0% for GPI DBS and 54.3% for STN DBS [120]. The difference between the two groups was not significant ($p = 0.09$).

UPDRS scores for rigor, bradykinesia and tremor improved by GPI stimulation at an average of 43.1 ± 18.3, 33.6 ± 5.7, and $65.5 \pm 20.0\%$ [4, 16, 27, 48, 61, 118], and by STN stimulation at an average of 52.9 ± 15.5, 43.5 ± 14.0 and $79.2 \pm 6.6\%$ [16, 33, 40, 45, 59, 62, 74, 76, 95, 112, 117]. Axial symptoms (scores for ''gait'', and ''postural instability'') improved in STN studies [16, 33, 40, 45, 59, 62, 74, 76, 95, 112, 117] more effectively (average: $52.9 \pm 17.6\%$) compared to GPI studies (average improvement: $35.8 \pm 4.8\%$) [4, 16, 27, 48, 61, 118]. Speech was addressed in only one GPI series [118] and improved by 56% at 1 year FU. In STN studies, speech seemed to be the least responding of all motor symptoms (average improvement: 24.0 ± 4.9) [33, 40, 59, 62, 74, 95, 117]).

Activities of daily living. Activities of daily living (ADL, UPDRS part II) improved by GPI DBS at an average of $33.1 \pm 19.4\%$ (range: 5–68% [4, 16, 27, 48, 52, 53, 61, 75, 118], Table 4) and by STN DBS at an average of $47.9 \pm 14.1\%$ (range: 28–66% [13, 16, 25, 33, 37, 40, 45, 52, 59, 62, 67, 74, 76, 95, 105, 111, 112, 117], Table 6). In the meta-analysis of Weaver *et al.* [120] the calculated mean ADL score reductions were in the same range (GPI: 38.6%, STN: 47%).

Dyskinesia and medication. Independent of the stimulation site, on-medication/on-stimulation dyskinesia

Table 4. *Clinical studies on the treatment of advanced Parkinson disease with bilateral GPI stimulation*

Citation	No. of pts.	Follow-up	UPDRS III (% change)	ADL (% change)	Dyskinesia (% change)	Change of medication
Siegfried [94]	3	6–12 months	3/3 pts. improved	NA	NA	NA
Pahwa [75]	3	minimum 3 months	21	19	NA	slightly increased[1]
Tronnier [108]	6	2–15 months	no change	NA	significant	12% decrease[1]
Ghika [27]	6	2 years	50	68	29	11% decrease[1]
Krack [48]	5	6 months	39	46	82	29% increase[1]
Kumar* [53]	17	6 months	31	39	66	not significant[1]
DBS study group [16]	38	6 months	33	36	67	unchanged[1]
Krause [52]	6	1 year	41	5	58	increased over time[1]
Scotto di Luzio [93]	5	1 year	42	NA	55	6% increase[1]
Loher [61]	10	1 year	41	34	71	5% increase[2]
Anderson [4]	10	1 year	39	18	89	3% decrease[1]
Volkmann [118]	10	1 year	55	50	75	23% decrease[2]
	9	3 years	49	26	68	unchanged[2]
	6	5 years	23	0	70	21% decrease[2]

* Multicenter study; *NA* not addressed: *UPDRS* Unified Parkinson's Disease Rating Scale; *ADL* activities of daily living.
Examination conditions: UPDRS Part III, ADL: baseline (medication OFF) vs. end of study (medication OFF/stimulation-ON), dyskinesia: baseline (medication ON) vs. end of study (medication ON/stimulation-ON). Reduction of medication: [1] change of L-Dopa dose; [2] change of levodopa equivalent dose (*LED*); [3] Levodopa equivalent dose (*LED*) without considering COMT inhibitors.

severity at follow-up investigations decreased significantly compared to on-medication dyskinesia severity at baseline. The average reduction was $64.4 \pm 18.3\%$ for GPI DBS (range: 29–89%, Table 4 [4, 16, 27, 48, 52, 53, 61, 93, 108, 118]) and $76.9 \pm 12.6\%$ for STN DBS (range: 58–91%, Table 6 [16, 33, 37, 40, 45, 52, 59, 62, 67, 74, 95, 105, 111, 112, 117]).

GPI DBS acts directly on L-Dopa induced dyskinesia; neuromodulation is therefore independent of medication reduction whilst in the case of STN stimulation, medication has to be reduced to gain dyskinesia improvement. Either expressed as change of L-Dopa dose or change of levodopa equivalent dose (LED) the reduction in STN patients was on average $52.2 \pm 16.1\%$ (range: 22–80% [13, 16, 25, 33, 37, 40, 45, 52, 59, 67, 74, 76, 95, 105, 111, 112, 117], Table 6) with reference to baseline. In the above cited meta-analysis [120], the average reduction of 52% was significant. In contrast, in none of the listed studies addressing GPI DBS, dopaminergic medication was significantly

Table 5. *Clinical studies on the treatment of advanced Parkinson disease with bilateral GPI stimulation: improvement in UPDRS III subscales (18–31) assessed at baseline (medication OFF) and at end of study (medication OFF/stimulation-ON)*

Citation	Follow-up	Score (% change) (UPDRS item no.)					
		Rigidity (22)	Bradykinesia (23–26)	Tremor (20–21)	Gait (30)	Postural instability (29)	Speech (18)
Siegfried [94]	6–12 months	NA	NA	NA	NA	NA	NA
Pahwa [75]	minimum 3 months	NA	NA	NA	NA	NA	NA
Tronnier [108]	2–15 months	NA	NA	NA	NA	NA	NA
Ghika [27]	2 years	46	37[6]	84	40[7]		
Krack [48]	6 months	52	31	60	41		
Kumar* [53]	6 mth	NA	NA	NA	NA	NA	NA
DBS study group [16]	6 months	30	26	59	35	36	NA
Krause [52]	1 year	NA	NA	31	NA	NA	NA
Scotto di Luzio [93]	minimum 1 year	NA	NA	NA	NA	NA	NA
Loher [61]	1 year	41	41	80	32	26	NA
Anderson [4]	1 year	47	33	79	40[1]		
Volkmann [118]	1 year	42	47	100	36[4]		56[5]
	3 years	50	53	100	47[4]		25[5]
	5 years	70	0	100	22[4]		0[5]

NA Not addressed; * multicenter study; [1] "axial motor signs" not specified; [2] mean of items 27–30; [3] sum of items 13–15, 29, 30; [4] posture + gait; [5] speech + swallowing; [6] sum of items 19, 23–26, 31; [7] sum of items 27–30.

Table 6. *Clinical studies on the treatment of advanced Parkinson disease with bilateral STN stimulation (studies with >10 patients)*

Citation	No. of pts.	Follow-up	UPDRS III (% change)	ADL (% change)	Dyskinesia (% change)	Reduction of medication (% change)
Limousin [59]	24	1–2 years	60	60	63	50[1]
Houeto [37]	23	6 months	NA	66	77	61[2]
Molinuevo [67]	15	6 months	66	72	81	80[1]
Broggi [13]	17	8 months (mean)	36	31	NA	33[1]
DBS study group* [16]	96	6 months	51	44	58	37[2]
Krause [52]	12	1 year	40	26	58	significant
Lopiano [62]	16	3 months	57	57	67	NA
Volkmann [117]	16	1 year	61	62	90	65[2]
Figueras-Mendez [25]	22	1 year	63	41	NA	32[1]
	9	2 years	49	47		
Ostergaard [74]	26	1 year	64	64	86	22[1]
Simuni [95]	12	1 year	47	49	64	55[2]
Thobois [105]	18	6 months	55	52	91	66[2]
	14/18	12 months	62	60	91	
Vesper [111]	38	1 year	38	66	58	53[1]
Vingerhoets [112]	20	2 year	45	37	92	79[2]
Herzog [33]	48	6 months	51	53	83	49[2]
	32	1 year	58	49	87	42[2]
	20	2 year	57	43	85	68[2]
Kleiner-Fisman [45]	25	24 months (range: 12–52)	41	24	82	36[2]
Pahwa [76]	33	1 year	38	33	NA	44[2]
	19	2 years	28	28		57[2]
Jaggi [40]	28	1 year	42	38	71	63[1]
Romito [85]	22	3 years	50	68	"improved"	66[2]
Krack [51]	49	5 years	54	49	58	63[2]
Rodriguez-Oroz* [84]	49	3–4 years	50	43	58	35[2]
Schüpbach [91]	30	5 years	54	40	79	58[2]
Visser-Vandevalle [113]	20	4 years	43	59	74	47[2]

NA Not addressed; *UPDRS* Unified Parkinson's Disease Rating Scale; *ADI* activities of daily living; * multicenter Study.
Examination conditions: UPDRS Part III, ADL: baseline (medication OFF) vs. end of study (medication OFF/stimulation-ON), dyskinesia: baseline (medication ON) vs. end of study (medication ON/stimulation-ON). [1] Reduction of medication: change of L-Dopa dose; [2] change of levodopa equivalent dose (*LED*); [3] levodopa equivalent dose (*LED*) without considering COMT inhibitors.

reduced [4, 16, 27, 48, 52, 53, 61, 75, 93, 108, 118] (Table 4).

Studies with follow-up periods >2 years

GPI-stimulation. Volkmann *et al.* published 5-year follow-up data of 6 out of 10 consecutive patients treated for PD with GPI DBS [119]. Only dyskinesia remained significantly reduced until the last assessment. Off-period motor symptoms and the beneficial effects of stimulation on activities of daily living started to decline after the first year. Two other studies with maximum follow-up times of 3 years confirmed this observation [21, 27].

Changes in stimulation response over time occurred despite a sustained L-Dopa response (59% at 5 years). Volkmann *et al.* hypothesized a loss of stimulation effect rather than progression of the underlying disease [119]. This assumption is supported by the finding that, in patients in whom GPI electrodes were replaced by STN electrodes due to significant reduction of the stimulation effect, the initial good clinical response to neurostimulation was restored [36, 119].

Twenty patients treated with pallidal stimulation in a multicenter study [84] presented with a relatively more stable outcome. Assessed 3–4 years after surgery in the medication-off state, motor functions were still significantly improved (39.0%), Also ADL scores (28.4%) and the severity of "on-medication" dyskinesia were still improved (75.9%). Postural stability and speech at no observation point (1-year and 3–4 years follow-up) did respond significantly. Between the first and last follow-up, the total motor score, and in particular rigidity, bradykinesia and gait, had worsened, and the stimulation effect on ADL and dyskinesias had declined. All these changes, however, were not significant [84].

The majority of stimulation electrodes are programmed in the monopolar mode (62% [119], 70% [84]). Changes of implantable pulse generator (IPG) settings over a 3–5 year-follow-up period were not significant [84, 119]. In the literature, only few authors comment on IPG

replacement due to battery exhaustion when PD is treated with GPI DBS. In one long-term study, mean durability of IPG batteries was 48.5 months (range: 24–67 months) [119].

STN stimulation. In a follow-up of 3–4 years, bilateral STN stimulation (49 patients) offered significant improvement in total motor score (50%) and UPDRS II scores (43%) (compared to baseline off-medication state) and reduced the severity of ''on-medication'' dyskinesia by 59% [84]. Speech in the off- and on-medication state had worsened between the first and fourth year with respect to baseline. Gait, posture, and ADL responded significantly less well to STN stimulation if the follow-up at 1 year was compared to the follow-up at 3–4 years [84].

Krack *et al.* assessed 49 consecutive patients treated with bilateral STN stimulation at five years [51]. Motor function scores during off-medication significantly improved by 54% and ADL scores by 49% compared to baseline values. There was an ongoing positive stimulation effect on dyskinesia during on-medication (57.9%) with the dose of dopaminergic medication still significantly reduced. Consistent with the natural course of PD, however, akinesia, speech, postural stability, and freezing of gait all worsened between the first and fifth year [51].

The preferred stimulation mode is monopolar (77% of the electrodes [91] or 90% of the patients [51]). Changes of the stimulator setting after the first year were not significant in two studies [51, 91]. In one study, the amplitude had to be increased significantly between 3 and 12 months postoperatively [84]. Within an observation period of five years, the frequency of IPG replacement due to battery exhaustion varied from 2% (1/49 patients [51]) to 35% (13/37 patients [91]). Table 8 lists IPG settings in long-term studies.

Adverse events following GPI DBS or STN DBS

Summarizing the data from cited studies [4, 16, 27, 48, 52, 53, 61, 93, 108, 118], permanent side effects of GPI stimulation were: hypophonia (4%), gait freezing (2.3%), limb dystonia (2.3%), eyelid apraxia (1.6%), increased libido (1.6%), dysarthria (0.8%), and choreiform foot movement (0.8%). General neurological and psychiatric complications of GPI stimulation were depression (0.8%) and perioperative confusion (7%) [4, 16, 27, 48, 52, 53, 61, 93, 108, 118].

Table 7. *Clinical studies on the treatment of advanced Parkinson disease with bilateral STN stimulation (studies including >10 pts.): improvement of UPDRS III subscales (18–31) assessed at baseline (medication OFF) and at end of study (medication OFF/stimulation-ON)*

Citation	Follow-up	Score (% change) (UPDRS item no.)					
		Rigidity (22)	Bradykinesia (23–26)	Tremor (20–21)	Gait (30)	Postural instability (29)	Speech (18)
Limousin [59]	1–2 years	68	61	80	55	61	22
Houeto [37]	6 months	NA	NA	NA	NA	NA	NA
Molinuevo [67]	6 months	NA	NA	NA	NA	NA	NA
Broggi [13]	8 months (mean)	NA	NA	NA	NA	NA	NA
DBS study group* [16]	6 months	59	43	80	56	50	NA
Krause [52]	1 year	NA	NA	NA	NA	NA	NA
Lopiano [62]	3 months	54	61	68	57	28	33
Volkmann [117]	1 year	75	48	89	59[4]		24[5]
Figueiras-Mendez [25]	1 year	53	NA	71	NA	NA	NA
	2 years	51		78			
Ostergaard [74]	1 year	72	55	90	64	62	25
Simuni [95]	1 year	33	40	83	52	84	26
Thobois [105]	6 months	NA	NA	NA	NA	NA	NA
	12 months						
Vesper [111]	1 year	NA	NA	NA	NA	NA	NA
Vingerhoets [112]	2 years	62	30	77	46[1]		
Herzog [33]	6 months	59	53	72	55[2]	NA	20
	1 year						
	2 years						
Kleiner-Fisman [45]	24 months (12–52 months)	42	40	85	[3]55		
Pahwa [76]	2 years	24	16	79	28	44	NA
Jaggi [40]	1 year	36	32	77	13	84	18

NA Not addressed; * multicenter study; [1] axial motor signs: not specified; [2] mean of items 27–30; [3] addition of items 13–15, 29, 30; [4] posture + gait; [5] speech + swallowing.

Table 8. *Stimulator settings for bilateral STN stimuation at 3–5 years follow-up (mean values ± SD)*

Citation	Voltage (V)	Frequency (Hz)	Pulse width (μs)
Rodriguez-Oroz* [84]	3.1 ± 0.5	151 ± 23	72 ± 20
Krack [51]	3.1 ± 0.4	145 ± 19	64 ± 12
Schüpbach [91]	[1]2.8 ± 0.4	150 ± 27	64 ± 10
	[2]2.9 ± 0.4	148 ± 26	62 ± 8

[1] Right electrodes; [2] left electrodes; * multicenter study.

In a systematic review of the clinical literature [29], the most frequent adverse effects of bilateral STN stimulation in PD patients ($n = 537$) were: hypophonia (5.8%), eyelid apraxia (4.6%), increased libido (0.8%), sialorrhea (0.9%), and decreased memory (1.1%). Other symptoms were reported but not quantified (dystonia, paresthesia, diplopia, dyskinesia, dysarthria). Modulations of mood and behavior were more frequently reported in STN DBS (depression: 4.7%, mania/hypomania: 2.0%, perioperative confusion: 13,7% [29]) than in GPI DBS. Depression during the first postoperative months led to suicidal ideation in some patients [11, 19]. With longer follow-up, however, depression in STN stimulated patients seems to improve [5, 26, 54, 89, 117]. Other adverse reactions caused by STN stimulation were apathy [20, 87, 117], abulia [59, 67, 117], anhedonia [117], and hypersexuality [52, 85]. Psychiatric problems were in most cases transient, starting immediately after implantation of the stimulation system and lasted for a few weeks. These complaints may in part be related to the acute withdrawal of dopaminergic medication.

Body weight was not regularly registered in the cited GPI studies. Following STN DBS, body weight increased in 72–100% of patients [25, 51, 59, 62, 68, 85, 117] (mean weight increment: 4.0–16 kg) [25, 51, 59, 68, 85, 109]. Ongoing severe (>10 kg) weight gain at 12 months after surgery was found in 27% of the patients with GPI and in 37.5% of patients with STN stimulation [117].

Quality of life

In a recently presented article [18], the literature was reviewed from 1965 to 2005 for publications on patient's health related quality of life (HRQoL). Eight studies were selected assessing the outcome in PD patients treated with STN DBS [23, 42, 54, 58, 64, 78, 96, 107]. In one of these studies fulfilling the criteria of class 1b evidence, 34 patients were randomized to unilateral pallidotomy or bilateral STN DBS [23]. Although the improvement of HRQoL in STN stimulated patients was not superior compared to the group of pallidotomy, there was a trend towards significance ($p = 0.15$).

The remaining seven studies had all class 2 evidence [42, 54, 58, 64, 78, 96, 107]. In one of them assessing 16 patients [96], the Sickness Impact Profile total score and the physical dimensions of a generic HRQoL instrument improved significantly at 6 months. The Grenoble group [54] used the Parkinson's Disease Quality of Life questionnaire (PDQL) in their analysis of 60 consecutive patients. At 12 months, the total PDQL improved significantly by 43% and all dimensions of the PDQL like social function (63%), PD related symptoms (48%), systemic symptoms (34%), and emotional functioning (29%). Other class 2 studies utilizing the Parkinson's disease questionnaire-39 (PDQ-39) in a total of 84 patients reported improvements of up to 62% in the PDQ-39 summary index relative to preoperative scores [42, 58, 64, 78, 107]. The improvements of PDQ-39 sustained in the long-term course (≥12 months follow-up) [63].

Complications of DBS surgery and implanted hardware

A systemic review of the clinical literature evaluated a total of 737 PD patients treated with bilateral STN DBS; mortality was 0.4% [29]. The frequency of intracranial hemorrhage (ICH) was 2.8%, and caused permanent neurological deficits in 1% of patients. Other frequently observed problems were: seizures (0.9%), pulmonary embolism (0.5%), meningitis (0.1%), and CSF leakage (0.1%). The implanted leads gave rise to problems (migration, breakage) in 4.5% of cases. Infection of the hardware (3.4%) required removal of the system in 1.8% of patients [29].

In our experience (262 consecutive patients operated on from 02/1996 to 03/2003 by DBS), we had only one asymptomatic ICH (0.2%) [115]. The rate of permanent neurological deficits caused by direct injury to brain tissue was 0.4%. In a mean follow-up of 36.3 ± 20.8 months, the total infection rate of hardware components was 5.7% requiring system removal in 4.6% of the cases [115].

Conclusions

Since its first application, DBS has become a standard therapy for patients with advanced PD. Although clinical efficacy of both GPI and STN stimulation is obviously comparable, it has become widely accepted to prefer STN over GPI DBS. The rationale STN tar-

geting includes: (i) the stimulation energy required to gain maximum clinical improvement seems to be lower compared to GPI [49, 117]. (ii) STN stimulation seems to have a more prominent and stable effect on L-Dopa responsive off-period symptoms in the long-term [36, 51, 110, 118].

In contrast, STN stimulation is more difficult to adjust [117]; in one comparative study, adverse events were more frequently observed in the STN DBS group than the GPI group [84]. In particular, STN stimulation seems to bear a higher risk of cognitive and neuropsychiatric adverse events [38, 87, 117].

The fact that STN stimulation is paralleled by significant reduction of specific medication, at first sight, seems attractive but can give rise to difficulties, particularly in patients who are equally disabled by motor and by non-motor disturbances (e.g. hypersalivation, vegetative instability). In these cases, the required reduction of medication may narrow the therapeutic window for dopaminergic therapy of parkinsonian symptoms that are less well alleviated by stimulation than by drug therapy; as a consequence, GPI stimulation may be an alternative to STN stimulation.

Deep brain stimulation was developed empirically. To achieve a therapeutic benefit which is commercially available, IPGs deliver a permanent high frequency periodic pulse train stimulation. At present, the mechanism of this stimulation technique is still not fully understood [65] but from clinical and experimental data, it can be concluded that it strongly modulates the firing pattern of both normal and pathological neurons. To overcome limitations associated with the conventional, unspecific stimulation more specifically acting stimulation techniques are required. One innovative approach, based upon mathematical simulation is multi-site coordinated reset stimulation (MCRS) [102]; this allows selective desynchronization of pathological synchronization processes (one hallmark of PD associated tremor [57, 77]), or shifting of the dynamics of affected neuronal populations to the healthy mode of function [104].

Applied intraoperatively as test stimulation in a few patients with tremor due to PD or multiple sclerosis, MRCS led to significantly better tremor suppression with significantly lower total stimulation energy compared to conventional DBS [103]. Indicated by mathematical modeling this new stimulation technique may also have powerful antikindling effects enabling the stimulated network to unlearn pathologically strong synaptic interactions [104].

References

1. Alesch F, Pinter MM, Helscher RJ, Fertl L, Benabid AL, Koos WT (1999) Stimulation of the intermediate thalamic nucleus in tremor dominated Parkinson's disease and essential tremor. Acta Neurochir (Wien) 136: 75–81
2. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 9: 357–381
3. Alusi SH, Worthington J, Glickman S, Bain PG (2001) A study of tremor in multiple sclerosis. Brain 124: 720–730
4. Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP (2005) Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson's disease. Arch Neurol 62: 554–560
5. Ardouin C, Pillon B, Peiffer E, Bejjani P, Limousin P, Damier P, Arnulf I, Benabid AL, Agid Y, Pollak P (1999) Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 46: 217–223
6. Bejjani B, Damier P, Arnulf I, Bonnet AM, Vidailhet M, Dormont D, Pidoux B, Cornu P, Marsault C, Agid Y (1997) Pallidal stimulation for Parkinson's disease. Two targets? Neurology 49: 1564–1569
7. Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J (1987) Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 50: 344–346
8. Benabid AL, Pollak P, Gross C, Hoffmann D, Benazzouz A, Gao DM, Laurent A, Gentil M, Perret J (1994) Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. Stereotact Funct Neurosurg 62: 76–84
9. Benabid AL, Pollak P Gao D, Hoffman D, Limousin P, Gay E, Payen P, Benazzouz A (1996) Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 84: 203–214
10. Benabid AL, Koudsie A, Benazzouz A, Le Bas JF, Pollak P (2002) Imaging of subthalamic nucleus and ventralis intermedius of the thalamus. Mov Disord 17 [Suppl 3]: S123–S129
11. Berney A, Vingerhoets F, Perrin A, Guex P, Villemure JG, Burkhard PR, Benkelfat C, Ghika J (2002) Effect on mood of subthalamic DBS for Parkinson's disease: a consecutive series of 24 patients. Neurology 59: 1427–1429
12. Blond S, Siegfried J (1991) Thalamic stimulation for the treatment of tremor and other movement disorders. Acta Neurochir [Suppl 52]: 109–111
13. Broggi G, Franzini A, Ferroli P, Servello D, D'Incerti L, Genitrini S, Soliveri P, Girotti F, Caraceni T (2001) Effect of bilateral subthalamic electrical stimulation in Parkinson's disease. Surg Neurol 56: 89–96
14. Caparros-Lefebvre D, Blond S, Vermersch P, Pecheux N, Guieu JD, Petit H (1993) Chronic thalamic stimulation improves tremor and levodopa induced dyskinesias in Parkinson's disease. J Neurol Neurosurg Psychiatry 56: 268–273
15. Cuny E, Guehl D, Burbaud P, Gross C, Dousset V, Rougier A (2002) Lack of agreement between direct magnetic resonance imaging and statistical determination of a subthalamic target: the role of electrophysiological guidance. J Neurosurg 97: 591–597
16. Deep-Brain Stimulation for Parkinson's Disease Study Group (2001) Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 345: 956–963
17. Deuschl G, Wenzelburger R, Kopper E, Volkmann J (2003) Deep brain stimulation of the subthalamic nucleus for Parkinson's disease: a therapy approaching evidence-based standards. J Neurol 250 [Suppl 1]: I/43–I/46

18. Diamond A, Jankovic J (2005) The effect of deep brain stimulation on quality of life in movement disorders. J Neurol Neurosurg Psychiatry 76: 1188–1193
19. Doshi PK, Chhaya N, Bhatt NH (2002) Depression leading to attempting suicide. Mov Disord 17: 1084–1085
20. Dujardin K, Defebvre L, Krystkowiak P, Blond S, Destee A (2001) Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. J Neurol 248: 603–611
21. Durif E, Lemaire JJ, Debilly B, Dordain G (2002) Long-term follow-up of globus pallidus chronic stimulation in advanced Parkinson's disease. Mov Disord 17: 803–807
22. Ende G, Treuer H, Boesecke R (1992) Optimization and evaluation of landmark-based image correlation. Phys Med Biol 37: 261–271
23. Esselink RA, de Bie RM, de Haan RJ, Lenders MW, Nijssen PC, Staal MJ, Smeding HM, Schuurman PR, Bosch DA, Speelman JD (2004) Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. Neurology 62: 201–207
24. Fahn S, Elton RL (1987) Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden SD, Calne D, Goldstein M (eds) Recent development in Parkinson's disease. Mac-Millan Health Care Information, Florham Park, New York pp 153–163
25. Figueiras-Mendez R, Regidor I, Riva-Meana C, Magarinos-Ascone CM (2002) Further supporting evidence of beneficial subthalamic stimulation in Parkinson's patients. Neurology 58: 469–470
26. Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Kliniger H, Chabardes S, Foote K, Benabid AL, Pollak P (2004) Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 75: 834–839
27. Ghika J, Villemure JG, Fankhauser H, Favre J, Assal G, Ghika-Schmid F (1998) Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year follow-up review. J Neurosurg 89: 713–718
28. Hamani C, Richter EO, Andrade-Souza Y, Hutchinson W, Saint-Cyr JA, Lozano AM (2005) Correspondence of microelectrode mapping with magnetic resonance imaging for subthalamic nucleus procedures. Surg Neurol 63: 249–253
29. Hamani C, Richter EO, Schwalb JM, Lozano AM (2005) Bilateral subthalamic nucleus stimulation for Parkinson's disease: a systematic review of the clinical literature. Neurosurgery 56: 1313–1324
30. Hamel W, Fietzek U, Morsnowski A, Schrader B, Herzog J, Weinert D, Pfister G, Müller D, Volkmann J, Deuschl G, Mehdorn HM (2003) Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: evaluation of active electrode contacts. J Neurol Neurosurg Psychiatry 74: 1036–1046
31. Hassler R, Riechert T (1954) Indikationen und Lokalisationsmethode der gezielten Hirnoperationen. Der Nervenarzt 25: 441–447
32. Hassler R, Mundinger F, Riechert T (1970) Pathophysiology of tremor at rest derived from the correlation of anatomical and clinical data. Confin Neurol 32: 79–87
33. Herzog J, Volkmann J, Krack P, Kopper F, Potter M, Lorenz D, Steinbach M, Klebe S, Hamel W, Schrader B, Weinert D, Müller D, Mehdorn HM, Deuschl G (2003) Two-years follow-up of subthalamic deep brain stimulation in Parkinson's disease. Mov Disord 18: 1332–1337
34. Herzog J, Fietzek U, Hamel W, Morsnowski A, Steigerwald F, Schrader B, Weinert D, Pfister G, Müller D, Mehdorn HM, Deuschl G, Volkmann J (2004) Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease. Mov Disord 19: 1050–1099
35. Holloway KL, Gaede SE, Starr PA, Rosenow JM, Ramakrishnan V, Henderson JM (2005) Frameless stereotaxy using bone fiducial markers for deep brain stimulation. J Neurosurg 103: 404–413
36. Houeto JL, Bejjani PB, Damier P, Staedler C, Bonnet AM, Pidoux B, Dromont D, Cornu P, Agid Y (2000) Failure of long-term pallidal stimulation corrected by subthalamic stimulation in PD. Neurology 55: 728–730
37. Houeto JL, Damier P, Bejjani PB, Staedler C, Bonnet AM, Arnuilf I, Pidoux B, Dormont D, Cornu P, Agid Y (2000b) Subthalamic stimulation in Parkinson' disease. A multidisciplinary approach. Arch Neurol 57: 461–465
38. Houeto JL, Mesnage V, Mallet L, Pillon B, Gargiulo M, du Moncel ST, Bonnet AM, Pidoux B, Dormont D, Cornu P, Agid Y (2002) Behavioral disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 72: 701–707
39. Ilinsky IA, Kultas-Ilinsky K (2001) Neuroanatomical organization and connections of the motor thalamus in primates. In: Kultas-Ilinsky K, Ilinsky IA (eds) Basal Ganglia and Thalamus in health and movement disorders. Kluwer Academic Plenum Publishers, New York, pp 77–91
40. Jaggi JL, Umemura A, Hurtig HI, Siderowf AD, Colcher A, Stern MB, Baltuch GH (2004) Bilateral stimulation of the subthalamic nucleus I Parkinson's disease: surgical efficacy and prediction of outcome. Stereotact Funct Neurosurg 82: 104–114
41. Jezzard P, Balaban RS (1995) Correction for geometrical distortion in echo planar images from field variations. Magn Reson Med 34: 65–73
42. Just H, Ostergaard K (2002) Health-related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei. Mov Disord 17: 539–545
43. Karger CP, Hipp P, Henze M, Echner G, Höss A, Schad L Hartmann GH (2003) Stereotactic imaging for radiotherapy: accuracy of CT, MRI, PET and SPECT. Phys Med Biol 48: 211–221
44. Kitagawa M, Murata J, Kikuchi S, Sawamura Y, Saito H, Sasaki H, Tashiro K (2000) Deep brain stimulation of subthalamic area for severe proximal tremor. Neurology 55: 114–116
45. Kleiner-Fisman G, Fisman DN, Sime E, Saint-Cyr JA, Lozano AM, Lang AE (2003) Long-term follow-up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. J Neurosurg 99: 489–495
46. Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, Tuite P, Sime E, Lozano A, Hauser R, Malapira T, Smith D, Tarsy D, Miyawaki E, Norregaard T, Kormos T, Olanow CW (1997) High-frequency unilateral stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 42: 292–299
47. Koller WC, Hutton JT, Tolosa E, Capilledo R (1999) Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. Carbidopa/Levidopa Study Group. Neurology 53: 1012–1019
48. Krack P, Pollak P. Limousin P, Hoffmann D, Benazouzz A, LeBas JF, Koudsie A, Benabid AL (1998) Opposite motor effects of pallidal stimulation in Parkinson's disease. Ann Neurol 43: 180–192
49. Krack P, Pollak P. Limousin P, Hoffmann D, Benazouzz A, Benabid AL (1998) Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 121: 451–457
50. Krack P, Hamel W, Mehdorn HM, Deuschl G (1999) Surgical treatment of Parkinson's disease. Curr Opin Neurol 12: 417–425
51. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix Valerie, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P (2003) Five-year follow-up of bilateral

stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 349: 1925–1934
52. Krause M, Fogel W, Heck A, Hacke W, Bonsanto M, Trenkwalder C, Tronnier V (2001) Deep brain stimulation for the treatment of Parkinson's disease: subthalamic nucleus versus globus pallidus internus. J Neurol Neurosurg Psychiatry 70: 464–470
53. Kumar R, Lang AE, Rodriguez-Oroz MC, Lozano AM, Limousin P, Pollak P, Benabid AL, Guridi J, Ramos E, van der Linden C, Vandewalle A, Caemaert J, Lannoo E, van den Abeele D, Vingerhoets G, Woltersa M, Obeso JA (2000) Deep brain stimulation of the globus pallidus pars interna in advanced Parkinson's disease. Neurology 55 [Suppl 6]: S34–S39
54. Lagrange E, Krack P, Moro E, Ardouin C, Van Blercom N, Charbardes S, Benabid AL, Pollak P (2002) Bilateral subthalamic nucleus stimulation improves health-related quality of life. Neurology 59: 1976–1978
55. Laitinen LV, Bergenheim AT, Hariz MI (1992) Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg 76: 53–61
56. Lanotte MM, Rizzone M, Bergamasco B, Faccani G, Melcarne A, Lopiano L (2002) Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation. J Neurol Neurosurg Psychiatry 72: 53–58
57. Lenz F, Kwan H, Martin R, Tasker R, Dostrovsky J, Lenz Y (1994) Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain 117: 531–543
58. Lezcano E, Gomez-Esteban JC, Zarranz JJ, Lambarri I, Madoz P, Bilbao G, Pomposo I, Garibi J (2004) Improvement in quality of life in patients with advanced Parkinson's disease following bilateral deep-brain stimulation in subthalamic nucleus. Eur J Neurol 11: 451–454
59. Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, Benabid A (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 339: 1105–1111
60. Limousin P, Speelman JD, Gielen F, Janssens M, and study collaborators (1999) Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 66: 289–296
61. Loher TJ, Burgunder JM, Weber S, Sommerhalder B (2002) Effect of chronic pallidal deep brain stimulation on off-period dystonia and sensory symptoms in advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 73: 395–399
62. Lopiano L, Rizzone M, Bergamasco B, Tavella A, Torre E, Perozzo P, Valentini MC, Lanotte M (2001) Deep brain stimulation of the subthalamic nucleus: clinical effectiveness and safety. Neurology 56: 552–554
63. Lyons KE, Pahwa R (2005) Long-term benefits in quality of life provided by bilateral subthalamic stimulation in patients with Parkinson disease. J Neurosurg 103: 252–255
64. Martinez-Martin P, Valldeoriola F, Tolosa E, Pilleri M, Molinuevo JL, Rumia JJ, Ferrer E (2002) Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. Mov Disord 17: 372–377
65. McIntyre C, Savasta M, Kerkerian-Le Goff K, Vitek J (2004) Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol 115: 1239–1248
66. Medtronic website: www.medtronic.com/physician/activa/techmanuals.html
67. Molinuevo J, Valldeoriola F, Tolosa E, Rumia J, Valls-Sole J, Roldan H, Ferrer E (2000) Levodopa withdrawal after bilateral subthalamic nucleus stimulation in advanced Parkinson's disease. Arch Neurol 57: 983–988
68. Moro E, Scerrati M, Romito A, Roselli R, Tonali P, Albanese A (1999) Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 53: 85–90
69. Mundinger F (1969) Results of 500 subthalamotomies in the region of the zona incerta. In: Gilingham FL, Donaldson IML (eds) Third Symposium of Parkinson's Disease.: Livingston E & A, Edinburgh, pp 261–265
70. Murata J, Kitagawa M, Uesugi H, Saito H, Iwasaki Y, Kikuchi S, Tashiro K, Sawamura Y (2003) Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. J Neurosurg 99: 708–715
71. Nandi D, Aziz TZ, Liu X, Stein JF (2002) Brain stem motor loops in the control of movement. Mov Disord 17 [Suppl 3]: S22–S27
72. Nicolelis MA, Chapin JK, Lin RC (1992) Somatotopic maps within the zona incerta relay parallel GABAergic somatosensory pathways to the neocortex, superior colliculus, and brainstem. Brain Res 10: 134–141
73. Ondo W, Jancovic J, Scheartz K, Almagure M, Simpson RK (1998) Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. Neurology 51: 1063–1069
74. Ostergaard K, Sunde N, Dupont E (2002) Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson's disease and motor fluctuations. Mov Disord 17: 693–700
75. Pahwa R, Wilkinson S, Smith D, Lyons K, Miyawaki E, Koller WC (1997) High-frequency stimulation of the globus pallidus for the treatment of Parkinson's disease. Neurology 49: 249–253
76. Pahwa R, Wilkinson SB, Overman J, Lyons KE (2003) Bilateral subthalamic stimulation with Parkinson disease: long-term follow-up. J Neurosurg 99: 71–77
77. Pare D, Curro'Dossi R, Steriade M (1990) Neuronal basis of the parkinsonian resting tremor: a hypothesis and its implications for treatment. Neuroscience 35: 217–226
78. Patel NK, Plaha P, O'Sullivan K, McCarter R, Heywood P, Gill SS (2003) MRI directed bilateral stimulation of the subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 74: 1631–1637
79. Power BD, Kolmac CI, Mitrofanis J (1999) Evidence for a large projection from the zona incerta to the dorsal thalamus. J Comp Neurol 22: 554–565
80. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000) A five-year study of dykinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 342: 1484–1491
81. Rehncrona S, Johnels B, Widner H, Tornqvist AL, Hariz M, Sydow O (2003) Long-term efficacy for thalamic deep brain stimulation for tremor: double-blind assessments. Mov Disord 18: 163–170
82. Rezai AR, Finelli D, Nyenhuis JA, Hrdlicka G, Thkach J, Sharan A, Rugieri P, Stypulkowski PH, Shellock FG (2002) Neurostimulation systems for deep brain stimulation: in vitro evaluation of magnetic resonance imaging-related heating at 1.5 Tesla. J Magn Res Imaging 15: 241–250
83. Richter EO, Hoque T, Halliday W, Lozano AM, Saint-Cyr JA (2004) Determining the position and size of the subthalamic nucleus based on magnetic resonance imaging results in patients with advanced Parkinson's disease. J Neurosurg 100: 541–546
84. Rodriguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, Kulisevsky J, Albanese A, Volkmann J, Hariz MI, Quinn NP, Speelman JD, Guridi J, Zamarbide I, Gironell A, Molet J, Pascual-Sedano B, Pidoux B, Bonnet AM, Agid Y, Xie J, Benabid AL, Lozano AM, Saint-Cyr J, Romito L, Contarino MF, Scerrati M, Fraix V, Van Blercom N (2005) Bilateral deep

brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain 128: 2240–2249
85. Romito L, Sceratti M, Contarino M, Bentivoglio A, Tonali P, Albanese A (2002) Long-term follow-up of subthalamic nucleus stimulation in Parkinson's disease. Neurology 58: 1546–1550
86. Saint-Cyr JA, Hoque Tasnuva Pereira LCM, Dostrovsky JO, Hutchison WD, Mikulis DJ, Abosch A, Sime E, Lang AE, Lozano AM (2000) Localization of clinically effective stimulating electrodes in the human subthalamic nucleus in magnetic resonance imaging. J Neurosurg 97: 152–1166
87. Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE (2002) Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 123: 2091–2108
88. Schaltenbrand G, Wahren W (1977) Atlas for Stereotaxy of the Human Brain. Thieme, Stuttgart
89. Schneider F, Habel U, Volkmann J, Regel S, Kornischka J, Sturm V, Freund HJ (2003) Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson's disease. Arch Gen Psychiatry 60: 296–302
90. Schrag A, Quinn N (2000) Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain 123: 2297–2305
91. Schüpbach WM, Chastan N, Welter ML, Houeto JL, Mesnage V, Bonnet AM, Czernecki V, Maltete D, Hartmann A, Mallet L, Pidoux B, Dormont D, Navarro S, Cornu P, Mallet A, Agid Y (2005) Stimulation of the subthalamic nucleus in Parkinson's disease: a 5-year follow up. J Neurol Neurosurg Psychiatry 76: 1640–1644
92. Schuurman PR, Bosch DA, Bossuyt PMM, Bonsel GJ, van Sommeren E, De Bie RMA, Merkus MP, Speelman JD (2000) A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 342: 461–468
93. Scotto di'Luzio AE, Ammannati F, Marini P, Sorbi S, Mennonna P (2001) Which target for THS in Parkinson's disease? Subthalamic nucleus versus globus pallidus internus. Neurol Sci 22: 87–88
94. Siegfried J, Lippitz B (1994) Bilateral continuous electrostimulation of ventroposterolateral pallidum: a new therapeutical approach for alleviating all Parkinsonian symptoms. Neurosurgery 35: 1126–1130
95. Simuni T, Jaggi J, Mulholland H, Hurtig H, Colcher A, Siderowf A, Ravina B, Skolnick B, Goldstein R, Stern M, Baltuch G (2002) Bilateral stimulation of the subthalamic nucleus in patients with Parkinson disease: a study of efficacy and safety. J Neurosurg 96: 666–672
96. Spottke EA, Volkmann J, Lorenz D, Krack P, Smala AM, Sturm V, Gerstner A, Berger K, Hellwig D, Deuschl G, Freund HJ, Oertel WH, Dodel RC (2002) Evaluation of healthcare utilization and health status of patients with Parkinson's disease treated with deep brain stimulation of the subthalamic nucleus. J Neurol 249: 759–766
97. Starr PA, Vitek JL, DeLong M, Bakay RAE (1999) Magnetic resonance imaging-based stereotactic localization of the globus pallidus and subthalamic nucleus. Neurosurgery 44: 303–313
98. Starr PA, Christine CW, Theodosopoulos PV, Lindsey N, Byrd D, Mosley A, Marks WJ (2002) Implantation of deep brain stimulators into subthalamic nucleus: technical approach and magnetic resonance imaging – verified target locations. J Neurosurg 97: 370–387
99. Sturm V, Pastyr O, Schlegel W, Scharfenberg H, Zabel HJ, Netzeband G, Schabbert S, Berberich W (1983) Stereotactic computer tomography with a modified Riechert-Mundinger device as the basis for integrated neuroradiological investigations. Acta Neurochir (Wien) 68: 11–17
100. Talairach J, Szikla G, Tournoux P, Prossalentis A, Bordas-Ferrer M, Covello L, Iacob M, Mempel E (1967) Atlas d'anatomie stéréotaxique du télencéphale. Masson & Cie, Paris
101. Tasker RR, Munz M, Junn FSCK, Kiss ZHT, Davis K, Dostrovsky JO, Lozano AM (1997) Deep brain stimulation and thalamotomy for tremor compared. Acta Neurochir Wien [Suppl 68]: 49–53
102. Tass PA (2003) A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neuronal subpopulations. Biol Cybern 89: 81–88
103. Tass PA, Russel DF, Barnikol UB, Neiman AB, Yakusheva TA, Voges J, Sturm V, Freund HJ (2005) Selective disruption of neuronal synchronization by means of repeated transient phase reset (in press)
104. Tass PA, Majtanik M (2006) Long-term anti-kindling effects of desynchronizing brain stimulation: a theoretical study. Biol Cybern 94: 58–66
105. Thobois S, Mertens P, Guenot M, Hermier M, Mollion H, Bouvard M, Chazot G, Brousolle E, Sindou M (2002) Subthalamic stimulation in Parkinson's disease. Clinical evaluation of 18 patients. J Neurol 249: 529–534
106. Treuer H, Klein D, Mohammad M, Lehrke R, Voges J, Sturm V (2005) Accuracy and conformity of stereotactically guided interstitial brain tumour therapy using I-125 seeds. Radiother Oncol 77: 202–209
107. Tröster AL, Fields JA, Wilkinson S, Pahwa R, Koller WC, Lyons KE (2003) Effect of motor improvement on quality of life following subthalamic stimulation is mediated by changes in depressive symptomatology. Stereotact Funct Neurosurg 80: 43–47
108. Tronnier V, Fogel W, Kronenbürger M, Steinvorth S (1997) Pallidal stimulation: an alternative to pallidotomy? J Neurosurg 87: 700–705
109. Tuite PJ, Maxwell RE, Ikramuddin S, Kotzd CM, Billingtond CJ, Laseski MA, Thielen SD (2005) Weight and body mass index in Parkinson's disease patients after deep brain stimulation surgery. Parkinson Rel Disord 11: 247–252
110. Valdeoriolla F, Pilleri M, Tolosa E, Molinuevo JL, Rumia J, Ferrer E (2002) Bilateral subthalamic stimulation monotherapy in advanced Parkinson's disease: long-term follow-up of patients. Mov Disord 17: 125–132
111. Vesper J, Klostermann F, Stockhammer F, Funk T, Brock M (2002) Results of chronic subthalamic stimulation for Parkinson's disease: a 1- year follow-up study. Surg Neurol 57: 311–313
112. Vingerhoets FJG, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J (2002) Subthalamic DBS replaces levodopa in Parkinson's disease. Two-year follow-up. Neurology 58: 396–401
113. Visser-Vandewalle V, van der Linden C, Temel Y, Celik H, Ackermans L, Spincemaille G, Caemaert J (2005) Long-term effects of bilateral subthalamic nucleus stimulation in advanced Parkinson disease: a four year follow-up study. Parkinsonism Relat Disord 11: 157–165
114. Voges J, Volkmann J, Allert N, Lehrke R, Koulousakis A, Freund HJ, Sturm V (2000) Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson's disease: correlation of therapeutic effect with anatomical electrode position. J Neurosurg 96: 269–279
115. Voges J, Waerzeggers Y, Maarouf M, Lehrke R, Koulousakis A, Lenartz D, Sturm V (2006) Deep Brain Stimulation: long-term analysis of complications caused by hardware and surgery- a single centre experience. J Neurol Neurosurg Psychiatry (in press)
116. Volkmann J, Sturm V, Weiss P, Kappler J, Voges J, Koulousakis A, Lehrke R, Hefter H, Freund HJ (1998) Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. Ann Neurol 44: 953–961

117. Volkmann J, Allert N, Voges J, Weiss P, Freund HJ, Sturm V (2001) Safety and efficiency of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 56: 548–551
118. Volkman J (2004) Morbus Parkinson – Indikation und Auswahl des Zielpunktes. In: Krauss JK, Volkmann J (eds) Tiefe Hirnstimulation. Steinkopf, Darmstadt, pp 258–268
119. Volkmann V, Allert N, Voges J, Sturm V, Schnitzler A, Freund HJ (2004) Long-term results of bilateral pallidal deep brain stimulation in advanced Parkinson's disease. Ann Neurol 55: 871–875
120. Weaver F, Follett K, Hur K, Ippolito D, Stern M (2005) Deep brain stimulation in Parkinson disease: a meta analysis of patient outcome. J Neurosurg 103: 956–967
121. Yelnik J, Damier P, Bejjani BP, Francois C, Gervais D, Dormont D, Arnuls I, Bonnet A, Cornu P, Pidoux B, Agid Y (2000) Functional mapping of the human globus pallidus: contrasting effect of stimulation in the internal and external pallidum in Parkinson's disease. Neuroscience 101: 77–87
122. Yelnik J, Damier P, Demeret S, Gervais D, Bardinet E, Bejjani BP, Francois C, Hueto JL, Arnulf I, Dormont D, Galanaud D, Pidoux B, Cornu P, Agid Y (2003) Localization of stimulating electrodes in patients with Parkinson disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. J Neurosurg 99: 89–99
123. Yu C, Petrovich Z, Apuzzo M (2001) An image fusion study of the geometric accuracy of magnetic resonance imaging with the Leksell stereotactic localization system. J Appl Clin Med Phys 2: 42–50
124. Zonenshayn M, Rezai AL, Mogilner AY, Beric A, Sterio D, Kelly P (2000) Comparison of anatomic and neurophysiological methods for subthalamic nucleus targeting. Neurosurgery 47: 282–294

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Neuromodulation of prelemniscal radiations in the treatment of Parkinson's disease

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Summary

In patients with Parkinson's disease (PD), tetrapolar electrodes were implanted in the prelemniscal radiations (RAPRL) to treat tremor, rigidity and bradykinesia. Fifteen patients were implanted unilaterally and five patients bilaterally and followed-up for one year. The selection criteria included the presence of unilateral pronounced tremor and rigidity in patients implanted unilaterally or bilateral symptoms including severe bradykinesia in patients implanted bilaterally. In the operating room, the tremor decreased significantly or was abolished following the insertion of the electrode in the RAPRL. This effect was temporary and subsided when the stimulation was off. However, when the stimulator was turned on, the severity of the symptoms and signs decreased significantly. The post-implantation MRI confirmed that the electrode contacts used for stimulation were inserted in RAPRL, a group of fibers located between the red nucleus and subthalamic nucleus, above the substantia nigra, medially to the zona incerta and below the thalamus. The patients were evaluated using the UPDRS part III, before implantation and every 3 months during the first year. Global scores decreased significantly. The pre- and postoperative median values (range in round brackets) were as follows: tremor improved from 3 (2–16) to 1 (2–3) ($p < 0.001$); rigidity was either abolished or decreased markedly from 2 (1–16) to 0 (0–4) ($p < 0.001$); bradykinesia improved from 2 (0–4) to 1 (0–2) ($p < 0.001$). We conclude that RAPRL, an area anatomically different from STN, is a good target for electrical stimulation in order to treat effectively all the main symptoms of PD.

Keywords: Prelemniscal radiations; neuromodulation; Parkinson's disease; tremor; rigidity; bradykinesia.

Introduction

Prelemniscal radiations (RAPRL) is a compact group of fibers located in the posterior subthalamic area in front of the sensory or medial lemniscus, between the red nucleus (RN) and subthalamic nucleus (STN) [14]. This area has been used for many years as a target of leukotome or radiofrequency lesions for the surgical treatment of Parkinson's disease (PD) [3, 4, 6, 8, 18]. These interventions were particularly effective in treating contralateral tremor, which consistently, either stopped or decreased by the simple insertion of the probe in the RAPRL; this area was considered a better target compared to the thalamic ventralis intermedius (Vim), ventralis oralis anterior (Voa), or ventralis oralis posterior (Vop) nuclei to treat tremor [21]. Results were very consistent and the improvement lasted for a long time. The experience of our group in lesioning RAPRL extends over several decades [18–21]. However, bilateral RAPRL lesions may cause a worsening of the bradykinesia, and therefore, this procedure was offered only to patients with unilateral symptoms [21]. Following the application of neuromodulation techniques in other traditional targets like globus pallidus internus (GPi) and thalamus [2, 12, 15], the placement of electrodes in RAPRL seemed promising. Unilateral RAPRL stimulation in patients with PD decreased markedly and definitively, contralateral tremor and was also associated with a significant decrease in rigidity; with respect to bradykinesia, there was no change because these patients did not have bradykinesia [9, 22]. Bilateral application of neuromodulation has minimal side effects in most targets; we considered, therefore, the application of RAPRL neuromodulation in patients with bilateral tremor, rigidity and bradykinesia. In this article, we present the results of RAPRL neuromodulation (RAPRL-NM) in a group of patients with PD of various degrees of severity; the improvement of the motor symptoms was evaluated with the Unified Parkinson's Disease Rating Scale part III (UPDRS III).

Patients

Twenty patients with an age range from 50 to 68 years (mean: 60 ± 7.1) and a PD history with a duration from

2 to 10 years (mean: 6 ± 2.3) were included in the study. The patients had received different types of antiparkinsonian medications that invariably included L-Dopa preparates with carbidope or benserazide; they had an initial satisfactory response, which was not maintained over time. Other drugs including biperiden, trihexiphenidyl, amantadine and dopamine agonists in combinations of one or more drugs were also used. Before surgery, the ON-medication improvement of the patients was either limited or brief. Increases in the doses of medication did not result in significant improvement, but to side effects or intolerance instead. The patients were evaluated by the UPDRS III a few hours prior to surgery and at 3, 6, 9 and 12 months after chronic NM. Drugs were discontinued at least 24 hours prior to each evaluation, and the evaluations were performed with the patients being OFF medication. UPDRS III scores were compared to the baseline scores every three months until the end of the study at the completion of one postoperative year. The values were expressed as median, minimum and maximum values. The statistical significance was determined by the non-parametric Wilcoxon rank-sum test.

Surgical technique

The stereotactic frame was fixed on the patient's head and a burr-hole was performed 15 mm from the midline, in front of the coronal suture. In the past, we used either the Bertrand's stereotactic guide (Preci-Tools Inst, Montreal, Canada) [4] or the Todd-Wells stereotactic frame, (Trend Wells Instruments, South Gate California, USA), which are compatible with X-ray air ventriculography. More recently, targeting has been performed by imaging fusion of computed tomography and magnetic resonance (CT-MR), using the ZD stereotactic frame (Leibinger, Freiburg, Germany), microrecordings and microstimulation. The target coordinates were calculated using as reference the anterior commissure–posterior commissure (AC–PC) line in the lateral craniogram. Each coordinate (vertical: below AC–PC line, lateral: laterally to the midcerebral plane, and anterior–posterior: relatively to the midpoint of the AC–PC line) was expressed in $1/10^{\text{th}}$ of the length of the AC–PC line. This method defines the target coordinates as proportions of the AC–PC line in each patient in order to minimize the effects of individual patient variations. In the past, this method has been proven useful in targeting the RAPRL; the latter is constantly located at $3/10$ behind the AC–PC midpoint, $1/10$–$2/10$ below the AC–PC level, and $4.5/10$–$5.5/10$ laterally to the midline. As soon as the quadripolar electrodes (3387 DBS, Medtronic Inc., Minneapolis, MN, USA) reached the target, tremor stopped and rigidity decreased markedly on the contralateral side. After this, the electrode was secured in position and externalized. An MRI scan was performed to confirm the position and thereafter the electrode was internalized, under general anesthesia, and connected to an implantable pulse generator (IPG) in an infraclavicular subcutaneous pocket.

In bilateral procedures, a small burr-hole was made on the other side and the same method was used in order to implant the second electrode. The postoperative MRI scan in the area of interest consisted of sections 2.5 mm thick without space between them. The axial sections were orientated to be parallel to the axial plane of the AC–PC line; the coronal sections were perpendicular to the same plane and the sagital sections parallel to the sagital plane of the midline. The electrode was visualized clearly and the position of each contact was identified with respect to the AC–PC line and to the other anatomical structures [22].

Chronic stimulation

Implantable pulse generators (IPGs) were programmed at the parameters determined in the acute stimulation test, and the patients were discharged from the hospital. The deepest contact was used as the cathode. The pulse width was programmed from 90 to 330 μs, while the pulse amplitude was increased (0.5–5 V) maintaining the frequency unchanged (130 Hz). The patients returned each month for consultation, and every 3 months for evaluation, in an OFF medication-ON stimulation state.

Results

The introduction of the electrode in the RAPRL either unilaterally or bilaterally diminished markedly or abolished tremor and rigidity. Bradykinesia improved but to a lesser degree. These effects disappeared after several hours or days, and thereafter they reappeared occasionally and partially when the patient was in ''OFF stimulation'' state.

Figure 1 shows the imaging and plotting in one case of unilateral and another case of bilateral RAPRL implantation. The position of the electrodes is at the center of the distance between the RN (internal part) and STN (external part). A hyperdense zone around the electrode, can be seen and represents an imaging artifact.

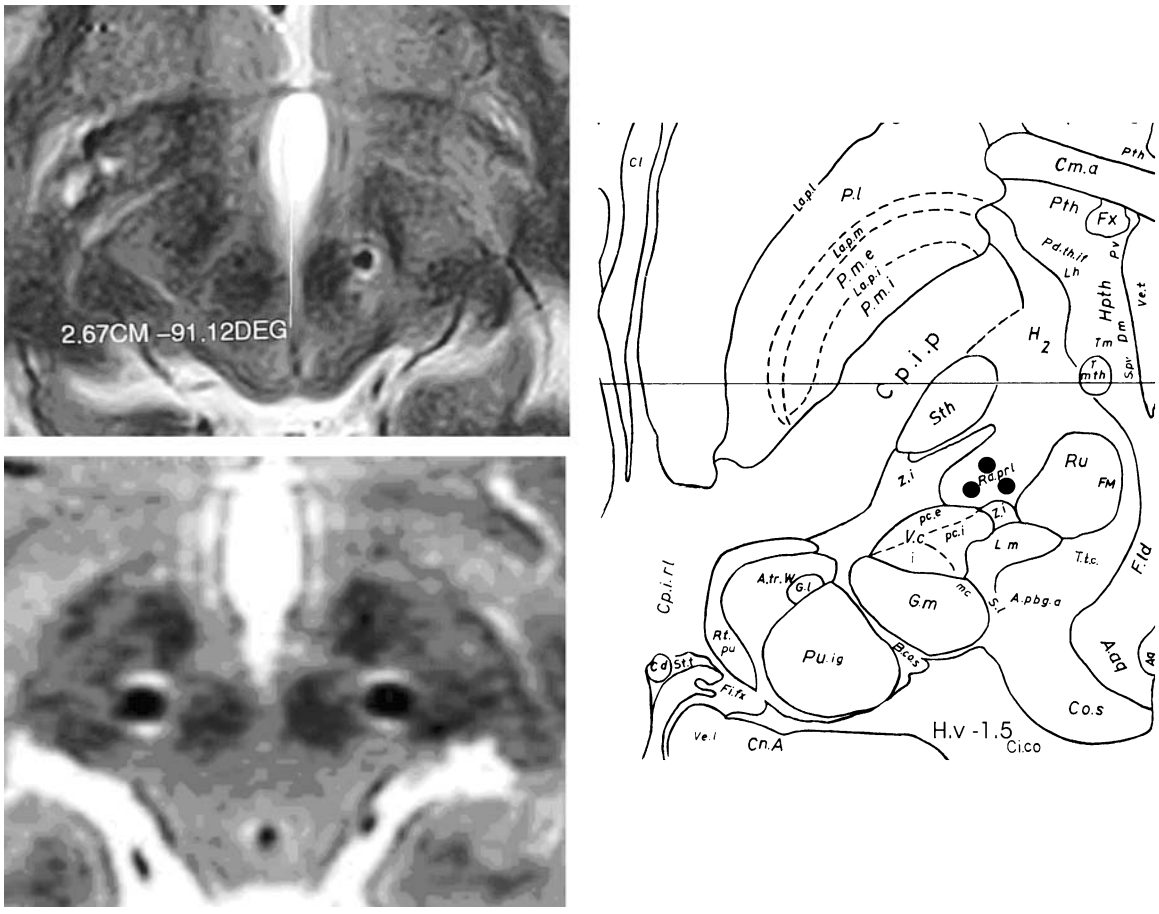

Fig. 1. MRI of unilateral and bilateral electrode implantations in RAPRL. The slice is 2.5 mm below the AC–PC line. On MRI, the electrode position is located between the red nucleus (*RN*) and the subthalamic nucleus (*STN*) in a patient with unilateral implantation (*top*) and in another patient with bilateral implantation (*bottom*). Plotting shows that all the electrode contacts were inserted in the subthalamic area including RAPRL, zona incerta (*ZI*) and Substantia Q. Black circles, at the plotting, indicate the unilateral electrode (*upper circle*) and bilateral electrodes (*lower circles*) in RAPRL

Bipolar stimulation between the two lowest contacts of the electrodes (0–1, 1–2) induced similar beneficial effects in tremor, rigidity and bradykinesia. However, stimulation through contacts placed lower than 7 mm below the AC–PC level and closer to the posterior commisure, often induced side effects such as paresthesias in the contralateral side, and diplopia or dizziness. The ideal position of the electrodes is 11–13 mm laterally to the midline, 5–8 mm behind the mid-commissural point and 5 and 2 mm below the AC–PC line for the cathode and anode, respectively.

Figure 2 demonstrates the difference between the baseline values of UPDRS III and the changes in values observed in the patients after stimulation at 3, 6, 9 and 12 months. The preoperative median value was 38 (15–84); during the first postoperative year, the value decreased to 28.5 (9–48). All the changes, with the exception of those at the 6-month evaluation, were statistically significant ($p<0.05$–$p<0.01$).

Figures 3–5 demonstrate separately the improvement in different motor signs. Figure 3 shows the effect on item no. 20 of the UPDRS III. Tremor is represented by additive scores of 4 points for each limb, and the head, with a maximum value of 20. In the graphic representation of the benefits observed in our patients, the median value of baseline tremor was 3 (range: 2–16) (included in a box-plot manner). This shows the wide range of tremor severity in this group of patients. In a subsequent evaluation, the range was greatly reduced and virtually eliminated by the end of the year, as tremor came under control in almost all cases ($p<0.001$).

Figure 4 shows the scores of rigidity, i.e. the item no. 22 of UPDRS III. Rigidity was evaluated by additive scores of 4 points summed for each limb and head with 20 being the highest score. With respect to rigidity, the median value was 2 with a range from 1 to 16. In the course of the evaluations, rigidity decreased markedly

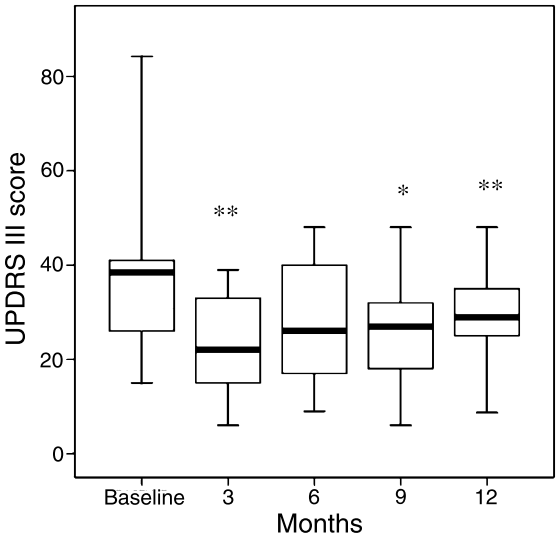

Fig. 2. Graphic representation of changes in UPDRS III, from baseline to postoperative evaluations at 3, 6, 9 and 12 months. The median value is represented by the horizontal bar, the box plot shows the 75% of the values and the outliers show the distribution. Statistical significance is indicated by $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$

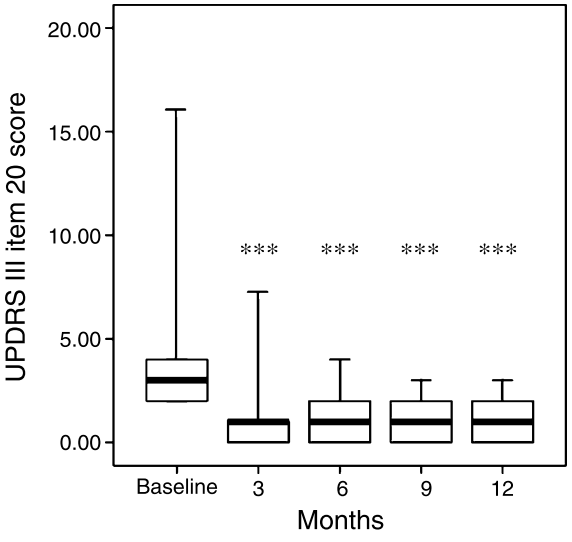

Fig. 3. Graphic representation of the changes in tremor evaluated by the UPDRS III scale (item no. 20) from baseline to evaluation at 3, 6, 9, and 12 months. The graphic representation is similar to Fig. 2 (for explanation see legend of Fig. 2)

and virtually stopped being present by month 12; the median value became 0 ($p<0.001$).

Figure 5 shows the effects on bradykinesia (UPDRS III item no. 31). The values were expressed in a scale from 0 to 4, with 0 being the value for normal subjects and 4 the value for very bradykinetic individuals. This group of patients had a baseline median value of 2 (0–4). Bradykinesia improved during the year and the final score became 1 (0–2) ($p<0.01$–0.001).

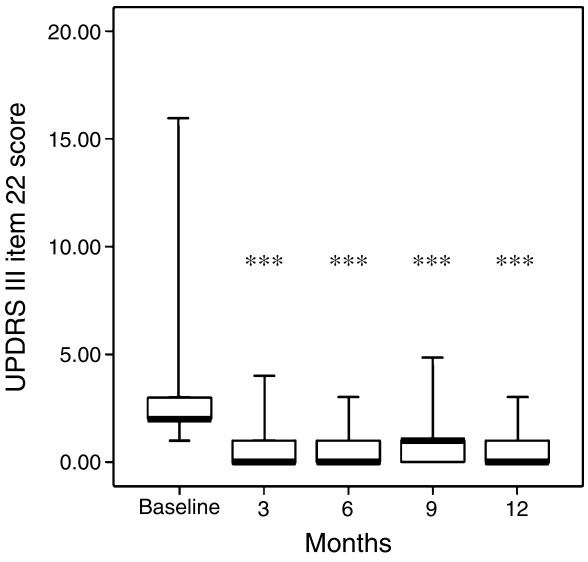

Fig. 4. Graphic representation of the changes in rigidity evaluated by the UPDRS III scale (item no. 22) from baseline to evaluation at 3, 6, 9 and 12 months. The graphic representation is similar to Fig. 2 (for explanation see legend of Fig. 2)

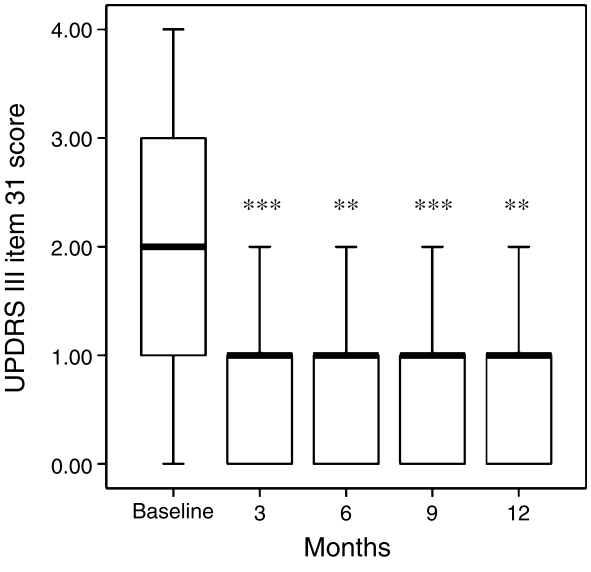

Fig. 5. Graphic representation of the changes in bradykinesia evaluated by UPDRS III (item no. 31) from baseline to evaluation at 3, 6, 9, and 12 months (for explantation see legend of Fig. 2)

Discussion

During the era of RAPRL lesioning, efforts were made not to lesion the STN because experience had shown that spontaneous or surgically induced lesions of STN could cause ballismus or flapping. Therefore, the procedure was restricted to the more posteriorly located subthalamic area, close to the posterior commissure and certainly not in the area where the anatomical atlases

and the standardised models place the STN [1, 7, 17]. It is true, that at that time, the methods of imaging did not allow a detailed analysis of the position and size of the surgical lesions; however, microelectrode recordings in and around the target area, indicated that this area consists of a group of fibers with few neurons [5, 9]. These findings were very different compared to the recordings obtained from STN [10, 12]. Surgically made bilateral lesions can increase bradykinesia, somnolence and cause worsening of balance. This was supported by recordings of large P300 components of the propioceptive event-related evoked potentials from the mesencephalic reticular formation and the RAPRL. P300 potentials reached maximal amplitude during the paradigm of selective attention [20].

How this knowledge can be used in RAPRL-NM? First, in order to obtain, similar to lesioning, clinical control of tremor, all the electrodes should be inserted at exactly the same site as the site where the original lesions have been made for four decades [3, 6, 7, 18]. If the electrode is located a few millimeters in front of the right location, i.e. towards STN, stimulation would loose its efficacy in controlling tremor and rigidity. If the electrode is inserted behind this location, stimulation would induce dysesthesias because of the proximity to the medial lemniscus. If the electrode is inserted more deeply, the effect on tremor and rigidity would be jeopardized by either paresthesias caused by stimulation of the lemniscus or diplopia due to the proximity of the electrode to the IIIrd nerve fibers. When the contacts are near or above the AC–PC level the effect on tremor and rigidity decreases [8, 22].

Neuromodulation of RAPRL not only improved tremor, but also stopped rigidity. The rates of improvement in tremor, and rigidity were 81–90 and 88–100%, respectively. Severe bradykinesia improved by 50–60% compared to the baseline. In the literature, there are few reports on RAPRL-NM. Murata et al reported amelioration of tremor in 80% of patients with essential tremor [13]; Kitawaga *et al.* reported that in PD patients the motor deficits improved at two years, as follows: contralateral tremor by 78%, contralateral rigidity by 93% and akinesia by 65% [11].

The bilateral implantation of the electrodes was followed by a transient state of somnolence that lasted for hours to days. MRI ruled out severe edema or bleeding around the electrodes tracts. It is likely, however, that somnolence was due to either microlesioning or mild edema. The effect on the conscious level was attributed to a possible participation of the lesioned fibers in an ascending reticulo-thalamic system which mediates propioceptive attention [20]. Perhaps, unilateral implantation is not associated with this adverse effect because the ascending reticular fibers are bilateral and have extensive ipsi- and contralateral representation. In order to knock out this system, this effect which is probably due to either swelling or lesioning, must be bilateral. Preoperatively, in these patients, the scores of tremor, rigidity and bradykinesia were high. The result of RAPRL neuromodulation was excellent in such patients. We believe that RAPRL is a different target compared to other targets that are used in the treatment of PD. It is an old target that has probably been described by other different names. Procedures such as the campotomy of Spiegel *et al.* [16] or the Andy's perirubral fibers lesion are related to RAPRL lesioning or neuromodulation [1]. In the few autopsy reports of patients treated by RAPRL lesioning, it has been demonstrated that this target corresponds to an area of fibers behind the STN and lateral to the RN [1, 14, 16]. It would be important to identify the origin of such fibers and analyze their relationship to the pathophysiology of tremor, rigidity and bradykinesia [23–25].

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References

1. Andy O, Jurko MF, Sias FR (1963) Subthalamotomy in treatment of Parkinsonian tremor. J Neurosurg 20: 860–870
2. Benabid AL, Pollak P, Louveau A, Henry S, De Rougemont J (1989) Combined (thalamotomy and stimulation) stereotactic surgery of the Vim thalamic nucleus for bilateral Parkinson's disease. Appl Neurophysiol 50: 344–356
3. Bertrand C, Hardy J, Molina-Negro P, Martínez N (1969) Optimum physiological target for the arrest of tremor. In: Gillingham FJ, Donaldson ML (eds) IIIrd symposium of Parkinson's disease. E & S Livingston, Edinburgh, pp 251–254
4. Bertrand C, Molina-Negro P, Martínez N, Velasco F (1974) Stereotaxic surgery in Parkinson's disease. In: Krayenbuhl H, Maspes P, Sweet W (eds) Progress in neurological surgery, vol. V. Year Book Medical Publishers
5. Birk P, Struppler A (1989) Functional neuroanatomy of the target area for the treatment of pathological tremor: an electrophysiological approach. Stereotact Funct Neurosurg 52: 164–170
6. Driollet R, Schvarcz JR, Orlando J (1974) Optimum target for tremor arrest. Confin Neurol 36: 355
7. Hullay J (1971) Subthalamotomy in Parkinson's disease. Acta Med Acad Sci Hung 28: 57–68
8. Ito Z (1975) Stimulation and destruction of the prelemniscal radiation or its adjacent area in various extrapyramidal disorders. Confin Neurol 37: 41–48

9. Jiménez F, Velasco F, Velasco M, Brito F, Morel C, Márquez I, Pérez ML (2000) Subthalamic prelemniscal radiation stimulation for the treatment of the Parkinson's disease: electrophysiological characterization of the area. Arch Med Res 31: 270–281
10. Katayama Y, Kasai M, Oshima H, Fukaya C, Yamamoto T, Ogawa K, Mizutani T (2001) Subthalamic nucleus stimulation for Parkinson disease: benefits observed in levodopa-intolerant patients. J Neurosurg 95: 213–221
11. Kitawaga M, Murata J, Uesugi H, Kikuchi S, Saito H, Tashiro K, Sawamura Y (2005) Two-year follow-up of chronic stimulation of the posterior subthalamic white matter for tremor-dominant Parkinson's disease. Neurosurgery 56: 281–289
12. Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R (1997) Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Ann Neurol 42: 283–291
13. Murata JI, Kitawaga M, Uesegi H, Hisatoshi S, Iwasaki Y, Kikuchi S, Tashiro K, Sawamura Y (2003) Electrical stimulation of the posterior subthalamic area for the treatment of intractable proximal tremor. J Neurosurg 99: 708–715
14. Schaltenbrand G, Wahren W (1977) Introduction to stereotaxis with an atlas of the human brain, vol. 2. Georg Thieme, Stuttgart
15. Siegfried J, Lippitz B (1994) Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery 35: 1126–1129
16. Spiegel EA, Wycis HT, Szekely EG, Adams J, Flanagan M, Baird HW (1962) Campotomy in various extrapyramidal disorders. Trans Am Neurol Asoc 87: 240–242
17. Struppler A, Burg D, Lücking CH, Velho F (1974) The mode of innervation following thalamotomy and subthalamotomy. Confin Neurol 36: 347–354
18. Velasco F, Molina-Negro P, Bertrand C, Hardy J (1972) Further definitions of the subthalamic target for the arrest of tremor. J Neurosurg 36: 184–191
19. Velasco F, Velasco M, Machado JP (1975) A statistical outline of the subthalamic target for the arrest of tremor: Applied Neurophysiol 38: 38–46
20. Velasco F, Velasco M (1979) A reticulo-thalamic system mediating propioceptive attention and tremor in man. Neurosurgery 4: 30–36
21. Velasco F, Velasco M, Ogarrio C (1986) Neglect induced by thalamotomy in man: a quantitative appraisal of the deficit. Neurosurgery 19: 744–751
22. Velasco F, Jiménez F, Pérez ML, Carrillo-Ruiz J, Velasco AL, Ceballos J, Velasco M (2001) Electrical stimulation of prelemniscal radiation in the treatment of Parkinson's disease. An old target revised with new techniques. Neurosurgery 49: 293–308
23. Yelnik J, Damier P, Demeret S, Gervais D, Bardinet E, Bejjani B-P, Francois C, Houetto JL, Arnulf I, Dormont D, Galanaud D, Pidoux B, Cornu P, Agid Y (2003) Localization of stimulating electrodes in patients with Parkinson's disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. J Neurosurg 99: 89–99
24. Yokoyama T, Sugiyama K, Nishizawa S, Yokota N, Ohta S, Akamine S, Namba H (2001) Optimal stimulation site for chronic stimulation of the subthalamic nucleus in Parkinson's disease. Stereotact Funct Neurosurg 77: 61–67
25. Zincone A, Landi A, Piolti R (2001) Physiologic study of the subthalamic volume. Neurol Sci 22: 111–112

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Deep brain stimulation for torsion dystonia

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Summary

Deep brain stimulation (DBS) at the globus pallidus pars internus (GPi) is an effective treatment for some patients with medically refractory torsion dystonia. In this chapter we review the classification and treatment of torsion dystonia including the current indications for DBS surgery. Details of the DBS procedure and programming of the DBS devices are discussed. Pallidal DBS is most effective in patients with primary generalized dystonia. Children and adolescents possessing the DYT1 gene mutation may respond best of all. Patients with cervical dystonia may also improve with pallidal DBS but definitive clinical evidence is lacking. As a group, patients with secondary dystonias respond less well to DBS than do patients with primary dystonia; however, patients with dystonia secondary to anoxic brain injury who have grossly intact basal ganglia anatomy, and patients with tardive dystonia may represent secondary dystonia subtypes for whom pallidal DBS is a viable option.

Keywords: Neuromodulation; deep brain stimulation; dystonia; globus pallidus; tardive dystonia; DYT1; stereotactic surgery.

Introduction

Torsion dystonia is a movement disorder characterized by twisting, repetitive movements which result in abnormal, often painful postures [9]. Different muscle groups may be involved to a variable extent and severity. Dystonia is not one disease; rather, it is a neurological manifestation of numerous pathophysiological conditions, many of which are poorly characterized. The prevalence estimates for primary dystonia in the general population range from two to 50 cases per million for early onset dystonia and from 30 to 7320 cases per million for late onset dystonia [6]. However, prevalence rates are significantly higher in some ethnic groups [3, 6]. Surgery for torsion dystonia is not new. Due to a lack of effective medical therapies a variety of procedures, targeting both the peripheral and central nervous systems, have been attempted with the hope of alleviating this debilitating condition. The dystonia literature is filled with case reports and studies of small cohorts, mostly relating mixed or conflicting outcomes. Long-term results are virtually absent. In the recent past, the successful use of deep brain stimulation (DBS) for medically refractory Parkinson's disease (PD) and Essential Tremor (ET) led to investigations of its utility for treating dystonia. Moreover, the observation that pallidal interventions improve 'off-state' dystonia in PD patients [16] shifted attention from the thalamus to the globus pallidus pars internus (GPi) as the target of choice. The result has been one of the most successful applications of neuromodulation technology yet described. This chapter will focus on the current status of pallidal DBS for dystonia. Due to space constraints, discussion of alternative therapeutic targets will be limited.

Classification of dystonia

Dystonia may be classified in three ways: by the anatomical distribution of the abnormal movements; by the age at symptom onset (early vs. late); and by the absence or presence of a specific underlying etiology (primary vs. secondary) [9]. Intermittent contractions limited to a single body region define focal dystonia (e.g. writer's cramp, spasmodic torticollis). Segmental dystonia affects contiguous body parts. Widespread involvement of the axial and limb musculature characterizes generalized dystonia. Patients with early symptom onset (age <20) are more likely to have a heritable form of dystonia and are more likely to generalize. Patients with late symptom onset (age >20) are more likely to develop focal dystonia.

A dystonia is classified as primary or idiopathic when no structural brain abnormality or specific toxic, metabolic, or infectious etiology is identified. The heritable forms of dystonia are traditionally included in this group.

At least 13 different mutations have now been associated with dystonia, each mutation occurring at a unique gene locus [3]. The most common form of genetic dystonia results from a three base pair GAG deletion of the gene encoding the protein torsin A [3]. This mutation, referred to as DYT1, causes a form of childhood onset dystonia formerly known as dystonia musculorum deformans or Oppenheim's disease. DYT1-associated dystonia is inherited in an autosomal dominant pattern but with a penetrance of just 30–40%, suggesting that additional genetic and/or environmental factors contribute to its phenotypic expression [3].

When a structural brain abnormality or specific underlying etiology is identified, a dystonia is classified as secondary or symptomatic [9]. Symptomatic dystonia is more prevalent than primary dystonia and may arise from a variety of causes including static encephalopathy, stroke, traumatic brain injury, or any number of toxic, metabolic, or infectious disorders. Consequently, this is a heterogeneous patient population with highly varied pathophysiologies and responses to treatment.

Medical therapy for dystonia

For the majority of dystonia patients, medical therapy is limited to symptom control and is marginally effective [20]. Anticholinergic medications (e.g. trihexphenidyl) remain the mainstay of medical therapy but often yield only modest improvements and, in the high doses employed for dystonia, can cause significant side effects. Additional medications for dystonia include baclofen, benzodiazepines, and tetrabenazine. A minority of patients with symptomatic generalized dystonia will benefit from specific therapy. In particular, children and adolescents with clinically ''pure'' dystonia of unknown etiology should be evaluated for Wilson's disease and should undergo a trial of levodopa therapy, as a small subset of patients with Dopa-Responsive Dystonia will experience a profound and sustained response to this medication [20]. Local injections of botulinum toxin (BOTOX) can alleviate focal dystonias such as Writer's cramp, blepharospasm or torticollis, but this intervention is impractical in patients with generalized dystonia [9, 20]. Some patients will not respond to BOTOX injections initially and up to 10% may develop resistance through the production of blocking antibodies [11].

Surgical therapy for dystonia

Historically, surgery for dystonia has targeted both the peripheral and central nervous systems. Peripheral denervation procedures were extensively used prior to the advent of botulinum toxin therapy with some positive results, mainly in the treatment of cervical dystonia [1]. The chronic administration of intrathecal baclofen via subcutaneously implanted pumps can alleviate dystonic cramping of the lower extremities, but this intervention may not be appropriate for dystonias affecting the arms and neck, and positive responses may not result in significant functional gains [10].

Advances in stereotactic technique and the observation that pallidotomy improves 'off-state' dystonia in PD patients [16] renewed interest in basal ganglia interventions for torsion dystonia. Pallidotomy does improve symptoms of primary generalized dystonia (PGD) [17]; however, unilateral pallidotomy may not sufficiently treat generalized symptoms [17] and bilateral pallidotomy entails significant risk including cognitive dysfunction, dysarthria, dysphagia, and limb weakness [12]. Additionally, there is concern that irreversible ablative procedures may alter basal ganglia function in a manner that will interfere with therapies that are developed in the future. Consequently, deep brain stimulation, which is reversible and may be employed bilaterally with relative safety, has emerged as an alternative to neuroablation.

The DBS device

Presently, there is but one DBS device available commercially, the Activa™ system, manufactured by Medtronic Inc. (Minneapolis, MN, USA). The device consists of three components: (1) a lead, which is equipped with four electrodes (contacts) and is implanted within the deep brain target; (2) an intervening extension cable and; (3) a programmable pulse generator (PG), which

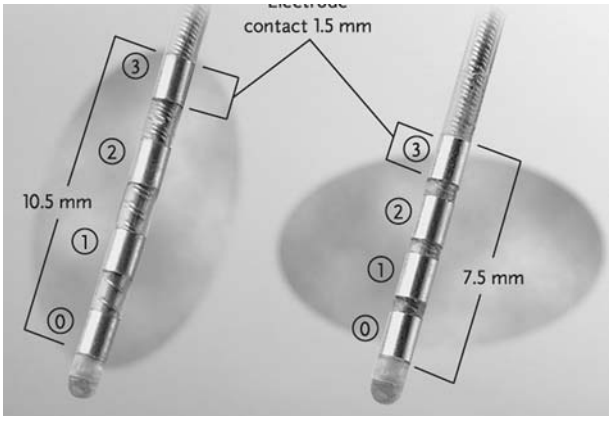


Fig. 1. DBS leads: Two quadripolar DBS leads are available from Medtronic, Inc. The only difference between the leads is the interelectrode spacing

delivers the therapeutic current. Two models of DBS lead are available, the only difference being the spacing of the contacts (Fig. 1). There are also two types of PG available, the Soletra™, which has four channels to accomodate one lead, and the Kinetra™, which has eight channels for two leads. Both may be interrogated and programmed transcutaneously by the treating physician.

The DBS procedure

Consistently successful DBS surgery is dependent upon three critical steps: (1) careful patient selection; (2) precise lead implantation; and (3) skillful device programming. Failure to perform any one of these three steps properly may lead to suboptimal results.

Patient selection

As discussed in the introduction, dystonia is a complex group of disorders, most of which are *not* responsive to DBS. Therefore, it is important to have all surgical candidates evaluated by a movement disorders neurologist. He/she will ensure that the diagnosis is correct, and that all reasonable medical therapies have been tried. At our center, the neurologist also programs the DBS devices after implantation, manages medication changes, and monitors patient progress. In the U.S. Activa™ is approved under a Humanitarian Device Exemption exclusively for the treatment of primary dystonia. All other uses are considered to be ''off-label''. Patients should not be offered surgery unless their symptoms are disabling and they have failed standard medical therapies. A recent MRI of the brain should be obtained to rule out structural lesions. Patients with childhood onset generalized dystonia should be tested for Wilson's disease and the DYT1 mutation, and should receive an adequate trial of levodopa.

Surgical technique

The device is implanted in two stages. During the first stage the lead(s) is implanted into the GPi stereotactically. The extension cable(s) and PG are implanted during the second stage, which may be performed on the same day or shortly thereafter. It is acceptable to implant DBS leads bilaterally during the same procedure. Dystonia patients are relatively young and, in our experience, tolerate the bilateral frontal lobe penetrations without difficulty. Moreover, the long implantation procedure is arduous for patients with generalized dystonia. Performing both lead implants in one session minimizes patient discomfort and hastens the time to the commencement of therapy. The first stage of the DBS procedure is ideally performed with the patient fully awake, but this may not be possible for children or patients with contorted postures. Anticholinergic medications, benzodiazepines, and baclofen should be withheld on the morning of surgery as these medications may interfere with intraoperative microelectrode recording (MER). If

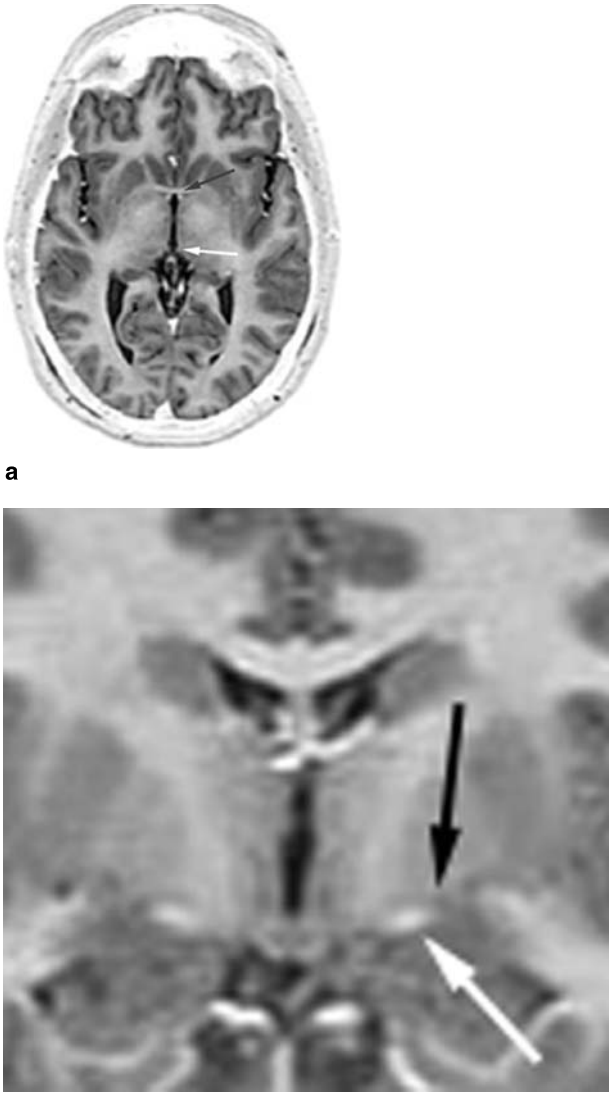


Fig. 2. Fast spin echo/inversion recovery MRI: We employ both axial (a) and coronal (b) FSE/IR images for targeting the GPi. The anterior (a; black arrow) and posterior (a; white arrow) commissures are readily visible on the axial image, as is the GPi. The target is the posteroventral GPi, approximately 20 mm lateral to the midline (b; black arrow), which lies 2–3 mm superior and lateral to the optic tract (b; white arrow)

painful muscular spasms or abnormal postures make awake surgery difficult, conscious sedation with propofol or dexmedetomidine can be instituted. Antibiotics are administered intravenously during application of the headframe, so that serum levels are therapeutic during the implantation procedure.

Anatomical targeting

Stereotactic headframes remain the gold standard for performing these surgeries; however, "frame-less" technologies are being employed with greater frequency. We employ axial and coronal fast spin echo/inversion recovery (FSE/IR) MRI for anatomic targeting because the images are acquired rapidly (6–9 minutes per scan) and provide superior resolution of the commissures and deep gray matter (Fig. 2). Additionally, this pulse sequence is reported to resist magnetic susceptibility artifact, minimizing the risk of targeting errors due to inaccurate fiducial registration. The thickness of the axial slices (3 mm) required to generate these high resolution images increases our initial targeting error along the Z-axis (i.e. depth); but this is compensated for by MER, which delineates the depth of specific structures along the implantation trajectory with a resolution of ~0.1 mm. The scanning parameters for FSE/IR MRI are given in Table 1. These images alone are sufficient for performing DBS implants with microelectrode guidance; however, additional image sets such as gadolinium-enhanced T1-weighted MRI, and/or computerized tomography may also be employed. The former assists in the selection of safe entry points by highlighting the cortical veins, while the latter provides the most geometrically accurate images for fiducial registration.

Table 1. *MRI scanning parameters for fast spin echo/inversion recovery images*

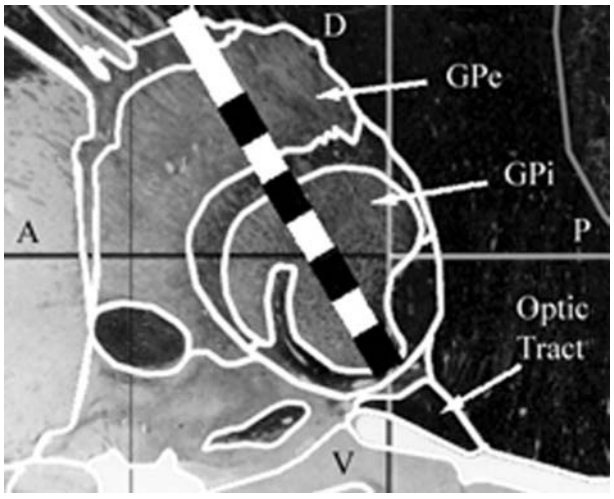
Excitation time (Te)	120 msec
Relaxation time (Tr)	10,000 msec
Inversion time (Ti)	2200 msec
Band width	20.83
Field of view (FOV)	24
Slice thickness	3 mm
Slice spacing	0 mm
Frequency	192 Hz
Phase	160
Number of excitations	1
Freqency direction	anteroposterior (AP)
Autocontrol frequency	water
Flow compensation direction	slice direction

Scanning parameters for fast spin echo/inversion recovery MRI are demonstrated. A scan of thirty slices can be obtained in 6–9 minutes employing these parameters.

The target coordinates may be calculated directly, employing the scanner's software. Alternatively, the imaging data sets may be transferred via internal network or CD-ROM to an independent workstation that is equipped with advanced stereotactic targeting software. These advanced software packages provide at least four distinct advantages: (1) target coordinates are calculated automatically, eliminating human mathematical errors; (2) a variety of image sets (e.g. CT and MRI) may be fused, allowing one to exploit the advantages of different types of imaging; (3) the entire trajectory may be visualized, allowing one to plan safer approaches to the target; and (4) digitized versions of stereotactic atlases may be overlaid and digitally "fit" to the patient's anatomy, helping to identify the desired target. We target the internal pallidal site first described by Leksell, which lies 19–22 mm lateral, 2–3 mm anterior, and 4 mm inferior to the mid-commissural point (MCP) [14]. The coordinates for the MCP are determined by calculating the arithmetic mean of the coordinates for the anterior and posterior commissures, which may be determined directly. The calculated target point should be visualized on both axial and coronal images and should lay 2–3 mm superior and lateral to the optic tract (Fig. 2b). Our preferred trajectory is 60–65° above the intercommissural plane and 0–5° lateral to the vertical axis. This trajectory allows one to avoid the lateral ventricle and still employ parasagittal trajectories, simplifying the process of mapping the intra-operative microelectrode recording data (see below).

Microelectrode recording

We employ single cell microelectrode recording (MER) to refine our anatomical targeting. The finer details of our MER technique are beyond the scope of this report but are provided elsewhere [18]. The need for MER is hotly debated; however, we find that MER provides important information that other neurophysiological localization techniques do not. First, MER delineates the borders and expanses of the GPe and Gpi along a given trajectory with a spatial resolution of ~100 μ. These data are mapped onto scaled sagittal sections of stereotactic atlases in order to determine anatomical location of the recording trajectory. Acceptable trajectories for implantation include a 3–4 mm span of globus pallidus pars externa (GPe) and at least 7.5 mm of GPi. Such a trajectory will pass through the heart of the GPi and will allow three or four contacts to be positioned comfortably within the nucleus, depending on the lead employed



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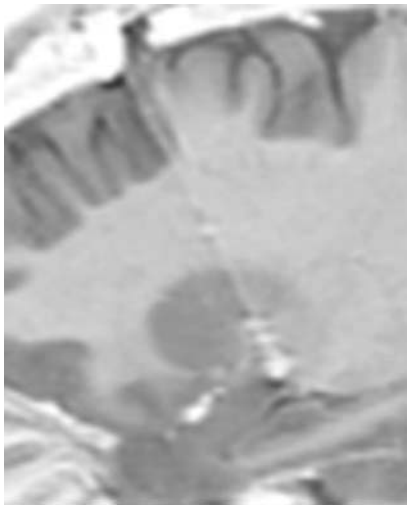


b

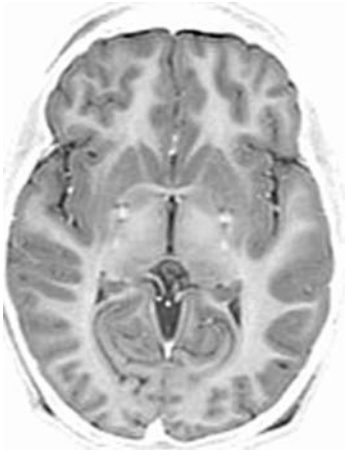
Fig. 3. Pallidal lead implantation: Our preferred lead position within the GPi is depicted. (a) A schematic representation of the model 3387 lead (Medtronic Inc.), with 1.5 mm inter-electrode spacing, is superimposed on a sagittal image, 20 mm lateral of midline, from the Schaltenbrand and Wharen Atlas. With the deepest contact (contact 0) positioned at the inferior border of the GPi, three contacts can fit within the nucleus. (b) Post-implantation image

(Fig. 3). Second, the detection of kinesthetic cells confirms that the trajectory traverses the sensorimotor sub-region of the GPi. Third, delineating the inferior border of the GPi refines the depth of implantation. And fourth, identifying the optic tract 2–3 mm inferior to the GPi exit point confirms that the trajectory exits the nucleus inferiorly, not posteriorly into the internal capsule. Identification of the optic tract provides an additional level of confidence that the lead will be well-positioned; but this should not be viewed as an absolute requirement for implantation, as the optic tract may not be identified in many cases.

Macroelectrode stimulation

The DBS lead is inserted along the desired trajectory leaving the deepest contact (contact 0) at the physiologically defined inferior border of the GPi (Fig. 3). C-arm fluoroscopy is employed to confirm that the lead has traveled to the desired point, relative to the frame. Before it is secured, the acute effects of stimulation via the lead are tested. Testing is performed in bipolar mode employing the following parameters: pulse width – 60 μsec; frequency – 130 Hz, amplitude – 0–4 V. Stimulation amplitudes greater than 4 V are not used as we have never required amplitudes this great for therapy. The initial test is performed with the deepest pair of contacts (i.e. 0−, 1+), as these are most likely to generate adverse effects (AE). If no AE are observed, testing continues in a ventral to dorsal sequence. Unlike Parkinson's disease, dystonia requires days to weeks of stimulation therapy before improvements are apparent. Therefore, a lack of improvement in response to intraoperative stimulation should not be viewed as an indicator of poor lead placement. Rather, one must have faith that if the microelectrode recording data is consistent with good placement and there are no adverse effects with up to four volts of stimulation, the lead is well positioned.

Sustained, time- and voltage-locked contractions of the contralateral hemi-body and/or face indicate that stimulation is activating the fibers of the internal capsule, in which case the lead is placed too medially and/or posteriorly. The induction of phosphenes in the contralateral visual field suggests that stimulation is activating the optic tract and that the lead is too deep. Stimulation within the sensorimotor GPi may induce transient paresthesiae; however, sustained paresthesiae at low stimulation amplitudes indicate that the lead is positioned very posterior, and is activating thalamo-cortical projections in the posterior limb of the internal capsule. If any of these adverse effects occur, the lead should be re-positioned accordingly. The lead is secured at the skull employing a 'cap' that also covers the burr hole. Fluoroscopy is used to confirm that the lead was not displaced from its desired position during fixation. The free end of the lead is encircled around the burr hole cap and left in the sub-galeal space. The incision is irrigated with antibiotic saline and closed anatomically. After removing the stereotactic frame, the patient is transported to radiology where postoperative MRI is performed to confirm that the leads are well-positioned and that there has been no hemorrhage (Fig. 4). Patients are observed overnight in the



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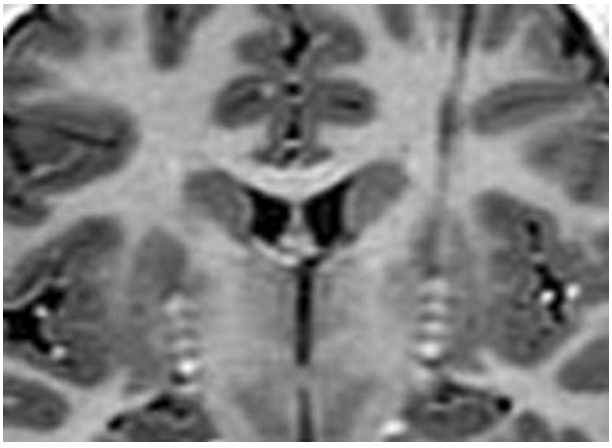

b

Fig. 4. Post-implantation MRI: Axial (a) and Coronal (b) FSE/IR images of a patient immediately after surgery. The DBS leads are positioned within the posteroventral GPi

neurosurgical intensive care unit and discharged the following day.

Implantation of the PG

The remainder of the DBS system(s) is implanted 10–14 days after the lead(s) is implanted. This is an ambulatory procedure that is performed under general anesthesia. We have found that placing the connection between the lead and the extension cable under the galea, just lateral to the cranial incision significantly reduces the incidence of lead fracture and wound erosion.

Programming the device

The device(s) is activated 7–10 days after implantation, allowing the surgical incisions to heal. The clinician controls four stimulus parameters: (1) amplitude; (2) pulse width; (3) frequency; and (4) the active contact(s). There is no consensus regarding the optimal settings for treating dystonia as systematic evaluations of varying stimulus parameters have not been conducted. Instead, therapy is currently guided by published case series, which report positive responses with wide pulses (210–400 μsec) and high frequencies (130 Hz or higher) [5]. Though effective, these parameters rapidly deplete the PGs, necessitating their frequent replacement (12–24 months). With experience, we have found that stimulation at lower frequencies (60–80 Hz) and narrower pulses (210 μsec) may be just as effective as high frequency stimulation (unpublished results). These settings deliver less electrical energy to the brain, enhancing the tolerability of stimulation, and should prolong battery life.

At the initial programming session, the effects of unipolar stimulation with each of the contacts are assessed. In particular, the stimulation thresholds for inducing AEs are noted. Our approach to implantation positions the deepest three contacts within the GPi proper (Fig. 3). We employ for therapy the most ventral contact that does not induce adverse effects with stimulation of up to 3.5 V. We prefer to treat with unipolar stimulation but will use bipolar settings if unipolar stimulation is not tolerated. Patients are initially treated at 2.0–2.5 V. The stimulation amplitude may be increased over time; however, the amplitude should never exceed 3.5 V, as the PG must invoke a 'doubling circuit' to deliver this amplitude, shortening battery life out of proportion to the energy delivered. If more energy is required, it is better to increase frequency or pulse width from the standpoint of battery preservation. Patients return every two weeks for evaluation during the first three months, and every three to six months after that. During each visit the patient is assessed employing the Burke-Fahn-Marden dystonia rating scale (BFMDRS) [23]. For patients with adult onset cervical dystonia, the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is preferred [23]. These scales can be used to assess patient progress relative to their baseline scores, which are obtained one week prior to surgery.

Clinical results

Pallidal DBS for primary dystonia

Initial case reports of pallidal DBS for dystonia employing contemporary technology were published in 1999. Coubes *et al*. reported the case of an 8-year-old

girl with generalized torsion dystonia whose symptoms were so severe she required sedation and mechanical ventilation. Thirty-six months after surgery she had returned to school with near normal neurologic function [5]. Kumar *et al*. also reported a dramatic improvement in one patient with severe generalized primary dystonia and correlated the clinical response to normalization of motor cortical activity on positron emission tomography [15]. Krauss *et al*. noted improvements of 78 and 70% in the BFMDRS scores of two patients with PGD two years after surgery [13].

Larger series of patients have supported these preliminary results. Yianni *et al*. reported on 25 patients with various forms of dystonia, finding that all sub-groups were improved [24]. Coubes *et al*. have published the largest and most comprehensive single-center experience to date, reporting a mean 79% improvement in the BFMDRS motor subscore two years after surgery in 31 patients with PGD [4]. The mean improvement in the BFMDRS disability subscore was 65%. The authors noted a steady improvement in the BFMDRS scores over the first year of therapy. They found no difference in outcomes between those who did or did not possess the DYT1 mutation. Children fared marginally better than adults. Vidailhet *et al*. prospectively examined 22 patients with PGD who were treated with bilateral pallidal DBS [22]. One year after surgery, the mean BFMDRS motor score was improved by 51% with one third of the patients experiencing a greater than 75% improvement. The authors noted that phasic symptoms improved more rapidly than fixed postures, the presence of which may limit functional recovery.

Our experience mirrors these results. Table 2 summarizes the clinical results we achieved in 17 primary dystonia patients treated with pallidal DBS with at least 12 months of follow-up. One year after surgery the group as a whole was improved 50–60% as measured by the BFMDRS. Statistically, there was no difference between the patients with primary idiopathic dystonia and those who were DYT1+. Interestingly, three DYT1+ patients who had undergone prior thalamotomies exhibited inferior responses as compared to DYT1+ patients without prior ablation. The role of pallidal DBS in the management of medically refractory cervical dystonia (i.e. spasmodic torticollis) is less clear, although the reported results in small series of patients are encouraging. For example, Bittar *et al*. [2] have observed a mean 59% improvement in the total TWSTRS scores of six patients with cervical dystonia, two years after bilateral GPi DBS surgery. The response to stimulation was gradual as in PGD. The authors report the use of high stimulation frequencies (>100 Hz) and very high amplitudes (∼5 V). Larger series of patients with long-term follow-up must be studied before the true value of DBS in this dystonia subgroup is understood.

Pallidal DBS for secondary dystonia

Reports of DBS for secondary dystonia are scarce and include relatively few patients. Nevertheless, it seems clear that secondary dystonia patients, as a group, respond less robustly to pallidal interventions than do patients with primary dystonia [8]. Our own experience treating five patients with secondary dystonia of various

Table 2. *Pallidal DBS for torsion dystonia: clinical results*

Cohort	Six months		Twelve months	
	BFMDRS-M % Improvement (range)	BFMDRS-D % Improvement (range)	BFMDRS-M % Improvement (range)	BFMDRS-D % Improvement (range)
Primary dystonia	49.0	42.6	58.7	62.2
$N=17$	(9.1–93.6)	(0–80.0)	(16.7–97.4)	(9.5–100)
Primary idiopathic	66.4	47.7	70.3	64.6
$N=5$	(55.8–93.6)	(28.6–71.4)	(51.9–97.4)	(28.6–100)
DYT1+	44.0	40.5	53.9	47.0
$N=12$	(9.1–83.3)	(0–80.0)	(16.7–85.2)	(9.5–84.0)
DYT1+; No prior surgery	53.5	48.5	63.5	72.7
$N=9$	(16.7–83.3)	(0–80.0)	(16.7–85.2)	(33.3–94.0)
DYT1+; Prior thalamotomy	11.9	16.7	25.5	16.7
$N=3$	(9.1–25.5)	(9.5–34.0)	(22.6–27.3)	(9.5–34.0)
Secondary dystonia	23.2	22.1	32.9	26.2
$N=5$	(12.6–32.5)	(9.5–33.3)	(15.2–35.7)	(12.6–33.3)

Clinical results for 22 dystonia patients treated between December 2000 and April 2004. Each patient has been followed for at least one year. The percentage improvement in the Burke-Fahn-Marsden dystonia rating scale motor (*BFMDRS-M*) and disability (*BFMDRS-D*) subscores are given, six and twelve months after the commencement of stimulation therapy

causes confirms that responses in this group are more modest than the results obtained in primary dystonia (Table 2). However, we recently operated a 12-year-old boy with severe generalized dystonia secondary to an anoxic brain injury at birth, who responded quickly (within two weeks) and dramatically to bilateral GPi DBS (results not shown). Despite his prolonged anoxia and the severity of his dystonia, his brain anatomy was well preserved. His outcome and that of other sporadic cases, suggest that there are some patients with anoxic or traumatic brain injuries who will respond favorably to DBS; however, the pre-operative indicators of a positive response are currently unknown.

Trottenberg *et al*. have reported excellent responses to pallidal DBS in five patients with severe tardive dystonia (TD) [21]; however, this result was not corroborated by Krauss *et al*. [13]. These authors did note a dramatic improvement in one patient with Hallervorden-Spatz disease. Unfortunately, the response lasted for just two years [13].

Subthalamic DBS for primary dystonia

Sun *et al*. performed the only study to date comparing bilateral GPi to bilateral subthalamic nucleus (STN) stimulation for dystonia [19]. Four patients were implanted at each target. All four of the patients treated with STN DBS improved as compared to two of the four patients treated with GPi DBS. Furthermore, the patients treated at the STN improved immediately while the patients receiving GPi improved over a period of months. In contrast, Detante *et al*. found no improvement in three dystonia patients who underwent DBS at the STN [7].

Complications of DBS therapy

Overall, both DBS surgery and chronic electrical stimulation of the internal pallidum are well tolerated. The senior author (RLA) has now implanted 76 DBS devices in 36 dystonia patients. There have been no intracerebral hemorrhages and no patient has suffered a new neurological deficit of any kind. Four patients (11%) have developed peri-operative infections that necessitated removal of five devices (6.6%). Each patient was successfully treated and underwent re-implantation surgery without any additional adverse events. Two patients have developed fractures of an extension cable, a complication that is reported to occur more frequently in dystonia than in Parkinson's disease or essential tremor [25]. Only one patient with DYT1-associated dystonia has required lead repositioning due to an inadequate response. The repositioning was performed successfully and has resulted in a rapid and dramatic improvement in his contralateral dystonia.

Conclusions

Deep brain stimulation at the internal pallidum has emerged as the treatment of choice for medically refractory primary torsion dystonia. Multiple open-label studies demonstrate that pallidal DBS is highly effective in patients with PGD and is well tolerated. Patients who are DYT1+ may fare best of all. The response to stimulation is more gradual than that observed in Parkinson's disease or Essential Tremor and the full benefit of surgery may not be realized for a year or more. When prolonged dystonia has resulted in fixed contractures, additional orthopedic surgery may be required to maximize functional gains. Preliminary results in patients with spasmodic torticollis are promising but larger case series are required before the true efficacy of pallidal DBS for this entity can be ascertained.

Patients with secondary dystonia respond more modestly and inconsistently than do primary dystonia patients, reflecting the physiological and anatomical heterogeneity of this population. Among these, patients with tardive dystonia and individuals with dystonia secondary to anoxic brain injury, but with preserved basal ganglia anatomy, represent subgroups that may respond well to DBS therapy. Conversely, patients with obvious structural abnormalities and those with metabolic disorders appear to be poor DBS candidates.

Standard stimulation parameters for treating dystonia currently include frequencies of 130 Hz or more and pulse widths of 210–400 μsec, settings that may rapidly deplete the implanted pulse generators. Stimulation at lower frequencies may prove to be as efficacious as high frequency stimulation, may make stimulation more tolerable in some cases, and should prolong battery life. Therefore, a more complete evaluation of low frequency stimulation for primary dystonia should be undertaken.

Additional research efforts should be directed toward developing a greater understanding of dystonia pathophysiology and the neurophysiological changes induced by chronic electrical stimulation. This will lead to more rational stimulation paradigms and better clinical results. Pre-operative indicators of a positive response to DBS must be sought in order to improve patient selection. In particular, functional imaging studies of dystonia patients, pre- and post-DBS surgery, are currently lack-

ing and should be pursued. Finally, continued explorations of other targets for therapy are appropriate, particularly for the many patients with secondary dystonia who are not candidates for pallidal DBS.

References

1. Bertrand CM, Molina-Negro P (1988) Selective peripheral denervation in 111 cases of spasmodic torticollis: rationale and results. Adv Neurol 50: 637–643
2. Bittar RG, Yianni J, Wang SY, Liu X, Nandi K, Joint C, Scott R, Bain PG, Gregory R, Stein J, Aziz T (2005) Deep brain stimulation for generalized dystonia and spasmodic torticollis. J Clin Neurosci 12: 12–16
3. Bressman SB (2003) Dystonia: phenotypes and genotypes. Rev Neurol (Paris) 159: 849–856
4. Coubes P, Cif L, El Fertit H, Hemm S, Vayssiere N, Serrat S, Picot MC, Tuffery S, Claustres M, Echenne B, Frerebeau P (2004) Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: long-term results. J Neurosurg 101: 189–194
5. Coubes P, Echenne B, Roubertie A, Vayssiere N, Tuffery S, Humbertclaude V, Cambonie G, Claustres M, Frerebeau P (1999) Treatment of early-onset generalized dystonia by chronic bilateral stimulation of the internal globus pallidus. Apropos of a case. Neurochirurgie 45: 139–144
6. Defazio G, Abbruzzese G, Livrea P, Berardelli A (2004) Epidemiology of primary dystonia. Lancet Neurol 3: 673–678
7. Detante O, Vercueil L, Krack P, Chabardes S, Benabid AL, Pollak P (2004) Off-period dystonia in Parkinson's disease but not generalized dystonia is improved by high-frequency stimulation of the subthalamic nucleus. Adv Neurol 94: 309–314
8. Elthaway H, Saint-Cyr J, Giladi N, Lang A, Lozano AM (2004) Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. Neurosurg 54: 613–621
9. Fahn S (1994) Idiopathic torsion dystonia. In: Calne DB (ed) Neurodegenerative diseases. Saunders WB, Philadelphia, pp 705–715
10. Ford B, Greene P, Louis ED, Petzinger G, Bressman SB, Goodman R, Brin MF, Sadiq S, Fahn S (1996) Use of intrathecal baclofen in the treatment of patients with dystonia. Arch Neurol 53: 1241–1246
11. Greene P, Fahn S, Diamond B (1994) Development of resistance to botulinum toxin type A in patients with torticollis. Mov Disord 9: 213–217
12. Hua Z, Guodong G, Qinchuan L, Yaqun Z, Qinfen W, Xuelian W (2003) Analysis of complications of radiofrequency pallidotomy. Neurosurgery 52: 89–99
13. Krauss JK, Loher TJ, Weigel R, Capelle HH, Weber S, Burgunder JM (2003) Chronic stimulation of the globus pallidus internus for treatment of non-dYT1 generalized dystonia and choreoathetosis: 2-year follow up. J Neurosurg 98: 785–792
14. Laitinen LV, Bergenheim AT, Hariz MI (1992) Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J Neurosurg 76: 53–61
15. Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM (1999) Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. Neurology 53: 871–874
16. Lozano AM, Lang AE, Galvez-Jimenez N, Miyasaki J, Duff J, Hutchinson WD, Dostrovsky JO (1995) Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 346: 1383–1387
17. Ondo WG, Desaloms JM, Jankovic J, Grossman RG (1998) Pallidotomy for generalized dystonia. Mov Disord 13: 693–698
18. Shils J, Tagliati M, Alterman R (2002) Neurophysiological monitoring during neurosurgery for movement disorders. In: Deletis V, Shils J (eds) Neurophysiology in neurosurgery. San Diego, Academic Press, pp 393–436
19. Sun B, Li D, Sun C, Liu D, Zhao Y, Shen J, Chen S (2003) Target selection for primary dystonia deep brain stimulation: GPi or STN? ASSFN Proceedings, New York, NY, p 91
20. Tagliati M, Blatt K, Bressman SB (2003) Generalized torsion dystonia. In: Noseworthy J (ed) Neurological therapeutics: principles and practice. Martin Dunitz Ltd., London
21. Trottenberg T, Volkmann J, Deuschl G, Kuhn AA, Schneider GH, Muller J, Alesch F, Kupsch A (2005) Treatment of severe tardive dystonia with pallidal deep brain stimulation. Neurology 64: 344–346
22. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, Lagrange C, Tezenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P, French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group (2005) Bilateral deep brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 352: 459–467
23. Volkmann J, Benecke R (2002) Deep brain stimulation for dystonia: patient selection and evaluation. Mov Disord 17 Suppl 3: S112–S115
24. Yianni J, Bain P, Giladi N, Auca M, Gregory R, Joint C, Nandi D, Stein J, Scott R, Aziz T (2003) Globus pallidus internus deep brain stimulation for dystonic conditions: a prospective audit. Mov Disord 18: 436–442
25. Yianni J, Nandi D, Shad A, Bain P, Gregory R, Aziz T (2004) Increased risk of lead fracture and migration in dystonia compared with other movement disorders following deep brain stimulation. J Clin Neurosci 11: 243–245

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Deep brain stimulation for treatment of cervical dystonia

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Summary

Pallidal deep brain stimulation is an efficient treatment option in those patients with cervical dystonia who do not benefit from conservative treatment including local botulinum toxin injections. Given the fact that other surgical treatment options such as selective peripheral denervation are available, it may be considered third-line treatment in most instances. Chronic bilateral pallidal stimulation improves dystonic posture and movements, pain caused by dystonia and disability related to dystonia. Preliminary data on longterm follow-up confirm its beneficial effect in the majority of patients. Given the frequency of cervical dystonia, pallidal deep brain stimulation will play a major role in the future.

Keywords: Cervical dystonia; deep brain stimulation; pallidum; spasmodic torticollis.

Introduction

Deep brain stimulation (DBS) for the treatment of dystonia has emerged only a decade ago [10, 26, 29]. Since then, it has been used in a variety of different dystonic disorders [6, 9, 45]. It has been shown that it is more effective in idiopathic and inherited forms of dystonia than in secondary dystonia due to insults such as perinatal hypoxia, trauma or stroke [12, 25, 27, 38]. The results of early pilot studies, more recently have been confirmed by prospective semi-controlled randomized studies [44]. Nowadays, pallidal DBS is a major therapeutic tool in the armamentarium to treat medically-refractory dystonia. Besides generalized dystonia, cervical dystonia has been one of the earliest indications for chronic pallidal DBS. Since its introduction in clinical routine in the late 1990s it is being performed widely now both in the Western and Eastern hemispheres.

While DBS may be considered second-line or even first-line treatment in some patients with severe idiopathic generalized dystonia, this is not the case, however, in cervical dystonia [1]. First, the mainstay in the treatment of cervical dystonia nowadays is local botulinum toxin injection [1, 19]. Second, it should be remembered that there are other less costintensive surgical options available such as selective peripheral denervation. Pallidal DBS has been thought to be indicated primarily in patients with complex cervical dystonia with marked phasic dystonic movements, sagittal or lateral shift, and associated head tremor or myoclonus who do not achieve adequate benefit from botulinum toxin injections [24, 26]. Since cervical dystonia is the most common manifestation of dystonia, however, it might well be that it will be the dystonic movement disorder considered most often for DBS in the future.

Clinical symptoms and epidemiology of cervical dystonia

Cervical dystonia is being used as a synonym for spasmodic torticollis. Note, however, that both terms are not mutually interchangeable. Cervical dystonia may consist of torticollis (neck turning), head tilt (laterocollis), neck flexion (anterocollis), neck extension (retrocollis), or sagittal and lateral shift. In about one-third of patients with cervical dystonia other body parts may become involved, most frequently the shoulder. Cervical dystonia is characterized by patterned repetitive, phasic (spasmodic) or sustained (tonic) muscle contractions resulting in involuntary abnormal neck movements or postures. Tremulous cervical dystonia results in oscillatory movements of the head. It has been shown that dystonic activity in various combinations may result in a similar abnormal head posture, and that actually the pattern of activation of dystonic muscles may change in

an individual patient [34]. About two thirds of patients suffer from neck pain which may be excruciating in some instances.

Cervical dystonia and other dystonic movement disorders affecting the neck may lead to premature cervical spondylosis causing cervical radiculopathies or even myelopathy, in the rare case [30]. Remarkably, in dystonic patients the upper cervical segments are involved more frequently than in degenerative spinal disorders related to aging. Scoliosis is frequent, and it has even been discussed as a risk factor for dystonia.

Cervical dystonia is the most frequent focal dystonia [18]. Its prevalence has been estimated to be 13 per 100,000 inhabitants. There is a slight preponderance of female gender, the mean age at symptom onset is in the early forties.

Treatment options for cervical dystonia

Pharmacotherapy is useful only in a limited number of patients with cervical dystonia [1]. The most effective drugs are anticholinergics but their efficacy is often limited by side effects. Local botulinum toxin injections are the therapy of choice in the majority of patients, nowadays. Botulinum toxin type A is regarded as first line treatment, while type B is being reserved for non-responders. Actual evidence is lacking on direct comparison of the clinical efficacy and safety of type A vs. type B. Primary or secondary resistance to botulinum toxin may occur in about 10% of patients.

Selective peripheral denervation has been recommended as a safe procedure with infrequent and minimal side effects [38]. This procedure should not be confused with intradural rhizotomy, which has a high incidence of complications. It is indicated in patients with cervical dystonia who do not achieve adequate response with medical treatment or repeated botulinum toxin injections. Additional myectomy may be carried out if necessary. In some patients selective peripheral denervation can also be an alternative to botulinum toxin injections. Overall, about one to two thirds of patients achieve useful improvement on long-term. Re-innervation can occur and may require further surgery.

Functional stereotactic surgery in cervical dystonia

Dystonia has been recognized to be a central movement disorder since decades. Therefore, it appeared to be logical to target structures such as the thalamus or the pallidum in order to modulate the circuitries thought to be involved in its pathophysiology. Thalamic surgery was the preferred procedure in ablative stereotactic neurosurgery for cervical dystonia until the early 1980s [16, 31, 35]. The GPi proper was targeted infrequently, and it was not considered at all to be a target after the general decline of pallidal surgery. There are several lessons to be learned from review of the experience with ablative stereotactic surgery for cervical dystonia, despite limitations in interpretation of the data. Amelioration of cervical dystonia was achieved in about 50–70% of patients in most studies. Bilateral surgery generally provided better outcomes than unilateral surgery. Postoperative benefit was reported to show up only after a delay in several studies. Some reports demonstrated sustained benefit after follow-up of more than 5 years. Bilateral procedures, in particular bilateral thalamotomies, were clearly associated with a higher rate of postoperative side effects, such as dysarthria, dysphagia, and ataxia, ranging from 20 to 70%. Functional stereotactic ablative surgery for cervical dystonia was abandoned in the late 1970s.

Rationales for pallidal DBS in cervical dystonia

Contemporary concepts shed some light on the pathophysiology of cervical dystonia. Nevertheless, its pathophysiology is still poorly understood, probably much less than that of Parkinson's disease (PD). Findings from functional neuroimaging studies indicate that there is bilateral striatal dysfunction regardless of the phenomenology of cervical dystonia [33, 36]. Dysfunction of other systems in addition to the basal ganglia circuitry has been considered to be relevant for the development of cervical dystonia. More recently, the interstitial nucleus of cajal (INC) has been rediscovered as an important key-structure for head control and it has been suggested that it may play an important role in the development of CD [22].

Opposing suggestions concerning the side to place the electrode were made for unilateral DBS in cervical dystonia patients based on the experience in single cases [7, 13]. We favor bilateral pallidal DBS over unilateral DBS in cervical dystonia for a variety of reasons. As indicated above, positron emission tomography (PET) investigations, for example, have demonstrated higher glucose metabolism in the lentiform nucleus bilaterally in cervical dystonia without significant differences regarding laterality, specific pattern, or severity [33]. Furthermore, transcranial magnetic stimulation studies revealed that there is considerable bihemispheric presentation of neck muscles [43].

Principles of DBS for cervical dystonia

The pallidal target for cervical dystonia is located in the posteroventral lateral GPi and it is the same that has been used for pallidal DBS in PD [23]. It is slightly anterior to the usual pallidotomy target to avoid spread of current to the internal capsule with higher intensity of stimulation which is necessary in many patients with dystonia. The target is chosen 20–22 mm lateral to and 4 mm below the intercommissural line, and 2–3 mm anterior to the intercommissural midpoint. We implant quadripolar 3387 electrodes bilaterally in the same surgical session under local anesthesia (Medtronic Minneapolis, Minn., USA). The preliminary target is defined by standard stereotactic imaging and refined by microelectrode recording. In awake patients macrostimulation directly via the DBS electrode allows for evaluation of extrinsic and intrinsic responses. Extrinsic responses can be evoked by spread of current to adjacent structures such as the optic tract which may result in phosphenes or the perception of flashes, and the internal capsule which may result in tonic contraction of the contralateral face or extremities. Intrinsic responses can include modulation of the patient's movement disorder and occasionally a feeling of tightness and fear at very high voltages. While there is no immediate effect on dystonic tonus, in some patients immediate improvement of phasic or myoclonic dystonic movements can be seen. Since battery depletion may result in sudden recurrence of dystonia our strategy is to use two implantable pulse generators (IPGs) (Soletra, Medtronic) instead of one dual channel IPG (Kinetra, Medtronic). Patients with dystonia are stimulated continuously. The improvement of dystonia in pallidal stimulation may be delayed, and it can take several months before the full benefit is evident [46]. The initial stimulation settings are based on a bipolar stimulation mode. Most frequently contact 1 is set to negative, and the next contact, usually contact 2 is set to positive, whilst the other electrodes remain neutral. Initial stimulation settings include a frequency of 130 Hz, a pulse width of 210 μsec, and amplitudes between 2.0 and 4.0 V as tolerated by the patient. During the next few months, the amplitude is gradually increased. The threshold for undesired effects shifts during progressive adjustment of stimulation amplitude. If no optimal benefit of the movement disorder is achieved upon chronic stimulation alternative electrode contacts or combinations are activated. Some centers also start with monopolar stimulation, or use two contacts as cathodal with case or another contact anodal. DBS settings are adjusted within the first year after surgery. In general, only minimal adjustment if any is required later. Energy consumption is much higher than in PD, which is due both to the broader pulse width and the relatively high amplitudes needed for symptomatic improvement. Side effects of stimulation are always reversible upon adjustment of DBS settings. If persistent side effects occur at a low amplitude that does not allow therapeutic stimulation to treat the movement disorder, reimplantation of the electrode is a feasible option. Weight gain is observed in some patients, but it appears to be unspecific and it has also been observed in pallidal surgery for other movement disorders [37].

While it may take several weeks to months until the full effect of pallidal DBS may be appreciated in cervical dystonia, it may recur minutes after cessation of stimulation. In a systematic study we have shown that phasic elements of dystonia recur earlier than tonic elements [30]. Hardware-related problems have been noted more frequently in early patient series of cervical dystonia but have been comparable to those of other movement disorder populations more recently due to some technical modifications such as avoiding to place the connector in the neck [20, 32, 40]. Distinct temporal patterns of synchronized neuronal activity in the pallidum were found in dystonia patients as compared to treated and untreated PD patients [41]. Dystonia patients had less local field potential (LFP) power in the 11–30 Hz band, but greater power in the 4–10 Hz band. The change in the latter spectrum was particularly manifest in more rostral contact pairs presumed to be within the globus pallidus externus (GPe). Thus, consistent with data from microelectrode recordings, abnormal patterned activity is present both in GPi and GPe in dystonia. These findings support the assumption that pallidal functional surgery could reduce dystonia by suppression of disruptive noisy activity across a number of frequency bands.

Clinical outcome of DBS in cervical dystonia

Pallidal stimulation results both in symptomatic and functional improvement of cervical dystonia including marked relief of pain [24, 26]. Several smaller series and case studies have confirmed the clinical benefit and negative outcome rather has been an exception [2–5, 14, 17, 21, 28, 39, 42]. The gradual improvement of cervical dystonia was reflected by the change of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) during follow-up. The mean TWSTRS scores were better at 1 year after surgery than at 3 months postoperatively. In the patients operated in Mannheim and Berne, follow-up

evaluation at 20 months after surgery demonstrated a 63% improvement of the TWSTRS severity score, a 69% improvement of the disability score, and a 50% improvement of the pain score. These figures are similar to the results obtained by the Oxford group who demonstrated amelioration for the subscores severity by 64%, disability by 60%, and pain by 60% at 19 months follow-up [45]. In single patients it was reported that relief of pain was greater than improvements in other aspects of the TWSTRS scale [28]. It appears that there is less interpatient variability in cervical dystonia patients than in patients with other dystonic disorders. In some series patients who presented with tonic rather than with phasic symptomatology tended to achieve more benefit [5]. Chronic pallidal stimulation has been used also as an adjunct in patients with cervical dyskinesias and secondary cervical myelopathy prior to performing spinal surgery [24].

Since relatively high currents and broad pulse widths are used for chronic pallidal stimulation in cervical dystonia patients costs are relatively high. Furthermore, it has to be considered that these patients are much younger than other movements disorder patients, e.g. those with PD. Mean IPG settings for chronic stimulation at follow-up of 3 years or more in our experience were as follows: voltage 4.0 V, pulse width 210 microsec, and frequency 135 Hz. It would be desirable to have new DBS strategies available to reduce costs. Such strategies might be the use of rechargeable IPG batteries – which is marketed already for chronic spinal cord stimulation –, the use of batteries which have longer lifetime, and the use of other stimulation modes such as cyclic stimulation.

Subthalamic nucleus stimulation has been reported to be efficacious in single cases with cervical dystonia, but systematic studies on this subject are lacking [8].

There is limited knowledge on the longterm effect of pallidal stimulation for cervical dystonia. The first patient from Berne now has reached 9-year follow-up, and she still has marked benefit from continuous stimulation. Initially, she underwent a total of three revisions to replace fractured leads. In our experience, the initial postoperative improvement has been sustained for three years or longer in four out of five patients.

Perspectives

Perspectives of DBS for treatment of dystonia include mainly the development of new technology, and the evaluation of carefully planned and conducted studies. At this time, two larger studies on this subject are under way. Preliminary results of the Canadian multicenter study have been published [21]. The German randomized double-blind multicenter study has started to recruit patients and the first patients have been operated on recently.

References

1. Albanese A, Barnes MP, Bhatia KP, Fernandez E, Fillipini G, Gasser T, Krauss JK, Newton A, Rektor I, Savoiardo M, Valls-Sole J (2006) A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force. Eur J Neurol 13: 433–444
2. Andaluz N, Taha JM, Dalvi A (2001) Bilateral pallidal deep brain stimulation for cervical and truncal dystonia. Neurology 57: 557–558
3. Bereznai B, Steude U, Seelos K, Botzel K (2002) Chronic high-frequency globus pallidus internus stimulation in different types of dystonia: a clinical, video, and MRI report of six patients presenting with segmental, cervical, and generalized dystonia. Mov Disord 17: 138–144
4. Bittar RG, Yianni J, Wang S, Liu X, Nandi D, Joint C, Scott R, Bain PG, Gregory R, Stein J, Aziz TZ (2005) Deep brain stimulation for generalised dystonia and spasmodic torticollis. J Clin Neurosci 12: 12–16
5. Botzel K, Steude U (2006) First experiences in deep brain stimulation for cervical dystonia. Nervenarzt 77: 940–945
6. Capelle HH, Weigel R, Krauss JK (2003) Bilateral pallidal stimulation for blepharospasm-oromandibular dystonia (Meige syndrome). Neurology 60: 2017–2018
7. Chang JW, Choi JY, Lee BW, Kang UJ, Chung SS (2002) Unilateral globus pallidus internus stimulation improves delayed onset post-traumatic cervical dystonia with an ipsilateral focal basal ganglia lesion. J Neurol Neurosurg Psychiatry 73: 588–590
8. Chou KL, Hurtig HI, Jaggi JL, Baltuch GH (2005) Bilateral subthalamic nucleus deep brain stimulation in a patient with cervical dystonia and essential tremor. Mov Disord 20: 377–380
9. Cif L, El Fertit H, Vayssiere N, Hemm S, Hardouin E, Gannau A, Tuffery S, Coubes P (2003) Treatment of dystonic syndromes by chronic electrical stimulation of the internal globus pallidus. J Neurosurg Sci 47: 52–55
10. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B (2000) Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 355: 2220–2221
11. Eltahawy HA, Saint-Cyr J, Giladi N, Lang AE, Lozano AM (2004) Primary dystonia is more responsive than secondary dystonia to pallidal interventions: outcome after pallidotomy or pallidal deep brain stimulation. Neurosurgery 54: 613–619
12. Eltahawy HA, Saint-Cyr J, Poon YY, Moro E, Lang AE, Lozano AM (2004) Pallidal deep brain stimulation in cervical dystonia: clinical outcome in four cases. Can J Neurol Sci 31: 328–332
13. Escamilla-Sevilla F, Minguez-Castellanos A, Arjona-Moron V, Martin-Linares JM, Sanchez-Alvarez JC, Ortega-Morenoa A, Garcia-Gomez T (2002) Unilateral pallidal stimulation for segmental cervical and truncal dystonia: which side? Mov Disord 17: 1383–1385
14. Goto S, Mita S, Ushio Y (2002) Bilateral pallidal stimulation for cervical dystonia. An optimal paradigm from our experiences. Stereotact Funct Neurosurg 79: 221–227
15. Grips E, Blahak C, Capelle HH, Baezner H, Weigel R, Sedlaczek O, Krauss JK, Wöhrle JC (2006) Chronic deep brain stimulation in

dystonia: patterns of reoccurrence after discontinuation. J Neurol Neurosurg Psychiatry (Epub ahead of print)
16. Hassler R, Dieckmann G (1970) Stereotactic treatment of different kinds of spasmodic torticollis. Confin Neurol 32: 135–143
17. Islekel S, Zileli M, Zileli B (1999) Unilateral pallidal stimulation in cervical dystonia. Stereotact Funct Neurosurg 72: 248–252
18. Jankovic J (2004) Treatment of cervical dystonia. In: Brin MF, Comella C, Jankovic J (eds) Dystonia: etiology, clinical features and treatment. Lippincott, Williams & Wilkins, Philadelphia, pp 159–166
19. Jankovic J, Schwartz K (1995) Response and immunoresistance to botulinum toxin injections. Neurology 45: 1743–1746
20. Joint C, Nandi D, Parkin S, Gregory R, Aziz T (2002) Hardware-related problems of deep brain stimulation. Mov Disord 17 Suppl 3: S175–S180
21. Kiss ZH, Doig K, Eliasziw M, Ranawaya R, Suchowersky O (2004) The Canadian multicenter trial of pallidal deep brain stimulation for cervical dystonia: preliminary results in three patients. Neurosurg Focus 15:17:E5
22. Klier EM, Wang H, Constantin AG, Crawford JD (2002) Midbrain control of three-dimensional head orientation. Science 295: 1314–1316
23. Krauss JK, Grossman RG (2001) Principles and techniques of movement disorders surgery. In: Krauss JK, Jankovic J, Grossman RG (eds) Surgery for Parkinson's disease and movement disorders. Lippincott, Williams & Wilkins, Philadelphia, pp 74–109
24. Krauss JK, Loher TJ, Pohle T, Weber S, Taub E, Barlocher CB, Burgunder JM (2002) Pallidal deep brain stimulation in patients with cervical dystonia and severe cervical dyskinesias with cervical myelopathy. J Neurol Neurosurg Psychiatry 72: 249–256
25. Krauss JK, Loher TJ, Weigel R, Capelle HH, Weber S, Burgunder JM (2003) Chronic stimulation of the globus pallidus internus for treatment of non-DYT1 generalized dystonia and choreoathetosis: 2-year follow up. J Neurosurg 98: 785–792
26. Krauss JK, Pohle T, Weber S, Ozdoba C, Burgunder JM (1999) Bilateral stimulation of the globus pallidus internus for treatment of cervical dystonia. Lancet 354: 837–838
27. Krauss JK, Yianni J, Loher TJ, Aziz TZ (2004) Deep brain stimulation for dystonia. J Clin Neurophysiol 21: 18–30
28. Kulisevsky J, Lleo A, Gironell A, Molet J, Pascual-Sedano B, Pares P (2000) Bilateral pallidal stimulation for cervical dystonia: dissociated pain and motor improvement. Neurology 55: 1754–1755
29. Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM (1999) Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. Neurology 53: 871–874
30. Loher TJ, Bärlocher CB, Krauss JK (2006) Dystonic movement disorders and spinal degenerative disease. Stereotact Funct Neurosurg 84: 1–11
31. Loher TJ, Pohle T, Krauss JK (2004) Functional stereotactic neurosurgery for treatment of cervical dystonia: review of the experience from the lesional era. Stereotact Funct Neurosurg 82: 1–13
32. Lyons KE, Koller WC, Wilkinson SB, Pahwa R (2001) Surgical and device-related events with deep brain stimulation. Neurology 56 Suppl: A147
33. Magyar-Lehmann S, Antonini A, Roelcke U, Maguire RP, Missimer J, Meyer M, Leenders KL (1997) Cerebral glucose metabolism in patients with spasmodic torticollis. Mov Disord 12: 704–708
34. Munchau A, Filipovic SR, Oester-Barkey A, Quinn NP, Rothwell JC, Bhatia KP (2001) Spontaneously changing muscular activation pattern in patients with cervical dystonia. Mov Disord 16: 1091–1097
35. Mundinger F (1977) New stereotactic treatment of spasmodic torticollis with a brain stimulation system (in German). Med Klin 72: 1982–1986
36. Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brucke T (1998) Imaging the pre- and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using (123I) epidepride and (123I) beta-CIT. Mov Disord 13: 319–323
37. Ondo WG, Ben-Aire L, Jankovic J, Lai E, Contant C, Grossman R (2000) Weight gain following unilateral pallidotomy in Parkinson's disease. Acta Neurol Scand 101: 79–84
38. Ondo WG, Krauss JK (2004) Surgical therapies for dystonia. In: Brin MF, Comella C, Jankovic J (eds) Dystonia: etiology, clinical features and treatment. Lippincott, Williams & Wilkins, Philadelphia, pp 125–147
39. Parkin S, Aziz T, Gregory R, Bain P (2001) Bilateral internal globus pallidus stimulation for the treatment of spasmodic torticollis. Mov Disord 16: 489–493
40. Rowe JG, Davies LE, Scott R, Gregory R, Aziz TZ (1999) Surgical complications of functional neurosurgery treating movement disorders: results with anatomical localisation. J Clin Neurosci 6: 36–37
41. Silberstein P, Kuhn AA, Kupsch A, Trottenberg T, Krauss JK, Wohrle JC, Mazzone P, Insola A, Di Lazzaro V, Oliviero A, Aziz T, Brown P (2003) Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. Brain 126: 2597–2608
42. Starr PA, Turner RS, Rau G, Lindsey N, Heath S, Volz M, Ostrem JL, Marks WJ Jr (2006) Microelectrode-guided implantation of deep brain stimulators into the globus pallidus internus for dystonia: techniques, electrode locations, and outcomes. J Neurosurg 104: 488–501
43. Thompson ML, Thickbroom GW, Mastaglia FL (1997) Corticomotor representation of the sternocleidomastoid muscle. Brain 120: 245–255
44. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, Lagrange C, Tezenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P, French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group (2005) Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 352: 459–467
45. Yianni J, Bain P, Giladi N, Auca M, Gregory R, Joint C, Nandi D, Stein J, Scott R, Aziz T (2003) Globus pallidus internus deep brain stimulation for dystonic conditions: a prospective audit. Mov Disord 18: 436–442
46. Yianni J, Bain PG, Gregory RP, Nandi D, Joint C, Scott RB, Stein JF, Aziz TZ (2003) Post-operative progress of dystonia patients following globus pallidus internus deep brain stimulation. Eur J Neurol 10: 239–247

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Subthalamic nucleus stimulation for primary dystonia and tardive dystonia

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Summary

With the renaissance of stereotactic pallidotomy for Parkinson's disease in 1990s, pallidotomy has become increasingly used as an effective treatment for various manifestations of medically refractory dystonia. More recently, deep brain stimulation of globus pallidus internus (GPi) has been replacing pallidotomy. Although GPi DBS has great promise for treating dystonia, there are some disadvantages. We introduce our experiences in subthalamic nucleus (STN) DBS for primary dystonia and tardive dystonia in this chapter. We propose that STN DBS has the following advantages over GPi DBS: (1) symptomatic improvement is seen immediately after stimulation, allowing us to quickly select the most suitable stimulation parameters; (2) the stimulation parameters for the STN are lower than those used for the GPi, resulting in longer battery life; and (3) STN DBS results in better symptomatic control than GPi DBS in dystonia patients when our STN data is compared to that obtained by others with using the GPi as the target. We suggest that STN DBS may be the most appropriate surgical technique for dystonia.

Keywords: Primary dystonia; tardive dystonia; deep brain stimulation; subthalamic nucleus; basal ganglia.

Introduction

Dystonia is a movement disorder characterized by twisting or involuntary movements and postures as a result of sustained involuntary muscle contraction. Dystonia can be classified by etiology, into primary and secondary dystonias, which require different therapeutic approaches [33]. Most cases of primary dystonia are inherited and begin in childhood or adolescence [37]. With advances in genomics and proteinomics, genes and proteins have been found that provide promising markers for early diagnosis [7, 8]. Primary generalized dystonia produces severe disability; traditional therapies are not effective enough to inhibit disease progression and relieve symptoms [1, 48].

Dystonia can also be a symptom of various neurological disorders, including neurodegenerative diseases, brain injury, inherent diseases and metabolic diseases. Differential diagnosis should be established because lesions present in basal ganglia, thalamus, subthalamus or the brainstem can cause secondary dystonia [3, 6]. Systematic evaluation should be used to identify the cause of secondary dystonias if patients will undergo surgical treatment.

Among traditional drug therapies, anticholinergics, dopamine antagonists and benzodiazepines are the most common drugs used to treat dystonic motor symptoms and can offer benefit to about 50% of patients younger than 20 years of age. Levodopa is effective in relieving the symptoms of dopa-responsive dystonia patients. Baclofen, a GABA-B agonist, can be administered intrathecally at a dosage of 200–2000 μg per day and may benefit up to 80% of primary and secondary dystonia patients; however, side effects include infection and leakage of cerebrospinal fluid [18, 26]. Botulinum toxin injections are still considered the most effective approach in treating focal dystonias such as blepharospasm, oromandibular and cervical dystonias [12, 43]. Unfortunately, more than 20% of patients do not respond well to these therapies or develop intolerable side effects.

Functional stereotactic neurosurgery has become increasingly used as an effective treatment for various manifestations of medically refractory dystonia. Since the early 1950s, surgical treatments have been applied in dystonia. Cooper reported significant improvement in 24.5% and mild improvement in 45.2% of patients undergoing thalamotomy [11]. With the resurgence of surgical treatments for Parkinson's disease in the 1990s, surgical treatment for refractory dystonia also received renewed attention. Many authors have reported that the long-term effects of pallidotomy were better than

thalamotomy. Besides improvement in control of arm and leg dystonias, pallidotomy also markedly improved speech, writing function and gait disturbance; but its side effects, such as dysarthria, were also significant, especially after bilateral lesions. More recently, deep brain stimulation (DBS) of the globus pallidus interna (GPi) has replaced pallidotomy as the surgical treatment of choice. Bilateral GPi DBS was seen to significantly decrease complications such as dysarthria, dysphasia and balance disturbances compared to bilateral pallidotomy. Some authors report that GPi DBS is 80% effective in intractable dystonia, and over 90% effective in dystonia caused by a DYT-1 mutation. Although GPi DBS has great promise for treating dystonia, there are still some disadvantages: (1) stimulation of GPi requires relatively high parameter settings (voltage, pulse width, etc.) which means battery life is relatively short; (2) it often takes weeks to months to see a positive effect, making stimulation programming difficult; and (3) since GPi is a relatively large structure, it is not clear which part of the nucleus is the best target. These concerns lead us to study new possible targets of DBS for dystonia. Subthalamic nucleus (STN) DBS has been established as an effective treatment for the motor symptoms of Parkinson's disease, and has also been demonstrated as improving levodopa-induced dyskinesias and off-period dystonic symptoms. In this chapter, we will discuss STN stimulation for generalized dystonia and tardive dystonia.

Surgical target selection

Relative to Parkinson's disease, DBS for dystonia is more difficult. Several reasons may explain this. (1) The etiology of dystonia is complicated and the clinical features are diverse. (2) So far there are no good predictors of efficacy prior to surgery (for instance, Parkinson patients with good levodopa response usually have good surgical results). (3) Many nuclei of the brain have been used for surgical treatment of dystonia, including thalamic nuclei [e.g., ventral oral anterior (Voa), ventral intermediate (Vim) and ventral lateral (VL)] and GPi, but the optimal site(s) for relief of a myriad of dystonic motor symptoms is still unknown. Although in recent years GPi has become a popular target for dystonia, GPi is relatively big and we do not yet know which subregion responds best to lesions or DBS. (4) DBS for dystonia requires weeks to months, sometimes even more than one year, to see an effect. This makes stimulation programming difficult because the beneficial effects of parameter changes are not seen immediately. That means there is an interval from weeks to months between programming sessions.

Although the mechanisms of primary and secondary dystonia still remain unclear, increasing evidence points to inappropriate over-activity of the striatofrontal projection and impaired activity of motor executive areas. Using PET regional blood flow studies, over-activity is seen in the contralateral premotor cortex, rostral sensory motor area, anterior cingulate, ipsilateral dorsolateral prefrontal cortex and bilateral lentiform nuclei.

Globus pallidus (GPi) in dystonia

Current studies document that GPi plays an important role in the pathophysiology of dystonia. Under normal conditions, GPi inhibits the function of the ventralis lateralis (VL) and ventralis anterior (VA) thalamic nuclei which are responsible for activation of the motor cortex. Data collected from microelectrode studies during pallidotomy in patients with primary dystonia show changes in neuronal firing rates within the basal ganglia which are not consistent with normal thalamocortical control. Starr and colleagues analyzed the activity of neurons recorded from GPi or the globus pallidus externa (GPe) in dystonic patients. They found the mean GPi firing rate in dystonia was significantly lower as compared to normal non-human primates and, perhaps surprisingly, Parkinson patients. In contrast, GPe activity was lower than that seen in normal non-human primates, but no different from that observed in Parkinson patients. They also observed oscillations in the 2–10 Hz range and increased bursting activity similar to that seen in Parkinson patients. Since Parkinson's disease normally results in decreased GPe activity (through increased inhibition of the indirect pathway) and increased GPi activity (through decreased inhibition of the direct pathway), the authors concluded that dystonia may represent a change in the basal ganglia leading to increased inhibition of *both* the direct and indirect pathways, but superimposed with the oscillations and bursting activity normally seen in Parkinson's disease [39]. Gernert and others have also demonstrated in rat models of dystonia that GPi neurons fire irregularly and show a burst-like firing pattern as compared with normal control rats [16]. As further evidence, intraoperative GPi activity in a clinical study decreased when a patient repeatedly made a fist, purposely aggravating the severity of dystonia [28]. GPi activity thus appears to correlate inversely with the severity of dystonia. This can reduce the ability of GPi to influence thalamocortical control, resulting in poor

cortical planning and executive function, and abnormal brain stem and spinal cord inhibitory control [40].

In addition to firing rate changes within GPi, Vitek and colleagues have presented evidence that dystonia also alters the responsiveness of GPi to somatosensory input [46]. They demonstrated that receptive fields of neurons in GPi of dystonic patients respond to movement in multiple directions about multiple joints in multiple limbs. In non-dystonic patients, neurons in GPi usually respond to only one direction about one joint in the contralateral limb. Based on these results, pallidotomy and GPi DBS may alleviate dystonia not only through reducing discharge rates, but also by blocking pathological response patterns in GPi. Bilateral GPi DBS in patients with severe primary generalized dystonia are already known to significantly improve dystonic symptoms. In one study, a patient treated with GPi DBS was asked to perform a task requiring specific joystick movements in response to auditory cues. DBS bilaterally reduced $^{15}O–H_2O$ PET activation in the primary motor, lateral premotor, supplementary motor, anterior cingulate and prefrontal areas, and ipsilaterally in the lentiform nucleus. These results indicate that GPi DBS reverses the over-activity of cortical areas responsible for producing the abnormal motor activity present in dystonia [24], and suggests a role for GPi in controlling these cortical areas. The study also highlights GPi as an effective surgical target site in the treatment of primary dystonia.

Thalamic nucleus in dystonia

In addition to the role played by GPi in the production of dystonic motor symptoms, Zhuang and colleagues report that the ventral oral posterior (Vop) and Vim thalamic nuclei and STN are also involved in the production of dystonic movement. Microelectrode recording in the Vop, GPi and STN demonstrates a close relationship between dystonic movements and activity in these regions. Cross-correlation analysis provides evidence that this activity is time-linked to EMG activity in affected muscle groups [50]. Lenz and others also confirm that thalamic nuclei are implicated in dystonic activity. Single-unit recordings reveal that the Vop exhibits activity that is time-linked to EMG activity during dystonia. A larger somatotopic representation of muscle groups in the Vim of dystonic patients is also observed as compared to control subjects. Microstimulation of Vim cells evokes EMG activity in multiple muscle groups, confirming that the cells in the Vim of dystonic patients have an enhanced and abnormal response pattern to peripheral sensory information [29, 30]. Lesions in the Vop and Vim can relieve dystonic movements, as can Vop/Vim DBS. Vop/Vim DBS is currently undergoing clinical evaluation in treating writer's cramp and idiopathic tremor since these nuclei receive fibrils from the dentate nucleus of the cerebellum. These surgical targets are undergoing more intensive clinical evaluation.

Abnormal neuronal activity and discharge rates are also observed in the STN [50]. Severe dyskinesias or ballism can occur following hemorrhagic events involving the STN which indicates a major role of STN in the pathophysiology of motor dysfunctions. It is now well-accepted that STN DBS is effective in the treatment of Parkinson's disease, especially for the relief of levodopa-induced dystonia and off-period dystonia. High-frequency stimulation of the STN in PD patients can induce intense dyskinesias that are similar to those induced by levodopa. STN has thus been considered as an important node in the circuitry involved in regulating movement. Although the connection and function of these nuclei still need further investigation, they are potential surgical sites in the treatment of several movement disorders, including primary dystonia, Parkinson's disease and tremor. Since inhibitory control of basal ganglia output to the thalamocortical projection plays an important role in normal cortical activity, excess or collapse of the basal ganglia output may result in hypokinetic or hyperkinetic movement disturbances and excessive and inappropriate muscle contraction (Fig. 1).

Thalamotomy for primary dystonia

Stereotactic neurosurgery has been used to treat dystonia as early as the 1950s. Patients were candidates for surgery if they had failed or were resistant to pharmacologic therapy, including levodopa and trihexyphenidyl, and did not have surgical contraindications. It was, and remains, very important to differentially diagnose primary vs. secondary dystonia prior to surgery. Reports have documented that the most dramatic improvements have been observed in primary dystonia with a mutation in the DYT-1 gene; patients with secondary dystonia have often shown a lesser degree of improvement.

Thalamotomy was the first surgical approach used for dystonia, but authors reported a great variability in outcome and a high incidence of operative side effects. In 1976, Cooper reviewed his surgical results of 226 patients with both primary and secondary generalized dystonia. Bilateral thalamotomy was performed in 54% of the patients and 67% of the patients had significant motor

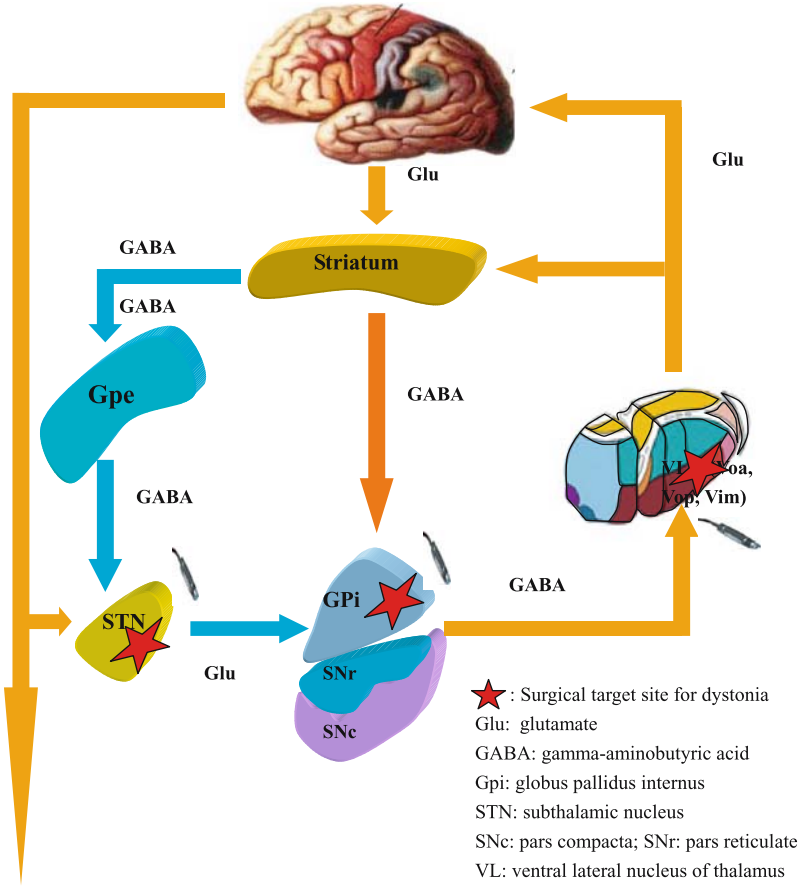

Fig. 1. Basal ganglia-thalamocortical circuitry and related surgical target sites for dystonia. The circuitry includes the direct pathway, which contains the striatum, GPi/SNr complex, and thalamus, and the indirect pathway, which contains the striatum, GPe, STN, GPi/SNr complex, and thalamus. Basal ganglia output is then directed toward the VL. These two pathways play an important role in movement regulation, and abnormalities here are partially responsible for dystonia. Surgical target sites may include the GPi, STN, and thalamus (Vim, Voa, and Vop). Although the exact mechanisms of DBS are not totally understood, these target sites show promise in the control of dystonia

improvement after surgery. However, only 60% of these patients exhibited persistent benefit from surgery when seen during long-term follow-up. Surgical complications included pseudobulbar dysfunction and dysarthria, but the mortality rate was less than 2%. In addition, Jewish Ashkenazi patients carrying mutations of the DYT-1 gene and a history of dystonia musculorum deformans (DMD) had a two-fold symptomatic improvement as compared to other patients [11]. Among these patients, age was a good prognostic factor, with those under 20 years of age doing better than those older than 20 years.

Andrew also used bilateral thalamotomy in 55 patients, but only 25% received long-term benefit, especially patients with focal and segmental dystonia [2]. Tasker reviewed 56 patients with different types of dystonia, including primary dystonia (32%), secondary dystonia (34%), and atypical DMD (14%) that underwent thalamotomy in Vimp and/or Voa [41]. Thalamotomy resulted in long-term improvement of limb function in more than 50% of the patients. Manual dexterity improved in 38% of DMD patients. As with other studies, a quarter of the patients improved by 25–50%, and nearly a third improved by more than 50%. Unfortunately, most patients had dystonic symptoms return within two years. Surgical complications included hemiparesis, dysarthria, and gait difficulties. Hydrocephalus was reported in some patients, especially in those with secondary dystonia.

Cardoso reported that thalamotomy caused improvement in about 50% of dystonia patients after short-term, and 35% after long-term, follow-up [9]. The long-term outcome was slightly better in patients diagnosed with secondary dystonia (50% moderately or markedly improved) vs. primary dystonia (43% moderately or markedly improved). Thalamotomy has recently been cited as effective for drug-induced tardive dyskinesia and task-specific focal hand dystonia (writer's cramp) [38]. These results have not yet been evaluated in long-term follow-up. In conclusion, although many report that thalamotomy benefits patients with primary and secondary generalized dystonia as well as several kinds of focal and segmental dystonia in short-term follow-up, long-term results have not been as favorable, and more recent studies have not had adequate time to evaluate long-term benefits. In addition, thalamotomy has been largely replaced by other surgical procedures in recent years because of its relatively high mortality and complication rates.

Pallidotomy and GPi DBS for dystonia

In 1996, Iacono reported on a surgery performed on a patient with primary generalized dystonia and with a history of DMD. He performed a bilateral pallidoansotomy and the patient reportedly showed rapid recovery of strength in all limbs and dramatic improvement in coordination [19]. Furthermore, he noted that bilateral posteroventral pallidotomy and pallidoansotomy were effective in treating parkinsonian symptoms, such as dyskinesia and dystonia. Compared to thalamotomy, bilateral pallidotomies reportedly had a lower rate of complications, such as language impairment. These results attracted attention and initiated a new avenue of dystonia treatment. One year later, Lozano documented that one generalized dystonic patient with bilateral pallidotomy displayed 80% improvement with significant relief of symptoms three months after surgery [32]. Ondo also reported post-pallidotomy improvements lasting up to nine months in eight patients, with a mean improvement of 60% [34]. In this study, primary dystonia patients had greater benefit than those with secondary dystonia. Vitek reported the results of three patients who underwent unilateral pallidotomy for generalized dystonia. All three patients improved after surgery, with two patients displaying sustained improvement [45].

Secondary dystonia, including those resulting from such neurodegenerative disorders as Hallervorden-Spatz disease and Wilson's disease, also can benefit from pallidotomy [25]. Complications have included hemiparesis, hemianopsia, dysarthria, dysphagia, and cognitive and mood alterations but these are seen less frequently after pallidotomy than after thalamotomy. Pallidotomy also appears to produce better results as compared to thalamotomy in patients with primary dystonia, especially those with mutations of the DYT-1 gene. Finally, the beneficial effects of pallidotomy on dystonic symptoms seem to last longer than with thalamotomy. Undoubtedly, the goal of pallidotomy and thalamotomy is to produce a permanent lesion within the intended target. The obvious problem with this strategy is that many of the surgical complications reviewed above are often permanent as well. In recent years, many neurosurgeons have responded to this problem by application of a much safer but more expensive approach: DBS. DBS involves the placement of permanent indwelling electrodes in the areas normally targeted for destruction. DBS is believed to produce either a functional lesion or, at a minimum, disruption of abnormal firing patterns within the target. The obvious advantage of this is that the most common side effects can be resolved through simple programming adjustments to the stimulation settings. Another advantage is that the DBS system can be explanted, almost always without incident.

Vidailhet treated 22 primary dystonia patients with bilateral GPi DBS. These patients demonstrated a 55% improvement in their dystonic symptoms, and a 45% improvement in disability scores one year after surgery without significant deficits in cognitive function [44]. A host of other centers have reported similar outcomes for patients afflicted with primary generalized dystonia and treated with GPi DBS [13, 23, 42]. Interestingly, Vitek reported the case of one generalized dystonic patient that had a worsening of symptoms one year after a bilateral pallidotomy [45]. This patient was then bilaterally implanted with DBS leads in the GPi. GPi DBS resulted in significant symptomatic improvement that persisted for more than four years. Long-term improvement is also seen in patients with segmental and focal dystonias. However, secondary dystonia tends to be less responsive.

STN DBS for dystonia: rationale

The STN is becoming recognized as a safe and effective surgical target for the treatment of several kinds of movement disorders. Dramatic effects have been observed in treating PD patients with STN DBS. Chronic STN DBS has been shown to result in up- and down-regulation of D1 and D2 receptors, respectively, which may help explain the mechanism of action of DBS [5]. Accumulating evidence indicates its efficacy in treating PD-related dystonia and dyskinesia. Krack has reported that bilateral STN DBS reduces off-period dystonia by 90% [22]. Furthermore, STN DBS reduces levodopa-induced dystonia by 50% and peak-dose dyskinesia by 30%. Reducing PD medication and also giving STN DBS reduces peak-dose dyskinesia by 52%. These results support the essential role of STN not only in Parkinson's disease but also in dystonia. Detante has also reported that bilateral STN DBS is successful in treating off-period dystonia in PD patients. STN DBS reduced the severity of off-period dystonia by 70% [14]. Bilateral STN DBS has also been used in the treatment of essential tremor, focal segmental dystonia, and primary dystonia. In a case report, Chou demonstrated that a patient treated with bilateral STN DBS recovered from medically refractory cervical dystonia and action tremor of the upper extremities [10]. Clinical investigations are currently underway to evaluate its effectiveness in the treatment of primary dystonia. Although the interaction

mechanisms between the STN and the GPi-SNr complex are not completely understood, STN is clearly a promising surgical site for dystonia.

STN DBS for generalized dystonia and tardive dystonia: our experience

Since early 2002, twelve patients with clinically intractable generalized dystonia and two patients with neuroleptic-induced tardive dystonia underwent bilateral STN DBS stimulation.

Patient selection

Twelve patients were clinically diagnosed with primary generalized dystonia (clinical characteristics are detailed in Table 1) in the absence of any secondary cause, including birth injury and head trauma. All of these patients presented with a normal neurological examination, including normal findings on magnetic resonance imaging (MRI), except for the presence of dystonia. Some patients (4/12) were tested for the DYT-1 mutation in the torsion A gene. Two patients with clinically diagnosed neuroleptic-induced tardive dystonia had a history of taking Risperdal.

Surgical procedure

The surgical procedures used for implantation of the DBS in the STN for dystonia is the same as for Parkinson's disease, and has been described in detail previously. Briefly, after the stereotactic frame is attached, a high-resolution volumetric MRI is used for STN targeting. The STN can be clearly seen on the MRI, especially with a T2-weighted sequence. Intraoperative macroelectrode stimulation is used to confirm the target position, and the DBS leads (Medtronic, Quadripolar 3389) are then fixed in position. Under general anesthesia, the leads are connected to extension wires (Medtronic, 7482) and the neurostimulator (Medtronic, Kinetra 7428), which is implanted in the subclavicular region.

Programming of DBS

One week after implantation, DBS is initiated. Initial stimulator parameters are approximately: 135–185 Hz, 90–120 μs, and 2.0–3.0 V. Bipolar contact settings in these patients produced the best therapeutic effects. In 90% of our patients, an immediate response to stimulation was observed; the symptoms improved from 30–90% in a few minutes to a few hours. This effect appears to improve over time. After several months to a year, patients usually do not need repeated programming and the effect of stimulation remains stable.

Results

The Burke-Fahn-Marsden Dystonia (BFM) Rating Scale was employed for evaluation of DBS effects. All patients were followed up from 6 months to 42 months (mean 28.8 months). Postoperative BFM scores demonstrated improvement ranging from 76 to 100% (mean 88.6%) as compared to their pre-operative baseline scores. There were no permanent surgical or stimulation-induced

Table 1. *The clinical features of seven patients with generalized dystonia (GD) and tardive dystonia (TD)*

Patient no.	Age at onset	Duration of disease	Clinical features	Response to medication
1 GD	21	14	torsion and involuntary movement in the neck, limbs, and trunk	light effect
2 GD	23	18	torsion and involuntary movement in the face, neck, trunk, and both upper extremities	no effect
3 GD	31	12	torsion and abnormal fixed posture in both upper extremities	no effect
4 GD	19	12	involuntary movement in the face, neck, trunk, and both upper extremities	good effect
5 GD	21	3	abnormal fixed posture in the neck and shoulder, and writing spasm in the right hand	light effect
6 GD	19	13	torsion in extremities and trunk	no effect
7 GD	30	4	torsion and involuntary movement in the neck and right upper extremity	light effect
8 GD	30	18	torsion and involuntary movement in the neck and trunk	light effect
9 GD	36	6	torsion and involuntary movement in the neck, trunk, and bilateral upper extremities	light effect
10 GD	50	12	torsion in the neck, trunk, and bilateral upper extremities	light effect
11 TD	41	3	torsion and involuntary movement in the face, neck, and trunk	no effect
12 GD	17	5	torsion in the neck, trunk, and right hand	light effect
13 TD	26	12	torsion in the neck, trunk, and extremities	light effect
14 GD	16	6	torsion in the face, neck, trunk and bilateral upper extremities	no effect

side effects or complications. This STN group had lower average stimulation parameters as compared to patients receiving GPi DBS.

Advantages of STN DBS

Based on our limited experience with STN DBS, we propose that STN DBS has the following advantages over GPi DBS: (1) symptomatic improvement is seen immediately after stimulation, allowing us to quickly select the most suitable stimulation parameters; (2) the stimulation parameters for STN are lower than those used for GPi, resulting in longer battery life; and (3) STN DBS results in better symptomatic control than GPi DBS in dystonia patients when our STN data is compared to that obtained by others with using GPi as the target. Based on our limited data, we suggest that STN DBS may be the most appropriate surgical technique for dystonia.

References

1. Anca MH, Zaccai TF, Badarna S, Lozano AM, Lang AE, Giladi N (2003) Natural history of Oppenheim's dystonia (DYT1) in Israel. J Child Neurol 18: 325–330
2. Andrew J, Fowler CJ, Harrison MJ (1983) Stereotaxic thalamotomy in 55 cases of dystonia. Brain 106(Pt 4): 981–1000
3. Asbury AK, Mckhann GM (2001) Disease of the nervous system, 3rd edn. Cambridge University Press, New York, pp 532–551
4. Asmus F, Salih F, Hjermind LE, Ostergaard K, Munz M, Kuhn AA, Dupont E, Kupsch A, Gasser T (2005) Myoclonus-dystonia due to genomic deletions in the epsilon-sarcoglycan gene. Ann Neurol 58: 792–797
5. Bergmann O, Winter C, Meissner W, Harnack D, Kupsch A, Morgenstern R, Reum T (2004) Subthalamic high frequency stimulation induced rotations are differentially mediated by D1 and D2 receptors. Neuropharmacology 46: 974–983
6. Bradley WG, Daroff RB, Fenichel GM, Jankovic J (2004) Neurology in clinical practice, 4th edn. Butterworth Heinemann, Philadelphia, USA, pp 2155–2160
7. Bressman SB (2003) Dystonia: phenotypes and genotypes. Rev Neurol 159(10 Pt 1): 849–856
8. Bressman SB (2004) Dystonia genotypes, phenotypes, and classification. Adv Neurol 94: 101–107
9. Cardoso F, Jankovic J, Grossman RG, Hamilton WJ (1995) Outcome after stereotactic thalamotomy for dystonia and hemiballismus. Neurosurgery 36: 501–507
10. Chou KL, Hurtig HI, Jaggi JL, Baltuch GH (2005) Bilateral subthalamic nucleus deep brain stimulation in a patient with cervical dystonia and essential tremor. Mov Disord 20: 377–380
11. Cooper IS (1976) 20-Year follow-up study of the neurosurgical treatment of dystonia musculorum deformans. Adv Neurol 14: 423–452
12. Costa J, Espirito-Santo C, Borges A, Ferreira JJ, Coelho M, Moore P, Sampaio C (2005) Botulinum toxin type A therapy for blepharospasm. Cochrane Database Syst Rev 25: CD004900
13. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B (2000) Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 355: 2220–2221
14. Detante O, Vercueil L, Krack P, Chabardes S, Benabid AL, Pollak P (2004) Off-period dystonia in Parkinson's disease but not generalized dystonia is improved by high-frequency stimulation of the subthalamic nucleus. Adv Neurol 94: 309–314
15. Evidente VG, Nolte D, Niemann S, Advincula J, Mayo MC, Natividad FF, Muller U (2004) Phenotypic and molecular analyses of X-linked dystonia-parkinsonism (''lubag'') in women. Arch Neurol 61: 1956–1959
16. Gernert M, Bennay M, Fedrowitz M, Rehders JH, Richter A (2002) Altered discharge pattern of basal ganglia output neurons in an animal model of idiopathic dystonia. J Neurosci 22: 7244–7253
17. Hjermind LE, Johannsen LG, Blau N, Wevers RA, Lucking CB, Hertz JM, Friberg L, Regeur L, Nielsen JE, Sorensen SA (2006) Dopa-responsive dystonia and early-onset Parkinson's disease in a patient with GTP cyclohydrolase I deficiency? Mov Disord 21: 679–682
18. Hou JG, Ondo W, Jankovic J (2001) Intrathecal baclofen for dystonia. Mov Disord 16: 1201–1202
19. Iacono RP, Kuniyoshi SM, Lonser RR, Maeda G, Inae AM, Ashwal S (1996) Simultaneous bilateral pallidoansotomy for idiopathic dystonia musculorum deformans. Pediatr Neurol 14: 145–148
20. Kabakci K, Hedrich K, Leung JC, Mitterer M, Vieregge P, Lencer R, Hagenah J, Garrels J, Witt K, Klostermann F, Svetel M, Friedman J, Kostic V, Bressman SB, Breakefield XO, Ozelius LJ, Pramstaller PP, Klein C (2004) Mutations in DYT1: extension of the phenotypic and mutational spectrum. Neurology 62: 395–400
21. Kabakci K, Isbruch K, Schilling K, Hedrich K, de Carvalho Aguiar P, Ozelius LJ, Kramer PL, Schwarz MH, Klein C (2005) Genetic heterogeneity in rapid onset dystonia-parkinsonism: description of a new family. J Neurol Neurosurg Psychiatry 76: 860–862
22. Krack P, Pollak P, Limousin P, Benazzouz A, Deuschl G, Benabid AL (1999) From off-period dystonia to peak-dose chorea. The clinical spectrum of varying subthalamic nucleus activity. Brain 122(Pt 6): 1133–1146
23. Krauss JK, Pohle T, Weber S (1999) Bilateral stimulation of globus pallidus internus fro treatment of cervical dystonia. Lancet 354: 837–838
24. Kumar R, Dagher A, Hutchison WD, Lang AE, Lozano AM (1999) Globus pallidus deep brain stimulation for generalized dystonia: clinical and PET investigation. Neurology 53: 871–874
25. Kyriagis M, Grattan-Smith P, Scheinberg A, Teo C, Nakaji N, Waugh M (2004) Status dystonicus and Hallervorden-Spatz disease: treatment with intrathecal baclofen and pallidotomy. J Paediatr Child Health 40: 322–325
26. Lara-Sires N, Chacon J, Garcia-Moreno JM (2005) The intrathecal baclofen pump in the long-term treatment of generalised dystonias. Rev Neurol 40: 30–33
27. Lee HY, Xu Y, Huang Y, Ahn AH, Auburger GW, Pandolfo M, Kwiecinski H, Grimes DA, Lang AE, Nielsen JE, Averyanov Y, Servidei S, Friedman A, Van Bogaert P, Abramowicz MJ, Bruno MK, Sorensen BF, Tang L, Fu YH, Ptacek LJ (2004) The gene for paroxysmal non-kinesigenic dyskinesia encodes an enzyme in a stress response pathway. Hum Mol Genet 13: 3161–3170
28. Lenz FA, Suarez JI, Metman LV, Reich SG, Karp BI, Hallett M, Rowland LH, Dougherty PM (1998) Pallidal activity during dystonia: somatosensory reorganisation and changes with severity. J Neurol Neurosurg Psychiatry 65: 767–770
29. Lenz FA, Jaeger CJ, Seike MS, Lin YC, Reich SG, DeLong MR, Vitek JL (1999a) Thalamic single neuron activity in patients with dystonia: dystonia-related activity and somatic sensory reorganization. J Neurophysiol 82: 2372–2392
30. Lenz FA, Byl NN (1999b) Reorganization in the cutaneous core of the human thalamic principal somatic sensory nucleus (Ventral caudal) in patients with dystonia. J Neurophysiol 82: 3204–3212

31. Lotze T, Jankovic J (2003) Paroxysmal kinesigenic dyskinesias. Semin Pediatr Neurol 10: 68–79
32. Lozano AM, Kumar R, Gross RE, Giladi N, Hutchison WD, Dostrovsky JO, Lang AE (1997) Globus pallidus internus pallidotomy for generalized dystonia. Mov Disord 12: 865–870
33. McNaught KS, Kapustin A, Jackson T, Jengelley TA, Jnobaptiste R, Shashidharan P, Perl DP, Pasik P, Olanow CW (2004) Brainstem pathology in DYT1 primary torsion dystonia. Ann Neurol 56: 540–547
34. Ondo WG, Desaloms JM, Jankovic J, Grossman RG (1998) Pallidotomy for generalized dystonia. Mov Disord 13: 693–698
35. Schiller A, Wevers RA, Steenbergen GC, Blau N, Jung HH (2004) Long-term course of L-dopa-responsive dystonia caused by tyrosine hydroxylase deficiency. Neurology 63: 1524–1526
36. Schule B, Kock N, Svetel M, Dragasevic N, Hedrich K, De Carvalho Aguiar P, Liu L, Kabakci K, Garrels J, Meyer EM, Berisavac I, Schwinger E, Kramer PL, Ozelius LJ, Klein C, Kostic V (2004) Genetic heterogeneity in ten families with myoclonus-dystonia. J Neurol Neurosurg Psychiatry 75: 1181–1185
37. Shang H, Clerc N, Lang D, Kaelin-Lang A, Burgunder JM (2005) Clinical and molecular genetic evaluation of patients with primary dystonia. Eur J Neurol 12: 131–138
38. Shibata T, Hirashima Y, Ikeda H, Asahi T, Hayashi N, Endo S (2005) Stereotactic Voa-Vop complex thalamotomy for writer's cramp. Eur Neurol 53: 38–39
39. Starr PA, Rau GM, Davis V, Marks WJ Jr, Ostrem JL, Simmons D, Lindsey N, Turner RS (2005) Spontaneous pallidal neuronal activity in human dystonia: comparison with Parkinson's disease and normal macaque. J Neurophysiol 93: 3165–3176
40. Tarsy D, Vitek JL, Lozano AM (2002) Surgical treatment of Parkinson's disease and other movement disorders, 1st edn. Humana Press, Totowa, New Jersey, USA, pp 266–272
41. Tasker RR, Doorly T, Yamashiro K (1988) Thalamotomy in generalized dystonia. Adv Neurol 50: 615–631
42. Tronnier VM, Fogel W (2000) Pallidal stimulation for generalized dystonia. Report of three cases. J Neurosurg 92: 453–456
43. Truong D, Duane DD, Jankovic J, Singer C, Seeberger LC, Comella CL, Lew MF, Rodnitzky RL, Danisi FO, Sutton JP, Charles PD, Hauser RA, Sheean GL (2005) Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. Mov Disord 20: 783–791
44. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, Lagrange C, Tezenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P, French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group (2005) Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 352: 459–467
45. Vitek JL, Zhang J, Evatt M, Mewes K, DeLong MR, Hashimoto T, Triche S, Bakay RA (1998) GPi pallidotomy for dystonia: clinical outcome and neuronal activity. Adv Neurol 78: 211–219
46. Vitek JL, Chockkan V, Zhang JY, Kaneoke Y, Evatt M, DeLong MR, Triche S, Mewes K, Hashimoto T, Bakay RA (1999) Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 46: 22–35
47. Waddy HM, Fletcher NA, Harding AE, Marsden CD (1991) A genetic study of idiopathic focal dystonias. Ann Neurol 29: 320–324
48. Walker RH, Shashidharan P (2003) Developments in the molecular biology of DYT1 dystonia. Mov Disord 18: 1102–1107
49. Ward CD (1993) Pathogenesis of focal and segmental dystonias: implications for rehabilitation. Baillieres Clin Neurol 2: 159–177
50. Zhuang P, Li Y, Hallett M (2004) Neuronal activity in the basal ganglia and thalamus in patients with dystonia. Clin Neurophysiol 115: 2542–2557

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DBS in Tourette syndrome: rationale, current status and future prospects

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Summary

Tourette syndrome is a neuropsychiatric disorder with onset in early childhood and characterized by tics, often associated with behavioural abnormalities. Symptoms often disappear before or during adulthood. Treatment consists of psychotherapy or pharmacotherapy. A small percentage of patients is treatment refractory. After the introduction of deep brain stimulation (DBS) of the thalamus as a new therapeutical approach in 1999, several other brain nuclei have been targeted in a small number of patients, like the globus pallidus internus, anteromedial and ventroposterolateral part, and the nucleus accumbens. In the published reports, a tic reduction rate of at least 66% is described. The effects of DBS on associated behavioural disorders are more variable. The number of treated patients is small and it is unclear whether the effects of DBS are dependent on the target nucleus. The pathophysiology of Tourette syndrome is not well understood. On the basis of our current knowledge of cortico-basal ganglia-thalamocortical circuits, an explanation for the beneficial effects of DBS on tics is proposed. It is concluded that a meticulous evaluation of the electrode position, and a blinded assessment of the clinical effects on tics and behavioural disorders, is absolutely mandatory in order to identify the best target of DBS for Tourette syndrome.

Keywords: Neuromodulation; Tourette syndrome; tics; deep brain stimulation; thalamus; globus pallidus internus; nucleus accumbens; obsessive-compulsive behaviour; self-injurious behaviour; attention deficit hyperactivity disorder.

Introduction

Clinical characteristics and prevalence

Tourette syndrome is a chronic neuropsychiatric disorder characterized by tics. Tics are involuntary, repetitive muscle contractions (motor tics) or sounds (vocal tics) [18]. They may be abrupt in onset, fast and brief (clonic tics) or may be slow and sustained (dystonic or tonic tics) [24]. The motor patterns of tics may involve individual muscles or small groups of muscles with discrete contractions (simple tics) or more muscles acting in a coordinated pattern to produce more complicated movements that may resemble purposeful voluntary movements (complex tics) [18]. Examples of simple tics include blinking of an eyelid, elevation of eyebrows, a sniff, or mouth opening. Complex tics include head shaking, scratching, throwing, touching, uttering phrases. Tics increase with stress and decrease with relaxation or when the individual is engaged in acts that need selective attention. Tics can be temporarily suppressed by an effort of will or concentration, but rebound afterwards [1].

The onset of tics in TS is during early childhood, with a mean of 7 years being commonly reported [24]. The tics typically increase to a maximum severity that occurs on average during the prepubescent years, and often decline in frequency and intensity by the beginning of adulthood. According to the ''Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [4], TS is defined by the presence of both multiple motor tics and one or more vocal tics throughout a period of more than one year, during which period there was never a tic-free period of more than 3 consecutive months [10]. The tic repertoire of an individual with TS typically changes over time [18]. Thus, a specific motor pattern may be present for months or years, and then suddenly cease, replaced by a completely different tic.

An important feature of TS is its association with a wide range of co-morbid behavioural abnormalities, which in certain patients may be more relevant than the tics themselves [10]. Especially obsessive-compulsive behaviour (OCB), self- injurious behaviour (SIB), and attention deficit hyperactivity disorder (ADHD) are strongly linked to TS and are probably an integral part of the syndrome. The occurrence of ADHD in TS patients ranges from 21 to 90% of clinical populations [24]. Symptoms consist of a short attention span and impulsivity, with or without hyperactivity. OCB is

characterized by persistent obsessions (recurrent, intrusive, senseless thoughts), or compulsions (repetitive and seemingly purposeful behaviours which are performed to certain rules or in a stereotyped fashion). The obsessions seen in TS have to do with sexual, violent, religious, aggressive and symmetrical themes; the compulsions are to do with checking, ordening, counting, repeating, forced touching, symmetry, and self-damage. Obsessive-compulsive traits may occur in up to 50% of TS patients. Robertson [24] reported that over one-third of clinical TS patients carried out SIB. The most frequent type of SIB is head banging.

At one time, TS was considered a rare syndrome. Nowadays, it is recognized as a relatively common disorder. An estimated worldwide prevalence of 4–5/10,000 individuals has been reported [23]. A recent study [11], however, revealed a prevalence of 31–157 cases per 1000 individuals in 13–14-year-old children attending mainstream secondary schools in the United Kingdom. There is a considerable variation in studies reporting on the prevalence of TS, most probably due to variations in sex, age, diagnostic criteria, and assessment methods [15].

Treatment

For many patients, especially those with mild symptomatology, supportive reassurance and psychobehavioural methods are sufficient. Pharmacological treatment, however, may be considered when symptoms begin to interfere with peer relationships, social interactions, academic or job performance, or with activities of daily living. The therapy must be individualised and the most troublesome symptoms should be targeted first. The most commonly prescribed medications for the motor and vocal tics are dopamine depleting (tetrabenazine) and dopamine blocking (haloperidol) agents [24]. Other drugs such as clonidine, clonazepam, and risperidone, and injections with botulinum toxin, or nowadays also widely used. Selective serotonin reuptake inhibitors are recommended for the treatment of obsessive-compulsive behaviour. Psychostimulants, such as methylphenidate, are the treatment of choice for attention deficit hyperactivity disorder [27].

For patients refractory to any medical treatment, surgery may be the treatment of last resort. Although no precise numbers are available, this is a small percentage of patients with TS.

In the past, various attempts have been made to treat these patients through neurosurgical ablative procedures [32]. The target sites have been diverse including the frontal lobe (prefrontal lobotomy and bimedial frontal leucotomy), the limbic system (limbic leucotomy and anterior cingulotomy), the thalamus and the cerebellum. Combined approaches have also been tried such as anterior cingulotomies plus infrathalamic lesions. The results have often been unsatisfactory or major side-effects have occurred such as hemiplegia or dystonia.

In 1999, deep brain stimulation (DBS) was introduced as a new surgical technique in the treatment of intractable TS [34].

Targets (Table 1)

Only few reports have been published on DBS in TS. The first patient described by Vandewalle *et al.* [34] underwent chronic bilateral stimulation of the medial part of the thalamus. This target was chosen on the basis of the good results of thalamotomies described by Hassler in 1970 [9]. The same group described the promising effects of bilateral thalamic DBS in three patients in 2004 [36]. In follow-up periods of 5 years, 1 year and 8 months, there was a good effect on tics with a tic reduction of 90, 72 and 83%, respectively with stimulation on compared to the stimulation off condition. Improvements were also seen on associated behavioural disorders. Side effects of stimulation consisted of drowsiness, and changes in sexual function [31, 36]. In 2005, Servello *et al.* reported on the beneficial effects of DBS of the same target in five patients with TS [26].

The effects of bilateral DBS of the internal segment of the globus pallidus (GPi) have been described by van der Linden *et al.* in 2002 [33]. The choice of this target was based on the observation that DBS of GPi has beneficial effects on hyperkinetic movements induced by medication in patients with Parkinson's disease (PD). At six months follow-up, a tic reduction of 95% was noticed, compared with the pre-operative situation. In 2004, Diederich *et al.* described the beneficial effects of chronic stimulation of the same target (posteroventrolateral part of the GPi), with a follow-up of 14 months [3]. However, there was no change in the ''very mild compulsive tendencies''.

Very recently, Houeto *et al.* described the effects of bilateral pallidal and thalamic stimulation in one patient [12]. The pallidal target, however, was not located in the posteroventrolateral (motor) part of the GPi as described by van der Linden *et al.* and Diederich *et al.*, but in the anteromedial (limbic) part. In this patient, both thalamic and pallidal stimulation had a similar effect on tics, but

Table 1. *Reports on deep brain stimulation in patients with Tourette syndrome*

First author, year	Target	No. of pt	F-U	Tic reduction	Effect on behavioral disorders	Side-effects	Complications
V. Vandewalle *Lancet, 1999*	Thal (med.)	1	4 m	90–100%	n.m.	n.m.	none
Ch. van der Linden *Mov Dis, 2002*	Thal (med.)/ GPi vpl	1	immed.postop/ 6 m	80/95%	n.m.	none	none
V. Visser-Vandewalle *J Neurosurg, 2003*	Thal (med.)	3	5y, 1y, 8 m	90, 72, 83%	very good	drowsiness, changes in sex.behav.(2 pt)	none
N. J. Diederich, *Mov Dis, 2005*	GPi vpl	1	14 m	66%	no effect on compulsions	impairment of left rapidly alternating movements	small H around right electrode tip
J. L. Houeto, *JNNP, 2005*	Thal (Cm-Pf)/ GPi am	1	24 m	70% (both)	very good (both)	with GPi DBS more depressed	none
M. Egidi, *Proc of 14th m. WSSFN, 2005*	Thal (med.)	1	6 m	78%	n.m.	mild dysarthria	none
D. Servello, *Proc of 14th m. WSSFN, 2005*	Thal (med.)	5	n.m.	n.m.	n.m.	n.m.	n.m.
D. Lenartz/V Sturm, *personal. communic., 2005*	NAC	3	2y, 4 m, 4 m	75% (average)	very good	none	none

Thal Thalamus; *med* medial part (CM-Spv-Voi); *CM* centromedian nucleus; *Spv* substantia periventricularis; *Voi* nucleus ventro-oralis internus; *Pf* Parafascicular nucleus; *GPi* globus pallidus internus; *vpl* ventroposterolateral part; *am* anteromedial part; *NAC* nucleus accumbens; *F-U* follow-up period; *y* year(s); *m* month(s); *immed.postop* immediately postoperatively; *behav* behaviour(al); *dis* disorders; *sex* sexual; *pt* patients; *H* hematoma; *Proc. of 14th m. WSSFN* Proceedings of the 14th meeting of the World Society for Stereotactic and Functional Neurosurgery; *personal communic* personal communication; *n.m.* not mentioned.

the thalamic stimulation had a more beneficial effect on behaviour.

Lastly, it has to be mentioned that also DBS of the nucleus accumbens has been performed in patients suffering from TS. These patients were included in a group of patients suffering from obsessive-compulsive disorder (OCD) (personal communication dd 29 July 05).

Neuroanatomical basis (Fig. 1)

It is widely believed that abnormalities in dopamine neurotransmission play a fundamental role in the pathogenesis of TS. This hypothesis arises from the clinical observation that dopamine-blocking agents decrease tics, while potentiation of dopamine transmission with

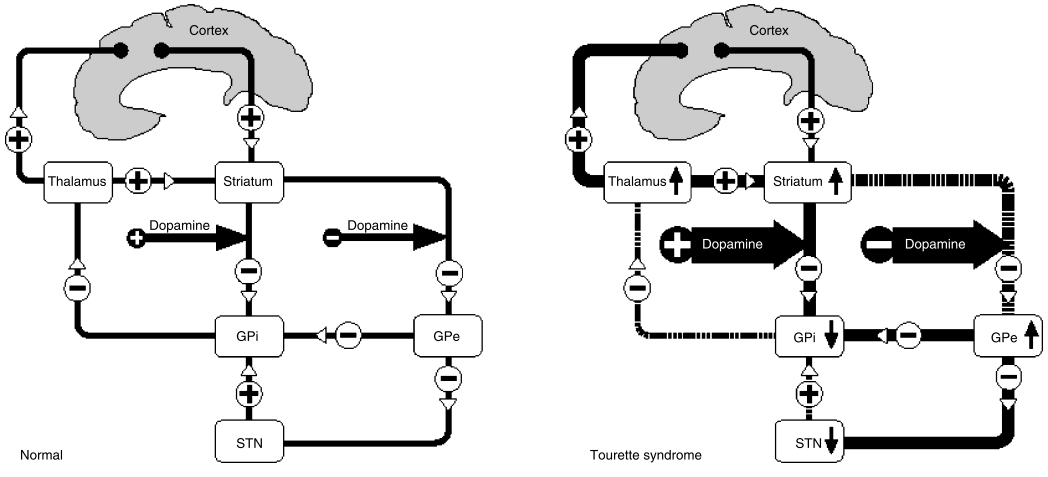

Fig. 1. Schematic representation of the activity of the striatal-basal ganglia thalamocortical circuits with normal (*left*) and excessive (*right*) dopamine activity. For detailed description see Neuroanatomical basis in the text. Doaminergic hyperactivity might facilitate the striatal output towards the GPi (*globus pallidus internus*), and inhibit the striatal output towards GPe (*globus pallidus externus*). A hypoactivity of GPi is the result, leading to a reduced inhibition of the thalamocortical drive. The feedback loop of the thalamus towards the striatum is also hyperactive so that the pathological mechanism leading to a thalamic hyperactivity, maintains itself. With this model the beneficial effect of deep brain stimulation (*DBS*) of the thalamus in TS (in which there is mainly an alteration of D2 receptor activity at the level of the indirect pathway) can be explained, as well as the beneficial effect of DBS of the ventral striatum (nucleus accumbens). The effects of GPi DBS need further clarification, analogous to the unexplained effects of DBS of the GPi on hyperkinesias in Parkinson disease

stimulant medications may elicit tics [18]. Moreover, a number of functional neuroimaging studies have shown abnormalities in dopamine transporter and dopamine receptor binding in the striatum of TS patients [28]. Dopamine has a strong regulatory function on striatal activity [7]. The striatum, consisting of the caudate nucleus, the putamen, and the nucleus accumbens (ventral striatum), is the input structure of the basal ganglia, receiving information from the cortex. The striatum projects to the globus pallidus, and further via the thalamus, back to the (pre)frontal cortex, thus forming a circuit. Within the brain, there are anatomically segregated, parallel circuits representing different functions (motor, oculomotor, cognitive, limbic). They all traverse the cortex, striatum, globus pallidus and thalamus. The sensorimotor circuit runs through the putamen, the dorsal part of the globus pallidus, and the VA/VL complex of the thalamus. The limbic loop projects to the ventral striatum, the ventral pallidum, and the subparafascicular nucleus of the thalamus [7]. Each circuit has a direct and an indirect pathway. In the direct pathway, information is sent from the striatum to the internal part of the globus pallidus (GPi). In the indirect pathway, the striatum projects towards the external part of the globus pallidus (GPe). GPe neurons project to the subthalamic nucleus (STN), which sends its projections to the GPi.

The modulatory effect of dopamine is different at the level of the direct and the indirect pathway: through D1 receptor binding, dopamine facilitates striatal output towards GPi, and through D2 receptor binding, dopamine inhibits striatal output towards GPe. The GPi is electrically the most active nucleus within the basal ganglia. It inhibits the thalamus, which excites the cortex. Thus, the GPi can be symbolically seen as a brake, which slows down the thalamocortical drive. Inhibition of GPi by the striatum is stimulated by the cortex. Thus, through the direct pathway, the inhibition of the thalamocortical drive by the GPi is counteracted, thus facilitating the activity of the thalamus. In the indirect pathway, GPi activity is stimulated by the STN. The inhibitory effect of the striatum on the GPe, which in turn inhibits the STN, leads to a facilitation of GPi activity, and thus an inhibition of the thalamocortical drive. In normal circumstances, there is a balance between the direct and the indirect pathway. For motor function, this means that the execution of the intended movement is enabled through the direct pathway, while, through the indirect pathway, competing movements are prevented from interfering with the desired one [18].

Dopaminergic hyperactivity might facilitate the direct pathway and inhibit the indirect pathway. Both lead to an overactivity of the thalamocortical drive. Besides the above mentioned circuits, there are smaller circuits or loops, interacting with the main circuits. An important one is the excitatory feedback loop from the thalamus towards the striatum, originating from the centromedian-parafascicular complex (CM-Pf), and the midline thalamic nuclei (substantia periventricularis or Spv). CM and Pf are very large in the primate brain. CM strongly projects to the sensorimotor region of the putamen, while Pf projects to the associative regions of both caudate nucleus and putamen. Spv projects to the limbic related parts of the striatum. Through these feedback loops, the thalamic hyperactivity as described above would lead to an hyperactivity of the striatum. In the direct pathway, this hyperactivity would be reinforced by dopamine, thus leading to a hypoactivity of GPi. In the indirect pathway, this striatal hyperactivity would be inhibited by the excess of dopamine, even so resulting in a hypo-activity of GPi. Several studies have suggested that both the sensorimotor and the limbic-innervated parts of the basal ganglia including the dorsal and ventral striatum, are involved in the pathophysiology of TS [8, 20, 21, 29]. In conclusion, a dopaminergic hyperactivity might dysregulate at least the sensorimotor and limbic circuits within the basal ganglia, leading to a thalamic hyperactivity. This thalamic hyperactivity would lead to an excessive stimulation of the cortex, and maintain itself through a feedback loop towards the striatum which is inappropriately modulated by an excess of dopamine.

Rationale for targeting the medial part of the thalamus

In 1970, Hassler and Diekman reported on the beneficial effects of lesioning the intralaminar and midline thalamic nuclei in patients suffering from TS, and also the Voi (nucleus ventro-oralis internus of the thalamus) in patients suffering from facial tics [9]. High frequency stimulation of a nucleus has the same effect on symptoms as a lesion, the effect of stimulation is reversible [17]. Thus, it was an attractive hypothesis to postulate that DBS of the intralaminar and midline thalamic nuclei, and Voi, might have a good effect on the symptoms of TS. The difficulty was that Hassler made up to ten coagulations in each hemisphere; it was necessary, therefore, to find a ‘‘strategic point’’ in order to stimulate by one electrode in each hemisphere the maximum num-

ber of nuclei targeted by Hassler. On the Schaltenbrand-Wahren atlas [25], this ''strategic point'' was found on a coronal slice 4 mm posterior to the midpoint of the line connecting the anterior commissure (AC) (AC–PC line) with the posterior commissure (PC) and 5 mm lateral to the AC–PC line. At this point, the CM, Spv and Voi form a triangle that can be reached by one electrode. As outlined above, it is hypothesized that a hyperactivity of the thalamus in TS, as a consequence of alterations in the dopaminergic transmission, leads to an overdrive of the (pre)frontal cortex, and maintains itself through an excitatory feedback loop towards the striatum. In line with this hypothesis, high frequency stimulation of the thalamus, and more specifically of the nuclei projecting to the cortex on one side and back to the striatum on the other, would decrease the cortical drive, and break the self-maintaining circle that enhances thalamic hyperactivity. The Voi projects directly to the facial part of the premotor cortex. CM projects back to the dorsal (motor) striatum, and Spv projects back to the ventral (limbic) striatum. Thus, DBS of the medial part of the thalamus, at 5 mm lateral and 4 mm posterior to mid-AC–PC, is hypothesized to have a good effect on motor and limbic symptoms in patients with intractable TS. In three patients, this has been confirmed.

Rationale for targeting the globus pallidus

Posterolateral part

Before the STN DBS era, DBS of the posteroventrolateral part of the GPi was performed in patients suffering from advanced PD. The effect on akinesia was disappointing, but their seemed to be a strong and lasting effect on dyskinesias [6]. On the other hand, GPi DBS is nowadays widely performed in patients suffering from dystonia [14, 35]. The good results are not so much a consequence of the effect on muscular tonus, as on the associated hyperkinetic movements. According to this, and reasoning that tics are even so hyperkinesias, clinicians have decided to target the motor (posteroventrolateral) part of the GPi [33].

Anteromedial part

The GPi is a rather big nucleus, in which the posterior located, motor part, is relatively far from the anterior located, limbic related part. With ''relatively far'' is meant: too far to be reached by one electrode. In other words: one has to choose whether the motor or limbic part of the GPi will be targeted. This stands in contrast to the thalamus, in which motor and limbic-related nuclei are lying close together. As mentioned above, both the motor-, and limbic innervated parts of the basal ganglia have been implicated in the pathophysiology of TS. While van der Linden *et al.* have chosen to target the motor part of the thalamus, other authors have reported the good results of DBS of the anterior, limbic-related, part of the GPi.

Rationale for targeting the nucleus accumbens

TS and Obsessive-Compulsive Disorders (OCD) share many clinical similarities and show a strong comorbidity. A recent study using event-related brain potentials indicated that frontal inhibitory mechanisms are altered in similar ways in TS and OCD [13]. DBS of the nucleus accumbens (NAC) has been performed in patients suffering from OCD [30]. It is known, from oral communications, that in addition to OCD patients, patients suffering from TS were also treated by NAC DBS and had beneficial effects on tics. It has even been proposed to center the pathophysiological model of TS on the NAC. This model assumes that external and internal events occurring during the development of the nervous system induce modular changes in the NAC [2].

Clinical and surgical considerations

Patient selection

As mentioned in the first section, in most cases, TS symptoms wane before or at onset of adolescence. Not all patients require therapy, and of those who do, only a minority seem not to respond to conservative treatment. Only a small percentage of TS patients are potential candidates for surgery. The Dutch-Flemish Tourette Surgery Study Group has established guidelines for DBS in TS. These guidelines can be found in detail elsewhere [37]. They include the following selection criteria. The TS patients considered for DBS should comprise only very severe cases who have already fruitlessly received standard therapies. This has the following implications for patient selection:

Inclusion of patients

1. The patient has a definite Tourette's syndrome, established by two independent clinicians. The diagnosis is being established according to DSM- IV criteria [2] and with the aid of the Diagnostic Confidence Index (DCI) [4].

2. The patient has severe and incapacitating tics as his primary problem. The treatment of these tics, not of other co-morbid behaviors such as OCD, SIB or ADHD is the main aim of the therapy.
3. The patient is treatment refractory. This means that the patient either has not or very partially responded to 3 different medication regimes each during at least 12 weeks in adequate doses, or has proven not to tolerate medication due to side-effects after serious attempts at taking medication have been made. With regard to the types of medication tried, three different groups can be distinguished that should have been tried: a) "classic" Dopamine-2 antagonists (haloperidol, pimozide) or clonidine b) modern anti-psychotic medication (f.i. risperidone, olanzapine, tiapride, sulpiride) c) experimental drugs (f.i. quetiapine, aripiperazole, pergolide). Finally, a trial of at least 12 sessions behavioral therapy for tics has been attempted and failed. Behavioral therapy techniques should entail either self-control procedures (habit reversal) or exposure therapy to premonitory urges.
4. The patient is over 25 years of age.

Exclusion of patients:

a. Tic disorder other than TS.
b. Severe psychiatric co-morbid conditions (psychotic, dissociative, depressive disorders, substance use disorders), cognitive disorders, mental deficiency.
c. Common contra-indications for surgery such as severe cardiovascular, pulmonary or haematological disorders.
d. Structural MRI abnormalities.

Surgical procedure

The technique of DBS applied to TS is similar to the one used for more classical indications, like PD. The preference and experience of the surgeon play a key role in choosing the imaging technique for the target localization. MR, or fused CT/MR-images are often used. The most frequently used target nucleus for PD is the STN, which can be visualized on coronal T2-weighted MR-images. However, the target for TS, such as the nuclei of the medial part of the thalamus, are invisible in current imaging techniques. The procedure becomes more complicated and difficult making the intra-operative findings like the effects of stimulation more important. Moreover, TS patients might pull themselves out of the stereotactic frame because of the high ratio of motor tics occurring in the head region. One solution would be to operate with the patient being under general anesthesia [12]. Because of the uncertainty of the ideal target and the importance of intra-operative findings, the patient should be cooperative during surgery. To avoid general anesthesia, the patients can be sedated with a combination of lormetazepam and clonidine [36], or with a Propofol Target Controlled Infusion [33], sufficiently reducing the tics and their implications for the stereotactic procedure. At the same time, the patient can be interrogated so that acute negative stimulation-induced side effects can be detected and the position of the electrode adapted. This is illustrated by the following two cases of bilateral thalamic stimulation. In the first patient, test stimulation of the target on the left side evoked a pleasant feeling, while test stimulation of the same target on the right side, elicited a feeling of acute anxiety, after which the electrode was repositioned 2 mm more medially. In the second patient, test stimulation of the target on the right side evoked an acute depressive state, after which the position of the electrode was changed [36].

Perioperative evaluation

It is of paramount importance that in all TS patients treated by DBS, the exact location of the electrode is precisely determined, and all effects are meticulously described. In order to do a proper clinical assessment, it is absolutely necessary to record a description of the effect on tics and the associated behavioural disorders, the stimulation-induced side-effects, and the complications. For tic rating, the most commonly used scale is the Yale Global Tic Severity Scale (YGTSS) [16]. For a more objective evaluation, the patient should also be recorded on videotape with and without stimulation. The tics should be rated on these tapes by two independent investigators. Also, the patient should be blinded to the status of the stimulation. A careful psychiatric and neuropsychological evaluation should be performed at regular intervals (for example at 6 and 12 months postoperatively). A more comprehensive survey of guidelines for the perioperative assessment of the effects of DBS in TS can be found elsewhere [19].

The clinical effects should be correlated to the exact position of the electrode. MRI in subjects with implanted DBS systems may induce heating of the electrode or other untoward effects [22]. Therefore, the most prudent approach is to perform a postoperative CT scan, and fuse these images with preoperative MR images. Only if these prerequisites are fulfilled and a maximum of data is exchanged between centres, the optimal target can be established in due time.

Discussion

The last few years, TS has attracted the attention of clinicians who are active in the field of neuromodulation. After the initiation of thalamic DBS as a potential treatment for patients with refractory TS, several other targets have been used in a relatively small period of time. The published reports however are sparse. In total, one newsletter has been published [34], one article [36], one brief report [3], one short report [12], and 3 abstracts [5, 26, 33]. Without any doubt, this has to do with the small percentage of patients that are potential candidates for surgery. Up until now, five targets have been used for DBS for TS, in 15 patients: a) medial part of the thalamus, at the cross point of CM-Spv-Voi, b) medial part of the thalamus, CM-Pf, c) GPi posteroventrolateral part, d) GPi anteromedial part, and e) NAC. In all the reports in which the effects on tics are described, there is a tic reduction of at least 66% (see Table 1). With the exception of a small hematoma around the tip of one electrode, no complications have been reported. Stimulation-induced unexpected side effects are described in the majority of cases: drowsiness in 3 patients, changes in sexual behaviour in 2, and mild dysarthria in 1 patient subjected to thalamic medial DBS. One patient who received bilateral thalamic and bilateral GPi(vpl) DBS appeared to be more depressed when the pallidal stimulation was on. The stimulation-dependent changes in the execution of movements in one case of anteromedial pallidal stimulation very probably have to do with a small hematoma. One comparative study between anteromedial pallidal and thalamic stimulation in one patient showed that thalamic stimulation had a better effect on associated behavioural disorders. Also, in one patient receiving posteroventral pallidal stimulation, there was no effect on the behavioural disorders. It is not mentioned whether the other patient, in whom the effects of chronic posteroventral pallidal stimulation are described, suffered from any behavioural disorder. In six patients who received thalamic stimulation, the effect on behaviour was not described. In conclusion, the published data on the effects of DBS in TS are incomplete.

There are no exact figures about the number of TS patients who appear to be treatment refractory and thus are potential candidates for DBS, but it is low compared with other indications for DBS like PD. The impact on the patient's quality of life and his socio-economical functioning however is often so devastating that this disease deserves strong efforts by clinicians who are experienced in DBS. There are no good animal models for TS and the pathophysiology is not well understood. Currently, the selection of any specific target is based on the effects of lesions of that same target, or on the effects of DBS in that target on comparable symptoms of other diseases, like hyperkinesias in PD. With the proposed pathophysiological model (Fig. 1), the beneficial effects on tics by DBS of the thalamus or NAC, can be explained, because high frequency stimulation reduces the activity of a nucleus. This does not explain the effects of DBS in the GPi, since GPi is hypoactive in TS. This effect of stimulation is similar to the poor understanding of the mechanisms of DBS in PD. In this latter disease, STN and GPi are hyperactive. High frequency stimulation of these nuclei leads to a reduced inhibition of the thalamocortical drive or a facilitation in the execution of movements. Conversely, the beneficial effects of DBS in the GPi on levodopa-induced dyskinesias are inexplicable.

In conclusion, DBS in TS is still experimental, the best target has not yet been determined, and the effects of stimulation of the currently used targets are not fully understood. A surgical procedure with the patient being sedated but cooperative during test stimulation makes the intraoperative detection of stimulation-induced acute side effects possible and the electrode can be repositioned before its final fixation. However, the other negative effects like changes in sexual behaviour may become prominent later in the course of the postoperative follow-up. Patients should be very carefully informed about this risk prior to surgery. On the other hand, the use of the current advanced techniques available to perform DBS can reduce major complications such as intracerebral hematomas to a minimum. Appropriate programming of the stimulator can reverse the stimulation-induced unwanted effects. DBS in TS, although experimental, is a safe procedure. If it remains in the hands of experienced neurosurgeons working with a team of scientists who have expertise in diagnosing and treating TS and there is continuous assessment and timely exchange of clinical experience, DBS can become a standard treatment procedure for selected intractable patients with TS.

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References

1. Berardelli A, Curra A, Fabbrini G, Gilio F, Manfredi M (2003) Pathophysiology of tics and Tourette syndrome. J Neurol 250: 781–787
2. Brito GN (1997) A neurobiological model for Tourette syndrome centered on the nucleus accumbens. Med Hypotheses 49: 133–142

3. Diederich NJ, Bumb A, Mertens E, Kalteis K, Stamenkovic M, Alesch F (2004) Efficient internal segment pallidal stimulation in Gilles de la Tourette syndrome: a case report. Mov Disord 19 Suppl 9: S440
4. DSM-IV task force: Tic Disorders (1994) In: Frances A, Pincus HA, First MB (eds) American Psychiatric Association, Washington DC, pp 100–105
5. Egidi M, Carrabba G, Priori A, Rampini P, Locatelli M, Bossi B, Cogiamanian F, Mrakic-Sposta S, Prada F, Tamma F, Caputo E, Gaini SM (2005) Thalamic DBS in Tourette's syndrome: case report. Proceedings of the 14th meeting of the WSSFN, Rome, Italy, June 13–17, 2005
6. Follett KA (2004) Comparison of pallidal and subthalamic deep brain stimulation for the treatment of levodopa-induced dyskinesias. Neurosurg Focus 17(1): E3
7. Graybiel AM (2000) The basal ganglia. Curr Biol 10: R509–R511
8. Groenewegen HJ, van den Heuvel OA, Cath DC, Voorn P, Veltman DJ (2003) Does an imbalance between the dorsal and ventral striatopallidal systems play a role in Tourette's syndrome? A neuronal circuit approach. Brain Dev 25 Suppl 1: S3–S14
9. Hassler R, Dieckmann G (1970) Traitement stereotaxique des tics et cris inarticulés ou coprolaliques considérés comme phénomène d'obsession motrice au cours de la maladie de Gilles de la Tourette. Rev Neurol Paris 123: 89–100
10. Hoekstra PJ, Anderson GM, Limburg PC, Korf J, Kallenberg CG, Minderaa RB (2004) Neurobiology and neuroimmunology of Tourette's syndrome: an update. Cell Mol Life Sci 61: 886–898
11. Hornse H, Banerjee S, Zeitlin H, Robertson M (2001) The prevalence of Tourette syndrome in 13–14-year-olds in mainstream schools. J Child Psychol Psychiatry 42: 1035–1039
12. Houeto JL, Karachi C, Mallet L, Pillon B, Yelnik J, Mesnage V, Welter ML, Navarro S, Pelissolo A, Damier P, Pidoux B, Dormont D, Cornu P, Agid Y (2005) Tourette's syndrome and deep brain stimulation. J Neurol Neurosurg Psychiatry 76: 904
13. Johannes S, Wieringa BM, Nager W, Rada D, Muller-Vahl KR, Emrich HM, Dengler R, Munte TF, Dietrich D (2003) Tourette syndrome and obsessive-compulsive disorder: event-related brain potentials show similar mechanisms [correction of mechanisms] of frontal inhibition but dissimilar target evaluation processes. Behav Neurol 14: 9–17
14. Krause M, Fogel W, Kloss M, Rasche D, Volkmann J, Tronnier V (2004) Pallidal stimulation for dystonia. Neurosurgery 55: 1361–1368
15. Leckman JF (2002) Tourette's syndrome. Lancet 360: 1577–1586
16. Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, Cohen DJ (1989) The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 28: 566–573
17. Lozano AM, Mahant N (2004) Deep brain stimulation surgery for Parkinson's disease: mechanisms and consequences. Parkinsonism Relat Disord 10 Suppl 1: S49–S57
18. Mink JW (2001) Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. Pediatric Neurology 25: 190–198
19. Mink JW, Walkup J, Frey KA, Como P, Cath D, DeLong MR, Erenberg G, Juncos J, Leckman JF, Swerdlow N, Visser-Vandewalle V, Vitek JL for the Tourette Syndrome Association, Inc. (2005) Recommended guidelines for deep brain stimulation in Tourette syndrome. Mov Dis 21(11): 1831–1838
20. Peterson BS, Skudlarski P, Anderson AW, Zhang H, Gatenby JC, Lacadie CM, Leckman JF, Gore JC (1998) A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. Arch Gen Psychiatry 55: 326–333
21. Peterson BS, Thomas P, Kane MJ, Scahill L, Zhang H, Bronen R, King RA, Leckman JF, Staib L (2003) Basal Ganglia volumes in patients with Gilles de la Tourette syndrome. Arch Gen Psychiatry 60: 415–424
22. Rezai AR, Finelli D, Nyenhuis JA, Hrdlicka G, Tkach J, Sharan A, Rugieri P, Stypulkowski PH, Shellock FG (2002) Neurostimulation systems for deep brain stimulation: in vitro evaluation of magnetic resonance imaging-related heating at 1.5 Tesla. J Magn Reson Imaging 15: 241–250
23. Riederer F, Stamenkovic M, Schindler SD, Kasper S (2002) Tourette's syndrome – a review. Nervenarzt 73: 805–819
24. Robertson MM (2000) Tourette syndrome, associated conditions and the complexities of treatment. Brain 123(Pt 3): 425–462
25. Schaltenbrand G, Wahren W (1977) Atlas for stereotaxy of the human brain, 2nd edn Thieme, Stuttgart
26. Servello D, Sassi M, Geremia L, Porta M (2005) Bilateral thalamic stimulation for intractable Tourette syndrome. Proceedings of the 14th meeting of the WSSFN, Rome, Italy, June 13–17, 2005
27. Silay YS, Jankovic J (2005) Emerging drugs in Tourette syndrome Expert Opin Emerg Drugs. 2005 May 10: 365–380
28. Singer HS, Szymanski S, Giuliano J, Yokoi F, Dogan AS, Brasic JR, Zhou Y, Grace AA, Wong DF (2002) Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET. Am J Psychiatry 159: 1329–1336
29. Stern E, Silbersweig DA, Chee KY, Holmes A, Robertson MM, Trimble M, Frith CD, Frackowiak RS, Dolan RJ (2000) A functional neuroanatomy of tics in Tourette syndrome. Arch Gen Psychiatry 57: 741–748
30. Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkotter J (2003) The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. J Chem Neuroanat 26: 293–299
31. Temel Y, van Lankveld JJ, Boon P, Spincemaille GH, van der Linden C, Visser-Vandewalle V (2004) Deep brain stimulation of the thalamus can influence penile erection. Int J Impot Res 16: 91–94
32. Temel Y, Visser-Vandewalle V (2004) Surgery in Tourette syndrome. Mov Disord 19: 3–14
33. Van der Linden C, Colle H, Vandewalle V, Alessi G, Rijckaert D, De Waele L (2002) Successful treatment of tics with bilateral internal pallidum (GPi) stimulation in a 27-year-old male patient with Gilles de la Tourette's syndrome. Mov Dis 17 Suppl 5: 1130 (S341)
34. Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J (1999) Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. Lancet 353: 724
35. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, Lagrange C, Tezenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P, French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group (2005) Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 352: 459–467
36. Visser-Vandewalle V, Temel Y, Boon P, Vreeling F, Colle H, Hoogland G, Groenewegen H, van der Linden Ch (2003) Chronic bilateral thalamic stimulation: a new therapeutic approach in intractable Tourette syndrome. J Neurosurg 99: 1094–1100
37. Visser-Vandewalle V, Ackermans L, van der Linden C, Temel Y, Tijssen MA, Schruers KR, Nederveen P, Kleijer M, Boon P, Weber W, Cath D (2006) Deep brain stimulation in Gilles de la Tourette's syndrome. Guidelines of the Dutch-Flemish Tourette Surgery Study Group. Neurosurgery 58: E590

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Extradural cortical stimulation for movement disorders

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Summary

Extradural cortical stimulation is a recent addition to the armamentarium of operative neuromodulation. Motor cortex stimulation (MCS) is offered by positioning a stimulating plate extradurally on the primary motor cortex. It is a minimally invasive technique that was originally proposed for the control of central neuropathic pain. Currently, its use has been extended to patients with movement disorders. The need for minimally invasive therapies, with low morbidity-mortality which can be applied to patients who are excluded from deep brain stimulation (DBS), led to the first attempt of MCS in Parkinson's disease (PD). Following the demonstration that transcranial magnetic stimulation (TMS) is beneficial in PD, we attempted direct extradural MCS on patients with advanced PD not meeting the criteria for DBS. The mechanisms of action may include "hyperdirect" motor cortex-subthalamic nucleus (MI-STN) input, inhibition, resynchronisation, plasticity changes, interhemispheric transfer of inhibition/excitation and modulation of other cortical areas. In this article, we review the mechanism of action of MCS in movement disorders, the predictive factors of MCS efficacy in PD, the indications, particularly in the elderly who are not suitable for DBS, the adverse effects, and the technique for localization of the central sulcus and for performing the procedure. The future prospects and developments are also discussed.

Keywords: Neuromodulation; motor cortex stimulation (MCS); Parkinson's disease; movement disorders.

Introduction and historical note

Extradural cortical stimulation is a recent addition to the armamentarium of operative neuromodulation. Motor cortex stimulation (MCS) is offered by positioning a stimulating plate extradurally on the primary motor cortex (BA4, MI). It is a minimally invasive technique that was originally proposed for the control of central neuropathic pain [7]. Currently, its use has been extended to patients with movement disorders [4–6, 8–10, 23, 24, 30].

In the first half of the 20th century, Paul C. Bucy relieved extrapyramidal symptoms such as tremor by surgical ablation of cortical areas BA4 and 6; this was done at the expense of inducing motor deficits [3]. Other groups relieved Parkinsonian tremor by pyramidotomy [19, 32]. These pioneering works showed that the primary motor cortex plays a role in the pathophysiology of extrapyramidal disorders; however, at the time, there was no practical way to modulate its function and the cortex was later disregarded as an important location in the pathogenesis of extrapyramidal disorders. In the early 1970s, drawing from animal experiments, showing that pressure on or cooling of MI could stop surgically-induced Parkinson-like tremor in monkeys, Alberts [1] reported that stimulation at 60 Hz with a 7-contact Delgado plate electrode of an area near the rolandic fissure, between motor and sensory sites, could initiate or augment Parkinsonian tremor in patients. Post-central cortical stimuli had the same effect at, above or below the sensory threshold. A few years later, Woolsey *et al.* [37] temporarily alleviated Parkinsonian rigidity and tremor in two patients by direct acute intraoperative stimulation of MI. They wrote that: "*. . .marked tremor and strong rigidity. . .The results suggest the possibility that subthreshold electrical stimulation through implanted electrodes might be used to control these symptoms in Parkinsonian patients*."

In the 1980s, two major advances followed; in 1985, Barker introduced cortical transcranial magnetic stimulation (TMS), a technique allowing focal activation of cortical areas by means of an external magnetic coil and, in Japan, Tsubokawa's group exploited available technology to stimulate MI extradurally for the relief of central pain, with the first patient undergoing surgery in 1989 [7]. In 1993, Benabid's group showed that bilateral subthalamic nucleus stimulation (STNS) provided dramatic relief of advanced Parkinson's Disease (PD) and in 1994 Siegfried reported similar results with pallidal stimulation. Ever since, STNS has become the neurosurgical

intervention of choice for advanced drug-resistant PD. Yet, patients who score less than 30–40 in the off condition on Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) or have an improvement of less than 40–50% when undergoing the levodopa challenge test are not suitable for STNS. Importantly, age 70 is an upper limit for surgery at several centers and patients with major cortical atrophy or focal lesions or patients showing severe psychiatric disturbances and cognitive decline in the off phase are generally excluded. All in all, rougly half the patients may be excluded from deep brain stimulation (DBS). Moreover, the risk of intracranial hemorrhage or cerebral abscess makes DBS not completely safe. This procedure can be complicated by hardware-related problems, persistent neurological deficits, infection, and perioperative mortality.

The need for minimally invasive therapies, with low morbidity-mortality which can be applied to cases that are excluded from DBS, led to the first attempt of MCS for PD. Following the demonstration that transcranial magnetic stimulation (TMS) was beneficial for PD (see review in [26]), we attempted direct extradural MCS for the first time in July 1998 on a patient with advanced PD not meeting the criteria for DBS [4–6, 8–10]. Further evidence that MCS could be effective for motor disorders was accumulated over the late 1990s–early 2000s. Katayama *et al.* and later other authors (see review in Refs. [9] and [23]) reported that MCS may be effective for hemichoreoathetosis, distal resting and/or action tremor, proximal postural tremor associated with brain and/or brainstem stroke, and focal post-stroke dystonia. Moreover, subjective improvement of motor performance was observed in patients in whom involuntary movements were associated with mild to moderate motor weakness [23].

Mechanisms of action

Several mechanisms of action are possible but they apply at variable degrees not only in PD, but also in dystonia and all relevant movement disorders described in this chapter.

Hyperdirect MI-STN input

In primates, MI has a direct, somatotopographically organized, input to the subthalamic nucleus-STN [20]; this corticosubthalamic pathway is in parallel with the corticostriatal path. A human study found electrophysiological evidence of such direct cortico-STN glutamatergic pathway [16]. The Oxford group [27], on the basis of human studies, proposed that the functional connection between the STN and arm muscles is mainly contralateral, but cross-talk may occur between the two subthalamic nuclei via a frequency-dependent pathway. This frequency-dependent pathway could contribute to the bilateral effects of unilateral high frequency STN DBS; the same may apply to MCS. In addition, MCS induces increases of rCBF in the thalamic motor nuclei ventral anterior, ventrolateral (VA-VL) [18] and these are the only thalamic nuclei directly connected to motor and premotor areas. It should be recalled how a modification of motor cortex metabolism contributes to the efficacy of several surgical procedures for Parkinson's disease [8, 9] and neurometabolic evidence from our studies suggests that MCS might be able to upregulate dopamine receptors in the striatum ([8] and unpublished observations). Strafella *et al.* using TMS during intraoperative single-unit recordings from STN in 6 patients with PD undergoing DBS, observed that the MI activation produced a long-term inhibition in the STN neuronal activity [34]. The importance of deep influences is highlighted by a clinical observation. In a central post-stroke pain patient with associated parkinsonian tremor, MCS (50–75 Hz, 120–210 msec) was analgesic, but neither relieved tremor nor improved the UPDRS score (Dario A, personal communication 2002); it is likely that the stroke had altered the motor loop upon which MCS acted. If STN is the primary target, this might explain the whole body effect from unilateral stimulation.

Inhibition

TMS studies suggest that cortical stimulation acts via an MI intracortical mechanism; cortical inhibitory neurons that surround pyramidal cells may be selectively activated by low intensity TMS [14] and a large coil activates all relevant surrounding interneurons. Also, pyramidal cells can be inhibited by TMS without previous excitation. Thus, MCS could reduce MI excitability, which is increased in several movement disorders including Parkinson disease (PD), as long trains of low frequency TMS do (see Refs. [8, 9]). MCS appears to activate axons in the cortex, which excite both corticospinal neurons and inhibitory neurons [21, 33]. In PD patients, TMS studies showed that there is excess excitability or reduced inhibition at MI levels [12]. During production of a voluntary output, motor cortex activation is defective or inadequately modulated, and this may be due to a dysfunction of GABAergic (both A and B) interneurons mediating the level of excitation within BA 4 [11].

GABA modulation is at the core of MCS effect on neurogenic pain [7]. Local cortical changes during MCS have been documented with neuroimaging [8].

Resynchronization

Disruption of oscillation and/or temporal synchronization is considered a fundamental mechanism of neurological diseases, including PD; just as cortical stimulation acts by resetting an out-of-balance thalamoparietal oscillatory loop in central pain [7], likewise MCS might actually act via an oscillatory repatterning of the corticoganglionar pathway; given that 15–30 Hz oscillations are observed during physiologic postural maintenance, it may be surmised that MCS marshals this frequency to reset the abnormal pattern [9].

Plasticity changes

These are suggested by findings in our first PD patient, in whom switching off the stimulator led to a slow, delayed decline of effect – unlike DBS-, and in central pain cases submitted to MCS [5, 7]; they may take place cortically and/or in the basal ganglia, at both synaptic or receptor levels [25].

Interhemispheric transfer of excitation/inhibition

Unilateral MCS improves Parkinsonian symptoms bilaterally, a consistent finding in all successfully operated cases. Several lines of evidence show that MI is involved in contra as well as ipsilateral hand movements, with greater involvement in more complex tasks and with the left hemisphere playing a greater role than the right; moreover, transmission of inhibitory and excitatory signals via the corpus callosum has been demonstrated [5, 15]. Transcallosal spread of electrically induced neuronal alterations by surface recordings from the opposite motor cortex has been observed in humans in a TMS study [13].

Modulation of other cortical areas

Neurometabolic studies have demonstrated hypofunction of the supplementary motor (SMA) and premotor areas (PMA) in the generation of rigidity and bradykinesia; it may be hypothesized that abnormal prolonged firing of preparatory movement-setting SMA and PMA cells cause disruption of the neuronal activity of MI. MCS may activate myelinated axons connecting SMA with MI both anti and orthodromically, thus rebalancing the disrupted SMA activity.

Functional considerations

The efficacy of MCS is strongly affected by the thickness of the cerebrospinal fluid (CSF) layer between the electrode and MI. When the CSF layer thickness is increased, both the current intensity in the cortex at a given voltage and the load impedance are reduced, thus increasing the energy needed for stimulation. In particular, when the CSF thickness is increased from 0 to 2.5 mm, the load impedance decreases by 28%, and the stimulation amplitude increases by 6.6 V for each millimetre of CSF [28]. On the other hand, variation of the width of MI and the central sulcus has a negligible effect on the current distribution in the cortex. During bipolar MCS, due to the rather large electrode distance (1 cm center-to-center), the cathodal and anodal fields in the cortex hardly interfere and have a shape similar to a monopolar field. Due to a different load impedance, however, the monopolar field has a larger extent than the bipolar one when the same voltage is applied [28] and monopolar MCS alleviates Parkinsonian symptoms in MPTP monkeys. Nerve fibers under the cathode and parallel to the electrode surface are depolarized and possibly excited, whereas fibers normal to its surface are hyperpolarized. Under the anode, the opposite effects are observed. Due to the curved shape of MI, the orientation of its afferent and efferent fibers varies, thereby changing their response to stimulation. Whereas efferents in MI are hyperpolarized by cathodal stimulation, they are depolarized in the walls of the (pre-) central sulcus. In addition, the magnitude of a fiber's response depends on its caliber and its distance from the electrode. Thus, hardly any difference will be present among the cathodal fields in mono- and bipolar stimulation, although monopolar stimulation is more energy efficient. To avoid potential anodal responses in a different motor cortex area interfering with cathodal responses in bipolar MCS, it is suggested that the anode should not be placed over MI [28]. Another study found that anodal stimulation over vertically oriented pyramidal cells induces depolarization at the initial segment. Since anodal stimulation activates corticospinal neurons mainly indirectly, it turns out to be less effective than cathodal stimulation; moreover, there is a lower threshold to cathodal than to anodal stimulation [21].

On subdural stimulation, although the muscles that are activated roughly correspond to the expected cortical representation, discrete somatotopic excitation of upper limb muscles does not exist [21]. Also, body areas represented only deep in a sulcus or fissure are unlikely to be stimulated by an electrode on the brain surface [28], but

this may not affect global efficacy. The combined worldwide experience up to now points to low frequency stimulation (below 80 Hz) as the standard of stimulation for movement disorders. This is an important distinguishing feature of MCS as compared to STN DBS, which is effective at the highest range (>100 Hz). Clearly, these two types of stimulation work differently.

Predictive factors for MCS effectiveness in PD

Dopa and apomorphine unresponsiveness are known poor predictors of STNS efficacy; hence, patients with levodopa-resistant Parkinsonism associated with ischemia-anoxia, multisystem atrophy or progressive supranuclear palsy are unlikely to draw a significant benefit from STNS. The same should apply to MCS: the benefit has been at best modest and/or transitory [9, 24], but optimization of the parameters (continuous versus cyclical stimulation, low versus high voltage, and low versus high frequency) might help a few patients. Propofol, a GABA-A agonist which is useful in selecting patients with central pain for MCS [7], appears not to renormalize dystonic symptoms [6]; therefore, it may be speculated that MCS acts differently on pain and dystonia, and other movement disturbances as well [7, 30]. Decreased striatal D2 receptor binding seems to be a predictor of nonresponse to STN surgery, but a patient of ours showing decreased IBZM binding had a successful response to implantation [9].

Adverse effects

MCS has proven to be a very safe neuromodulatory technique, with no reported mortality or long-term disabling morbidity [7]. In particular, the much-feared kindling of long-term epilepsy has never been substantiated at therapeutic stimulation parameters. On the other hand, PD patients submitted to MCS up to now tend to be older and often above the age of 70. Preliminary experience suggests that psychiatric and cognitive adverse effects may turn out to be more common in this age than in the younger patients submitted to DBS. Even if psychiatric symptoms and dementia frequently occur in PD patients as part of the natural history of the disease, caution must be exercised, particularly since the minimal invasiveness of the technique makes it potentially applicable to a much greater number of patients than DBS [8]. An evoked potentials study found a significant relationship of MCS efficacy with the patient's age; it showed a significant delay, during MCS, of the cognitive responses N2 (but not N1) and P3 (N200 and P300) in patients older than 50 years. This effect was rapidly reversible after MCS discontinuation. These results, together with experiments showing P300 alteration during rTMS, suggest that MCS may interfere with relatively simple cognitive processes such as those underlying target detection, and that the risk of abnormal cognitive effects related to cortical stimulation may increase with age, but also in the presence of pre-existent cerebral lesions [29].

Central sulcus localization and operative procedure

The target of MCS for PD is the hand area, on the side most affected. While in surgery for central pain somatotopography is important, even not as stringently as previously thought, in PD patients, hand area targeting is able to affect the whole body. The motor hand area in the axial plane on standard MRI, is a knob-like, broad-based, posterolaterally directed structure of the precentral gyrus. It usually has an inverted omega shape (90%) and sometimes a horizontal epsilon shape (10%), with a mean diameter of 1.4 cm. On average, it is located about 23 mm from the midline, just posterior to the junction of the superior frontal sulcus with the precentral sulcus and 19 mm from the lateral surface [39]. However, the motor hand area may extend to, or be located exclusively in SI, on functional magnetic resonance (fMRI) [38]. In particular, this area is most often located in the posterior bank of the precentral gyrus (80%), but it is seen additionally in the postcentral gyrus in 50% or exclusively in SI in 20% [31, 38], even during the simplest tasks. Other areas, e.g. the supplementary motor area, are also activated and, occasionally, bilateral activation of MI following unilateral hand activation is observed. It is well known how pyramidal cells are located in SI (particularly BA3a) and how direct electrical stimulation of all SI can also elicit motor responses in the contralateral skeletal muscles, as it was classically demonstrated by Penfield and replicated by others [35]. In these cases, SI stimulation may be as effective. A major issue should be taken into consideration. In a sizable minority of patients (20%) there are variations in the organization of MI, i.e. mosaicism (overlapping of functional areas), variability (inverted disposition of MI functional areas) or both [2]. These data challenge the orderly topography of MI and suggest that the motor homunculus may not always be considered a definite and absolute representation of MI. Also, BA44 (found 2 cm anterior to the

primary tongue motor area) has direct fast conducting corticospinal projections and has a role in voluntary hand movements [36]. Clearly, MCS is not a straightforward surgical procedure.

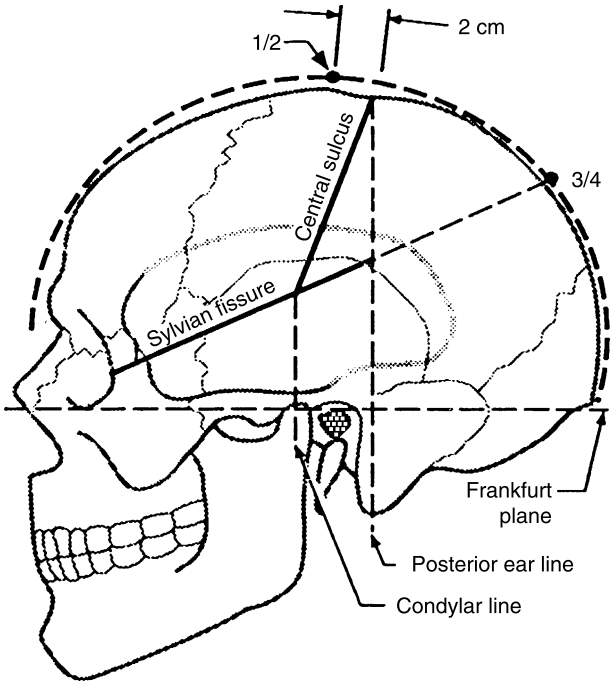


Fig. 1. Taylor-Haughton lines used for initial identification of the central sulcus

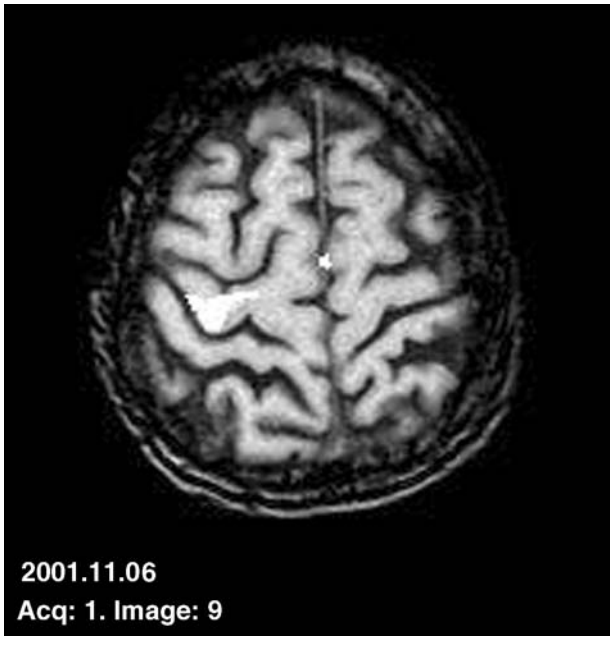
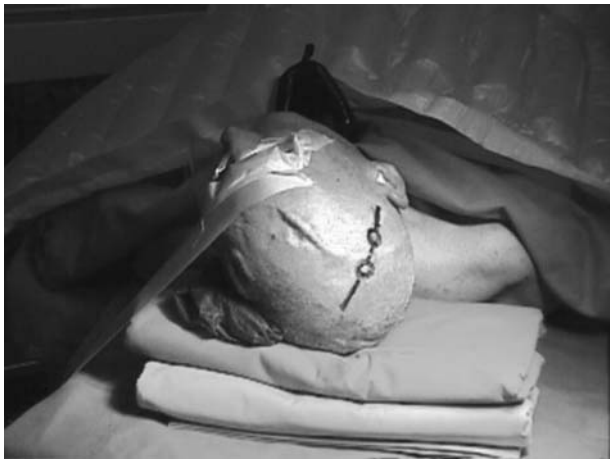
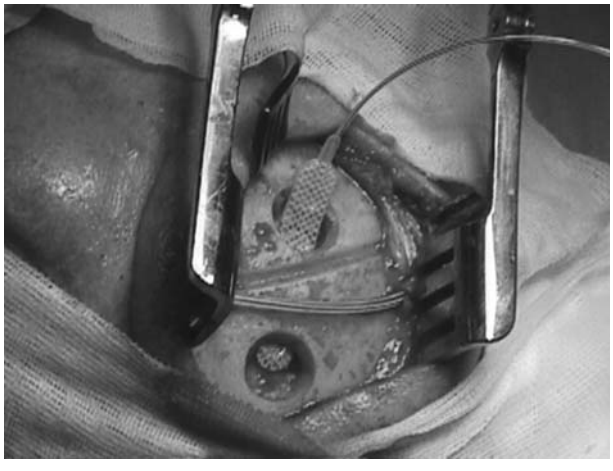


Fig. 2. Functional MR image showing the focus of motor hand activation in the appropriate area in BA4 (from Canavero *et al.*, 2002, with permission)

After shaving the patient's head, the approximate location of the central sulcus is marked on the skin along the Haughton-Taylor lines (Fig. 1). Motor area localization is confirmed by standard fMRI sequences while the patient makes repetitive self-paced opposition movements of the thumb to the rest of the fingers at an approximate rate of $1/\text{sec}$. The echoplanar multiphase acquisition in a 1-tesla MRI consists of a 3.31-minute sequence with 3×30 seconds of motor activation interleaved with 4×30 seconds of rest. A fiducial paramagnetic marker applied on the skin is adjusted under MR conditions until the skin marking and the actual target area match (Fig. 2). The operation is performed under local anesthesia, with mild i.v. sedation if required. We strongly discourage general anesthesia for electrode placement because of the added risks, particularly in elderly patients. After a linear incision along the projection of the central sulcus (arm area) is made (Fig. 3a),



a



b

Fig. 3(a, b). Patient in position for surgery (a) and implantation of the stimulating paddle through a pair of burr holes (b)

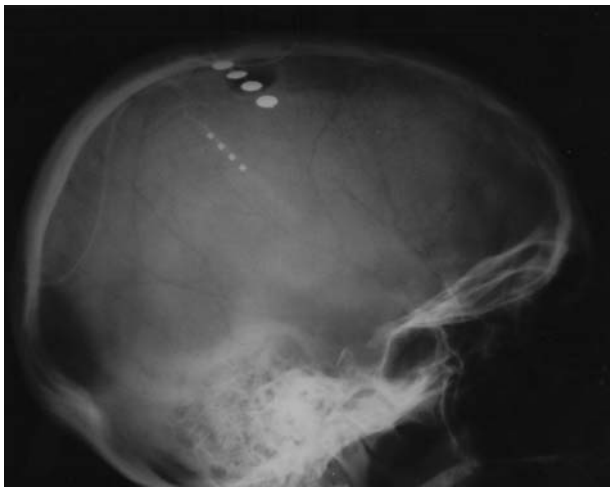


Fig. 4. Radiograph showing the MCS apparatus in place

two burr holes are drilled in front of the projection of the central sulcus to accomodate the length of the stimulation paddle. After dural hemostasis is achieved, the paddle is slid under the bone over the primary motor area (Fig. 3b). Intraoperative stimulation to elicit motor responses is the usual next step. Once the surgeon is satisfied with positioning, the electrode is externalized behind the ear. We usually drill a groove in the bone parallel to the paddle's long axis in order to accommodate the joint between the paddle and the electro-catheter. After a stimulation test period generally lasting a few weeks, during which the most beneficial parameters are sought, the pulse generator (IPG) is implanted in the subclavicular area under general anesthesia, or local anesthesia under mild sedation, and connected to the subcutaneous electrode (Fig. 4). Alternatively, both the paddle and the IPG can be implanted simultaneously during the same surgical session.

Indications

Parkinson disease and Parkinsonism

Worldwide, more than 50 patients have been implanted up to now (congress and privileged data). The first three patients have been implanted by the authors between 1998 and 2002 ([4, 5, 8–10]; Fig. 5). These were all patients above the age of 70 and excluded from DBS due to MR evidence of atrophy, ventricular enlargement, ischemic white matter disease, neuropsychiatric deficits or poor medical conditions. All the relevant observations regarding MCS for PD were obtained in these patients, notably bilateral effects from unilateral stimulation (e.g. the tapping test improved in both hands) with minimal asymmetry, efficacy of stimulation at low frequency (beneficial) versus high (>100 Hz) frequency (disruptive or not beneficial), and the effect on all three cardinal signs of PD, i.e. tremor, rigidity, bradykinesia. An interesting finding was that after a few weeks of continuous stimulation, the stimulator could be switched off at night without losing benefit (up to weeks), an observation which is relevant to energy sparing. Further experience shows that MCS also improves verbal understanding and fluidity, spatial orientation, dysphagia, void and fecal control. Dyskinesias are the one symptom which responds dramatically to stimulation. L-Dopa may be reduced in many patients. Currently, patients must meet the following criteria for implantation: UPDRS in OFF $\geq$40/180, Hoehn and Yahr (H/Y) $\geq$3, motor fluctuations plus disabling dyskinesias, UPDRS improvement to L-Dopa challenge test $\geq$30%. Although voltage should not exceed 3–3.5 V, some patients drew benefit at higher voltages. Pulse width varies from low (150 msec) to high (e.g. 400 msec); effective frequencies are usually in the low range (10–60 Hz). We, and others, have found that, with a few exceptions, the best electrode setting tends to encompass as much cortex as possible (0–3).

Slight adjustments of parameters may be necessary over time, although much less often than in pain patients.

In several cases improvement is around 30% on UPDRS, but can be lower or higher. However, due to the abolition of disabling dyskinesias and improvement of axial symptoms (standing, walking, falling, swallowing, facial hypomimia, swallowing), life quality and self-grooming are improved – sometimes dramatically – with lesser degrees of assistance, a fact often noted by family members. A few patients have benefited from MCS after ineffective DBS. Longest follow-up is now several years. Similarly to DBS, some symptoms remain relieved, while others tend to worsen with time. Although rigidity and, less so, tremor are abolished within several minutes of stimulation, the full effect on bradykinesia and gait grows with time (days, weeks, and even months). Thus, compared to DBS, additional time should be allowed for in searching for effective parameters. Failures have been noted, perhaps due to extensive atrophy (see *Functional considerations* above). While the experience with parkinsonism associated with multiple system atrophy has been disappointing up to now, vascular parkinsonism may respond.

Post-stroke movement disorders

Movement disorders are one of the most disabling sequelae of stroke. In the mid- and late-1990s, Katayama

a b

Fig. 5(a, b). Images of the first patient ever to receive MCS for Parkinson's disease at 1 year follow-up

et al. reported on the effects of MCS in patients with post-stroke involuntary movements (in most of whom MCS was performed for controlling central pain) [23]. MCS appreciably attenuated hemichoreathetosis associated with thalamic stroke and completely abolished distal resting and/or action tremor associated with multiple lacunar, striatal or thalamic infarcts, independent of analgesia. Proximal postural tremor was not well controlled by MCS and SI and supplementary motor area (SMA) stimulation had no effect on hemichorea and resting tremor. In patients with Wallenberg's syndrome, MCS was effective in improving pain, tremor, dysarthria and paresis. Postural tremor and frozen gait seemed resistant to stimulation. MCS effect, when present, began immediately after the start of stimulation; after its termination, the effect reappeared at stimulation intensity below the threshold for muscle contraction and a frequency of more than 15 Hz. Thus, post-stroke motor disorders seem to respond to higher frequencies (50–125 Hz) than pain (25–75 Hz) and at intensities below the threshold for muscle contraction. Subjective improvement of voluntary motor performance, which had been impaired in association with mild or moderate hemiparesis, was reported during MCS by approximately 20% of patients with post-stroke pain, independent of analgesia. Such an effect on voluntary motor performance appears to be caused by an inhibition of their rigidity. No improvement occurred in patients who demonstrated severe motor weakness and/or no muscle contraction in response to MCS at a higher intensity. MCS completely

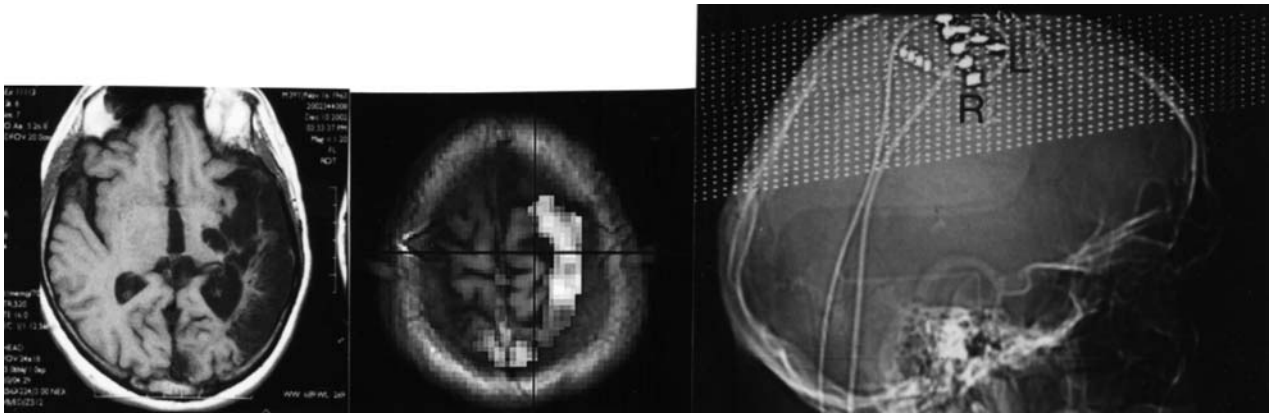


Fig. 6. MR image of a patient with stroke (a), fMR image following motor activation of the paretic arm (b) and double cortical stimulator ion motor areas (c) (Ref. [10b])

relieved both pain and tremor for at least 32 months in a patient with severe upper limb action tremor and facial pain following removal of an acoustic Schwannoma [30]. In this patient, tremor increased by decreasing the frequency below 50 Hz. In other series, a few patients experienced reversible improvements in facial sensory discrimination, motor strength and post-stroke dysarthria after successful stimulation for neuropathic pain.

Dystonias

We reported the effects of MCS on a female patient with spasmodic torticollis who later developed post-thalamotomy painful paroxysmal hemidystonia [9]; lesions of the thalamus, including surgical lesions of the posterior-posterolateral or paramedian thalamus, may originate dystonia, including paroxysmal dystonic attacks. During the trial period, stimulation at low frequency (10 Hz), at long impulse duration (450 msec) and low voltage (1 V) relieved the pain and dystonia almost completely, while the neck symptoms were not affected or slightly worsened. Duration of paroxysms and free intervals were not affected. Increasing the frequency to 60 Hz and even more to 130 Hz at short impulse duration (60 msec) worsened both pain and dystonia and increased the duration of her crises up to 40 min. In addition, previously never reported rebound crises lasting 5–10 min were triggered. A second plate positioned over the neck-head area at effective parameters as above worsened both pain and dystonia; the picture was even worse at 700 msec. Other experience suggests that MCS may affect post-stroke pain and dystonia (thalamic hand) variably, with dystonia responding to high frequency (130 Hz) [6], but also other dystonic syndromes.

Post-stroke motor rehabilitation

In 2002, we were the first to submit a plegic patient to bilateral cortical stimulation for post-stroke motor rehabilitation (Fig. 6) and found modest effects. Similarly to another recent controlled US study, it seems that cortical stimulation of areas undergoing plastic changes as evidenced on fMR may help rehabilitation of patients who have been left with disabling deficits after intensive physiotherapy [11].

Future prospects and developments

MCS holds great promise for the treatment of selected motor disorders, notably Parkinson's disease and several

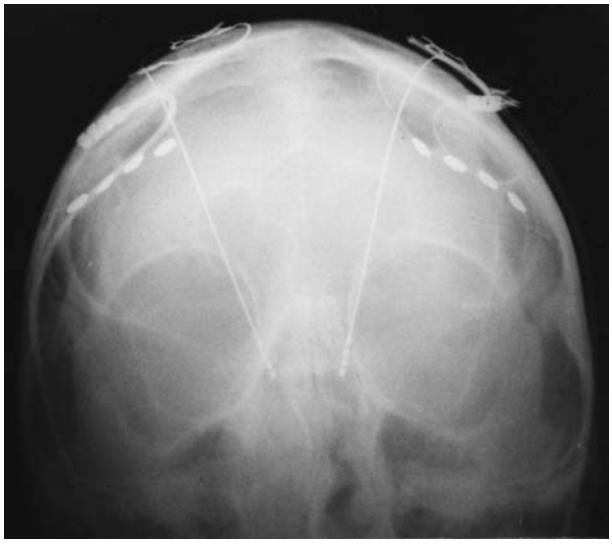


Fig. 7. Radiograph of a Parkinsonism case with a double STN and MCS stimulator (Ref. [9])

post-stroke disorders. Bilateral Parkinson's disease appears to be controlled by unilateral MCS, making it cost-effective compared to DBS. Although bilateral stimulation may be additive (Fig. 7), contralateral stimulation, on the least affected side, may be attempted in failures. SMA is not accessible to extradural MCS, but premotor areas could be targeted in future studies. Old data point to a motor suppressing area (BA4a) (see McCullock in [3]) and this region should be better explored. Finally, STN DBS does not prevent cell death and glutamate excitotoxicity [22] and it would be interesting to assess MCS for this effect. It seems every movement disorder that responds to TMS will also respond to MCS, including a wide range of dystonias, such as writer's cramp, tics (as in Tourette's syndrome), myoclonus (primary and secondary) and others. Lack of mortality and disabling surgical morbidity (due to lack of insertion of electrodes into the brain) plus cost-effectiveness (no need for stereotactic equipment) may contribute towards a massive resort to this technique, which is likely to spill over to psychiatric neuromodulation; epilepsy is now undergoing experimental treatment with closed-loop cortical stimulation [17]. Even if future head-to-head studies find DBS more effective, MCS will remain an option for all those patients who are not suitable for DBS, i.e. a huge population.

References

1. Alberts WW (1972) A simple view of parkinsonian tremor. Electrical stimulation of cortex adjacent to the rolandic fissure in awake man. Brain Res 44: 357–369
2. Branco DM, Coelho TM, Branco BM, Schmidt L, Calcagnotto ME, Portuguez M, Neto EP, Paglioli E, Palmini A, Lima JV, Da Costa JC (2003) Functional variability of the human cortical motor map: electrical stimulation findings in perirolandic epilepsy surgery. J Clin Neurophysiol 20: 17–25
3. Bucy PC (1949) Extirpation in man. In: Bucy PC (ed) The precentral motor cortex. University of Illinois Press, Urbana, pp 355–393
4. Canavero S, Bonicalzi V, Paolotti R, Cerutti A (1998) Extradural cortical stimulation for neurogenic pain and Parkinson's disease. The Turin experience. In: Meadows P (ed) IFESS Conference proceeding: electronic edition. IFESS CD
5. Canavero S, Paolotti R (2000) Extradural motor cortex stimulation for advanced Parkinson's disease: case report. Mov Disord 15: 169–171
6. Canavero S, Bonicalzi V (2001) Motor cortex stimulation. J Neurosurg 94: 688–689
7. Canavero S, Bonicalzi V (2002) Therapeutic extradural cortical stimulation for central and neuropathic pain: a review. Clin J Pain 18: 48–55
8. Canavero S, Paolotti R, Bonicalzi V, Castellano G, Greco-Crasto S, Rizzo L, Davini O, Zenga F, Ragazzi P (2002) Extradural motor cortex stimulation for advanced Parkinson's disease. Report of two cases. J Neurosurg 97: 1208–1211
9. Canavero S, Bonicalzi V, Paolotti R, Castellano G, Greco-Crasto S, Rizzo L, Davini O, Maina R (2003) Therapeutic extradural cortical stimulation for movement disorders: a review. Neurol Res 25: 118–122
10. Canavero S, Bonicalzi V (2004) Cortical stimulation for Parkinsonism. Arch Neurol 61: 606
11. Canavero S, Bonicalzi V, Intonti S, Crasto S, Castellano G (2006) Effects of bilateral extradural cortical stimulation for plegic stroke rehabilitation. Case report. Neuromodulation 9: 28–33
12. Cantello R, Tarletti R, Civardi C (2002) Transcranial magnetic stimulation and Parkinson's disease. Brain Res Rev 38: 309–327
13. Chiappa KH, Cros D, Kiers L, Triggs W, Clouston P, Fang J (1995) Crossed inhibition in the human motor system. J Clin Neurophysiol 12: 82–96
14. Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P, Rothwell JC (1998) Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. Exp Brain Res 119: 265–268
15. Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali F, Rothwell JC (1999) Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. Exp Brain Res 124: 520–524
16. Dinner DS, Neme S, Nair D, Montgomery EB Jr, Baker KB, Rezai A, Lueders HO (2002) EEG and evoked potential recording from the subthalamic nucleus for deep brain stimulation of intractable epilepsy. Clin Neurophysiol 113: 1391–1402
17. Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD (2005) Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy. Stereotact Funct Neurosurg 83: 153–158
18. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
19. Guiot G, Pecker J (1949) Traitement du tremblement parkinsonien par la pyramidotomie pedonculaire. Sem Hop Paris 25: 2620–2624
20. Haber SN, Gdowski MJ (2004) The basal ganglia. In: Paxinos G, Mai JK (eds) The human nervous system, 2nd edn. Elsevier Academic Press, Amsterdam, pp 677–738
21. Hanajima R, Ashby P, Lang AE, Lozano AM (2002) Effects of acute stimulation through contacts placed on the motor cortex for chronic stimulation. Clin Neurophysiol 113: 635–641
22. Hilker R, Portman AT, Voges J, Staal MJ, Burghaus L, van Laar T, Koulousakis A, Maguire RP, Pruim J, de Jong BM, Herholz K, Sturm V, Heiss WD, Leenders KL (2005) Disease progression continues in patients with advanced Parkinson's disease and effective subthalamic nucleus stimulation. J Neurol Neurosurg Psychiatry 76: 1217–1221
23. Katayama Y, Oshima H, Fukaya C, Kawamata T, Yamamoto T (2002) Control of post-stroke movement disorders using chronic motor cortex stimulation. Acta Neurochir [Suppl] 79: 89–92
24. Kleiner-Fisman G, Fisman DN, Kahn FI, Sime E, Lozano AM, Lang AE (2003) Motor cortical stimulation for parkinsonism in multiple system atrophy. Arch Neurol 60: 1554–1558
25. Lee L, Siebner HR, Rowe JB, Rizzo V, Rothwell JC, Frackowiak RS, Friston KJ (2003) Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23: 5308–5318
26. Lefaucheur JP (2005) Motor cortex dysfunction revealed by cortical excitability studies in Parkinson's disease: influence of antiparkinsonian treatment and cortical stimulation. Clin Neurophysiol 116: 244–253
27. Liu X, Ford-Dunn HL, Hayward GN, Nandi D, Miall RC, Aziz TZ, Stein JF (2002) The oscillatory activity in the parkinsonian sub-

thalamic nucleus investigated using the macro-electrodes for deep brain stimulation. Clin Neurophysiol 113: 1667–1672
28. Manola L, Roelofsen BH, Holsheimer J, Marani E, Geelen J (2005) Modelling motor cortex stimulation for chronic pain control: electrical potential field, activating functions and responses of simple nerve fibre models. Med Biol Eng Comput 43: 335–343
29. Montes C, Mertens P, Convers P, Peyron R, Sindou M, Laurent B, Mauguiere F, Garcia-Larrea L (2002) Cognitive effects of precentral cortical stimulation for pain control: an ERP study. Neurophysiol Clin 32: 313–325
30. Nguyen JP, Pollin B, Feve A, Geny C, Cesaro P (1998) Improvement of action tremor by chronic cortical stimulation. Mov Disord 13: 84–88
31. Pujol J, Conesa G, Deus J, Vendrell P, Isamat F, Zannoli G, Marti-Vilalta JL, Capdevila A (1996) Presurgical identification of the primary sensorimotor cortex by functional magnetic resonance imaging. J Neurosurg 84: 7–13
32. 30-Putnam TJ (1940) Treatment of unilateral Paralysis Agitans by section of the lateral pyramidal tract. Arch Neurol Psych 44: 950
33. Schlag J, Balvin R (1964) Sequence of events following synaptic and electrical excitation of pyramidal neurons of the motor cortex. J Neurophysiol 27: 334–365
34. Strafella AP, Vanderwerf Y, Sadikot AF (2004) Transcranial magnetic stimulation of the human motor cortex influences the neuronal activity of subthalamic nucleus. Eur J Neurosci 20: 2245–2249
35. Uematsu S, Lesser R, Fisher RS, Gordon B, Hara K, Krauss GL, Vining EP, Webber RW (1992) Motor and sensory cortex in humans: topography studied with chronic subdural stimulation. Neurosurgery 31: 59–71
36. Uozumi T, Tamagawa A, Hashimoto T, Tsuji S (2004) Motor hand representation in cortical area 44. Neurology 62: 757–761
37. Woolsey CN, Erickson TC, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg 51: 476–506
38. Yousry TA, Schmid UD, Schmidt D, Hagen T, Jassoy A, Reiser MF (1996) The central sulcal vein: a landmark for identification of the central sulcus using functional magnetic resonance imaging. J Neurosurg 85: 608–617
39. Yousri TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P (1997) Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain 120: 141–157

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Motor cortex stimulation for Parkinson's disease

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Summary

In 2000, Canavero and Paolotti reported the improvement of symptoms in a case of advanced Parkinson disease (PD), following chronic epidural motor cortex stimulation (MCS). In 2002, the same group reported the results obtained in 2 patients with PD. Unilateral MCS proved to be beneficial bilaterally. They concluded that MCS may represent a cost-effective alternative to deep brain stimulation. In 2003, Pagni promoted an Italian Multicenter Study and in June 2005 the results in the first 29 cases were reported. Any symptom of PD could be modulated by MCS, but improvement of different symptoms was variable and unpredictable, with some patients being unresponsive. L-Dopa induced dyskinesias, painful dystonia and motor fluctuations were satisfactorily controlled. In the author's series, 2 patients were unresponsive and 5 patients showed a clinical improvement, particularly evident in the off-medication state; UPDRS-III mean improvement was 30% at 3 months and 22% at 12 months. Quality of life (QOL) also improved. Assessment by the Parkinon's disease quality of life (PDQL) scale showed a mean decrease by 26% at 12 months. No complication or adverse events were observed. These preliminary data indicated the possibility to modulate PD symptoms by MCS. Several unsettled issues remain such as the optimal electrode position, the best stimulation parameters, the usefulness of unilateral versus bilateral stimulation, the prognostic factors for best selection of patients, and the optimal assessment of clinical effects. The mechanisms of MCS may be only the subject of hypothesis.

Keywords: Neuromodulation; epidural motor cortex stimulation; Parkinson's disease; intraoperative neurophysiological monitoring.

Introduction

Currently, the primary surgical treatment for Parkinson disease (PD) is deep brain stimulation (DBS). This therapy offers improvement ranging from 30 to 80% in patients when in the 'OFF' medication state and ameliorates both parkinsonian symptoms and L-Dopa-induced dyskinesias. However, DBS therapy is not free of complications. The implantation of the electrode is associated with 1–3% risk of haemorrhage depending on the surgical technique used. It also requires a well-trained and specialized team, with rather expensive equipment for the targeting and the implantation of the DBS electrode. Moreover, age more than 70 years, brain atrophy, cognitive impairment, psychiatric symptoms, and medical co-morbidities are contraindications to DBS. Furthermore, recent evidence suggests that subthalamic nucleus (STN) DBS is not effective in controlling any motor deficits, particularly speech-related and axial motor symptoms such as posture, postural instability and freezing of gait. This may lead to dissatisfaction with the treatment and a small benefit in activities of daily living. Finally, side effects such as dysphonia, dysphagia, and psychotic crisis leading even to suicide, may limit the clinical application of the DBS procedure. Therefore, other approaches to the treatment of PD patients should be considered, and the motor cortex may be one of the possible targets for therapeutic neuromodulatory interventions.

Why the motor cortex?

Many old and new data suggest a strong involvement of the motor cortex in PD:

1) Extirpation of motor cortex abolishes parkinsonian tremor [6].
2) Intraoperative MCS, subthreshold for movements, relieves tremor and rigidity in PD patients [33].
3) Repetitive Transcranial Magnetic Stimulation (rTMS) of the motor cortex improves motor performances in PD [13, 15, 17, 18, 25, 29, 30]. Many of these studies assessed the effects of rTMS by UPDRS (Unified Parkinson's Disease Rating Scale). Lefaucheur *et al.* [17] used real and sham stimulation in 12 "off-med" patients with PD and compared the results with those obtained by a single dose of L-Dopa. Real rTMS but not sham stimulation, improved motor performances.

They concluded that these results support the stimulation of the primary motor cortex for neuromodulation in PD.

4) rTMS of the motor cortex increases dopamine release in the nigrostriatal system [20, 31].
5) Bilateral overactivity of the motor cortex is present in PD [28] and is reduced by dopaminergic treatment and by DBS [26].
6) Abnormal synchronization between cortical and basal ganglia oscillatory activity has been demonstrated in human PD using coherence analysis and movement-related frequency-specific changes in synchronization [5]. This activity is modulated by STN DBS [9].
7) Animal studies suggest that the cerebral cortex plays an important role in regulating the activity of STN. Indeed, the STN represents the second entry point of cortical information to the basal ganglia [19, 24].
8) The most extensive cortical innervation of STN originates from motor areas through a direct pathway and an indirect multisynaptic basal ganglia circuit [1].
9) Strafella *et al.* in 2004 [32], demonstrated that 75% of the neurons in dorsolateral STN respond to TMS of the motor cortex in humans. This response is characterized by a short-latency short-duration excitation followed by a long lasting inhibition (more than 100 ms). They concluded that these findings ''clearly indicate that the human motor cortex exerts a powerful modulatory influence over the STN''.
10) Drouot *et al.* [10] described a functional recovery of Parkinson's motor signs in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) baboons following MCS. High-frequency MCS significantly reduced akinesia and bradykinesia. The effect was present only in animals displaying moderate and severe 18F-Dopa striatal uptake depletion. The behavioral benefit was associated with an increased metabolic activity in the supplementary motor area (SMA) as assessed with 18-F-deoxyglucose PET, a normalization of mean firing rate in the internal globus pallidus (GPi) and the STN, and a reduction of synchronized oscillatory neural activities in these two structures.
11) MCS has been reported to be effective not only in relieving pain but also in improving the associated movement disorders in patients with thalamic hand [12] or post-stroke movement disorders [14]. Brown *et al.* [4] reported a case of enhanced motor recovery after stroke following MCS.

Review of the literature

In 2000, Canavero and Paolotti [7] were the first to report an improvement of symptoms in a 72-year-old woman with advanced PD following unilateral extradural MCS. The clinical improvement was bilateral. UPDRS (Unified Parkinson's Disease Rating Scale) in ''on-med'' decreased as follows: section I: −10%, section II: −50%, section III: −48%, section IV: −62%. Levodopa was reduced by 80%. These results were confirmed by the same group in 2002 [8], when they added a second patient to the first case. In 2003, Pagni *et al.* described 3 new cases [22]. In 2005, the same group [23] summed up the results obtained in 6 patients affected by advanced PD and submitted to unilateral MCS, opposite to the worst clinical side. Chronic electrical stimulation was delivered bipolarly at 2.5–6 V, 150–180 μs, 25–40 Hz, continuously. The global UPDRS score decreased by 42–62%; UPDRS III (evaluating motor performances) decreased by 32–83%. Notably, the patients were evaluated only in the ''on-med'' state. L-Dopa was reduced by 11–33% in 3 and by 70–73% in 2 patients. The symptoms of long term L-Dopa treatment were improved markedly.

In 2003, Pagni commenced, on behalf of the Italian Society of Neurosurgery, a multicenter study to evaluate the efficacy of MCS in advanced PD. The preliminary results of the multicenter study have been published [2, 3, 21]. Twenty-nine patients were treated, confirming that any symptom of PD (tremor, rigor, motor dexterity, bradykinesia, posture and gait, freezing) may improve. In addition, L-Dopa daily dosage could be reduced. On assessment at 6 and 12 months, the mean UPDRS III in ''off-med'' (8 cases) (which was 53 before surgery) decreased by 21 and 13%, respectively; while UPDRS III in ''on-med'' (12 cases) decreased by 34 and 21%, respectively. The stimulation parameters differed in the various centers and were 2–8 V, 60–400 μs, 20–120 Hz, continuously or only during daytime. On MRI, many of these patients had findings of leucoencephalopathy, white matter ischemic foci or cerebral athrophy. Notably, several patients were unresponsive to MCS. Furthermore, an article appeared in 2003 [16], evaluating the efficacy of subdural MCS in 5 patients with refractory Parkinsonism due to multiple systemic atrophy (MSA). The stimulation parameters were 3–3.6 V, 40–90 ms (note: the authors repeatedly wrote milliseconds, but probably they intended to write microseconds), 145–185 Hz. They concluded that ''MCS using these parameters fails to improve the motor disability in MSA. Worsening of motor scores was likely a function of disease progression''.

Author's experience

In 2003, we started a prospective study to evaluate the efficacy of MCS in Parkinson patients. The inclusion criteria were: idiopathic PD, history at least 5 years long, and advanced state (UPDRS in off $\geq$40/180; Hoehn and Yahrs $\geq$3; motor complications: fluctuations and disabling dyskinesias), positive response to L-Dopa, DBS not acceptable by the patient or contraindicated, and patient's ability to give informed consent. The exclusion critera were: history of epilepsy or EEG epileptic activity, alcohol or drug abuse, mental deterioration, psychiatric symptoms, previous basal ganglia surgery, and other major illness. Seven patients met the above mentioned criteria and were submitted to the implantation of an epidural plate electrode (Resume, Medtronic) over the motor cortex controlaterally to the worst clinical side (in 3 cases) or bilaterally (4 cases). The implantation was performed under general totally intravenous anaesthesia (Propofol and Remifentanyl).

The precise location of the plate electrode was verified anatomically and electrophysiologically. We used craniometer landmarks (10–20 EEG system) to draw the central sulcus over the scalp. The anatomical location of the motor strip was confirmed by an MRI with fiducial markers and by neuronavigation. A burr hole was made in front of the central sulcus, medially to the presumed hand motor area. A plate multicontact electrode (Resume, Medtronic) was slipped epidurally, over the motor strip at the hand knob. Then, the position of the electrode was verified neurophysiologically. We used the phase reversal technique to identify the central sulcus. We stimulated the controlateral median nerve at the wrist and recorded from each contact of the strip electrode. A cortical N20 potential was recorded over the sensory cortex and a cortical P20 potential was recorded over the motor cortex; the central sulcus is located between the two contacts showing the phase reversal. The motor mapping was obtained by motor cortex focal anodal stimulation through two adjacent contacts of the same strip electrode with short train of stimuli (5 stimuli, 0.5 ms, ISI 4 ms, 10–30 mA). Muscle responses were recorded from muscle bellies of the controlateral hemibody with needle electrodes. The electrode strip was connected to a totally implantable stimulator (Kinetra, Medtronic). Therapeutic stimulation during the first year was made by the electrode controlateral to the worst clinical side and the parameters were: 120 µs, 80 Hz, 3–4 V (subthreshold for movements and motor or sensory feelings), delivered continuously through contacts 0 and 3. The clinical assessment before implantation and at 1, 3, 6, and 12 months included: UPDRS, finger tapping, walking time, Parkinson's disease quality of life (PDQL) scale, Mini Mental State Evaluation (MMSE), EEG, current oral medications, and adverse events. The clinical evaluation was performed both in the ''off'' and in the ''on'' medication state and the motor assessment was videotaped.

Five (71.4%) patients showed an improvement during MCS, while 2 were unresponsive. At 3 months of follow-up, UPDRS III in ''off-med'' showed a mean decrease of 30.2%, UPDRS III in ''on-med'' decreased by 21.5%, UPDRS IV by 49% and PDQL by 26.7%. The effect of MCS seems to decline with time. At follow-up, 12 months post-operatively, UPDRS III in ''off-med'' decreased by 22%, UPDRS IV by 46%, PDQL by 16.2% (Fig. 1). Hence, it was possible to decrease the drug treatment. Early morning dystonia, walking and freezing, dyskinesias were ameliorated particularly well. The effect of unilateral MCS was bilateral, with no significant difference between the two sides and was evident after 1–2 weeks of stimulation. In a case of accidental switching ''off'' of the stimulator, the patient became aware of something going wrong after 3–4 weeks. After 1 year of unilateral stimulation, 2 patients underwent bilateral MCS. Bilateral stimulation seems to restore the clinical effect (Fig. 2). There were no complications or adverse events; epileptic seizures or EEG epileptic activity did not occur.

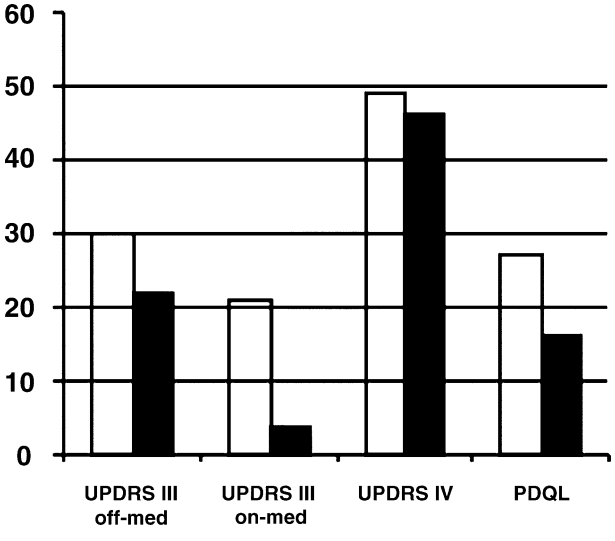

Fig. 1. Mean percentage decrease of UPDRS and PDQL scores after 3 and 12 months of continuous extradural unilateral MCS. At 12 months, the clinical effect of MCS seems to decline slightly. □ 3 months, ■ 12 months

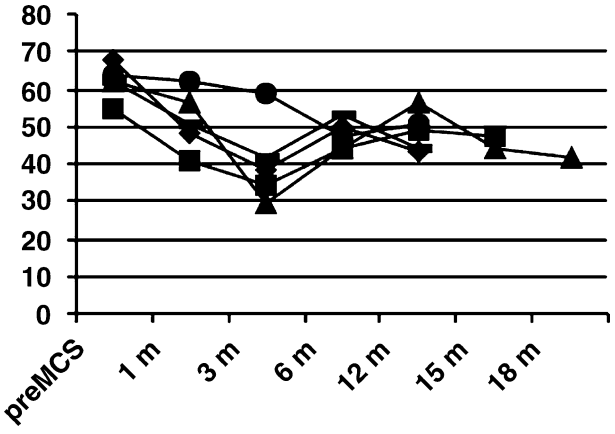

Fig. 2. UPDRS III in ''off-med'' before and following unilateral MCS (until 12 months) and bilateral stimulation (from 12 to 18 months), for each patient. At 6 months, the stimulators of patients a and e were accidentally ''off'' and UPDRS III scores increased. MCS was restarted and the motor effect was restored. At 12 months, patients b and c underwent bilateral stimulation and following this, UPDRS III scores showed a tendency to decrease. —◆— a, —■— b, —▲— c, —●— d, —■— e

Unsettled issues

Currently, the questions regarding the efficacy of MCS are certainly more numerous than the answers. The most important unsettled issues are described below.

Inclusion criteria

On the basis of the present inclusion criteria, we select patients in whom DBS is usually contraindicated such as patients with cerebral atrophy or other cerebral lesions at MRI, and often patients with Parkinsonism or Parkinson plus. This makes it difficult to compare the results of MCS with those obtained by what is currently considered the ''gold standard'' of treatment, i.e. STN DBS. Furthermore, these ''expanded'' inclusion criteria may be responsible for the lack of success of MCS in a few patients. More strict inclusion criteria, such as those applied to DBS, are advisable.

Prognostic factors

Not all patients respond to MCS. This may be due to the rather large inclusion criteria, or the different electrode position and different stimulation parameters. The effect of rTMS may be a predictor of the clinical response to MCS. However, the frequency and the duration of rTMS certainly differ from that used for MCS. In candidates for pain treatment by MCS, a positive response to rTMS encourages the use of MCS, but this is not sufficient for ensuring success; on the other hand, a negative rTMS test does not predict failure of MCS. With regard to the electrode's position and stimulation parameters, the number of patients treated by MCS is still small to allow a statistical analysis.

Surgery

Techniques used to place the epidural cortical electrode may differ in the following areas: general versus local anaesthesia, burr hole versus craniotomy, craniometer landmarks versus neuronavigation with MRI or fMRI. Regardless of the technique used, we believe that a neurophysiological precise localisation is mandatory if we want to know exactly where our electrode is. Our method allows motor mapping under general anaesthesia with a very low incidence of epileptic seizures, i.e. 4–5% compared to the 20–25% of the Penfield's technique. The need for bilateral implantation has still to be demonstrated. In our experience unilateral MCS improves motor performances bilaterally, but bilateral stimulation seems to enhance such an improvement.

Stimulation parameters

The choice of the stimulation parameters is made on an empirical basis, as for all therapeutic neurostimulations. Various groups use different stimulation parameters. The amplitude of stimulation is common for all treated patients and is subthreshold for movements or sensations. In some cases, a low frequency is used, while in other cases a high frequency is selected; the result can be positive in both situations. The clinical effect of unilateral MCS shows a slight decline with time, with the maximum benefit observed at 3 months. At 12 months, two of our patients underwent bilateral MCS, and after this the amelioration of symptoms became more pronounced. Usually, the stimulation is delivered continuously. The slight decline in the clinical benefit may be due to habituation of the cortex. A change of the type of stimulation may restore the previous effect. If this is the case, alternate stimulation, i.e. right side or left side, may be a solution.

MCS vs. DBS

We cannot compare the results obtained with the 2 procedures, because of the small number of patients treated by MCS and because of the different selection criteria. Nevertheless, in such a comparison, we should take into consideration not only the clinical improvement but also the complication rate and the side effects of the two techniques.

Mechanisms

The mechanisms of MCS may only be a matter of speculation. In animals, direct cortical stimulation, activates the neuronal cell as well as very diffuse complex systems of interneurons [27]. The motor cortex is connected to the basal ganglia via an indirect corticostriatal pathway and through a direct cortico-subthalamic pathway. MCS may exert its effect modulating the STN directly or through the loop cortex-striatum- lateral globus pallidus-STN. MCS may also modulate the activity of SMA. Furthermore, MCS may activate the so called ''suppressor cortical system'' [11].

Conclusions

We believe that MCS may have a place in the treatment of Parkinson's disease. A large multicenter, randomized, double blind study may answer many of the existing questions and settle many of the unsettled issues.

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References

1. Afsharpour S (1985) Topographical projection of the cerebral cortex to the subthalamic nucleus. J Comp Neurol 236: 14–28
2. Bentivoglio AR, Cavallo MA, Cioni B, Contarino F, Eleopra R, Lavano A, Mazzone P, Meglio M, Signorelli CD, Sturiale C, Valzania F, Zeme S, Zenga F, Pagni CA (2005) Motor cortex stimulation for movement disorders In: Meglio M, Krames E (eds) Proceedings of the 7th Meeting of the International Neuromodulation Society. Medimond, Bologna, pp 5–14
3. Bentivoglio AR, Cavallo MA, Cioni B, Contarino F, Eleopra R, Lavano A, Mazzone P, Meglio M, Signorelli CD, Sturiale C, Valzania F, Zeme S, Zenga F, Pagni CA (2005) Motor cortex stimulation for movement disorders In: Meglio M (ed) Proceedings of the 14th Meeting of the World Society for Stereotactic and Functional Neurosurgery. Medimond, Bologna, pp 89–97
4. Brown JA, Lutsep H, Cramer SC, Weinand M (2003) Motor cortex stimulation for enhancement of recovery after stroke: case report. Neurol Res 25: 815–818
5. Brown P (2003) Oscillatory nature of human basal ganglia activity. Relationship to the pathophysiology of Parkinson's disease. Mov Disord 18: 357–363
6. Bucy PC (1945) Special article: the neural mechanisms of athetosis and tremor. Ann Surg 122: 943–954
7. Canavero S, Paolotti R (2000) Extradural motor cortex stimulation for advanced Parkinson's disease. Mov Disord 15: 169–171
8. Canavero S, Paolotti R, Bonincalzi V, Castellano G, Greco-Crasto S, Rizzo L, Davini O, Zenga F, Ragazzi P (2002) Extradural motor cortex stimulation for advanced Parkinson's disease: report of two cases. J Neurosurg 97: 1208–1211
9. Devos D, Labyt E, Derambure P, Bourriez JL, Cassim F, Reyns N, Blond S, Guieu JD, Destec A, Defevre L (2004) Subthalamic nucleus stimulation modulates motor cortex oscillatory activity in Parkinson's disease. Brain 127: 408–419
10. Drouot X, Oshino S, Jarraya B, Besret L, Kishima H, Dauquet J, Lefaucheur JP, Dolle F, Condè F, *et al* (2004) Functional recovery in a primate model of Parkinson's disease following motor cortex stimulation. Neuron 44: 769–778
11. Dusser de Barenne JG, McCulloch WS (1941) Suppression of motor responses obtained from a area 4 by stimulation of area 4s. J Neurophysiol 4: 311–323
12. Franzini A, Ferroli P, Servello D, Broggi G (2000) Reversal of thalamic hand syndrome by long term motor cortex stimulation. J Neurosurg 94: 873–875
13. Ikeguci M, Touge T, Nashiyama Y, Takeuchi H, Kurijama S, Ohkawa M (2003) Effects of successive repetitive transcranial magnetic stimulation on motor performances and brain perfusion in idiopathic Parkinson's disease. J Neurol Sci 209: 41–46
14. Katayama Y, Oshima H, Fukaya C, Kawamata T, Yamamoto T (2002) Control of post-stroke movement disorders using chronic motor cortex stimulation. Acta Neurochir Suppl 79: 89–92
15. Khedr EM, Farweez HM, Islam H (2003) Therapeutic effect of repetitive transcranial magnetic stimulation on motor function in Parkinson's disease patients. Eur J Neurol 10: 567–572
16. Kleiner-Fisman G, Fisman DN, Kahn FI, Sime E, Lozano A, Lang AE (2003) Motor cortical stimulation for Parkinsonism in multiple systemic atrophy. Arch Neurol 60: 1554–1558
17. Lefaucheur JP, Drouot X, Von Raison F, Menard-Lefaucheur I, Cesaro P, Nguyen JP (2004) Improvement of motor performances and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease. Clin Neurophysiol 115: 2530–2541
18. Mally J, Stone TW (1999) Improvement in Parkinsonian symptoms after repetitive transcranial magnetic stimulation. J Neurol Sci 162: 179–184
19. Nambu A, Tokuno H, Hamada I, Kita H, Imanishi M, Akazawa T, Ikeuki Y, Hasegawa N (2000) Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. J Neurophysiol 84: 289–300
20. Ohnishi T, Hayashi T, Okabe S, Nonaka K, Matsuda H, Imabayashi E, Watabe H, Miyake Y, Ogawa M, Teramoto N, Ohta Y, Ejima N, Sawada T, Ugawa Y (2004) Endogenous dopamine release induced by repetitive transcranial magnetic stimulation over the primary motor cortex: an (11C) raclopride positron emission tomography study in anesthetized macaque monkeys. Biol Psychiatry 55: 484–489
21. Pagni CA, Altibrandi MG, Bentivoglio AR, Caruso G, Cioni B, Contarino F, Insola A, Lavano A, Maina R, Mazzone P, Signorelli CD, Sturiale C, Valzania F, Zeme S, Zenga F (2005) Extradural motor cortex stimulation for Parkinsin's disease: history and first results by the study group of the Italian Neurosurgical Society. Acta Neurochir Suppl 93: 113–119
22. Pagni CA, Zeme S, Zenga F, Maina R, Mastropietro A, Papurello D (2003) Further experience with extradural motor cortex stimulation for treatment of advanced Parkinson's diseases. Report of 3 new cases. J Neurosurg Sci 47: 189–193
23. Pagni CA, Zeme S, Zenga F, Maina R (2005) Extradural motor cortex stimulation in advanced Parkinson's disease: the Turin experience. Neurosurg 57 ONS Suppl 3: ONS–402
24. Parent A, Hazrati LN (1995) Functional anatomy of the basal ganglia. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Rev 20: 128–154

25. Pascual-Leon A, Valls-Sole J, Brasil-Neto JP, Cammarota A, Grafman J, Hallett M (1994) Akinesia in Parkinson's disease. Effects of subthreshold ripetitive transcranial megnetic stimulation of the motor cortex. Neurology 44: 892–898
26. Payoux F, Remy P, Damier P, Miloudi M, Loubinoux J, Pidoux B, Gaura V, Rascol O, Samson Y, Agid Y (2004) Subthalamic nucleus stimulation reduces abnormal motor cortical overactivity in Parkinson's disease. Arch Neurol 61: 1307–1313
27. Patton HD, Amassian VE (1954) Single and multiple unit analysis of cortical stage of pyramidal tract activation. J Neurophysiol 17: 345–363
28. Ridding MC, Inzelberg R, Rothwell JC (1995) Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann Neurol 37: 181–188
29. Shimamoto H, Takasaki K, Shigemori M, Imaizumi T, Ayabe M, Shoji H (2001) Therapeutic effect and mechanism of repetitive transcranial magnetic stimulation in Parkinson's disease. J Neurol 248 Suppl 3: 48–52
30. Siebner HR, Mentschel C, Auer C, Conrad B (1999) Repetitive transcranial stimulation has a beneficial effect on bradykinesia in Parkinson's disease. Neuroreport 10: 589–594
31. Strafella A, Paus T, Fraraccio M, Dagher A (2003) Striatal Dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 126: 2609–2615
32. Strafella A, Vanderwerf Y, Sadikot AF (2004) Transcranial magnetic stimulation of the human motor cortex influences the neural activity of subthalamic nucleus. Eur J Neurosci 20: 2245–2249
33. Woolsey CN, Erickson T, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg 51: 476–506

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Stereotactic stimulation of the anterior lobe of the cerebellum in cerebral palsy from a suboccipital approach

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Summary

The anatomical connections of the anterior lobe of the cerebellum with the reticular formation in the brainstem, upper motor neurons and the limbic system, as well as the results of experimental and clinical observations indicate that this region is a proper area for modulation of certain types of central motor disorders but also of limbic functions. Through a direct stereotacticaly suboccipital approach electrodes were introduced into the anterior lobe of the cerebellum in four patients (3 females and one male, 24, 29, 45 and 19 years old, respectively) suffering from cerebral palsy and being confined to a wheelchair with severe spastic choreoathetoid movements, with minimal hand function, but in good mental state. After a period of test stimulation (up to 10 days), the pulse generators were implanted and chronic high-frequency stimulation was applied (for 37, 58, 9 and 32 months, respectively). In agreement with our previous experience (transtentorial approach in 30 patients), noticeable improvements in spasticity were immediate and a gradual reduction in choreoatetoid movements was observed in the following days to weeks. Improvements in speech, swallowing, respiration, posture, ambulation, and mood states were combined with development of new motor skills. Caution with the proper positioning of the electrode in the target and the selection of optimal program for stimulation are of paramount importance.

Keywords: Neuromodulation; deep brain stimulation; cerebellum; spasticity; dyskinesia; cerebral palsy.

Introduction

Cooper *et al.* [1] was the first, who implanted an electrode array and applied chronic stimulation to the cortex of the anterior lobe of the cerebellum in patients suffering from cerebral palsy in order to reduce muscular hypertonia. Various degrees of effectiveness of this method have been reported [2, 11]. The specific anatomical and functional arrangement of the anterior lobe of the cerebellum can contribute to the unpredictability of this procedure [7]. The anterior lobe of the cerebellum has precise spatial rostrocaudal organization of afferent and efferent pathways into cortical and subcortical zones, where each particular zone has specific and identifiable functional correlates with specific afferent and efferent connections. The cortical efferents, using criteria of fiber diameter in subcortical white matter, were divided by Voogd [12] to at least seven ipsilateral zones, from midline – A, B (vermal), C1, C2, C3 (paravermal), D1, D2 (hemispheral). Each zone includes a specific deep cerebellar nucleus except zone B, from where fibers bypass cerebellar nuclei and enter the vestibular complex. Zone A contains the nucleus fastigii, zone C1 and C3 the emboliform nucleus, zone C2 the globose nucleus and zones D1, D2 the dentate nucleus.

The afferent fibers are arranged in a similar way [6]. The climbing fibers of the medial accessory olive project as follows: the caudal part project into the cortical zone A and the fastigial nucleus, and the rostral part in the zone C2 and the globose nucleus. The caudal part of the dorsal accessory nucleus sends fibers into zone B and the lateral vestibular nucleus, but the rostral part to zones C1 and C3 and the emboliform nucleus. Principal olivary nucleus projects into zones D1, D2 and the dentate nucleus. Spinocerebellar fibers terminate specifically in sagitally oriented zones either differentially distributed within particular zones or coexist with input from other sources. Detailed analyses of spinoolivocerebellar pathways by Oscarsson [10] identified 9 ipsilateral sagital zones in the anterior lobe. Zones A, C1 and C3 received input from the ipsilateral limbs (hind limb rostrally, forelimb caudally), while zones B and C2 bilaterally from both sides. All these sagitally oriented zones in rostral portions of the anterior lobe are becoming very narrow and converge toward the midline.

The anterior lobe of cerebellum is situated rostrally to the primary fissure. The culmen and the anterior quadrangular lobule face the tentorium, but the rostral part of culmen and the lobulus centralis anteriorly face towards the inferior colliculi. This specific organization of the cerebellum into zones and the morphological configuration of the anterior lobe allow activation of one set of points on cerebellar cortex to elicit a set of responses while activation of an immediately adjacent area may produce no response, or a modified version of the first response or a completely different, possibly antagonistic response as it was stressed by Haines [7]. From this point of view, the optimal placement of an array of electrodes to the cortex of the anterior lobe could be questionable, especially if there are no facilities for intraoperative neurophysiological evaluation of the position of the electrode. About 15% of the cortex is exposed to the outer surface, whereas 85% faces the sulcal surface between the folia and is not accessible for direct cortical stimulation. It is crucial which zones of the anterior lobe are activated during electrical stimulation. The stereotactic method enables precise positioning of the electrode into deep regions of the anterior lobe; according to our experience, it allows intraoperative verification of proper position of the electrode by means of electrical stimulation.

Materials and methods

Our previous stereotactic approach to the deep structures of the anterior lobe of the cerebellum was transtentorial from the occipitoparietal region. In order to do chronic stimulation, we have used the radiofrequency-linked system TESLA LSP 330. The coil of the electrode was placed over a burr hole which excluded the application of the system in the suboccipital region. During effective stimulation, a reduction of spasticity and an improvement in motor performance was observed in 30 patients suffering from cerebral palsy [3, 4], but, in general, malfunction of the radiofrequency-linked system occurred within 16 months. The Medtronic system for deep brain stimulation (DBS) allowed us to implant the electrodes directly to the anterior lobe of the cerebellum through a suboccipital approach [5]. We applied this system in 4 patients suffering from cerebral palsy (3 females and one male, 24, 29, 45, and 19 years old, respectively), who were confined to a wheelchair, being severely spastic with minimal hand function, but in good mental state. The electrode implantation was unilateral in three patients and bilateral in one patient. High frequency stimulation (HFS) was applied for 37, 58, 9, and 32 months, respectively.

Surgical procedure

A few days before surgery, T1- and T2-weighted magnetic resonance imaging (MRI) sequences in axial, sagittal and coronal sections are obtained according to the sterotactic protocol. Under short-acting opioids in combination with propofol, the Riechert-Mundinger sterotactic frame in the negative position is placed on the patient's head and CT with contrast is performed. After fusion of preoperative MRI and intraoperative CT, the target is calculated. In the direct suboccipital approach, the target is defined to a point 8 mm (or ¾ of the height of 4th ventricle) rostral from the fastigium, parallel to the floor of the 4th ventricle in the midline if one electrode is used, and 1 mm from the midline for bilateral insertion of electrodes. The target was set after our previous assessment of the optimal positions of the electrode in the lobus anterior of the cerebellum. The entry burr hole is localized in the lateral suboccipital area 1 cm below the transverse and 1 cm medially to the sigmoid sinuses.

The intraoperative stimulation test is performed using the quadripolar electrode model 3387 or two electrodes model 3389 (Medtronic) for bilateral stimulation. The monopolar stimulation to the deepest contact of electrode (intracranially negative polarity) at frequency 200 Hz, pulse width 0.5 ms and voltage from 0.5 to 4.0 V in steps of progressively increasing voltage (usually by 0.5 V) is given with sudden application of current (no soft start) to induce a motor response, i.e. a jerk in the muscles mostly affected by the disease. According to our experience [3, 4], if the motor response is obtained during the test, the electrode is in position from where the effective chronic stimulation for the treatment of the disabling motor symptoms can be achieved. The response is evaluated also 2 and 4 mm in front and behind the target. If motor response to stimulation is present, the electrode is fixed in the burr hole with the cap, fluoroscopy is used to evaluate the position of electrode. The electrode is temporarily connected to a transcutaneous extension and externalised in the frontal region for further clinical and neurophysiological examination. Postoperative CT images with the frame fixed are obtained.

The monopolar stimulation of any contact of implanted electrodes and their bipolar combinations are performed during the test period. The rectangular stimuli at frequency of 200 Hz, 0.5 ms width, in progressively increasing voltage, are gradually applied at any contact of electrodes for few seconds. The level of voltage at which the motor jerk is achieved is called the "threshold level". The continuous application of the stimulation at slightly higher voltage (0.2–0.6 V) transiently aggravates the pathological postural pattern and is accompanied with the patient's intense feeling of pleasure. A higher voltage of stimulation causes an overall increase in muscular tone and the patient feels profound, unpleasant fear. At the beginning of stimulation, the muscular response is more pronounced at the side of electrode, but at a higher

voltage the muscle response becomes bilateral. Just bellow the threshold level of stimulation, a transient feeling of pleasure is followed by immediate relaxation and reduction of spasticity. The effect of relaxation is intensive for approximately 10–15 minutes, then is diminishing but the patient is still aware of the stimulation (slight tingling in the legs, and eventually in the upper extremity, more pronounced at the side of stimulation). The decrease of spasticity persists approximately for another 2–6 hours. Then it is necessary to repeat the stimulation. For chronic stimulation, the parameters are chosen in order to reduce spasticity but also to avoid effects on motor performance. At the beginning of stimulation, higher voltage can cause a strong decrease of muscular tone associated with imbalance. In our experience, a lower voltage that does not induce relaxation is ineffective for chronic stimulation. The parameters of stimulation must be set precisely and re-evaluated every 3–6 months. The phenomenon of adaptation may require a slight increase in the voltage of stimulation. The patient is aware of the stimulation and feels it when it starts (slight tingling and relaxation). The interruption of stimulation for 2–3 weeks may be required (after a period of 1–3 years), if the voltage for receiving effective stimulation is too high.

After the test period (approximately one week), the internal pulse generator (IPG) (Soletra or Kinetra models, Medtronic) is implanted infraclavicularly at a second stage. After implantation of IPG, the parameters for chronic stimulation are set as follows: frequency at 185–200 Hz, pulse width at 0.210 ms and voltage is individualized according to the threshold level at 0.5–2.5 V to evoke relaxation and program is set at cycling mode, usually with 15–20 min ON time and 2–6 hours OFF time. When the Kinetra model neurostimulator is implanted for two active DBS electrodes, the dual-program pulses are delivered alternately.

Illustrative case

A female patient suffering from cerebral palsy developed severe spastic quadruparesis and involuntary movements affecting the neck and the upper extremities (choreoathetosis more pronounced on the left side). She underwent DBS in the anterior lobe by a radiofrequency-linked TESLA 330 system at the age of 16 years. During application of stimulation, the spasticity and hyperkinesias were reduced, but a malfunction of the system after 12 months required the removal of the electrode. One year later, stereotactic thalamotomy ((ventral intermedius (VIM) and ventral caudalis posterior (VCP)) thalamic nuclei and centrum medianum) at the right side partially reduced the severe choreoathetosis of the left upper extremity. Because of progression of the disabling spasticity and involuntary movements, the patient demanded to repeat the cerebellar DBS.

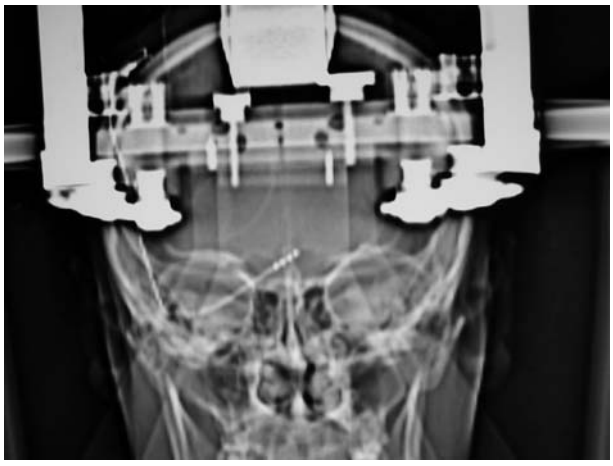

Fig. 1. AP skull X-ray; the electrode in the anterior lobe of the cerebellum was implanted from the right side

At the age of 29, the Medtronic system was implanted through a direct suboccipital approach on the right side. During surgery, the stereotactic frame was fixed, and the quadripolar electrode model 3387 was inserted and the intraoperative stimulation test was completed. The first contact of the electrode (deepest pole) was situated at the opposite side, the second was in the midline, the third and the fourth on the right (Fig. 1). The electrode was externalised. On the 3rd postoperative day, test stimulation was performed to assess the acute effects of monopolar and bipolar stimulation (frequency: 185 Hz, pulse width: 0.210 ms). When monopolar stimulation was applied to pole 0 (negative, the deepest contact on the left) the response was observed at 1.7 V in the left lower limb; further increase of voltage (2.1 V) induced bilateral aggravation of an abnormal motor pattern of the patient with rotation of the head and upper part of the body homolaterally to the side of stimulation, i.e. to the left (Fig. 2a). A similar response, starting at 2.0 V, but without deviation of the head developed when stimulation was applied to pole 1 localized in midline (Fig. 2b). Following stimulation on the right side, at pole 2 (1.7 V) and pole 3 (2.0 V), the muscular response began at the right lower extremity and at 2.3 V the head was turned to the right (Fig. 2c). An even higher voltage of stimulation (2.8 V) was associated with intense feeling of fear. The patient asked not to repeat such strong stimulation. However, the voltage just above the threshold level

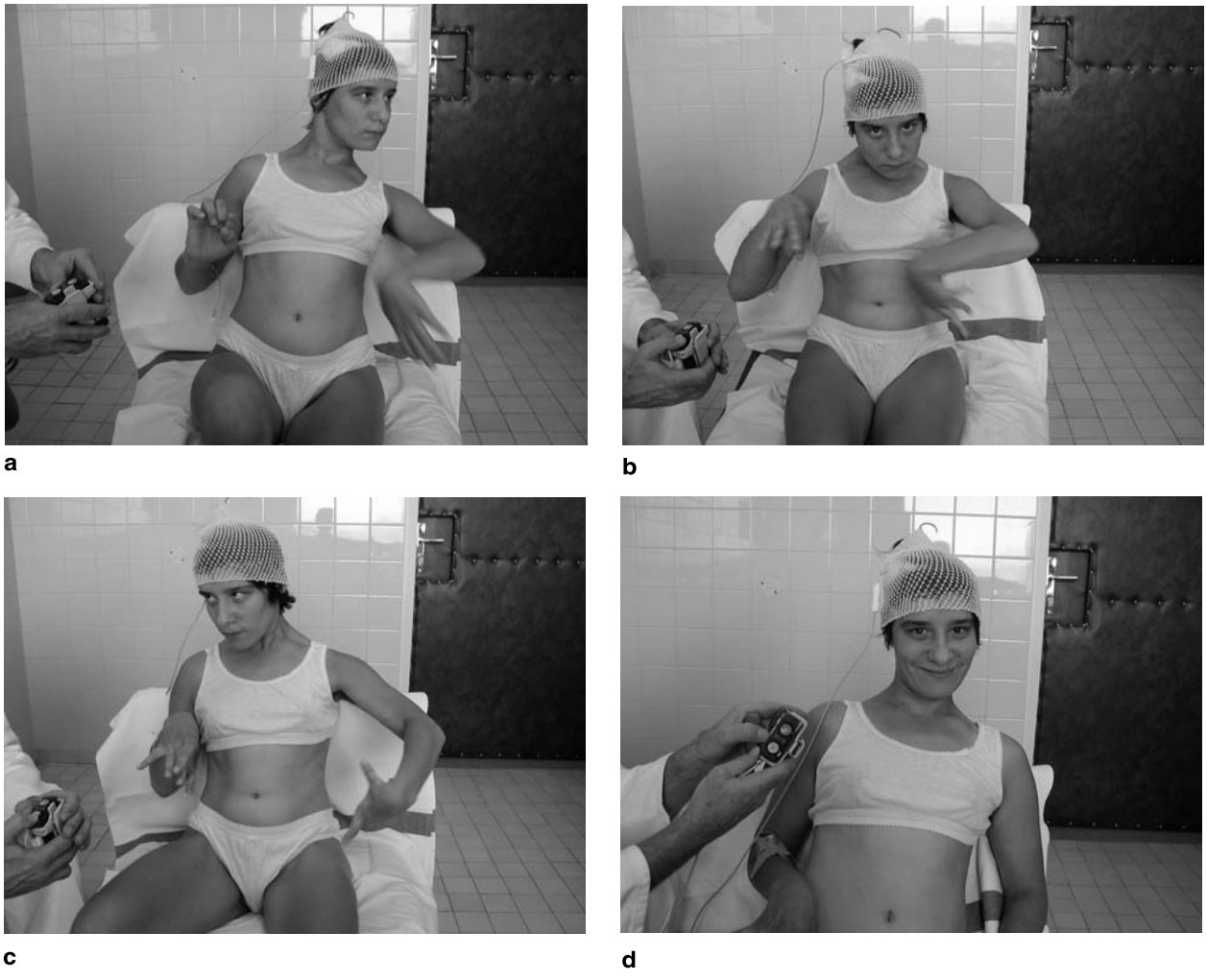

Fig. 2. Induced aggravation of the abnormal postural pattern by monopolar moderate overstimulation (patient Fig. 1) applied to pole 0 – left side (a), to pole 1 – midline (b) and to pole 2 – right side (c). Slight overstimulation induced feeling of pleasure and relaxation (d)

(0.1–0.2) was appreciated very much by the patient; she reported intense feelings of pleasure (Fig. 2d). Just below the threshold level, a transient feeling of pleasure was associated with overall relaxation of the patient and reduction of spasticity. Optimal set up for the bipolar stimulation was pole 3 negative, pole 0 positive and the threshold level at 1.5 V. We evaluated also effectiveness of the frequency of stimulation in this setting. Up to 70 Hz, the patient reported no response, at 80–90 Hz slight tingling in the whole body excluding the head, at 100 Hz also a motor response at the left lower limb, which at 185 Hz was bilateral and subsequently was followed by a decrease of the hypertonia, persisting for another 15 minutes. After having the stimulator switched off symptoms did not return to the baseline. The effect was long lasting, enduring up to 7 hours after HFS was stopped. On the 8th day after the stereotactic operation, an IPG Soletra (model 7426, Medtronic) was implanted infraclavicularly under general anesthesia. The parameters of stimulation were set: 0 pole positive, 3 pole negative, amplitude 1.7 V, pulse width 0.210 ms, frequency 185 Hz, 20 minutes ON, 4 hours OFF.

Marked decrease in spasticity and choreoathetosis and improvements in speech and mood were observed after a few weeks. These were followed by development of new hand skills (she began to feed and dress herself) and improved ambulation (she is able to walk without crutches at home, before she was just crawling), which became appreciable after months of therapeutic HFS. The evaluations were made every 3–6 months; the voltage was progressively increased to the present 2.6 V and OFF period was reduced to 3 hours to achieve the optimal effect of stimulation. She is doing well 3 years after DBS.

Results

The benefit was observed in all 4 patients undergoing chronic HFS treatment through a direct suboccipital approach to the anterior lobe of the cerebellum by the Medtronic totally implantable DBS system. The noticeable improvement on spasticity was immediate, bilateral and more evident in the limbs on the stimulated side. The gradual reduction in athetoid movements was observed in the following days to weeks. Unilateral high-frequency stimulation (HFS) has bilateral effects, but bilateral stimulation is more efficient. Improvements in speech, swallowing, respiration, posture, ambulation, and mood were combined with decrease of muscle tone, spasms and primitive reflexes. Motor skill progress was observed after few months of HFS. There is a need to increase the voltage (0.2–0.5 V) usually after 6–9 months of chronic stimulation to keep the treatment efficient or eventually to temporarily interrupt the stimulation (this was done in one patient after 42 months for 2 weeks). If the patient is not aware of the stimulation, the HFS is not likely to be effective and any achieved effects will gradually subside.

Discussion

A thoroughly documented review of chronic cerebellar stimulation applied to the superio-medial cortex in patients suffering from cerebral palsy has demonstrated the effectiveness of this method [2]. Instead of cortical stimulation, however, we applied stereotactic HFS to the subcortical structures of the anterior lobe taking into account its specific anatomical and functional arrangement. In this target, it is possible immediately, during test stimulation to demonstrate involvement of neural circuits that could modify the symptoms of patients with cerebral palsy. Induced changes in muscular tone, posture, emotions (pleasure, fear), and autonomic responses are dependent on the quality and quantity of electrical stimuli delivered to the target. The therapeutic window of effective parameters is narrow and must be set up individually. The stereotactic method offers the option to do so. The immediate and generalized changes in muscular tone can be explained by the strong connections of the anterior lobe of the cerebellum with the pontine and medullary reticular formation, and the vestibular system, which have significant role in maintenance of posture, control of muscular tone and reflex activity [9]. HFS in the anterior lobe of cerebellum has been shown to have widespread effects on various symptoms including spasticity (reduced), dyskinesias, speech (improved), respiration, attention, mood, and wakefulness. This reflects its powerful modulation capacity and indicates that stimulation of the anterior lobe of the cerebellum deserves further attention from neuroscientists and neurosurgeons. HFS is safe and reproducible and has the advantage that its effects can be modulated in accordance with the patient's needs and be evaluated immediately and objectively.

Conclusion

Chronic stereotactic stimulation of the anterior lobe of the cerebellum seems to be an effective and safe treatment for patients with cerebral palsy; it reduces spasticity and dyskinesias and improves activities of daily living. Caution with proper positioning of the electrode and selection of the optimal program for stimulation are necessary.

References

1. Cooper IS, Riklan M, Amin I (1976) Chronic cerebellar stimulation in cerebral palsy. Neurology 26: 744–753
2. Davis R (2000) Cerebellar stimulation for cerebral palsy spasticity, function, and seizures. Arch Med Res 31: 290–299
3. Galanda M, Zoltan O (1987) Motor and psychological responses to deep cerebellar stimulation in cerebral palsy (Correlation with organization of cerebellum into zones). Acta Neurochir Suppl 39: 129–131
4. Galanda M, Horvath S (1997) Different effect of chronic electrical stimulation of the region of the superior cerebellar peduncle and the nucleus ventralis intermedius of the thalamus in the treatment of movement disorders. Stereotact Funct Neurosurg 69: 116–120
5. Galanda M, Horvath S (2003) Effect of stereotactic high-frequency stimulation in the anterior lobe of the cerebellum in cerebral palsy: a new suboccipital approach. Stereotact Funct Neurosurg 80: 102–107
6. Groenewegen HJ, Voogd J (1977) The parasagittal zonation within the olivocerebellar projection. I. Climbing fiber distribution in the vermis of cat cerebellum. J Comp Neurol 174: 417–488
7. Haines DE (1981) Zones in the cerebellar cortex. Their organization and potential relevance to cerebellar stimulation. J Neurosurg 55: 254–264
8. Heath RG (1977) Modulation of emotion with a brain pacemaker. Treatment for intractable psychiatric illness. J Nerv Ment Dis 165: 300–317
9. Moruzzi G (1950) Effects at different frequencies of cerebellar stimulation upon postural tonus and myotatic reflexes. EEG Clin Neurophys 2: 463
10. Oscarsson O (1979) Functional units of the cerebellum-sagittal zones and microzones. Trends Neurosci 2: 143–145
11. Penn RD, Gottlieb GL, Agarwal GC (1978) Cerebellar stimulation in man. Quantitative changes in spasticity. J Neurosurg 48: 779–786
12. Voogd J (1969) The importance of fiber connections in the comparative anatomy of the mammalian cerebellum. In: Llinas R (ed) Neurobiology of cerebellar evolution and development. AMA Education and Research Foundation, Chicago, pp 493–514

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Electrical stimulation devices in the treatment of epilepsy

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Summary

Over the last ten years there has been a progressively increasing interest in the research and clinical application of implantable electrical brain stimulation devices in the treatment of drug-resistant epilepsy. The concept is not new, but the efforts were strengthened and accelerated after the efficacy of vagus nerve stimulation in controlling epilepsy was first demonstrated in the early 1990s and gained subsequently the approval of the USA Food and Drug Administration in 1997. This chapter reviews the progress made in this field. Special emphasis is given to the most important available evidence from animal and human studies, the neuroanatomical pathways and the role of the relevant neurotransmitters, the stimulation devices and the significance of correct programming of the stimulation parameters. The chapter also examines the antiepileptic efficacy of stimulation in all the known targets including vagus nerve, cerebellum, thalamus, subthalamic nucleus, locus ceruleus, and epileptogenic cortex. On the basis of the current evidence, the future directions of this exciting field are described.

Keywords: Neuromodulation; epilepsy; seizures; electrical stimulation; implanted device; review.

Introduction

Over the past decade, there has been a proliferation of medications for the treatment of seizures. When seizures do not respond well to medications, options such as epilepsy surgery or the ketogenic diet may be considered. Currently, there is only one electrical stimulation device that has been approved by the Food and Drug Administration (FDA) for the treatment of medication-resistant seizures. Other devices have been studied, and several are currently under investigation in randomized, multicenter trials. Much still has to be learned about these devices. However, in combination with the greater number of other therapies, these devices offer the promise of an improved quality of life for those with difficult-to-treat seizures.

Types of epilepsy

There are many causes of seizures, a variety of seizure types (Table 1), and a long list of epilepsy syndrome diagnoses. Seizures are divided into two main categories: those that are *partial* in onset, and those that are *generalized* in onset. Correct identification of the types of seizures, through a careful history, examination, and with help from medical testing, will allow the physician to select treatment options which are most likely to be of benefit (Table 2). For instance, virtually all of the available medications have been shown to be effective in the treatment of partial seizures. A smaller number is effective against generalized seizures. Epilepsy surgery is more effective in certain partial epilepsies, but may be also considered for specific types of generalized seizures. The vagus nerve stimulator has been best studied as a treatment for partial seizures; however, there is evidence to suggest that it works for generalized seizures as well.

The treatment of epilepsy: an overview

In all types of epilepsy, the goal of treatment is to improve the person's quality of life. Though simple in concept, there are very few studies which use *quality of life* as the primary outcome measure. Instead, endpoints which are easier-to-measure, such as seizure frequency, are used. For a long time, it has been assumed that if the treatment leads to fewer seizures or seizure freedom, the person would automatically experience an improved quality of life. Recent studies have shown, however, that this is not the case. In addition to seizure control, there must also be an elimination of adverse events or side effects. Notably, Gilliam *et al.* showed that aggressive

Table 1. *Seizure types*

Seizures with partial onset
– Simple partial seizures
– Complex partial seizures
– Secondarily generalized tonic-clonic seizures
Seizures with generalized onset
– Absence seizures (typical and atypical)
– Myoclonic seizures
– Tonic seizures
– Clonic seizures
– Atonic seizures
– Generalized tonic-clonic seizures

Table 2. *Epilepsy syndromes: usual features that can be found by history (a description of the seizure types that the person experiences), physical examination, and the results of commonly perfomed medical testing*

Idiopathic generalized epilepsy	*Idiopathic localization related epilepsy*
Generalized from onset tonic-clonic, myoclonic, and absence seizures	Partial seizures with characteristic features, secondarily generalized tonic-clonic seizures
Neurological exam is normal	Neurological exam is normal
Intellect is normal	Intellect is normal
MRI is normal	MRI is normal
EEG has a normal background	EEG has a normal background
EEG may show generalized epileptiform discharges (typically $\geq$3 Hz), and a photoparoxysmal response	EEG may show characteristic focal epileptiform discharges, and a photoparoxysmal response
Symptomatic generalized epilepsy	*Symptomatic localization related epilepsy*
Generalized from onset tonic-clonic, atonic, tonic, clonic, myoclonic, atypical absence	Partial seizure with characteristic features, secondarily generalized tonic-clonic seizures
Neurological exam is abnormal	Neurological exam is abnormal
Intellect is impaired	Intellect may be impaired
MRI is often abnormal	MRI is often abnormal
EEG background is diffusely slowed	EEG background shows focal slowing
EEG may show multifocal and generalized epileptiform discharges	EEG may show focal epileptiform discharges

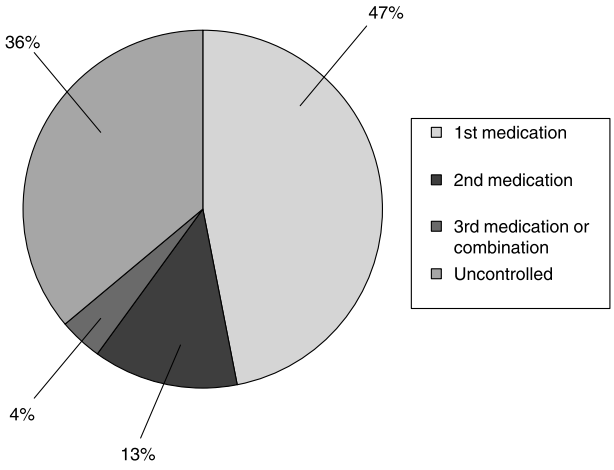

Fig. 1. Percentage of newly diagnosed people with epilepsy who respond to medical therapy

treatment of *comorbid conditions* such as depression directly improves the person's quality of life. In fact, in his study, persons who experienced *little or no change* in their seizure frequency reported a significantly improved quality of life when their depression was adequately addressed [30, 31, 43]. When the diagnosis of epilepsy has been made, a single medicine (*monotherapy*) is usually selected first. The choice of medicine may be based on several factors; however, the most important factor in selecting an optimal therapy is the correct identification of the patient's seizure type or epilepsy syndrome. When the first medication fails to control the seizures or causes side effects, a second medication may be tried. Following this, the physician may elect to try another medication or begin a combination of therapies (*polytherapy*) [45, 46]. If polytherapy fails, the chance that any combination of medications will stop the seizures is 1–4% [51]. When seizures are unlikely to respond to medications, they are referred to as *refractory* or *intractable*. It is now known that up to 36% of people have seizures that will not respond to medication(s) (Fig. 1) [51]. When seizures are identified as refractory, non-medical therapies should be considered [45, 46].

Epilepsy surgery has become a widely used treatment for refractory partial epilepsies (also called *localization related epilepsy*). The goal of surgery is simple: to remove the seizure-causing region of the brain (epileptogenic region or epileptogenic zone) thereby stopping the seizures [22]. This treatment is very effective in certain epilepsy syndromes such as mesial temporal sclerosis. In this condition, the chance of becoming seizure-free is 75–85%. However, epilepsy surgery is not always the answer for intractable seizures. Some people experience seizures which arise from more than one brain location. Others may have seizures that start in regions of the brain which are important to everyday life (*eloquent cortex*), such as within the language area or motor area. In these instances, surgery would result in permanent neurological deficits, such as the inability to communicate or move, and hence, would not be considered a reasonable option. Other epilepsy syndromes cause seizures which are *generalized* at onset. In other words, there is no focal epileptogenic region which can be resected. In the generalized epilepsies, corpus callosotomy, a sur-

gery which divides the major connection between the cerebral hemispheres, may be considered. This type of surgery may reduce the occurrence of certain injurious seizure types, such as tonic or atonic [28]. For reasons that are unclear, corpus callosotomy produces freedom from seizures in 5–10% [28, 44].

In 1997, a new option emerged when the Food and Drug Administration approved the use of the first device for the treatment of refractory partial epilepsy, the vagus nerve stimulator (VNS) [42, 52, 53]. Since its approval, VNS has been applied to generalized forms of epilepsy as well, including refractory idiopathic generalized epilepsy syndromes [8, 67]. In addition, it has been used in certain symptomatic generalized epilepsy syndromes as well [8, 27, 42, 44]. Finally, although not approved for use in children, there is growing evidence of its effectiveness and tolerability in this population [38, 65]. Generally considered a palliative treatment, as it is used in combination with medication, we now better understand that it has effectiveness in the treatment of depression as well [59, 66]. In other words, if treating epilepsy and its comorbidities is important to improving quality of life, this therapy may be an ideal adjunct in someone who has *both* refractory seizures *and* depression. Although VNS was the first to be approved, it is not the first or only device to be studied for the treatment of epilepsy. Many investigators have been interested in the possibility of using neural stimulators to treat seizures. Several sites for stimulation have been studied in both animals and humans. Some of the proposed sites include the cerebellum [9, 12–14, 16–18, 37, 82], thalamus [7, 10, 15, 25, 34, 41, 47, 62, 79, 84, 85], locus coeruleus [23], and subthalamic nucleus [3, 54, 86], and more recently, direct stimulation of the cerebral cortex [48–50, 68]. Compared to all proposed sites, we have gained the greatest experience with stimulation of the vagus nerve with over 30,000 patients to date. Despite the experience with these therapies, there remain many unanswered questions regarding the use of stimulation devices in the treatment of epilepsy: is there one site that affords optimal seizure control? What frequency or duration of stimulation is needed? Does continuous stimulation work better than intermittent stimulation?

The basics: neuroanatomy

Introduction

In order to understand the concept behind neural stimulation, it is important to study the substrate of stimulation: the brain. By definition, seizures are abnormal organized electrochemical events that involve the cerebral cortex. However, the cerebral cortex itself is complex. In addition, it is intimately connected to collections of neurons (nuclei) which are situated deep within the brain and brainstem. Together, these potentially distant regions of brain work together to produce normal thinking and neurological function. However, these regions can also work together to perpetuate abnormal signals such as seizures. In other words, the brain is to some degree compartmentalized; however, complex behaviors and function are mediated through groups of functional units. The coordinated effort between disparate brain regions has been loosely termed *neural networks*.

The cerebral cortex

The basic building block of any function occurs within the cerebral cortex itself. Though we are only just beginning to understand the complexity of the cortex, it appears that the cortex is arranged in columns of neurons [11]. By connecting more and more of these basic ''columns,'' complex functions can be accomplished. However, more is needed than just adding ''memory cards,'' as one might do to improve the function of a computer. Instead, there are an amazing number of connections between columns of neurons within one brain region. Different brain regions are connected locally. In addition, via connection through the corpus callosum, the major ''highway'' of information between the two halves of the brain, areas of brain that are geographically distant can communicate very rapidly.

Thalamo-cortical connections

Of the information sent to the cerebral cortex, 80–95% comes directly from other cortical regions; however, the remainder of information is transmitted through a central ''switchboard'' consisting of a large group of deeply situated nerve cells called the *thalamus* [11]. The cerebral cortex and the thalamus ''talk'' to each other constantly. In fact, there are many redundant and reciprocal connections between the two. During wakefulness, the thalamus faithfully sends signal from the brain to the body (and vice versa). However, during sleep, the thalamus changes to an oscillating or bursting pattern. One theory is that this helps to ''disrupt'' all of the information which would otherwise be transmitted to the cortex during sleep. Though the reason for sleep is still poorly understood, the thalamic ''disruption or oscilla-

tion'' during sleep may be required for a truly restorative rest. On the other hand, these oscillations, when abnormal, can lead to the generation of 3–4 Hz spike-and-wave discharges which are characteristic of certain kinds of seizures and are pathonomonic for specific epilepsy syndromes (see Table 2) [15].

Basal ganglia and brainstem nuclei

In addition to the cortex-to-cortex and thalamo-cortical connections, there are important links between the cerebral cortex and deep nuclei such as the subthalamic nucleus, the locus coeruleus, and the dorsal raphe nuclei. Not thought to be able to generate seizures on their own, these deep nuclei may be important to ''modulate'' the occurrence of seizures by adjusting or regulating the seizure threshold (Table 3) [70]. Each of these nuclei has widespread connections to the cerebral cortex, and deeper brain structures. It is through these connections that their influence is exerted. For instance, the secretion of norepinephrine from the locus coeruleus acts to *increase* the seizure threshold, making the occurrence of seizure *more difficult*. If one were to stimulate this area, causing release of norepinephrine, one might be able to ''block'' seizures. Serotonin from the dorsal raphe nuclei has a similar effect. If these neurons could be targeted, seizures would be expected to decrease. The subthalamic nucleus is a little more complex: it receives input from the cerebral cortex and certain deep brain nuclei, and sends its fibers primarily to the substantia nigra pars reticularis. Although the exact mechanism for seizure reduction is unknown, animal studies have shown that stimulating the subthalamic nucleus will suppress certain kinds of seizures [54].

Table 3. *Brain regions and the respected released neurotransmitters with possible antiepileptic action*

Cerebral cortex
– The majority of neurons in the cerebral cortex (70–85%) release excitatory neurotransmitters like aspartate and glutamate
– 15–30% of the neurons release the inhibitory neurotransmitter gamma-aminohydroxybutyric acid (GABA)
Thalamus
– Primarily excitatory (aspartate and glutamate)
– A group of neurons provide inhibitory feedback by releasing GABA
Locus coeruleus
– Norepinephrine
Dorsal raphe
– Serotonin
Subthalamic nucleus and dorsal tegmental nucleus
– Acetylcholine

Cell connections can change

Of course, there are far many more connections between brain areas than described above. In addition, connections between these areas can change. It is this ability for the brain to change its interconnectedness that probably accounts for *learning*. As certain tasks are performed repeatedly, the brain can change the number and type of connections between brain regions. In this way, disparate brain areas learn to work more efficiently. However, the brain may not be able to distinguish between normal electrochemical signals and those that are abnormal, e.g. seizures. In fact, it has been suggested based on animal data, that the brain ''learns'' how to have seizures. In other words, the longer seizures are allowed to continue, the ''better'' the brain becomes at having them. Although not conclusively proven in people, this raises a very real concern over the need to control seizures as quickly as possible in order to prevent the ''abnormal learning'' process. Therapies which could disrupt this process, thereby preventing the occurrence of epilepsy, are called *neuroprotectants*: this is an active and interesting area of current investigation [69, 78].

Cranial nerve X: vagus nerve stimulation

VNS: the device and its implantation

The vagus nerve stimulator (VNS) is the only device that is currently approved for use by the United States Food and Drug Administration (FDA) for the treatment of refractory or intractable epilepsy [1]. There is an incomplete understanding of the way that VNS works. However, controlled clinical trails have proven its safety and efficacy in the treatment of the partial epilepsies [89]. In addition, several smaller uncontrolled trials have demonstrated its effectiveness against both refractory symptomatic and idiopathic generalized epilepsies [8, 42, 44, 52, 53, 67]. Over the past 10 years, there have been several models of VNS generators. Models NCP 100 and NCP 101 are no longer produced. Model 100 had an estimated battery life of 5–7 years. Model 101 extended the battery life to 7–10 years, and reduced the volume of the generator by 33%. The next Model 102 further reduced the size of the generator (Fig. 2) and included a one-prong lead that simplifies the connection of the generator and the electrode; the battery life continues to last between 5–8 years, assuming typical settings. The generator is connected to a bipolar platinum lead intraoperatively and placed either subcutaneously

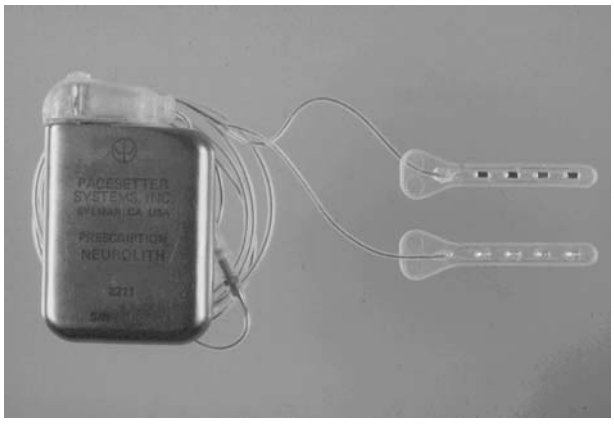

Fig. 2. A cerebellar stimulator with attached electrodes. Reprinted with permission of Ross Davis, MD

over the left chest wall, or under the left pectoralis muscle [89]. A second incision is made over the left neck, the vagus nerve is carefully exposed, and the electrode is attached. A ''tunnel'' is made from the neck incision to the chest and the leads are connected to the generator, and the system's integrity is tested in the operating room. Depending on the surgeon's approach, in most patients, the cosmetic appearance is excellent. The procedure can be done under either local or general anesthesia, it takes about 1–2 h at most, and many patients are home within several hours. The device can be initiated immediately after implantation (e.g., in the operating room or recovery area). The risk of bleeding or infection is low, occurring in less than 1% of implantations [36].

Anatomy and possible mechanism of action

The mechanism of action of VNS in epilepsy is incompletely understood. The vagus nerve and its interconnections throughout the brain suggest certain possibilities. For instance, the vagus nerve is comprised of approximately 20% *efferent* and 80% *afferent* fibers [39, 73, 89]. If an electrical stimulus is placed on the vagus nerve, 80% of the applied stimulation travels back to the brainstem where the vagus nerve originates [39]. When the signal reaches the brainstem, it is transmitted to the nucleus and tract solitarius (NTS) on *both* sides and hence, to both hemispheres [70]: in this way, stimulation of one vagus nerve is able to affect seizures which might arise from either of the cerebral hemispheres. The signal from the brainstem is relayed to many areas such as the hypothalamus, amygdala, dorsal raphe, and especially the thalamus. The thalamus sends signals to many regions of the cerebral cortex [5, 11, 15, 55, 73, 89, 90]. VNS may work by modifying the complex signals that are sent from the thalamus to the cerebral cortex. This is supported by the observation that long-term VNS stimulation causes changes of blood flow in the thalamus [40]. A second possibility is that the overall effect of VNS is the *inhibition* of cortical excitability [89]. Ben-Menachem showed that stimulation of the vagus causes an increase in CSF concentration of the inhibitory neurotransmitter GABA and decreases levels of the excitatory amino acid aspartate [6]; these mechanisms may influence seizure generation and propagation.

Other functions of the vagus nerve

The remaining 20% of vagus nerve fibers, the efferent fibers, originate in two brainstem nuclei: nucleus ambiguous (NA) and dorsal motor nucleus (DMN). Cell bodies in NA send special visceral efferent fibers to the striated muscle of the palate, pharynx, larynx, and esophagus. They are important in the coordination of swallowing [5, 39, 73, 89]. Cell bodies in the DMN are parasympathetic, and send general visceral efferent fibers to the heart, lungs, and gastrointestinal tract. Parasympathetic innervation of these viscera decreases heart rate, increases gastric and pancreatic secretion, and increases gut peristalsis [5, 73]. Although early studies showed that VNS could attenuate epileptic seizures, there was concern that stimulation might interrupt vagus normal function and that regulation of heart rate. More specifically, the parasympathetic fibers in the vagus nerve decrease heart rate and there was a real concern that VNS could slow heart rate even to asystole. However, the distribution of fibers in the vagus nerve is asymmetric; the majority of the afferent *and* efferent cardiovagal fibers run through the *right* nerve [73]. As VNS therapy emerged, stimulation was applied to the *left* vagus in order to minimize the potential detrimental effects on cardiac rhythm. Carefully studies of heart rate showed no significant effects of left VNS [89]. Another function of the vagus nerve is the careful beat-to-beat regulation of cardiac rhythm. This is accomplished through a complex, tightly regulated feedback system that involves both afferent and efferent vagal pathways. Pressure/stretch receptors and chemoreceptors in the aorta and lungs send information to the NTS. This information is transmitted to the DMN which sends signals back to the cardiopulmonary system [5]. During VNS there are subtle changes in both heart rate and variability [26]. Since VNS is intermittent,

the clinical significance of these subtle cardiophysiologic changes is unknown. Interestingly, right VNS has been attempted in very rare cases. In three children who underwent VNS implantation in the right vagus, none had cardiac arrhythmias but two experienced respiratory events; this suggests that extreme caution is required if right VNS is contemplated [61]. Another important function of the vagus nerve is its control of gastric and pancreatic secretion. Again, a feedback system is employed: when the stomach is distended, gastric stretch receptors send a signal of satiety to the brainstem and hypothalamus. In response, vagal efferents increase gastric acid and pancreatic insulin secretion, and promote emptying of the stomach [5, 73]. Early studies found no significant increase in hydrochloric acid secretion as a result of vagus nerve stimulation [89] and later studies have not shown an increase in the occurrence of stomach ulcers among people who receive VNS.

VNS, EEG, and seizures

Since the 1930s, it has been known that stimulation of the vagus nerve causes changes in the electroencephalogram (EEG) [2, 73]. In the 1950s, high frequency (50 Hz) stimulation of the vagus was found to cause desynchronization of the EEG and attenuation of sleep spindle formation, and to block the occurrence of interictal epileptiform discharges [73, 93]. In the 1960s, experiments using high frequency (greater than 30 Hz) stimulation of the NTS provided similar results [58, 73]. These early observations in animals led to the first clinical trials in humans in the late 1980s. Two pilot studies (EO1 and EO2) enrolled 16 patients with partial epilepsy, 15 of whom were implanted with a vagus nerve stimulator. Patients were followed for 14–35 months. In this group, there was a mean reduction in seizure frequency of 46.6% [80]. These results led to two randomized, controlled clinical trials (EO3 and EO5). The double-blinded trial used an ''active placebo'' design, and compared low-dose vagus nerve stimulation to high-dose stimulation as add-on therapy (i.e., in combination with the patients' existing antiseizure medication). EO3 enrolled 126 patients with partial epilepsy of whom 115 were implanted. All were over the age of twelve, and had a mean duration of epilepsy greater than 20 years. Following a three-month baseline period where seizure frequency was calculated, the patients were randomized to low- or high-dose stimulation. The treatment period was three months. The mean reduction in seizures frequency was 24.5% in the high-dose group, and 6.1% in the low-dose group. The most common side effects were hoarseness of voice (37.2% in high-dose, 13.3% in low-dose) and throat pain (11.1% in high-dose, 11.7% in low-dose) [74]. EO5 was identical to EO3 in design. EO5 enrolled 262 patients with partial epilepsy of whom 199 were implanted. As with EO3, the patients were at least 12 years old, and had a mean duration of epilepsy greater than 20 years. Three months of treatment were compared to the three-month baseline. The mean reduction in seizures frequency was 27.8% in the high-stimulation group, and 15.3% in the low-dose (placebo) group. Voice hoarseness, throat pain, and cough were the most common side effects of vagus nerve stimulation [36].

In between EO3 and EO5, there was a non-randomized open label study known as EO4. EO4 investigated the effectiveness of VNS in patients with different types of epilepsy syndromes, including refractory idiopathic/primary generalized epilepsy. In addition, EO4 included younger patients (older than 2 years old). Of 133 enrolled patients, 124 were implanted. Compared to a one-month baseline, the mean reduction in seizure frequency was 21.8%. The side effects were similar to those reported in the controlled clinical trials. When the 24 patients with primary/idiopathic generalized seizures were separately analyzed, the median reduction in seizures frequency after three months of treatment was 46% [52]. One issue that arose from these trials was that the observation period of 3 months was short. A last-visit-carrier-forward analysis of the 454 patients in the initial 5 trials showed that the effect of VNS was not only sustained over time, but seemed to improve [64]. Morris reported his results in terms of a responder rate, i.e. the percentage of people who experienced a greater than 50% reduction in the frequency of seizures. The responders were 36.8% at two years, 44.3% at one year, and 44.1% at three years. The studies showed a direct relationship between the intensity of the vagal stimulation and a reduction in seizure frequency (high versus low stimulation). In the controlled trials, the range of ''high-dose'' stimulation was defined as 1.25–1.75 mA (milliamperes). In most clinical practices, this remains the target range for treatment. However, similar to the way that medications are adjusted, some physicians have suggested that higher ''doses'' may have greater effectiveness. Like medications, if lower settings (i.e., lower ''doses'') fail, the amplitude of the stimulation is increased to the maximum tolerated amount [20]. Although this approach is logical and reasonable, it is not known whether ''doses'' higher than 1.75 mA are

more effective in the treatment of epilepsy. Obviously, prolonged use of higher ''doses'' shortens the generator's battery life.

Although it is clear that there is a direct relationship between the intensity of the electrical stimulation and a reduction in the number of seizures a person experiences, less is known about how other parameters like pulsewidth, frequency, and duty cycle affect seizure control. The commonly used pulsewidth and frequency is 500 us (microseconds) and 30 Hz (Hertz) respectively. These original parameters were derived from early observations in rats, cats, dogs, and monkeys. However, early experiments in animals suggest that new non-traditional settings of 20 Hz frequency and 250 μs pulse width should be equally effective. In order to improve tolerability and to possibly lengthen battery life, many physicians now advocate using these new parameters. However, the effectiveness of these new parameters has not been studied in a prospective, controlled clinical trial in humans. The issue of changing the duty cycle on seizure control has also been debated. The usual settings are 30 s ''on'' and 5 min ''off'' which translates to a duty cycle of about 10%. When a patient does not respond to the targeted ''dose'' of stimulation, it is reasonable to reduce the interval between stimuli: i.e., *increase* the duty cycle [19, 20] to the commonly referred to as ''rapid cycling''; there is, however, relatively few data regarding the impact of higher duty cycles on seizure control. DeGiorgio retrospectively analyzed the VNS settings of 154 patients. He concluded that a subset of patients whose seizure frequency did not change using the typical VNS duty cycle (10%) *did* respond to higher duty cycles [20]. Later, he studied 64 patients, randomized to different duty cycles (14, 28, and 50%). All duty cycles were equally effective as initial settings but when non-responders had their duty cycles increased, the number of responders increased, supporting his earlier findings [19].

In conclusion, studies in people with epilepsy have shown VNS to be safe, well-tolerated, and with very few complications. In the United States, it is approved for use in refractory partial epilepsy in people over 12 years old. However, many studies show that VNS therapy is effective in other types of epilepsy and in children as well. After implantation, the usual settings should be tried first but when these fail to improve the control of seizures, a higher duty cycle should be tried. This, however, reduces the battery life. Despite what is still unknown about VNS, this therapy is important for people whose seizures do not respond to medication.

Cerebellar stimulation

Clinical evidence, devices, and implantation technique

Most of the studies have been retrospective, lacked controls, or have included only a small number of patients, making interpretation of the results difficult. The results have been variable but it is possible that cerebellar stimulation reduces seizure frequency [12–14, 17, 18, 82]. A controlled trial in the United States by VanBuren and Wright showed no benefit to this therapy [81, 91], essentially halting further investigation. A more recent study in 5 patients by Velasco suggested a ''significant and sustained'' effect from cerebellar stimulation over a greater than 2 year period [82]. Although cerebellar stimulation is currently considered ineffective in the treatment of epilepsy, additional research is needed to resolve conflicting study results. There have been several models of cerebellar generators, going back to the 1970s. The first system was a radio frequency-coupled device. The device operated without an internal battery and was powered by radio frequencies which were transmitted through the skin by an antenna that was taped to the skin. This system was cumbersome and associated with frequent failures of the external equipment [87]. The next generation of cerebellar stimulators was completely implantable (Fig. 2), similar to modern pacemakers. The implantation is similar to VNS. However, the leads are different, using two four-contact electrodes. A craniotomy or two burr holes are made to expose the superior cerebellar surface. The paired electrodes are implanted symmetrically over the superomedial surface of the cerebellum [37, 82]. The leads are then tunneled under the skin, and attached to the generator which is implanted subcutaneously, usually over the chest wall.

Anatomy and possible mechanism of action

The mechanism of action of cerebellar stimulation is unclear. Examination of cerebellar function and anatomy suggests certain possibilities. The main functions of the cerebellum are to coordinate the execution of motor tasks and to maintain motor tone [88]. The cerebellum is richly interconnected with structures within the brain and brainstem. The cerebellum receives and compares input from the cerebral cortex and brainstem (e.g. commands from the motor cortex) to sensory input from the periphery (e.g., information regarding body position). It coordinates this with data transmitted from the vestibular nuclei, important structures that help to maintain

balance. When the data are put together, smooth, graceful movements are the result [29, 35]. However, in order to accomplish this, the cerebellum must send information to many different brain structures. The cerebellar efferent fibers travel through the superior cerebellar peduncle to synapse on the thalamus and brainstem [88] where they exert a predominantly inhibitory effect. Because of this, most believe that stimulation of the cerebellum *increases* this inhibition. In other words, cerebellar stimulation increases inhibitory outflow, thereby causing a reduction of seizures [9, 24]. Some authors have disputed this simple explanation, citing evidence that suggests that the mechanism of action is much more complex [71].

Effects of cerebellar stimulation on EEG and seizures

Cerebellar stimulation has been studied in animals since the middle of the 20th century. Early experiments showed that cerebellar stimulation affected the EEG; it enhanced low-voltage fast activity, and decreased the occurrence of epileptiform discharges in the hippocampus [24]. However, there was conflicting information: some studies in animal epilepsy models showed that cerebellar stimulation terminated seizures which arose from different areas of the cerebral cortex and hippocampus [17]. About an equal number of other studies demonstrated that cerebellar stimulation was ineffective [24]. Most human studies were uncontrolled and used different stimulator models, various stimulation parameters, and in patients with different types of epilepsy. The results of the uncontrolled trials vary, but most reported some improvement. The most extensive series was presented by Davis. Since 1974, he has implanted 332 patients with a cerebellar stimulator of whom 90% were implanted for spasticity due to cerebral palsy (Fig. 2). In this group, 33 patients (10%) had intractable epilepsy. Of the 33, 27 patients (82%) had ''improved'' seizure frequency using 0.9–2.5 microCoulombs/sq. cm delivered at between 10 and 30 Hz [17]. Seven patients (21%) became seizure-free [24].

There have been two controlled clinical trials of cerebellar stimulation. Van Buren studied 5 patients [81], and Wright presented data of 9 patients with intractable epilepsy [91]. The trials showed that cerebellar stimulation had no effect on the occurrence of seizures. These results convinced most physicians that cerebellar stimulation was an ineffective treatment of epilepsy and virtually halted further research in this area. However, when Davis reviewed Van Buren's data, he pointed out that 4 of the 5 were improved, with seizure reductions between 73 and 85%. More recently, Velasco implanted 5 patients with a cerebellar stimulator [82]. For three months, two of the patients were randomized to ''off'' (i.e., no stimulation), while the other three were assigned as ''on''. After a three month period, all patients had their stimulators turned ''on''. He found that patients whose stimulators were ''on'' experienced a 66% reduction of seizures while the ''off'' group had a 7% reduction ($p = 0.023$). After all were ''on'', the seizure reduction was 59% at 6 months, and 76% at 24 months (however, one person dropped out due to infection at 11 months). Although this is a small number of people, the results of this trial may re-invigorate the investigation of cerebellar stimulation in the treatment of refractory seizures. With respect to future prospects it is encouraging that cerebellar stimulation appears to be safe: there is a small risk of bleeding (0.6%) and wound infection (2.7%) [18]. The autopsy of one patient with chronic cerebellar stimulation for 16 months found non-specific fibrosis over the electrodes: there was no underlying neuronal loss, suggesting that long-term electrode implantation does not damage microscopic cerebellar structure [92]. Further research is needed to resolve the uncertainty of whether cerebellar stimulation is effective in humans.

Thalamic stimulation

Evidence, devices and implantation technique

Whether discussing the vagus nerve stimulator or cerebellar stimulators, one interesting similarity emerges: both structures are intimately connected with the thalamus. This raises the possibility that the two devices share a common mechanism of action. As we have seen, the thalamus seems to be involved in the *generation* of certain seizure types (generalized from onset) as well as in the *propagation* of others (partial onset) [15, 24, 77]. Within the thalamus, several sites have been stimulated: the anterior thalamic nucleus in humans [62], centromedian nucleus in humans [83–85], and the mediodorsal nucleus in rats [10]. Mondragon lesioned the ventroposterolateral nucleus (VPL) in monkeys. Because of the direct connection of the VPL with the motor cortex, he proposed that either ablation or stimulation of VPL would reduce or stop seizures arising from the motor cortex [63]. Different generators and electrodes have been used in thalamic stimulation but the surgical approach is nearly the same for all. Bilateral electrodes were inserted through a craniotomy or bilateral burr

holes using either MRI or CT-guided stereotaxis [15, 41, 47] or using the Radiological Proportion System [85]. Correct electrode placement within the thalamic nuclei was confirmed by intraoperative electrophysiologic recordings and postoperative CT or MRI [41, 47]. Platinum leads were either connected in the operating room [25, 41, 47], or externalized 10–15 days prior to being internalized for chronic stimulation [85]. The leads were then tunneled under the skin, and connected to generators, which in most cases were implanted in the anterior chest wall [25].

Anatomy and mechanism of action

The thalamus has been a site of interest for the treatment of epilepsy for many years. It is known to be involved in the initiation of generalized seizures, and is thought to be important in the propagation of partial seizures [15]. The thalamus can be divided into three gross anatomic nuclei: the anterior, medial, and lateral nuclear groups. All three areas have been studied in animals and humans to investigate their role in the generation and propagation of seizures and as a potential site for neural stimulation in the treatment of epilepsy [15]. However, the lateral and intralaminar nuclei have been most often sited as the regions which generate 3–4 Hz spike-and-wave of generalized epilepsy syndromes. The anterior thalamus, perhaps through connections with the limbic system, has been implicated both in the generation of generalized-from-onset seizures as well as the propagation of partial-onset seizures [15]. The nuclei of the thalamus are connected to virtually all regions of the brain and brainstem. The thalamus acts as a relay for sensory information. Its role changes depending on whether the person is awake or asleep. During wakefulness, the thalamus integrates sensory information from the body (the spinothalamic tracts) and combines this with information from the cerebellum, an organ which helps to coordinate smooth, sophisticated movements. In order for graceful movements to occur, these systems are then integrated with motor function via input from the thalamus. During sleep, the thalamus switches to an oscillatory mode: many believe that this is an important role in order to interrupt sensory input that would otherwise impair the ability to obtain restful sleep. During sleep, the thalamus generates normal rhythmic discharges such as sleep spindles. Through a similar mechanism, the thalamus also may generate pathologic rhythms such as generalized spike and wave discharges [15]. One possible mechanism for the generation of pathologic rhythms is based on the rich connectivity between the thalamus and the cerebral cortex. The thalamocortical connections are reciprocal, and use the excitatory neurotransmitters glutamate and aspartate. Within the thalamus, inhibitory GABA-containing interneurons synapse in the thalamocortical neurons. There is a balance between excitation and inhibition which is carefully regulated by several feedback mechanisms [15]. If there is increased excitability or diminished inhibition, seizures are more likely to occur.

Effects of thalamic stimulation on the EEG and seizures

The effect that thalamic stimulation has on seizures and the EEG depends on the location, frequency, and intensity of stimulation. Two sites have been studied both in animals and in people: the anterior thalamic nucleus, and the centromedian thalamic nucleus. In rats, low frequency stimulation (8 Hz) of the anterior thalamus was proconvulsant [62]. High frequency stimulation of the same nucleus raised the seizure threshold in rats that were given pentyleneterazol (PTZ), an intravenous chemical which very quickly induces seizure activity [62]. In humans, low frequency (6 Hz), high intensity stimulation of the centromedian produces pathological rhythms [85]. High-frequency (60 Hz) stimulation caused desynchronization of the EEG [85]. This suggests that high frequency stimulation acts to reduce seizures.

In the 1980s, Velasco *et al.* reported promising results in uncontrolled trials of centromedian thalamic nuclear stimulation in persons with refractory epilepsy. The group was mixed: some had partial and secondarily generalized seizures (frontal and temporal onset), while others carried the diagnosis of Lennox-Gastaut Syndrome. Initially, they reported a seizure reduction of up to 80–100% [83]. In addition, they reported normalization of the EEG and improvements in psychological performance [85]. In 2001, Velasco reported positive results using frequencies between 60 and 130 Hz in the centromedian thalamic nucleus, intermittently stimulating each side in an alternating pattern. He studied 49 patients, followed from 6 months to 15 years, and concluded that certain seizure types (tonic-clonic, atypical absence, and tonic) responded better than others (complex partial seizures) [84]. The results of the earlier uncontrolled studies prompted a double-blind pilot study in the United States. Seven patients were implanted. All had refractory seizures, and were not candidates for resective epilepsy surgery. The patients had multifocal or generalized seizure foci, carried different diagnoses and causes of their

seizures. Using the patients as their own controls, the seizure frequency was calculated during times when the stimulator was ''on'' versus ''off.'' These numbers were then compared to baseline values. A reduction of seizures by 30% was observed when the stimulator was ''on'' compared to an 8% reduction when the stimulator was ''off.'' Although a trend toward improvement was observed, the results were not statistically significant [25]. The controlled trial showed no statistically significant difference while the uncontrolled trials showed a very strong response to centromedian thalamic stimulation. It is unclear why there should be such a disparity between these results. Several possible explanations have been proposed, including the method for electrode implantation and the intensity of stimulation. Velasco activated each device sequentially, while Fisher activated both stimulators simultaneously. The number of patients in each study was small and eroded the power of the findings. The conclusion of the double-blind study was that thalamic stimulation was promising, but further study was needed to clearly demonstrate efficacy [25].

Stimulation of the anterior thalamus has been studied in animals [62] and humans [25, 34, 79]. In these studies, 100 Hz stimulation was selected due to the fact that in rats, 100 Hz thalamic stimulation raised the seizure threshold. In an initial study, Sussman found that of 5 patients with refractory seizures followed for 1–2 years, 100 Hz stimulation ''improved'' the seizure frequency in 3 [79]. Hodaie *et al.* reported the results of anterior thalamic nuclear stimulation in 5 patients. High frequency stimulation (100 Hz) was used, alternating the stimulation of each anterior thalamic nucleus. They reported an average reduction of seizures of 53.8% (range 24–89%) [41]. Kerrigan *et al.* reported 5 patients with alternating 100 Hz anterior thalamic nuclear stimulation for the treatment of their refractory epilepsy. In this group, 4 of the 5 had a statistically significant reduction of their generalized tonic-clonic seizures; only one had a statistically significant reduction of all seizure types [47].

In conclusion, the thalamus has been shown to be involved in both seizure generation and propagation. The exact mechanism remains unclear but it seems logical to target the thalamus for stimulation therapy. It is unknown which region of the thalamus is the ''best'' site for stimulation and what the optimal settings should be. Currently, a multicenter prospective trial is underway, rigorously investigating the usefulness of this type of electrical stimulation in refractory partial epilepsy. Hopefully, the multicenter trial will answer some of these questions.

Subthalamic nucleus

Subthalamic nucleus (STN) stimulation has been successfully and safely used to treat symptoms of refractory movement disorders such as Parkinson's disease [4, 57]. In rats, bilateral high frequency subthalamic nucleus stimulation (130 Hz) was shown to suppress absence seizures as well [86]. In 2003, Lado reported the results of bilateral simultaneous STN stimulation in 8 rats. Three stimulation frequencies were used (130, 260, and 800 Hz). 130 Hz seemed to increase the seizure threshold, while 800 Hz may have facilitated seizures by reducing the seizure threshold [54]. In 2002, four patients with refractory partial seizures were treated with STN stimulation. Their EEGs showed focal sharp waves ipsilateral to the side of stimulation. Because of this, Dinner proposed that the mechanism of action of STN stimulation was mediated by direct STN-cortical glutaminergic connections [21]. In 2002, Benabid reported seizure reduction in a 5-year-old child who underwent left subthalamic nuclear stimulation for refractory and frequent left parietal onset seizures. The frequency of 130 Hz was used and reduced the seizures by 80.7% [4]. Although animal studies suggest that STN stimulation may reduce seizures, more study is needed to answer this question.

Cerebral cortex

If seizures occur in the cerebral cortex, it seems reasonable to attempt stimulation of the cortex itself. During the presurgical evaluation of patients with refractory partial seizures, cortical mapping is often performed in order to identify epileptogenic zones or regions of eloquent cortex. A goal of mapping is to determine the extent of a safe resection. During this procedure, seizures are sometimes induced by the electrical stimulation. One observation is that if a second stimulation is applied to the test-induced discharges, called afterdischarges, many of them will stop. In addition to this, there have been reports that electrical stimulation will suppress epileptiform discharges i.e. abnormal electrical brain wave patterns. The epileptiform discharges are not seizures themselves but are markers for seizures (and epilepsy). In 2004, Kinoshita reported that both high-frequency (50 Hz) and low-frequency stimulation of the epileptogenic region reduced the frequency of epileptiform discharges in one patient [48]. In 2005, he reported similar results in four patients and suggested that electrical cortical stimulation ''suppressed epileptogenicity'' [49]. In 2004, Kossoff *et al.* reported the abatement of seizures in 4 patients who received cortical electrical

stimulation [50]. During intracranial EEG recording, he used an automated system to detect and respond to seizures which he called ''an external responsive neurostimulator''. Because the numbers were so small, he was unable to comment on efficacy; however, the system was able to ''alter or suppress'' some of the patients seizures. In the following year, Osorio reported the results of automated cortical electrical stimulation in 8 patients. The group was mixed, and some underwent deep brain (anterior thalamic) stimulation; he reported a mean reduction of seizures of 40.8–55.5% [68]. The interesting aspect of these reports, different from all other devices, is that these devices were designed to respond to seizure discharges as opposed to sending either a continuous or intermittent electrical stimulation. In other words, as technology advances, it may be possible to develop devices that respond to the person's events: if a person had seizures infrequently, their device would operate accordingly.

Other sites

Two patients with epilepsy have had unilateral stimulation of the locus coeruleus which presumably increased the release of norepinephrine. In both these patients the seizures were ''reduced in severity and intensity'' [23]. The small number does not provide conclusive proof that this is a safe and effective treatment for refractory seizures.

Conclusions

Recently, much attention has been focused on neurostimulators in the treatment of epilepsy. Two important questions remain: where to stimulate and how to optimize stimulation. If we assume that neural networks are responsible for seizure generation and propagation [10, 70], it seems reasonable to assume that seizures can be affected by electrical stimulation of more than one brain region. As research continues, we may discover that stimulation of a particular brain region is more effective for specific types of epilepsy. In addition to finding the ''ideal'' site for treatment, the optimum stimulation parameters must be defined. We may find, for instance, that different brain regions require different stimulation parameters. To date, most research has focused on the effectiveness of intermittent or continuous neural stimulation. However, some researchers are investigating ways to develop treatments that either *respond* to or *anticipate* the occurrence of seizures [32, 33, 50, 56, 60, 68, 75, 76]. The device would only be active when needed, and would not require the participation of the patient. In other words, the device would be designed to automatically deliver an electrical stimulus in response to or in anticipation of a seizure. Although this idea seems farfetched, it is clear that we are just starting to understand the usefulness of devices in the treatment of epilepsy. As our understanding of epilepsy grows, we are likely to see new approaches to the treatment of epilepsy, including the application of sophisticated electronic devices.

References

1. Aiken SP, Brown WM (2000) Treatment of epilepsy: existing therapies and future developments. Front Biosci 5: E124–E152
2. Bailey P, Bremer F (1938) A sensory cortical representation of the vagus nerve with a note on the effects of low blood pressure on the cortical electrogram. J Neurophysiol 1: 405–412
3. Benabid AL, Benazzouz A, Hoffmann D, Limousin P, Krack P, Pollak P (1998) Long-term electrical inhibition of deep brain targets in movement disorders. Mov Disord 13 Suppl 3: S119–S125
4. Benabid AL, Minotti L, Koudsie A, de Saint Martin A, Hirsch E (2002) Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luysi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. Neurosurgery 50: 1385–1392
5. Benaroch EE (1997) Central autonomic network: functional organization and clinical correlations. Futura Publishing Co. Inc., Armonk, New York
6. Ben-Menachem E, Hamberger A, Hedner T, Hammond E, Uthman B, Slater J, Treig T, Stefan H, Ramsay E, Wernicke J, Wilder B (1995) Effects of vagus nerve stimulation on amino acids in the CSF of patients with partial seizures. Epilepsy Res 20: 221–227
7. Bertram EH, Mangan PS, Zhang D, Scott CA, Williamson JM (2001) The midline thalamus: alterations and a potential role in limbic epilepsy. Epilepsia 42: 967–978
8. Binnie CD (200) Vagus nerve stimulation for epilepsy: a review. Seizure 9: 161–169
9. Bloedel JR, Ebner TJ, Godersky JC, Huang C (1985) Physiologic mechanisms underlying the effects of cerebellar stimulation. In: Davis R, Bloedel JR (eds) Cerebellar stimulation for spasticity and seizures. CRC Press, Boca Raton, Florida, pp 35–51
10. Cassidy RM, Gale K (1998) Mediodorsal thalamus plays a critical role in the development of limbic motor seizures. J Neurosci 18: 9002–9009
11. Connors BW (1997) Neocortical anatomy and physiology. In: Engel J Jr, Pedley TA (eds) Epilepsy: a comprehensive textbook. Lippincott-Raven Publishers, Philadelphia, pp 307–321
12. Cooper IS, Amin I, Gilman S (1973) The effect of chronic cerebellar stimulation upon epilepsy in man. Trans Am Neurol Assoc 98: 192–196
13. Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP (1976) Chronic cerebellar stimulation in epilepsy. Clinical and anatomic studies. Arch Neurol 33: 559–570
14. Cooper IS, Upton AR (1978) Effects of cerebellar stimulation on epilepsy, the EEG, and cerebral palsy in man. Electroencephalogr Clin Neurophysiol Suppl 34: 349–354
15. Coulter DA (1997) Thalamocortical anatomy and physiology. In: Engel J Jr, Pedley TA (eds) Epilepsy: a comprehensive textbook. Lippincott-Raven Publishers, Philadelphia, pp 341–351

16. Davis R (2000) Cerebellar stimulation for cerebral palsy spasticity, function, and seizures. Arch Med Res 31: 290–299
17. Davis R (1997) Cerebellar stimulation for seizure control. In: Gildenberg P, Tasker R (eds) Stereotactic and functional neurosurgery. McGraw-Hill Publishers, New York, pp 1945–1951
18. Davis R, Barolat-Romana G, Engle H (1980) Chronic cerebellar stimulation for cerebral palsy – five-year study. Acta Neurochir Suppl 30: 317–332
19. DeGiorgio C, Heck C, Bunch J, Britton J, Green P, Lancman M, Murphy J, Olejniciak P, Shih J, Arrambide S, Soss J (2005) Vagus nerve stimulation for epilepsy: randomized comparisons of three stimulation paradigms. Neurology 65: 317–319
20. DeGiorgio CM, Thompson J, Lewis P, Anarabie S, Naritoku D, Handforth A, Labar D, Mullin P, Hech C (2001) Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. Epilepsia 42: 1017–1020
21. Dinner DS, Neme S, Nair D, Montgomery EB, Baker KB, Rezal A, Luders HO (2002) EEG and evoked potential recordings from the subthalamic nucleus for deep brain stimulation of intractable epilepsy. Clin Neurophysiol 113: 1391–1402
22. Engel J, Weiser H-G, Spencer D (1997) In: Engel J Jr, Pedley TA (eds) Epilepsy: a comprehensive textbook. Lippincott-Raven Publishers, Philadelphia, pp 1673–1676
23. Feinstein B, Gleason CA, Libet B (1989) Stimulation of locus coeruleus in man. Preliminary trials for spasticity and epilepsy. Stereotact Funct Neurosurg 52: 26–41
24. Fisher RS, Mirski M, Krauss G (1997) Brain stimulation. In: Engel J Jr, Pedley TA (eds) Epilepsy: a comprehensive textbook. Lippincott-Raven Publishers, Philadelphia, pp 1867–1875
25. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Swerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
26. Frei MG, Osori I (2001) Left vagus nerve stimulation with the neurocybernetic prosthesis has complex effects in heart rate and on its variability in humans. Epilepsia 42: 1007–1016
27. Frost M, Gates J, Helmers SL, Wheless J, Levinsohn P, Tardo C, Conry JA (2001) Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. Epilepsia 42: 1148–1152
28. Gates JR, Rosenfeld WE, Maxwell RE, Lyons RE (1987) Response of multiple seizure types to corpus callosum section. Epilepsia 28: 28–34
29. Ghez C, Fahn S (1985) The Cerebellum. In: Kandel E, Schwartz J (eds) Principles of neural science, 2nd edn. Elsevier Science Publishers Inc., New York, pp 502–512
30. Gilliam F, Hecmimovic H, Sheline Y (2003) Psychiatric comorbidity, health, and function in epilepsy. Epilepsy & Behavior 4 Suppl 40: S26–S30
31. Gilliam F, Mendiratta A, Pack AM, Bazil CW (2005) Epilepsy and common comorbidities: improving the outpatient epilepsy encounter. Epileptic Disord 7 Suppl 1: S27–S33
32. Glanz J (1994) Do chaos-control techniques offer hope for epilepsy? Science 265: 1174
33. Glanz J (1997) Mastering the nonlinear brain. Science 277: 1758–1760
34. Goldman HW, Sussman NM, Callanan M, Bergen J, Jackel RA, Kaplan L, Cooper IS, Harner RN (1988) Anterior thalamic stimulation for medically refractory epilepsy. Part I: Implantation and stimulation. Epilepsia 29: 677
35. Haines DE (1985) Organizational principles of cerebellar cortical systems. In: Davis R, Bloedel JR (eds) Cerebellar stimulation for spasticity and seizures. CRC Press, Boca Raton, Florida, pp 15–31
36. Handforth A, DeGiorgio CM, Schacter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilamrtin RC, Labar DR, Morris GL, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51: 48–55
37. Heimberger RF (1985) Cerebellar stimulator implantation. In: Davis R, Bloedel JR (eds) Cerebellar stimulation for spasticity and seizures. CRC Press, Boca Raton, Florida, pp 195–201
38. Helmers SL, Wheless JW, Frost M, Gates J, Levisohn P, Tardo C, Conry JA, Yalnizoglu D, Madsen JR (2001) Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. J Child Neurology 16: 843–848
39. Henry TR (2002) Therapeutic mechanisms of vagus nerve stimulation. Neurology 59 (6 Suppl 4): S3–S14
40. Henry TR, Bakay RA, Pennell PB, Epstein CM, Votaw JR (2004) Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. prolonged effects at high and low levels of stimulation. Epilepsia 45: 1064–1070
41. Hodaie M, Wennberg RA, Dostrovskjy JO, Lozano LM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
42. Hosain S, Nikolev B, Harden C, Li M, Fraser R, Labar D (2000) Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. J Child Neurol 15: 509–512
43. Jones J, Hermann BP, Woodard JL, Barry JJ, Gilliam F, Kanner AM, Meador K (2005) Screening for major depression in epilepsy with common self-report depression inventories. Epilepsia 46: 731–735
44. Karceski SC (2001) Vagus nerve stimulation and Lennox-Gastaut syndrome: a review of the medical literature and data from the VNS patient registry. CNS Spectrums 6: 766–770
45. Karceski SC, Morrell MJ, Carpenter C (2001) Expert consensus guidelines: treatment of epilepsy. Epilepsy & Behavior 2: A1–A50
46. Karceski SC, Morrell MJ, Carpenter C (2005) Treatment of epilepsy in adults: expert opinion 2005. Epilepsy & Behavior 7 Suppl 1: S1–S64
47. Kerrigan JF, Litt B, Fisher R, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45: 346–354
48. Kinoshita M, Ikeda A, Matsumoto R, Begum T, Usui K, Ymamato J, Matsuhashi N, Takamaya M, Mikuni N, Takahashi J, Miyamoto S, Shibasaki H (2004) Electrical stimulation on human cortex suppresses fast cortical activity and epileptic spikes. Epilepsia 45: 787–791
49. Kinoshita M, Ikeda A, Matsuhashi M, Matsumoto R, Hitomi T, Begum T, Usui K, Takayama M, Mikuni N, Miyamoto S, Hashimoto N, Shibasaki H (2005) Electrical stimulation suppresses epileptic and background activities in neocortical epilepsy and mesial temporal lobe epilepsy. Clin Neurophysiol 116: 1291–1299
50. Kossoff EH, Ritzl EK, Politsky JM, Murro AM, Smith JR, Duckrow RB, Spencer DD, Bergey GK (2004) Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. Epilepsia 45: 1560–1567
51. Kwan P, Brodie MJ (200) Early identification of refractory epilepsy. New England J Med 342: 314–319
52. Labar D, Murphy J, Tecoma E (1999) Vagus nerve stimulation for medication-resistant generalized epilepsy. EO4 Study Group. Neurology 52: 1510–1512
53. Labar D, Nikolev B, Tarver B, Fraser R (1998) Vagus nerve stimulation for symptomatic generalized epilepsy: a pilot study. Epilepsia 39: 201–205
54. Lado FA, Velisek L, Moshe S (2003) The effect of electrical stimulation of the subthalamic nucleus on seizures is frequency dependent. Epilepsia 44: 157–164

55. Landy HJ, Ramsay RE, Slater J, Casiano RR, Morgan R (1993) Vagus nerve stimulation for complex partial seizures: surgical technique, safety, and efficacy. J Neurosurg 78: 26–31
56. Le Van Quyen M, Adam C, Martiniere J, Baulac M, Clemenceau S, Varela F (2000) Spatio-temporal characterizations of non-linear changes in intracranial activities prior to human temporal lobe seizures. Eur J Neurosci 12: 2124–2134
57. Levesque MF, Taylor S, Rogers R, Le MT, Swope D (1999) Subthalamic stimulation in Parkinson's disease. Preliminary results. Steretact Funct Neurosurg 72: 170–173
58. Magnes J, Moruzzi G, Pompeiano O (1961) Synchronization of the EEG produced by low frequency electrical stimulation of the region of the solitary tract. Arch Ital Biol 99: 33–67
59. Martinez JM, Marangell LB, Hollrah L (2005) Vagus nerve stimulation: current use and potential applications in child and adolescent psychiatry. Child Adolesc Psychiatr Clin N Am 14: 177–191
60. Martiniere J, Adam C, Le Van Quyen M, Baulac M, Clemenceau S, Renault B, Varela FJ (1998) Epileptic seizures can be anticipated by non-linear analysis. Nature Medicine 4: 1173–1176
61. McGregor A, Wheless J, Baumgartner J, Bettis D (2005) Right-sided vagus nerve stimulation as a treatment for refractory epilepsy in humans. Epilepsia 46: 1152–1153
62. Mirski MA, Rossell LA, Terry JB, Fisher RS (1997) Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 28: 89–100
63. Mondragon S, Lamarche M (1990) Suppression of motor seizures after specific thalamotomy in chronic epileptic monkeys. Epilepsy Res 5: 137–145
64. Morris GL, Mueller WM (1999) Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The vagus nerve study group E01–E05. Neurology 53: 1731–1735
65. Nadkarni S, LaJoie J, Devinsky O (2005) Current treatments of epilepsy. Neurology 64 (12 Suppl 3): S2–S11
66. Nahaz Z, Marangell LB, Husain MM, Rush AJ, Sackheim HA, Lisanby SH, Martinez JM, George MS (2005) Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 66: 1097–1104
67. Ng M, Devinsky O (2004) Vagus nerve stimulation for refractory idiopathic generalized epilepsy. Seizure 13: 176–178
68. Osorio I, Frei M, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB (2005) Automated seizure abatement in humans using electrical stimulation. Ann Neurol 57: 258–268
69. Pitkanen A, Kubova H (2004) Antiepileptic drugs in neuroprotection. Expert Opin Pharmacother 5: 777–798
70. Proctor M, Gale K (1997) Basal ganglia and brainstem anatomy and physiology. In: Engel J Jr, Pedley TA (eds) Epilepsy: a comprehensive textbook. Lippincott-Raven Publishers, Philadelphia, pp 353–368
71. Rajjoub RK, Wood JH, Van Buren JM (1976) Significance of purkinje cell density in seizure suppression by chronic cerebellar stimulation. Neurology 26: 645–650
72. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, Rapaport MH, Zajecka J, Nierenberg AA, Husain MM, Ginsberg D, Cooke RG (2005) Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 58: 347–354
73. Rutecki P (1990) Anatomical, physiological, and theoretical basis for the antiepileptic effects of vagus nerve stimulation. Epilepsia 31 Suppl 2: S1–S6
74. Salinsky M, Wernicke VF, Rutecki P, Allen J (1995) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology 45: 224–230
75. Schiff SJ (1998) Forecasting brain storms. Nature Medicine 4: 1117–1118
76. Schiff SJ, Jerger K, Duong DH, Chang T, Spano ML, Ditto WL (1994) Controlling chaos in the brain. Nature 370: 615–620
77. Schwartzkroin PA, McIntyre DC (1997) Limbic Anatomy and physiology. In: Engel J Jr, Pedley TA (eds) Epilepsy: a comprehensive textbook. Lippincott-Raven Publishers, Philadelphia, pp 323–340
78. Stafstrom CE, Sutula TP (2005) Models of epilepsy in the developing and adult brain: Implications for neuroprotection. Epilepsy & Behavior 7 Suppl 3: 18–24
79. Sussman NM, Goldman HW, Jackel RA, Kaplan L, Callanan M, Berger J, Harner RMN (1988) Anterior thalamic stimulation in medically refractory epilepsy. Part II: Preliminary clinical results. Epilepsia 29: 677
80. Uthman BM, Wilder BJ, Penry JK, Dean C, Ramsay RE, Reid SA, Hammond EJ, Tarver WB, Wernicke JF (1993) Treatment of epilepsy by stimulation of the vagus nerve. Neurology 43: 1338–1345
81. Van Buren JM, Wood JH, Oakley J, Hambrecth F (1978) Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg 48: 407–416
82. Velasco F, Carillo-Ruiz JD, Brito F, Velasco M, Marquez I, Davis R (2005) Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable seizures. Epilepsia 46: 1071–1081
83. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28: 421–430
84. Velasco F, Velasco M, Jimenez F, Velasco AL, Marquez I (2001) Stimulation of the central median thalamic nucleus for epilepsy. Stereotact Funct Neurosurg 77: 228–232
85. Velasco M, Velasco F, Velasco AL, Brito F, Jiminez F, Marquez I, Rojas B (1997) Electrocortical and behavioral responses produced by acute electrical stimulation of the centromedian thalamic nucleus. Electroencephalogr Clin Neurophysiol 102: 461–471
86. Vercueil L, Banazzouz A, Deransart C, Bressand K, Marescaux C, Depaulis A, Benabid AL (1998) High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. Epilepsy Res 31: 39–46
87. Walker CF, Heath RG (1985) Testing and failure analysis of cerebellar implants. In: Davis R, Bloedel J (eds) Cerebellar stimulation for spasticity and seizures. CRC Press, Boca Raton, Florida pp 283–298
88. Waxman SG (1996) The brain stem and cerebellum. Correlative neuroanatomy, 23rd edn. Appleton & Lange, Stamford, CT, pp 83–105
89. Wilder BJ (1997) Vagal nerve stimulation. In: Engel J Jr, Pedley TA (eds) Epilepsy: a comprehensive textbook. Lippincott-Raven Publishers, Philadelphia, pp 1353–1358
90. Woodbury DM, Woodbury W (1990) Effects of vagal stimulation on experimentally induced seizures in rats. Epilepsia 31 Suppl 2: S7–S19
91. Wright GD, McLellan DL, Brice JG (1985) A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatry 47: 769–774
92. Wright GD, Weller RO (1983) Biopsy and post-mortem findings in a patient receiving cerebellar stimulation for epilepsy. J Neurol Neurosurg Psychiatry 46: 266–273
93. Zanchetti A, Wang SC, Moruzzi G (1952) The effect of vagal afferent stimulation on the EEG, pattern of the cat. Electroencephalogr Clin Neurophysiol 4: 357–361

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Brain stimulation for epilepsy

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Summary

Brain stimulation has been receiving increasing attention as an alternative therapy for epilepsy that cannot be treated by either antiepileptic medication or surgical resection of the epileptogenic focus. The stimulation methods include transcranial magnetic stimulation (TMS) or electrical stimulation by implanted devices of the vagus nerve (VNS), deep brain structures (DBS) (thalamic or hippocampal), cerebellar or cortical areas. TMS is the simplest and least invasive approach. However, the most common epileptogenic areas (mesial temporal structures) probably lie too deep beneath the surface of the skull for effective TMS. The efficacy of VNS in reducing the frequency or severity of seizures is quite variable and depends on many factors which are currently investigated. VNS is well-tolerated and approved in many countries. DBS is much more invasive than either TMS or VNS. Currently, a number of targets for DBS are investigated including caudate, centromedian or anterior thalamic nuclei, and subthalamic nucleus. Direct stimulation of the epileptic cortical focus is another approach to the neuromodulation in epilepsy. Finally, another line of research investigates the usefulness of implantable seizure detection devices. The current chapter presents the most important evidence on the above methods. Furthermore, other important issues are reviewed such as the selection criteria of patients for brain stimulation and the potential role of brain stimulation in the treatment of depression in epileptic patients.

Keywords: Neuromodulation; epilepsy; seizures; brain stimulation; implanted device; treatment; review.

Introduction

Epilepsy is one of the most common neurological disorders, affecting 0.5–1% of the world population; the proportion may be higher in developing regions [17, 97]. Epilepsy constitutes approximately 0.5% of the whole burden of disease in the world [72].

At least 30% of patients with epilepsy have uncontrolled seizures despite antiepileptic drug (AED) therapy, including the new agents introduced in the last decade [60]. Surgical therapy can be effective for carefully selected patients, but literally millions of people around the world need additional approaches [144]. Health-related quality of life among people with epilepsy is closely related to seizure control [71]. Moreover, the cost of epilepsy, and particularly uncontrolled epilepsy and complications such as status epilepticus, is high, justifying complex interventions [8, 106].

Among experimental alternative therapies, brain stimulation has been receiving increasing attention. The methods proposed range from intermittent, non-invasive techniques such as transcranial magnetic stimulation (TMS), to thalamic, hippocampal, or cerebellar surgical implants. One therapy, vagal nerve stimulation (VNS) is approved in many countries. However, as with other therapeutic modalities, it has been used for seizure types not evaluated in controlled clinical trials. Thus, it continues to be an unproven treatment for many patients who have used it.

Several important issues have to be considered when evaluating the effects of brain stimulation for epilepsy. It may be harder to perform true blinded studies, due to patients' ability to perceive when stimulation is 'on.' This problem may affect less invasive approaches such as TMS and VNS to a greater degree than deep brain stimulation (DBS), but side effects may provide clues even in the latter case. The phenomenon of 'reversion to the mean' may occur as well. Patients are more likely to enter an experimental trial when their seizure frequency is high, leading to the risk that decline in frequency during the trial, due to random variation, or physiological cyclical pattern, might be misinterpreted as a therapeutic effect. This risk might be greater for studies involving invasive procedures or surgery than AEDs.

Adequate trial length, and placebo controls, is crucial for proper interpretation.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is the simplest and least invasive approach to brain stimulation for epilepsy. It has been used widely in clinical neurophysiology as an investigational tool, to measure parameters related to cortical excitatory and inhibitory function [65]. In most studies, a simple hand-held magnet, or occasionally a frame that can be aligned to predetermined coordinates, is used. In clinical studies, contrasting with the human DBS data (see below), low frequency rTMS reduces motor cortex excitability, while high frequency (>10–20 Hz) stimulation can lead to seizures, even in normal controls [20].

The main parameters measured with TMS include motor threshold (MT), used to judge cortical excitability, and paired pulse facilitation and inhibition. These phenomena probably reflect widespread cortical and spinal neuronal membrane excitability, as well as intracortical synaptic and corticospinal connections, involving excitatory and inhibitory synaptic pathways, as well as neuronal membrane potentials [109]. Thus, it may be difficult to relate altered parameters measured with TMS to specific physiological processes. Moreover, the currents generated by the magnets, and thus their physiological effects, depend on a wide variety of factors, including coil construction (there are round, and figure-of-eight coils, for example) and positioning, brain conductivity, and neuronal orientation. The brain is not an ideal, uniform, conduction medium. Distribution of field strength and flux, and effects on cortical excitability, may be difficult to predict. PET blood flow studies, for example, showed multifocal bilateral activation from unilateral motor cortex stimulation [114].

A few rTMS experiments have been performed in animal models of epilepsy. Low frequency stimulation (0.5 Hz stimulation) increased latency to onset of pentylenetetrazol-induced seizures in rats [2]. Moreover, the opposite effect occurred using 50 Hz rTMS, which increased excitability, reducing pentylenetetrazol-induced clonic seizure latency [61]. In addition, a possible long term depression-like effect of low frequency stimulation has been demonstrated in resected specimens of human temporal lobe [21].

In patients with epilepsy, seizures may occur by chance during TMS studies. However, AEDs increase motor threshold, and it may actually be harder to induce a seizure during rTMS in epilepsy patients, unless drugs are being withdrawn during stimulation [69]. No significant endocrine effects, or unusual histologic changes attributable to TMS (in patients who had temporal lobectomy after participating in studies) have been reported [15, 47, 56]. Patients may experience sensations such as 'skin crawling' during stimulation, or complain of headache [45, 118, 141].

There have been scattered reports of the use of rTMS to treat patients with seizures, or cortical myoclonus. In an open study, eight of nine patients with complex partial seizures and temporal lobe epilepsy were reported to have a mean seizure reduction of $38.6 \pm 36.6\%$, comparing 4 weeks before and 4 weeks after five days of 0.33 Hz rTMS [117]. Another study reported that 1 session (600 pulses) of low-frequency 0.5 Hz rTMS ''focally targeting'' malformations of cortical development in eight patients significantly decreased the number of EEG epileptiform discharges and seizures, as compared to a four week baseline, at 15 and 30 days after rTMS treatment [44]. One patient with partial seizures due to focal cortical dysplasia treated with 100 stimulations at 0.5 Hz twice a week for four weeks had a 70% seizure decrease in seizure frequency [84]. However, initial reports of transient improvement in three patients with cortical myoclonus were not confirmed by additional studies, and the response was transient in the three original cases [142, 143].

Only one controlled study has been reported. This was a 'single blind' trial of 1 Hz for 15 min twice daily for one week at 120% of motor threshold in patients with mesial temporal or neocortical localization-related epilepsy [120]. Twenty-four subjects were randomized to blinded active or placebo stimulation (with the coil angled away from the scalp, while the patient still heard the clicking from the stimulator). The physician administering rTMS, but not evaluating the patient in the clinic, knew the treatment assignment. Sham-stimulated patients showed no change in seizure frequency when eight weeks before and after stimulation were compared. The active group had a 16% (non-significant) mean reduction, but only in the first two weeks after stimulation. There was a trend toward a greater effect in patients with neocortical rather than mesial temporal foci. Mesial temporal structures probably lie too deep beneath the surface of the scalp for effective stimulation using rTMS [7, 37].

Vagus nerve stimulation (VNS)

The vagus nerve projects widely and diffusely to thalamus, amygdala, and forebrain through the nucleus

tractus solitarius and the medullary reticular formation [138]. In animals, increased inhibition or decreased excitation in nucleus tractus solitarius reduces susceptibility to limbic motor seizures [140]. In primates, there is strong vagal input to the gustatory/visceral thalamic relay nucleus, as well as the adjacent parafascicular nucleus [59]. Thus, thalamocortical relay neurons appear to modulate cortical excitability, and may influence generation of generalized seizures and secondary generalization of focal seizures [24].

Human studies using positron emission tomography (PET) and ^{15}O-H_2O found that VNS produced both increases and decreases in cerebral blood flow (CBF); in some reports, thalamic effects correlated with decreased seizures [51–54, 64]. Single photon emission computed tomography studies have tended to show decreased CBF in comparable regions [123, 136]. There is one report of thalamic hypometabolism measured with PET and ^{18}F-fluorodeoxyglucose [108]. A functional MRI study showed relative VNS-induced bilateral thalamic, insular, basal ganglia, and occipital-temporal activation [96]. In another, five patients had frontal-temporal increased activity, but only the two whose seizures improved, thalamic activation [77]. These studies suggest that thalamic activation or deactivation may mediate VNS efficacy. However, it is important to remember that thalamic hypoperfusion and hypometabolism may be present ipsilateral to seizure foci in patients with localization-related epilepsy as part of the dysfunction related to the underlying seizure disorder itself.

Clinical efficacy

VNS may be more problematic to study clinically even than TMS, due to the difficulty of blinding the subjects. Patients can sense when stimulation is occurring. In order to obtain 'controlled' data, a dose-response design was adopted. High-dose stimulation (0.25–3.5 ma, 30 sec on, 5 min off, 30 Hz, 500 μs pulse duration) versus low dose (0.25–3.5 ma, 30 sec on, 180 min off, 1 Hz, 130 μs pulse duration) was used in several clinical trials for adults and children older than twelve with complex partial and secondarily generalized seizures [42]. The null hypothesis was no difference between the two doses. In these trials, mean reduction in seizure frequency was 25–30% for the ''high'' stimulation group versus 6–15% for the ''low'' stimulation group; these differences were statistically significant [13, 51, 119].

In open label extension studies, the therapeutic efficacy was sustained, over follow-up periods of up to 12 months [29, 112]. Uncontrolled data suggested that additional improvement might occur [31]. However, antiepileptic drug adjustments were allowed during the long-term extensions, so the results should be treated with caution. Several other potentially beneficial effects have been reported (particularly related to mood, which will be discussed below). VNS may improve day-time sleepiness independent of seizure control [81]. There may be a significant decrease in body mass during VNS [113]. One characteristic of VNS that may have indirect psychological as well as direct therapeutic advantages is the ability of patients to activate the stimulator using an external magnet, thus allowing an increased 'dose' during a aura, as well as providing a greater sense of personal control.

Children with complex partial seizures appear to show results from VNS similar to adults, although controlled trial data are very limited [90, 105]. In a clinical, uncontrolled series of 100 patients, 45% had greater than 50% seizure reduction [92]. Small studies have found promising effects in patients with tuberous sclerosis and hypothalamic hamartomas [93, 101]. However, other epilepsy syndromes, and patients with 'epileptic encephalopathies,' such as epilepsy associated with ring chromosome 20, have not responded [3, 16, 103]. There are scattered case reports of VNS used to treat status epilepticus refractory to AEDs [104].

Side effects

VNS has been generally well-tolerated [11]. There is no evidence of increased mortality or overall morbidity in patients receiving VNS compared with uncontrolled epilepsy as a whole [4]. Implanation of the stimulator, under the left clavicle, can be performed as an outpatient procedure under local anesthesia if necessary; the stimulating electrodes are placed on the left vagus nerve in the neck to limit the risk of bradycardia [12]. Three to six percent experience post-operative infections. Common side effects (most evident when the stimulator is on) are cough (15–20%), voice alteration (50–60%), hoarseness, dyspnea, pain, paresthesia, and headaches (about 15–20% each), and respond to alteration of the stimulation settings, particularly lowering pulse width [75]. Left vocal cord paralysis, lower facial weakness, sternocleidomastoid spasm and transient bradycardia or asystole during implantation have been rare complications [19, 60, 115]. In a study of seven patients on chronic VNS, no significant changes were observed in time-domain parameters of heart rate variability, although there was

a slight flattening of circadian effects [49]. It has been suggested that air way compromise or aspiration might be possible complications in patients with preexisting undiagnosed right vocal cord weakness, or associated with nasogastric tube feeding; however, no cases have been reported [80]. Aspiration did occur in two children with pre-existing swallowing difficulties [11, 91]. Vagus nerve damage associated with stimulation has not been documented in adults, but may be suggested by one report in a child [121]. MRI can be performed at current clinical settings (up to about 2 tesla) with VNS in place, although as MRI magnet strengths increase, additional safety data will have to be collected [10].

Trigeminal nerve stimulation

Stimulation of the infraorbital branch of the trigeminal nerve led to reduction of seizure activity triggered by intraperitoneal injection of pentylenetetrazole in awake rats [40]. Bilateral stimulation was more effective than unilateral stimulation, and seizure-triggered stimulation more effective than a fixed schedule. Two patients treated with infraorbital transcutaneous stimulation at 120 Hz, 20–30 sec on and 20–30 sec off were reported to have 39 and 76% reduction in seizure frequency at six months after starting stimulation [30]. Side effects included twitching of the orbicularis oculi and mild tooth pressure/tingling in the canine teeth, responding to a reduction in current. There was no effect on vital signs or ECG.

Deep brain stimulation

Deep brain stimulation (DBS) involves intracranial surgery, and thus is much more invasive than either TMS or VNS [1]. There are a variety of stimulation targets. Electrodes are connected subcutaneously by extension leads to a subcutaneous battery-powered programmable stimulator or stimulators on the chest wall. Stimulation parameters have not been tested systematically. Typical settings may be 1–10 V, 90 μs pulses in trains of 100–165 Hz, with either bipolar or referential stimulation. Both continuous patterns, or 1 min on and 5 min off have been tried. Parameters can be changed, and stimulus trains turned on or off, with an external device. A wide range of subcortical nuclei have been targeted for epilepsy treatment; unfortunately, few studies have been controlled rigorously, or even notionally.

The most important potential complication is hemorrhage, reported in approximately 5% of patients [41]. As with any intracranial surgery, infection is an additional possibility. Centromedian thalamic nucleus stimulation led to central nystagmus in one reported patient [116]. Right-sided stimulation evoked left beating nystagmus and left-sided stimulation evoked right beating nystagmus.

Cerebellum

Despite almost universally inhibitory cerebellar outflow, effects in animal models have been both pro and anticonvulsant [23, 67]. Variability in results may have been due to differences in stimulation location, as well as in the stimulation parameters used. Similar variability in technique, as well as uncertainty concerning what was done, makes interpretation of results in many human studies difficult. A review of uncontrolled studies of 115 patients found that 27% were seizure-free, 49% "improved," and 24% unchanged [25]. However, controlled trials of 14 showed that only 2 were improved and 12 unchanged [67, 122, 147]. As with TMS, both potential placebo effects and reversion to the mean could explain the difference between controlled and open trial results. However, the small number of patients ($n = 14$) in the controlled trials makes it difficult to draw conclusions. Moreover, in a recent double-blind, randomized controlled study of bilateral superomedial cerebellar cortex stimulation in five patients, significant seizure frequency reductions for generalized tonic clonic seizures were reported [124]. Stimulation had to be stopped in one patient due to infection. Thus, the possible therapeutic role of cerebellar stimulation remains uncertain.

Caudate nucleus

Some animal data suggest that caudate stimulation might have an inhibitory effect on seizure activity emanating from subcortical as well as cortical stimulation or penicillin foci [68, 94, 139]. However, in some models, such as aluminum hydroxide in primate motor cortex, 10–100 Hz stimulation was inhibitory, while 100 Hz stimulation increased seizure frequency [98]. This effect might be due to caudate activation of the substantia nigra reticulata [33]. One clinical study found that ventral caudate stimulation at 4–6 Hz reduced neocortical and mesial temporal EEG discharges, but clinical seizure data were not reported [22].

Thalamus

Widespread cortical projections make the thalamus an attractive target for stimulation. Early work suggested

that the thalamus might be a cortical ''pacemaker'' [32, 107]. Thalamic stimulation was shown to stop seizures in a primate epilepsy model [145]. More recently, high frequency oscillations, probably generated by thalamic neuromodulatory circuits, were detected in neocortical epileptic foci [146]. Some studies suggest that thalamic stimulation may activate rather than inhibit neuronal activity, particularly cerebellothalamocortical pathways [85]. In hippocampal foci, evidence for external modulation is increasing as well [102]. Both electrophysiologic and anatomic evidence suggests that midline thalamic nuclei in particular may participate in modulation and spread of limbic seizures [14].

Centromedian nucleus

Although there are no strong monosynaptic connections between the centromedian nucleus (CM) and cortex, their firing patterns appear highly correlated, particularly in sleep [110, 125]. Typical cortical spike wave discharges and clinical absences can be produced by three-per-second CM stimulation [127]. Results of CM stimulation carried out as part of 'clinical care,' rather than in the context of a formal research study, have been reported in patients with a variety of seizure types. Frequencies ranged from 60 to 130 Hz, 2.5 to 5.0 V, 0.2 to 1.0 ms duration. Stimulation usually was bilateral carried out intermittently for several hours per day [126]. Definite improvement, judged qualitatively, was said to occur for generalized tonic-clonic seizures and atypical absences, but not for either complex partial seizures or focal spikes in temporal regions [128–131]. In contrast, a small double-blind, cross-over, placebo-controlled study of CM stimulation showed no significant benefit, although GTCS frequency decreased 30% compared to baseline when the stimulator was on, versus a decrease of 8% when the stimulator was off [43]. Stimulation was on or off in 3-month blocks, with a 3-month washout period in between, in an attempt to avoid carry-over effects. The results of this study do suggest, however, that there might be a small beneficial effect of CM stimulation on at least some seizure types.

Anterior thalamic nucleus

The anterior thalamus is part of the circuit of Papez, and studies using 2-deoxyglucose found markedly increased metabolism in guinea pig anterior thalamus [87]. Sectioning the connection between the mammillary bodies and the anterior thalamus in the guinea pig substantially increases the threshold for PTZ-induced seizures [86]. Stimulation of anterior thalamus (as well as posterior hypothalamus) at 100 Hz had an anticonvulsant effect for PTZ-induced seizures in rats, while 10–50 Hz stimulation was proconvulsant [88, 89]. Bilateral anterior thalamic nucleus lesions, as well as high-frequency stimulation also protect against pilocarpine-induced seizures [55]. Two small series of human anterior thalamic stimulation for intractable epilepsy have been reported. In five patients, with a variety of seizure types, who had stimulation through bilateral electrodes in anterior thalamus, a statistically significant mean reduction of 54% in seizure frequency was reported (mean follow-up, 15 months). However, the observed benefits did not differ between stimulation-on and stimulation-off periods, suggesting that either a placebo or carry-over effect was present [55]. In another five patients, bilateral anterior thalamus stimulation parameters were 100 cycles per second, pulse width, 90 ms, and voltages ranging between 1.0 and 10.0 V. Four of five were said to have improved generalized tonic clonic, and one, total seizure frequency [63].

Subthalamic nucleus (STN)

In animal models of epilepsy, widespread non-specific anterior and intralaminar thalamic nuclear, as well as substantia nigra (SN) and STN connections to mesial frontal, temporal, and limbic structures have been documented. Stimulation of STN, anterior thalamus, and SN inhibit limbic seizures [89, 133, 135]. Basal ganglia structures may modify propagation and manifestations of seizures, although no evidence of actual seizure initiation in this region has been found [33]. STN sharp waves, that may be an expression of direct cortico-STN glutamatergic pathways that could modulate the anti-seizure effect of stimulation, are closely linked to scalp recorded epileptiform activity [34]. Some studies have led to the concept of a 'dorsal midbrain anticonvulsant zone', near the superior colliculi, whose output could be affected by upstream stimulation at various sites [78]. This zone is under inhibitory control of efferent fibers from the substantia nigra pars reticulata. Inhibition of the STN could block the inhibitory effect of the substantia nigra pars reticulata on the dorsal midbrain anticonvulsant zone and thus activate the latter, raising the seizure threshold.

About ten reported patients with intractable epilepsy have had STN stimulation in uncontrolled studies [9, 18, 28, 78]. While some patients showed no improvement,

others had up to 80% reduction in seizure frequency. Side effects included mild facial twitching and numbness in the extremities, alleviated by adjustment of the stimulation parameters [18]. Interestingly, STN stimulation had no significant effect on motor cortex excitability measured using paired-pulse transcranial magnetic stimulation (TMS) [28]. In two patients with frontal lobe epilepsy, who had marked seizure frequency reduction during STN stimulation, increased rCBF was found in the frontal epileptogenic zones on subtraction SPECT; one patient had additional superior and inferior temporal hyperperfusion [148].

Cortical stimulation

Direct stimulation of the epileptic focus is another approach to neuromodulation in epilepsy. It will likely to combined with seizure-detection devices. In hippocampus, long term depression can be produced by low frequency stimulation [35]. In amygdala, low frequency stimuli by themselves led to synaptic facilitation in rat amygdala, but to inhibition when preceded by a condition high frequency stimulus [74]. There was a strong anti-epileptogenic effect of stimulation at 1 Hz for 15 min in both adult and immature rats, as measured by reduction in both after discharge duration and seizure stage induced by 60 Hz kindling [134]. One Hz stimulation of hippocampal CA3 suppressed entorhinal cortex discharges in mice [6].

Ten patients scheduled to have temporal lobectomy, and who had bilateral, depth, hippocampal or unilateral subdural, basal temporal electrodes were given 2–3 weeks of continuous 130 Hz electrical stimulation, delivered 23 h per day [132]. AEDs had been stopped before stimulation started, in order to record seizures. Seven of the patients had electrode contacts within the hippocampal formation or gyrus, and stimulation was uninterrupted. Clinical seizures were said to be abolished, and the number of focal interictal EEG spikes significantly decreased after 5–6 days of stimulation. In contrast, the three patients in whom stimulation was either interrupted or the contacts were outside the hippocampus had no response. In another open small series, 130–200 Hz amygdalo-hippocampal stimulation was used for three patients with intractable CPS [137]. Over a mean follow-up of 5 months, all three patients reported marked reduction in seizure frequency as well as decreased seizure severity. In two of the patients, antiepileptic drugs could be reduced. None of the patients reported side effects. In 17 patients undergoing preoperative mapping with subdural grids, brief bursts of 0.3-ms 50 Hz pulses of alternating polarity stopped stimulation-induced after-discharges, and possibly clinical seizures [73]. The human trials of direct seizure focus stimulation, in contrast to animal studies, have all used high frequency approaches that parallel the paradigms of subcortical DBS. In human and animal rTMS, low frequency stimulation is also inhibitory, while high frequency stimulation can produce seizures de novo. Activation or inhibition of upstream or downstream structures, in addition to than the target region itself could clearly play a role. rTMS may lead to fairly diffuse effects, while hippocampal stimulation via depth electrodes, although more precise, could still have more widespread effects than seen in the animal models.

Implantable seizure detection devices

Implantable devices incorporating seizure detection algorithms are now being used in clinical trials [76]. Rather than altering cortical excitability on a chronic basis via scheduled stimulation, these devices are expected to deliver stimulation to epileptogenic zones when the onset of ictal activity is detected. In order to implement this approach, it will be essential to have devices capable of predicting seizure onset or susceptibility reliably. Several prediction algorithms have been able to predict impending seizures with reasonable accuracy in small trials, although others have not [38, 57]. One problem may be the marked inter-patient heterogeneity of EEG patterns; an algorithm would have to be 'trained' individually for each patient to be useful [27].

Much of the data on which prediction algorithms have been based derives from invasive recordings. Ironically, an international workshop lamented that ''a decline in invasive monitoring due to better patient selection and improved functional imaging would eventually make a diverse archive of intracranial EEG more difficult to acquire in the future'' [70]. Additional obstacles to progress discussed at this workshop included the basic question of what defines an electroclinical seizure, and what the outcome variable for prediction studies should be. The computational intensity of the methods may complicate clinical application.

One study has reported using 100–500 Hz electrical stimulation triggered by automated seizure detections in eight patients, directly to the epileptogenic zone in four, and through anterior thalami to the others [100]. Both groups had 40–50% reductions in seizure rate during

stimulation. Another group reported a decrease of about 40% in seizures with direct focus stimulation via a closed loop seizure-detection algorithm, in 27 patients evaluated during invasive monitoring; short-term stimulation was well-tolerated [66]. Several controlled trials are in progress for intermittent cycling stimulation of the anterior nuclei of the thalamus, and for cortical stimulation at a seizure focus, responsive to detection of seizure onset [99].

Brain stimulation for depression in epilepsy

Depression is significantly increased in people with epilepsy, compared to the general population, and appears to be more common than in other chronic diseases such as diabetes [26, 39]. Moreover, depressive symptoms have a significant adverse effect on quality of life in epilepsy, independent of seizure frequency [79]. Some brain stimulation approaches might be helpful for depression, and would thus be particularly appropriate for epilepsy patients suffering from depression, particularly if it has not responded to standard drug therapy. VNS is approved in several regions, including the US, parts of Europe, and Canada for the treatment of drug-resistant depression. In uncontrolled trials, about 40% of patients are improved [49]. A long-term open study showed a 22% remission rate at two years [95]. In a subset of 11 patients drawn from a larger epilepsy efficacy trial, significant positive mood effects were found at 3 and 6 months, independent of seizure frequency reduction [36]. Children treated with VNS for refractory seizures also have been reported to show improved mood ratings [48]. TMS may be effective in treating depression as well. Many studies have used higher rates of stimulation that might be contraindicated in patients with epilepsy but it is not clear that these are needed for antidepressant effects [82]. An intriguing small study reported that four of six patients with severe depression showed marked improvement on stimulation of white matter tracts adjacent to the subgenual cingulate gyrus [83].

Selection of patients for brain stimulation

Patients with refractory epilepsy who may be candidates for brain stimulation fall into several possible epilepsy syndromes (Table 1). The most common are probably localization-related temporal lobe epilepsy (TLE) with complex partial (CPS) and secondarily generalized seizures (GTCS), and secondary generalized epilepsies, with a variety of seizure types, including ato-

Table 1. *Classification of clinical types, diagnosis and therapy of epilepsy*

Epilepsy type	Etiology	Clinical seizure types	Other clinical features	EEG	Neuroimaging	Therapy
Primary generalized epilepsy	most unknown, presumed genetic; rare ion channel genes implicated	Absence Myoclonic seizures GTCS	neurologic and neuropsychologic exam usually normal	interictal normal ictal shows regular generalized spike-wave	usually normal	usually excellent response to AEDs
Secondary generalized epilepsy	wide range of etiologies including metabolic disorders, cortical malformations, phakomatoses; many unknown	'atypical absence' myoclonic, tonic, clonic infantile spasms GTCS, CPS	highly variable features related to underlying disease; often developmental, neuropsychological, impairment	interictal slowing and frequent widespread epileptiform discharges ictal records often show irregular generalized spike-wave discharges	may show wide range of structural and developmental abnormalities	poor response to AEDs. very limited surgical options
Focal (localization-related)	focal lesions: developmental trauma infection neoplastic	SPS, CPS, GTCS	may have functional deficits related to seizure focus; usually mild	focal interictal discharges ictal discharges begin locally, may generalize	focal abnormalities may include limited cortical dysplasia, tumors, 'mesial temporal sclerosis'	variable response to AEDs. good candidates may have excellent outcome after focal resection

GTCS Generalized tonic-clonic seizures, *CPS* complex partial seizures, *SPS* simple partial seizures, *AEDS* antiepileptic drugs.

nic, myoclonic, and GTCS. The potential enrollment of these patients in clinical trials, particularly involving DBS, raises ethical as well as clinical issues. Many patients with TLE or other localization-related epilepsies who have not responded to AEDs will be candidates for resective surgery, and it is crucial to identify such patients using neuroimaging and video-EEG monitoring. Neither VNS, nor experimental invasive stimulation studies such should be considered until the possibility of resection, particularly temporal lobectomy, has been considered [5].

Patients with refractory secondary generalized epilepsies often are children, or adults with impaired cognitive function, and thus particularly vulnerable subjects for clinical trials. When procedures with more than minimal risk are considered, special care needs to be taken to address ethical concerns. Large, controlled clinical trials of neurostimulation have been completed only for VNS, and only for patients with localization-related epilepsy characterized by complex partial and secondary generalized seizures. VNS should be considered only after focal resection has been ruled out. Like most AEDs, it is a palliative therapy; very few patients become seizure-free. However, it does not appear to have any cognitive or systemic side effects, and is a useful adjunctive therapy for patients with that do not respond to antiepileptic drugs, or have unacceptable toxicity, and are not surgical candidates. Its costs approach those of surgical resection in patients who do not need intracranial monitoring. Some authors have suggested that VNS would be particularly appropriate for patients with both depression and epilepsy [46]. The role of VNS in the treatment of patients with seizure types other than partial and secondary generalized seizures, and epilepsy syndromes other than localization-related epilepsy, has not been established, and most reports have been disappointing.

Brain stimulation for epilepsy is not new. The electric torpedo fish may have been used by Dioscorides in 76 AD, and Leyden jars were tried in the 18th century [62]. Even for more modern studies, the initial claims for therapeutic success have not been confirmed by the very few controlled studies that have been conducted so far. This experience parallels that of experimental approaches for a wide range of disorders: early reports of therapeutic success are not often confirmed by controlled clinical trials [111]. The best structures to stimulate are unknown. There is a wide range of potential stimulus paradigms to test. It is vital that patients being considered for unproven brain stimulation studied be enrolled in well-controlled clinical trials.

References

1. Abosch A, Lozano A (2003) Stereotactic neurosurgery for movement disorders. Can J Neurol Sci 30 Suppl 1: S72–S82
2. Akamatsu N, Fueta Y, Endo Y, Matsunaga K, Uozumi T, Tsuji S (2001) Decreased susceptibility to pentylenetetrazole-induced seizures after low frequency transcranial magnetic stimulaiton in the rat. Neurosci Lett 310: 153–156
3. Alpman A, Serdaroglu G, Cogulu O, Tekgul H, Gokben S, Ozkinay F (2005) Ring chromosome 20 syndrome with intractable epilepsy. Dev Med Child Neurol 47: 343–346
4. Annegers J, Coan SP, Hauser, WA (2000) Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia 41: 549–553
5. Attarian H, Dowling J, Carter J, Gilliam F (2003) Video EEG monitoring prior to vagal nerve stimulator implantation. Neurology 12; 61(3): 402–403
6. Barbarosie M, Avoli M (1997) CA3-driven hippocampal-entorhinal loop controls rather than sustains in vitro limbic seizures. J Neurosci 17: 9308–9314
7. Barker AT (1999) The history and basic principles of magnetic nerve stimulation. In: Paulus W, Hallett M, Rossini PM, Rothwell JC (eds) Transcranial magnetic stimulation. EEG Clin Neurophysiol Suppl 51: 3–21
8. Begley CE, Famulari M, Annegers JF, Lairson DR, Reynolds TF, Coan S, Dubinsky S, Newmark ME, Leibson C, So EL, Rocca WA (2000) The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. Epilepsia 41: 342–351
9. Benabid AL, Minotti L, Koudsie A, de Saint Martin A, Hirsch E (2002) Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luysi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. Neurosurgery 50: 1385–1391
10. Benbadis SR, Nyhenhuis J, Tatum WO IV, Murtagh FR, Gieron M, Vale FL (2001) MRI of the brain is safe in patients implanted with the vagus nerve stimulator. Seizure 10: 512–515
11. Ben-Menachem E (2001) Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol 18: 415–418
12. Ben-Menachem E (2002) Vagus nerve stimulation for the treatment of epilepsy. Lancet Neurology 1: 477–482
13. Ben-Menachem E, Manon-Espaillat R, Ristanovic R *et al* (1994) Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. Epilepsia 35: 616–626
14. Bertram EH, Mangan PS, Zhang D, Scott CA, Williamson JM (2001) The midline thalamus: alterations and a potential role in limbic. Epilepsy Epilepsia 42: 967–978
15. Bridgers SL (1991) The safety of transcranial magnetic stimulation reconsidered: evidence regarding cognitive and other cerebral effects. Electroencephalogr Clin Neurophysiol Suppl 43: 170–179
16. Buoni S, Mariottini A, Pieri S, Zalaffi A, Farnetani MA, Strambi M, Palma L, Fois A (2004) Vagus nerve stimulation for drug-resistant epilepsy in children and young adults. Brain Dev 26: 158–163
17. Burneo JG, Tellez-Zenteno J, Wiebe S (2005) Understanding the burden of epilepsy in Latin America: a systematic review of its prevalence and incidence Epilepsy Res 66: 63–74
18. Chabardès S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid A-L (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus Epileptic disorders 4 Suppl 3: 83–93
19. Charous SJ, Kempster G, Manders E, Ristanovic R (2001) The effect of vagal nerve stimulation on voice. Laryngoscope 111: 2028–2031
20. Chen R, Classen J, Gerloff C, Celnik P, Wasserman EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by

low-frequency transcranial magnetic stimulation. Neurology 48: 1398–1403
21. Chen WR, Lee S, Kato K, Spencer DD, Shepherd GM, Williamson A (1996) Long-term modifications of synaptic efficacy in the human inferior and middle temporal cortex. PNAS 93: 8011–8015
22. Chkhenkeli SA, Chkhenkeli IS (1997) Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. Stereotact Funct Neurosurg 69(1–4 Pt 2): 221–224
23. Cooper I (1978) Cerebellar stimulation in man. Raven Press, New York, pp 1–212
24. Cox CL, Huguenard JR, Prince DA (1997) Nucleus reticularis neurons mediate diverse inhibitory effects in thalamus. Proc Natl Acad Sci USA 94: 8854–8859
25. Davis R, Emmonds SE (1992) Cerebellar stimulation for seizure control: 17-year study. Stereotact Funct Neurosurg 58: 200–208
26. Davies S, Heyman I, Goodman R (2003) Depression and comorbidity in community-based patients with epilepsy or asthma. Dev Med Child Neurol 45: 292–295
27. D'Alessandro M, Vachtsevanos G, Esteller R, Echauz J, Cranstoun S, Worrell G, Parish L, Litt B (2005) A multi-feature and multi-channel univariate selection process for seizure prediction. Clin Neurophysiol 116: 506–516
28. Däuper J, Peschel T, Schrader C, Kohlmetz C, Joppich G, Nager W, Dengler R, Rollnik JD (2002) Effects of subthalamic nucleus (STN) stimulation on motor cortex excitability. Neurology 59: 700–706
29. DeGiorgio CM, Schachter SC, Handforth A *et al* (2000) Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 41: 1195–1200
30. DeGiorgio CM, Shewmon DA, Whitehurst T (2003) Trigeminal nerve stimulation for epilepsy. Neurology 61: 421–422
31. DeGiorgio CM, Thompson J, Lewis P, Arrambide S, Naritoku D, Handforth A, Labar D, Mullin P, Heck C, VNS U.S. Study Group (2001) Vagus nerve stimulation: analysis of device parameters in 154 patients during the long-term XE5 study. Epilepsia 42: 1017–1020
32. Dempsey EW, Morison RS (1942) The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. Am J Physiol 135: 293–300
33. Deransart C, Depaulis A (2002) The control of seizures by the basal ganglia? A review of experimental data. Epileptic Disord 4 Suppl 3: S61–S72
34. Dinner DS, Neme S, Nair D, Montgomery EB Jr, Baker KB, Rezai Rb, Hans O, Luders HO (2002) EEG and evoked potential recording from the subthalamic nucleus fordeep brain stimulation of intractable epilepsy. Clin Neurophysiology 113: 1391–1402
35. Dudek SM, Bear MF (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci 89: 4363–4367
36. Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE (2000) Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 42: 203–210
37. Epstein CM, Schwartzberg DG, Davey KR, Sudderth DB (1990) Localizing the site of magnetic brain stimulation in humans. Neurology 40: 666–670
38. Esteller R, Echauz J, D'Alessandro M, Worrell G, Cranstoun S, Vachtsevanos G, Litt B (2005) Continuous energy variation during the seizure cycle: towards an on-line accumulated energy. Clin Neurophysiol 116: 517–526
39. Ettinger A, Reed M, Cramer J, Epilepsy impact project group (2004) Neurology 28; 63(6): 1008–1014
40. Fanselow EE, Reid AP, Nicolelis MA (2000) Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. J Neurosci 20: 8160–8168
41. Fisher RS (2003) Anterior thalamic nucleus stimulation: issues in study design, chapter 25, pp 307–322. In: Lüders H (ed) Deep brain stimulation and epilepsy. Martin Dunitz Inc. London and New York (in press)
42. Fisher RS, Handforth A (1999) Reassessment: vagus nerve stimulation for epilepsy: a report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology 53: 666–669
43. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP *et al* (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
44. Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD (2005) Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy. Stereotact Funct Neurosurg 83: 153–158
45. Fregni F, Schachter SC, Pascual-Leone A (2005) Transcranial magnetic stimulation treatment for epilepsy: can it also improve depression and vice versa? Epilepsy Behav 7: 182–189
46. Fregni F, Thome-Souza S, Bermpohl F, Marcolin MA, Herzog A, Pascual-Leone A, Valente KD (2005) Antiepileptic effects of repetitive transcranial magnetic stimulation in patients with cortical malformations: an EEG and clinical study stereotact funct neurosurg 83: 57–62
47. Galli R, Limbruno U, Pizzanelli C, Giorgi FS, Lutzemberger L, Strata G, Pataleo L, Mariani M, Iudice A, Murri L (2003) Analysis of RR variability in drug-resistant epilepsy patients chronically treated with vagus nerve stimulation. Auton Neurosci 29; 107(1): 52–59
48. Gates JR, Dhuna A, Pascual-Leone A (1992) Lack of pathologic changes in human temporal lobes after transcranial magnetic stimulation. Epilepsia 33: 504–508
49. Groves DA, Brown VJ (2005) Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev 29: 493–500
50. Hallbook T, Lundgren J, Stjernqvist K, Blennow G, Stromblad LG, Rosen I (2005) Vagus nerve stimulation in 15 children with therapy resistant epilepsy; its impact on cognition, quality of life, behaviour and mood. Seizure 14: 504–513
51. Hamani C, Ewerton FI, Bonilha SM, Ballester G, Mello LE, Lozano AM (2004) Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery 54: 191–195
52. Handforth A, DeGiorgio CM Schachter SC *et al* (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51: 48–55
53. Henry TR, Bakay RA, Votaw JR, Pennell PB, Epstein CM, Faber TL *et al* (1998) Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation. Epilepsia 39: 983–990
54. Henry TR, Votaw JR, Bakay RAE, *et al* (1998) Vagus nerve stimulation induced cerebral blood flow changes differ in acute and chronic therapy of complex partial seizures. Epilepsia 9 Suppl 6: 92
55. Henry TR, Votaw JR, Pennell PB, Epstein CM, Bakay RA, Faber TL *et al* (1999) Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. Neurology 52: 1166–1173
56. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
57. Hufnagel A, Elger CE, Klingmuller D, Zierz S, Kramer R (1990) Activation of epileptic foci by transcranial magnetic stimulation: effects on secretion of prolactin and luteinizing hormone. J Neurol 237: 242–246

58. Iasemidis LD, Shiau DS, Pardalos PM, Chaovalitwongse W, Narayanan K, Prasad A, Tsakalis K, Carney PR, Sackellares JC (2005) Long-term prospective on-line real-time seizure prediction. Clin Neurophysiol 116: 532–544
59. Iriarte J, Artieda J, Alegre M *et al* (2001) Spasm of the sternocleidomastoid muscle induced by vagal nerve stimulation. Neurology 57: 2319–2320
60. Ito S-I, Craig AD (2005) Vagal-evoked activity in the parafascicular nucleus of the primate thalamus. J Neurophysiol 94: 2976–2982
61. Jacobs MP, Fischbach GD, Davis MR, Dichter MA, Dingledine R, Lowenstein DH, Morrell MJ, Noebels JL, Rogawski MA, Spencer SS, Theodore WH (2001) Future directions for epilepsy research. Neurology 13; 57(9): 1536–1542
62. Jennum P, Klitgaard H (1996) Repetitive transcranial magnetic stimulations of the rat. Effect of acute and chronic stimulations on pentylenetetrazole-induced clonic seizures. Epilepsy Res 23: 115–122
63. Kellaway P (1946) The part played by electric fish in the early history of bioelectricity and electrotherapy. Bull Hist Med 20: 112–137
64. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy Epilepsia 45: 346–354
65. Ko D, Heck C, Grafton S, Apuzzo ML, Couldwell WT, Chen T *et al* (1996) Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging. Neurosurgery 39: 426–430
66. Kobayashi M, Pascual-Leone A (2003) Transcranial magnetic stimulation in neurology. Lancet Neurology 2: 145–156
67. Krauss GL, Fisher RS (1993) Cerebellar and thalamic stimulation for epilepsy. Adv Neurol 63: 231–245
68. La Grutta V, Sabatino M, Gravante G, Morici G, Ferraro G, La Grutta G (1998) A study of caudate inhibition on an epileptic focus in the cat hippocampus. Arch Int Physiol Biochim 96: 113–120
69. Lee H-W, Seo HJ, Cohen LG, Bagic A, Theodore WH (2005) Cortical excitability during prolonged antiepileptic drug treatment and drug withdrawal. Clin Neurophysiology 116: 1105–1112
70. Lehnertz K, Litt B (2005) The first international collaborative workshop on seizure prediction: summary and data description. Clin Neurophysiol 116: 493–505
71. Leidy NK, Elixhauser A, Vickrey B, Means E, Willian MK (1999) Seizure frequency and the health-related quality of life of adults with epilepsy. Neurology 13; 53(1): 162–166
72. Leonardi M, Ustun TB (2002) The global burden of epilepsy. Epilepsia 43 Suppl 6: 21–25
73. Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, Cysyk B, Krauss G, Gordon B (1999) Brief bursts of pulse stimulation terminate after discharges caused by cortical stimulation. Neurology 53: 2073–2081
74. Li H, Weiss SRB, Chuang D-M, Post RM, Rogawski M (1998) Bidirectional synaptic plasticity in the rat basolateral amygdala: characterization of an activity-dependent switch sensitive to the presynaptic metabotropic glutamate receptor 2S-a-ethylglutamic acid. J Neuroscience 18: 1662–1670
75. Liporace J, Hucko D, Morrow R *et al* (2001) Vagal nerve stimulation: adjustments to reduce painful side effects. Neurology 11; 57(5): 885–886
76. Litt B, Echauz J (2002) Prediction of epileptic seizures. Lancet Neurology 1: 22–30
77. Liu W-C, Mosier K, Kalnin AJ Marks D (2003) BOLD fMRI activation induced by vagus nerve stimulation in seizure patients. J Neurol Neurosurg Psychiatry 74: 811–813
78. Loddenkemper T, Pan A, Neme S (2001) Deep brain stimulation in epilepsy. J Clin Neurophysiol 18: 514–532
79. Loring DW, Meador KJ, Lee GP (2004) Determinants of quality of life in epilepsy. Epilepsy Behav 5: 976–980
80. Lundgren J, Ekberg O, Olsson R (1998) Aspiration: a potential complication to vagus nerve stimulation. Epilepsia 39: 998–1000
81. Malow BA, Edwards J (2001) Vagus nerve stimulation reduces daytime sleepiness in epilepsy patients. Neurology 11; 57(5): 879–884
82. Martin JL, Barbanoj MJ, Schlaepfer TE, Clos S, Perez V, Kulisevsky J, Gironell A (2002) Transcranial magnetic stimulation for treating depression. Cochrane Database Syst Rev (2): CD003493
83. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. Neuron 3; 45(5): 651–660
84. Menkes DL, Gruenthal M (2000) Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. Epilepsia 4: 240–242
85. Molnar GF, Sailer A, Gunraj CA, Cunic DI, Lang AE, Lozano AM, Moro E, Cehn R (2005) Changes in cortical excitability with thalamic deep brain stimulation. Neurology 64: 1913–1919
86. Mirski MA, Ferrendelli JA (1984) Interruption of the mammillothalamic tract prevents seizures in guinea pigs. Science 226: 72–74
87. Mirski MA, Ferrendelli JA (1986) Anterior thalamic mediation of generalized pentylenetetrazol seizures. Brain Res 399: 212–223
88. Mirski MA, Fisher RS (1994) Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. Epilepsia 35: 1309–1316
89. Mirski MA, Rossell LA, Terry JB, Fisher RS (1997) Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 28: 89–100
90. Murphy JV (1999) Left vagal nerve stimulation in children with medically refractory epilepsy. Pediatric VNS Study Group J Pediatr 134: 563–566
91. Murphy JV, Hornig GW, Schallert GS, Tilton CL (1998) Adverse events in children receiving intermittent left vagal nerve stimulation. Pediatr Neurol 19: 42–44
92. Murphy JV, Torkelson R, Dowler I, Simon S, Hudson S (2003) Vagal nerve stimulation in refractory epilepsy: the first 100 patients receiving vagal nerve stimulation at a pediatric epilepsy center. Arch Pediatr Adolesc Med 157: 560–564
93. Murphy JV, Wheless JW, Schmoll CM (2000) Left vagal nerve stimulation in six patients with hypothalamic hamartomas. Pediatr Neurol 23: 167–168
94. Mutani R (1969) Experimental evidence for the existence of an extrarhinencephalic control of the activity of the cobalt rhinencphalic epileptogenic focus. Part 1: the role played by the caudate nucleus. Epilepsia 10: 337–350
95. Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, Martinez JM, George MS (2005) Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 66: 1097–1104
96. Narayanan JT, Watts R, Haddad N, Labar DR, Li PM, Filippi CG (2002) Cerebral activation during vagus nerve stimulation: a functional MR study. Epilepsia 43: 1509–1514
97. Ndoye NF, Sow AD, Diop AG, Sessouma B, Sene-Diouf F, Boissy L, Wone I, Toure K, Ndiaye M, Ndiaye P, de Boer H, Engel J, Mandlhate C, Meinardi H, Prilipko L, Sander JW (2005) Prevalence of epilepsy its treatment gap and knowledge, attitude and practice of its population in sub-urban Senegal an ILAE/IBE/WHO study. Seizure 14: 106–111
98. Oakley JC, Ojemann GA (1982) Effects of chronic stimulation of the caudate nucleus on a preexisting alumina seizure focus. Exp Neurol 75: 360–367

99. Oommen J, Morrell M, Fisher RS (2005) Experimental electrical stimulation therapy for epilepsy. Curr Treat Options Neurol 7: 261–271
100. Osorio I, Frei MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB (2005) Automated seizure abatement in humans using electrical stimulation. Ann Neurol 57: 258–268
101. Parain D, Penniello MJ, Berquen P, Delangre T, Billard C, Murphy JV (2001) Vagal nerve stimulation in tuberous sclerosis complex patients. Pediatr Neurol 25: 213–216
102. Parish LM, Worrell GA, Cranstoun SD, Stead SM, Pennell P, Litt B (2004) Long-range temporal correlations in epileptogenic and non-epileptogenic human hippocampus. Neuroscience 125: 1069–1076
103. Parker AP, Polkey CE, Binnie CD, Madigan C, Ferrie C, Robinson RO (1999) Vagal nerve stimulation in epileptic encephalopathies. Pediatrics 103(4 Pt 1): 821
104. Patwardhan RV, Dellabadia J Jr, Rashidi M, Grier L, Nanda A (2005) Control of refractory status epilepticus precipitated by anticonvulsant withdrawal using left vagal nerve stimulation: a case report. Surg Neurol 64: 170–173
105. Patwardhan RV, Stong B, Bebin EM, Mathisen J, Grabb PA (2000) Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. Neurosurgery 47: 1353–1357
106. Penberthy LT, Towne A, Garnett LK, Perlin JB, DeLorenzo RJ (2005) Estimating the economic burden of status epilepticus to the health care system. Seizure 14: 46–51
107. Penfield W, Jasper H (1954) Epilepsy and the functional anatomy of the human brain. Little Brown and Co., Boston
108. Petrucci M, Hoh C, Alksne JF (2003) Thalamic hypometabolism in a patient undergoing vagal nerve stimulation seen on F-18 FDG PET imaging. Clin Nucl Med 28: 784–785
109. Reid AE, Chiappa KH, Cros D (2002) Motor threshold, facilitation and the silent period in cortical magnetic stimulation. In: Pascual-Leone A, Davey NJ, Rothwell J, Wasserman EM, Puri BK (eds) Handbook of transcranial magnetic stimulation. Arnold, London, pp 97–111
110. Royce GJ (1983) Single thalamic neurons which project to both the rostral cortex and caudate nucleus studied with the fluorescent double labeling method. Exp Neurol 79: 773–784
111. Sacks HS, Chalmers TC, Smith H Jr (1983) Sensitivity and specificity of clinical trials. Randomized v historical controls. Arch Intern Med 143(4): 753–755
112. Salinsky MC, Uthman BM, Ristanovic RK, Wernicke JF, Tarver WB, Vagus nerve stimulation study group (1996) Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Arch Neurol 53(11): 1176–1180
113. Sobocki J, Krolczyk G, Herman RM, Matyja A, Thor PJ (2005) Influence of vagal nerve stimulation on food intake and body weight – results of experimental studies. J Physiol Pharmacol 56 Suppl 6: S27–S33
114. Speer AM, Kimbrell TA, Wassermann EM, Repella DJ, Willis MW, Herscovitch P, Post RM (2000) Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 48: 1133–1141
115. Tatum WO 4th, Moore DB, Stecker MM, Baltuch GH, French JA, Ferreira JA, Carney PM, Labar DR, Vale FL (1999) Ventricular asystole during vagus nerve stimulation for epilepsy in humans. Neurology 52: 1267–1269
116. Taylor RB, Wennberg RA, Lozano AM, Sharpe JA (2000) Central nystagmus induced by deep-brain stimulation for epilepsy. Epilepsia 41(12): 1637–1641
117. Tergau F, Naumann U, Paulus W, Steinhoff BJ (1999) Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. Lancet 353: 2209
118. Tergau F, Neumann D, Rosenow R, Nitsche MA, Paulus W, Steinhoff BJ (2002) Low frequency repetitive transcranial magnetic stimulation for treatment of drug-resistant epilepsy. Interim analysis of a placebo-controlled study. Epilepsia 43 Suppl 7: S53
119. The Vagus Nerve Stimulation Study Group (1995) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology 45: 224–230
120. Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer R, Werhahn K, Kelley KR, Cohen L (2002) Transcranial magnetic stimulation for the treatment of seizures: a controlled study. Neurology 59: 560–562
121. Tubbs RS, Patwardhan R, Palmer CA, Kelly DR, Elton S, Blount JP, Bebin M, Grabb PA (2001) Histological appearance of a chronically stimulated vagus nerve in a pediatric patient. Pediatr Neurosurg 35: 99–102
122. van Buren JM, Wood JH, Oakley J, Hambrecht F (1978) Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg 48: 407–416
123. Van Laere K, Vonck K, Boon P, Brans B, Vandekerckhove T, Dierckx R (2000) Vagus nerve stimulation in refractory epilepsy: SPECT activation study. J Nucl Med 41: 1145–1154
124. Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, Davis R (2005) Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 46: 1071–1081
125. Velasco F, Velasco M, Cepeda C, Munoz H (1979) Wakefulness-sleep modulation of thalamic multiple unit activity and EEG in man. Electroencephalogr Clin Neurophysiol 47: 597–606
126. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28: 421–430
127. Velasco F, Velasco M, Marquez I, Velasco G (1993) Role of the centromedian thalamic nucleus in the genesis, propagation and arrest of epileptic activity. An electrophysiological study in man. Acta Neurochir Suppl 58: 201–204
128. Velasco F, Velasco M, Velasco AL, Jimenez F (1993) Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity. Epilepsia 34: 1052–1064
129. Velasco F, Velasco M, Jimenez F, Velasco AL, Brito F, Rise M *et al* (2000) Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery 47: 295–304
130. Velasco F, Velasco M, Jimenez F, Velasco AL, Marquez I (2001) Stimulation of the central median thalamic nucleus for epilepsy. Stereotact Funct Neurosurg 77: 228–232
131. Velasco M, Velasco F, Velasco AL, Jimenez F, Brito F, Marquez I (2000) Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. Arch Med Res 31: 304–315
132. Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F *et al* (2000) Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41: 158–169
133. Velísek L, Velísková J, Moshé SL (2002) Electrical stimulation of substantia nigra pars reticulata is anticonvulsant in adult and young male rats. Exp Neurol 173: 145–152
134. Velíšek L, Velíšková J, Stanton PK (2002) Low-frequency stimulation of the kindling focus delays basolateral amygdala kindling in immature rats. Neurosci Lett 326: 61–63
135. Vercueil L, Benazzouz A, Deransart C, Bressand K, Marescaux C, Depaulis A, Benabid AL (1998) High-frequency stimulation of the

subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. Epilepsy Res 31: 39–46
136. Vonck K, Boon P, Van Laere K, D'Have M, Vandekerckhove T, O'Connor S *et al* (2000) Acute single photon emission computed tomographic study of vagus nerve stimulation in refractory epilepsy. Epilepsia 41: 601–609
137. Vonck K, Boon P, Achten E, De Reuck J, Caemaert J (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 52: 556–565
138. Vonck K, Van Laere K, Dedeurwaerdere S, Caemaert J, De Reuck J, Boon P (2001) The mechanism of action of vagus nerve stimulation for refractory epilepsy. J Clin Neurophysiol 18: 394–401
139. Wagner HR, Feency DM, Gullotta FP, Cote IL (1975) Suppression of cortical epileptiform activity by generalizing and localized EcoG desynchronization. Electroencephalogr Clin Neurophysiology 39: 499–506
140. Walker BR, Easton A, Gale K (1999) Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. Epilepsia 40: 1051–1057
141. Wassermann EM, Lisanby SH (2001) Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 112: 1367–1377
142. Wasserman EM (2002) Safety and side effects of transcranial magnetic stimulation and repetitive transcranial magentic stimulation. In: Pascual-Leone A, Davey NJ, Rothwell J, Wasserman EM, Puri BK (eds) Handbook of transcranial magnetic stimulation. Arnold, London, pp 39–49
143. Wedegaertner F, Garvey M, Cohen LG, Hallett M, Wasserman EM (1997) Low frequency repetitive transcranial magnetic stimulation can reduce action myoclonus (abstract). Neurology 48 Suppl: A19
144. Weibe S, Blume WT, Girvin JP, Eliasziw M (2001) The effectiveness and efficiency of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 345: 311–318
145. Wilder BJ, Schmidt RP (1965) Propagation of epileptic discharge from chronic neocortical foci in monkey. Epilepsia 6: 296–309
146. Worrell GA, Parish L, Cranstoun SD, Jonas R, Baltuch G, Litt B (2004) High-frequency oscillations and seizure generation in neocortical epilepsy. Brain 127(Pt 7): 1496–1506
147. Wright GD, McLellan DL, Brice JG (1984) A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatr 47: 769–774
148. Shon YM, Lee KJ, Kim HJ, Chung YA, Ahn KJ, Kim YI, Yang DW, Kim BS (2005) Effect of chronic deep brain stimulation of the subthalamic nucleus for frontal lobe epilepsy: subtraction SPECT analysis. Stereotact Funct Neurosurg 83: 84–90

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Clinical experience with vagus nerve stimulation and deep brain stimulation in epilepsy

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Summary

Patients with refractory epilepsy present a particular challenge to new therapies. Vagus nerve stimulation (VNS) for the control of intractable seizures has become available since 1989. VNS is a relatively non-invasive treatment. It reduces seizure frequency by $\geq$50% in 1/3 of patients; an additional 1/3 of patients experience a worthwhile reduction of seizure frequency between 30 and 50%. In the remaining 1/3 of the patients there is little or no effect. Efficacy has a tendency to improve with longer duration of treatment up to 18 months postoperatively. Deep brain stimulation (DBS) or direct electrical stimulation of brain areas is an alternative neurostimulation modality. The cerebellum, various thalamic nuclei, the pallidum, and, more recently, medial temporal lobe structures have been chosen as targets. DBS for epilepsy is beyond the stage of proof-of-concept but still needs thorough evaluation in confirmatory pilot studies before it can be offered to larger patient populations. Analysis of larger patient groups and insight in the mode of action may help to identify patients with epileptic seizures or syndromes that respond better either to VNS or to DBS. Randomized and controlled studies in larger patient series are mandatory to identify the potential treatment population and optimal stimulation paradigms. Further improvements of clinical efficacy may result from these studies.

Keywords: Neuromodulation; epilepsy; vagus nerve stimulation; deep brain stimulation; amygdalohippocampal stimulation; VNS; DBS.

Introduction

Epilepsy is the second most common chronic neurological disorder affecting 0.5–1% of the population [21]. Approximately, 70% of patients become seizure-free when adequately treated with antiepileptic drugs (AEDs). However, 30–40% of patients continue to have seizures and/or experience unacceptable side effects. These patients have 'refractory epilepsy' [51]. Alternative treatment modalities for such patients include trials with newly developed AEDs, epilepsy surgery and neurostimulation. The administration of a *new AED* to refractory patients results in seizure freedom in only a small percentage of patients [24]. Repeated inclusion in trials with newly developed AEDs may be associated with a low quality of life. *Epilepsy surgery* is a treatment for medically refractory patients in whom the 'epileptogenic zone' that is responsible for the generation of the habitual seizures can be identified and resected. Epilepsy surgery requires a thorough presurgical evaluation including long-term video-EEG monitoring, optimum MRI, FDG-PET and neuropsychological evaluation [5]. In about 10% of patients, invasive video-EEG monitoring using subdural and/or depth electrodes is mandatory to localize the epileptogenic zone. Epilepsy surgery results in seizure freedom in 60–95% of cases. However, at least 50% of presurgical candidates will eventually not undergo resective surgery because a single and resectable epileptogenic zone could not be identified. These patients have little therapeutic options left. *Vagus nerve stimulation* (*VNS*) for the control of intractable seizures has become available since 1989. It consists of the electrical stimulation of the tenth cranial nerve in the neck by means of an implantable NCP^{TM} device. Compared to epilepsy surgery VNS is a relatively non-invasive treatment. It reduces seizure frequency with $\geq$50% in one third of patients and has minor side effects such as intermittent hoarseness [7].

Deep brain stimulation (*DBS*) or direct electrical stimulation of brain areas is an alternative neurostimulation modality. In the past, central nervous system structures such as the cerebellum, various thalamic nuclei and the pallidum have been chosen as targets [26]. DBS in medial temporal lobe structures for control of seizures has only recently been described [44]. In a small number of patients with complex partial seizures requiring invasive

video-EEG monitoring for localizing purposes, stimulation proved to be efficacious during a two-week period of stimulation using temporary depth electrodes. In these patients a temporal lobectomy was subsequently performed as the recording electrodes that were used for invasive video-EEG monitoring were unsuitable for long-term stimulation. In an open pilot trial, amygdalohippocampal DBS significantly reduced seizure frequency during long-term follow-up without important side effects but no controlled studies have been performed.

Vagus nerve stimulation

Historical and anatomical considerations

The first vagus nerve stimulator was implanted in humans in 1989. However, the historical basis of peripheral stimulation for treating seizures dates back to centuries ago. In the sixteenth and seventeenth century physicians described the use of a ligature around the limb in which a seizure commences to arrest its progress. Gowers reported several ways by which sensory stimulation could prevent seizures from spreading e.g. pinching of the skin and inhalation of ammonia. Almost a hundred years later, Rajna and Lona demonstrated that afferent sensory stimuli can abort epileptic paroxysms in humans [33]. The vagus nerve is a mixed cranial nerve that consists of ~80% afferent fibers originating from the heart, aorta, lungs and gastrointestinal tract and of ~20% efferent fibers that provide parasympathetic innervation of these structures and also innervate the voluntary striated muscles of the larynx and the pharynx [1, 12, 32]. Somata of the efferent fibers are located in the dorsal motor nucleus and nucleus ambiguus, respectively. Afferent fibers have their origin in the nodose ganglion and primarily project to the nucleus of the solitary tract. The nucleus of the solitary tract has widespread projections to numerous areas in the forebrain as well as the brain stem including important areas for epileptogenesis such as the amygdala and the thalamus. There are direct neural projections into the raphe nucleus, which is the major source of serotonergic neurons and indirect projections to the locus coeruleus and A5 nuclei that contain noradrenegic neurons. Finally, there are numerous diffuse cortical connections. The diffuse pathways of the vagus nerve mediate important visceral reflexes such as coughing, vomiting, swallowing, control of blood pressure and heart rate [36].

The current rationale for vagus nerve stimulation to treat epileptic seizures is that stimulation of its diffuse connections to the brain can have a widespread influence on numerous CNS structures. There is substantial evidence that the nucleus of the solitary tract as well as the locus coeruleus are involved when the vagus nerve is stimulated [23, 31, 50]. Evoked potentials during stimulation of the vagus nerve were recorded in the cerebral cortex, hippocampus, thalamus and cerebellum [17]. Results of research in the mechanisms of action will be discussed in a separate chapter.

Results of clinical trials of vagus nerve stimulation in epilepsy

Acute effect and side effects

Five (EO1–EO5) acute-phase clinical studies involving the NCP System have been conducted in a total population of 454 patients. The purpose of the studies was to determine whether adjunctive use of electrical stimulation of the left vagus nerve could reduce seizure frequency in patients with refractory epilepsy [4, 16, 18, 34]. The stimulation parameters that were typically used are described in Table 1.

The EO1 and EO2 studies were two pilot studies that enrolled 15 patients with refractory partial epilepsy, of whom, 14 received stimulation. In one patient, the NCP device was explanted because of a surgical complication that resulted in unilateral vocal cord paralysis, which resolved 9 months later. The degree of response ranged from no improvement to complete cessation of seizures with a mean reduction of 46%. In none of the patients did the seizure disorder appear to have been exacerbated by VNS. Of 14 patients, 5 reported a reduction in seizure frequency of at least 50%. None of the patients reported transient or permanent serious side effects. The most common side effects were noted only during actual stim-

Table 1. *Stimulation parameters available with the NCP™ system*

Parameter	Units	Range	Typical parameter value
Output current	Milliamperes (mA)	0–3.5 mA	1.25 mA
Signal frequency	Hertz (Hz)	1–143 Hz	30 Hz
Pulse width	Microseconds (μs)	130–1000 μs	500 μs
Signal on-time	Seconds (s)	7 s (rapid cycle) – 270 s	30
Signal off-time	Seconds-minutes (s, min)	14 s (rapid cycle) – 180 min	5 min
Lead impedance	Kiloohms (Kohms)	<1–7 Kohms	3–4 Kohms

ulation of the nerve and consisted of hoarseness and local neck/throat paresthesia. These effects became milder after a few months of stimulation. No cardiac or gastrointestinal negative effects were observed on ECG monitoring and measurements of gastric acid output.

The EO3 (114 patients) and EO5 (196 patients) studies were both randomized, blinded, active control trials in which patients with refractory partial epilepsy were randomly assigned into two treatment groups. Patients assigned to treatment with 'high' stimulation parameters (30 Hz, 30 s on, 5 min off, 500 μs pulse width) were believed to receive therapeutic treatment. Treatment with 'low' stimulation parameters (1 Hz, 30 s on, 90–180 min off, 130 μs pulse width) was considered to be non-therapeutic. The primary efficacy endpoint was the percentage reduction in seizure rate measured over a period of 12 weeks. Adverse events were assessed at each patient visit. In the high stimulation groups, there was a mean reduction in seizure frequency of 24 and 28% in the EO3 and EO5 studies, respectively. This is a statistically significant decrease in seizure frequency when compared with baseline seizure frequency and seizure frequency reduction in the low stimulation groups (6 and 15%, respectively). The most common treatment related adverse events were attributable to vagal innervation of the larynx during current 'on' periods and consisted of voice alteration, coughing, throat paresthesia and discomfort and dyspnea. Treatment was well tolerated with 97% of patients continuing in the long-term follow-up phase of the study. Surgery-related complications included left vocal cord paralysis in two patients, lower facial muscle paresis in two patients, fluid accumulation over the generator requiring aspiration in one patient. All these complications resolved. Infection around the device occurred in three patients. VNS had no effect on concurrent AED serum levels or on body chemistry. Rigorous blinded collection of autonomic measures revealed no effect on weight, serum gastrin, cardiac or pulmonary function tests. Administered at levels that do not exceed comfort electrical stimulation of the left vagus nerve, VNS has no demonstrable effects on visceral functions.

The EO4 study was an open study in which 116 patients with all types of epilepsy and patients under 12 were stimulated. In this study, 29% of the implanted patients had a seizure reduction of more than 50%.

Long-term efficacy and safety

Long-term data (>3 months) were collected on all available EO1 through EO4 study patients. These long-term follow-up data are uncontrolled because they come from an open-label protocol in which both the AED medications and NCP device settings were allowed to be changed. Patients initially randomized to low stimulation parameters were changed to high stimulation parameters. George *et al.* reported 18-months efficacy analysis in 50 patients exiting the EO3 study and Salinsky *et al.* reported efficacy data in 100 of 114 patients from the EO3 study that were treated for 1 year [15, 35]. Results indicated that VNS remains effective over time; a trend towards improved seizure control with longer use of VNS was observed. Response during the first three months of treatment is predictive of long-term response. Chronic side effects were identical to those observed during the randomized trials and consisted mainly of mild hoarseness during stimulus delivery. Several other reports on long-term treatment with VNS confirm these findings [48]. Ben-Menachem recently published data on 64 patients with a follow-up up to 5 years [3]. The study included patients with partial seizures, Lennox-Gastaut syndrome (LGS) and primary generalized seizures (PGS). Forty-four percent of patients experienced a large reduction in seizure frequency and severity over long periods of time. VNS seems equally efficacious for LGS and PGS but results from larger patient groups are necessary. In a large patient series from two geographically distinct epilepsy centers located in two different continents, VNS proved to be efficacious and safe during long-term follow-up [49]. A total of 118 of 131 implanted patients had a mean reduction in monthly seizure frequency of 55% during a minimum post-implantation follow-up period of 6 months (mean: 33 months). Seven percent of patients were free of seizures with impaired consciousness, 50% of patients had a seizure frequency reduction of more than 50, and 21% of patients were non-responders. Fifteen patients reported stimulation-related side effects such as hoarseness or gagging.

From what is currently known from long-term studies VNS remains efficacious and safe. Little specific information on the effect of VNS on pregnancy is available but so far no teratogenic effects have been demonstrated and patients who became pregnant have given birth to healthy babies.

Experience in children

Experience with VNS in children is less extensive than in adults but results seem promising. Two studies report seizure frequency reductions of >60 in 80% of children and >50 in 38% of children [20, 27]. A study in 60 children with mean age of 15 years reported a

reduction in seizure frequency similar to that in adults [30]. Median reduction of seizure frequency was 44%. A gradual increase in efficacy up to 18 months postoperatively was observed. The predominant seizure type in this study was complex partial (57%) followed by generalized tonic-clonic seizures (27%). No seizure or epilepsy type appeared particularly sensitive or resistant to VNS. Adverse events during stimulation included fever, coughing, colds and voice alteration [28]. Randomized controlled trials are needed to more conclusively evaluate VNS in children.

Cost considerations

VNS is a costly treatment. Few cost-benefit data are available. One study showed that there is a significant decrease in epilepsy related direct medical costs (ERDMC) after implantation with the vagus nerve stimulator [8]. This decrease is mainly due to an important decrease in the number of hospital admission days after implantation. It is estimated that the cost of the device can be paid back by savings in ERDMC after 2.5 years. Battery life now exceeds 5 years. A subsequent study on hospital admission costs confirmed these findings [2].

Decision tree and current practical management

In most epilepsy centers, VNS has become a commonly performed treatment for patients with refractory epilepsy. Patients with refractory epilepsy who are referred to an epilepsy center are initially included in a presurgical evaluation protocol including video-EEG monitoring, optimum MRI, PET and neuropsychological examination. Video-EEG monitoring is especially important to exclude patients with non-epileptic seizures. A reasonable working definition of medical intractability would be: failure to respond adequately to three critically selected antiepileptic medications, appropriate for the patient's seizure type. Results of the presurgical investigations are discussed in the epilepsy surgery meeting by a multidisciplinary team. If a patient is considered an 'ideal focal resective surgical candidate' on the basis of these investigations, resective surgery should be offered to the individual, as preferred, instead of VNS. From recent studies, the results of the surgical intervention show a 70–75% seizure free rate with 1% morbidity [40]. Clearly this procedure offers a potentially superior outcome compared to VNS. Nonetheless, the patient should obviously be given the informed choice of the two procedures. In cases where functional tissue coexists with epileptogenic tissue as determined by surface recording, or where intracranial electrodes are required to clarify that point, VNS may be offered as a preferred option before proceeding to a resection or invasive recording with a greater inherent morbidity risk [38]. Similarly for neocortical epilepsy, whether temporal or extratemporal, in the absence of a demonstrable lesion in a clearly surgically accessible location, the published odds of seizure free surgical outcome are in the 30–50% range. Therefore, VNS is certainly a reasonable alternative to cortical resection, especially if intracranial electrodes are required [42]. With a clearly identifiable lesion on MRI located in a surgically accessible location, focal resection with 50–90% seizure-free results is seen [29]. For these cases, focal resection is preferred over VNS.

Recent studies strongly suggest that VNS may have significant efficacy comparable to corpus callosotomy that is associated with a somewhat higher morbidity rate of 3–5% [14]. In the absence of a cortical resection option, VNS can be considered a preferred alternative to callosotomy.

Patients who previously underwent epilepsy surgery with insufficient outcome may also be candidates for VNS. In these patients especially, the existence of non-epileptic seizures should be ruled out. Re-evaluation of the patient investigating the reason for insufficient outcome should be performed and re-operation should be considered [37]. If there is no sufficient evidence that a second operation can significantly improve the patients seizure control, VNS is a preferred alternative. There is limited information in the literature however how efficient VNS can be in these patients as well as on the number of patients becoming seizure free. Absolute contraindications for implantation of a vagus nerve stimulator are limited to previous left or bilateral cervical vagotomy. A stimulator will not be implanted when there is evidence of progressive intracerebral disease. Other conditions that need special attention are cardiac arrhythmias, respiratory diseases like asthma, pre-existing hoarseness, gastric ulcers, vasovagal syncope and coexisting neurological diseases other than epilepsy. Patients who were evaluated for epilepsy surgery several years ago, when treatment with a vagus nerve stimulator was not yet routinely available, are rediscussed during an epilepsy surgery team meeting and will be re-evaluated with MRI or other investigations when necessary. Consequently, for a patient who has failed three medications, who does not have non-epileptic seizures accounting for medical intractability and who is less than the ideal focal

resection candidate, VNS appears to be a viable option [13]. Certainly, if temporal lobectomy can be performed without risking functional cortex, this would be the preferred course of action. For lesional surgery where clear localization of epileptogenesis can be located by surface recording in neocortical locations, local cortical resection is the preferred route, due to higher incidence of seizure-free rates. However, even in these cases, VNS should be offered to patients as an option. Compared to corpus callosotomy, VNS is a much less invasive procedure with a lower morbidity rate and appears to have comparable efficacy.

Patients should be extensively informed about the efficacy, side effects, implantation procedure and ramping up procedure.

Deep brain stimulation for temporal lobe epilepsy

Historical and anatomical considerations

Deep brain stimulation (DBS) or direct electrical stimulation of specific brain areas could be another alternative neurostimulation modality. In the past, central nervous system structures such as the cerebellum, the anterior and centromedian thalamic nucleus, the caudate nucleus and the mammillary bodies have been chosen as DBS targets in different types of epilepsy in humans resulting in variable seizure control [10, 11, 41, 43, 53]. These studies targeted nuclei that have direct or indirect connections with structures playing an important role in seizure generation or propagation.

Amygdalohippocampal deep brain stimulation

Rationale

Electrical seizure onset in the amygdala and hippocampus (AH) is the key feature of the medial temporal lobe epilepsy syndrome [39]. About 10% of patients with refractory epilepsy are scheduled for *invasive* video-EEG monitoring to localize the ictal onset zone during presurgical evaluation [6]. Another approach consists of specifically targeting the area of presumed ictal onset e.g. medial temporal lobe structures in limbic epilepsy. Acute DBS in medial temporal lobe structures for control of seizures has only recently been described [45]. In a small number of patients, with complex partial seizures requiring invasive video-EEG monitoring for localizing purposes, unilateral DBS decreased interictal and ictal epileptic activity during a two-week period using temporary depth electrodes. The recording electrodes that were used for invasive video-EEG monitoring are unsuitable for long-term DBS and had to be removed. Subsequently all patients underwent a temporal lobectomy. Performing *chronic* DBS implies removal of recording electrodes and replacement by chronic DBS electrodes. Because the purpose is to stimulate the ictal onset zone, replacement of electrodes should be anatomically as accurate as possible. Even with currently available neuronavigation technology positioning of a second electrode in exactly the same position as the initial one is difficult. We have therefore studied the feasibility of recording intracranial EEG activity for localizing purposes and subsequent long-term DBS of the identified ictal onset zone using the same electrodes with the aim to evaluate the long-term efficacy and safety of chronic DBS in medial temporal lobe structures, and to investigate the feasibility of using chronic DBS electrodes for the localisation of the ictal onset zone prior to DBS to avoid an additional invasive procedure. An initial pilot study was performed to demonstrate proof-of-concept [47].

Patient study at Ghent University Hospital

Sixteen patients with refractory epilepsy were implanted with bilateral AH-DBS electrodes and/or subdural grids for ictal onset localization and subsequent stimulation. In 14 patients with ictal onset in the temporal lobe, AH-DBS was initiated at the side of ictal onset during an acute stimulation period with an external pulse generator. In 13 patients in whom a significant reduction of interictal spikes and/or seizures was shown during this period, an abdominally located pulse generator was implanted. One patient did not meet the chronic implantation criterion and underwent a selective amygdalo-hippocampectomy. Patients were followed-up at the epilepsy clinic every 2–4 weeks. In 10 patients follow-up was at least 12 months. Four of these patients had a left-sided focal medial temporal lobe onset. Three patients had a right-sided regional medial temporal lobe onset. One patient had a bilateral regional temporal lobe onset with predominant involvement of the left side. Two patients had a left-sided regional medial temporal lobe onset. The mean follow-up in these patients was 18 months (range: 12–31 months). Nine of ten patients underwent chronic DBS ipsilateral to the side of ictal onset; one patient with bilateral ictal onset was stimulated bilaterally. One patient has been completely free of CPS for over 2 years. One patient is entirely seizure free during the day and only has infrequent seizures

during the night; 5/10 patients have a >50% reduction in seizure frequency; 2/10 patients have a reduction of 25% in seizure frequency. In one patient, no change in seizure frequency occurred. Perioperative complications included asymptomatic hemorrhagic changes along the trajectory of one electrode and local infection. These side effects are discussed in detail in the chapter on ''Neurosurgical aspects of temporal lobe deep brain stimulation for epilepsy''. None of the patients reported any stimulation-related side effects. The patient who underwent resective surgery has been seizure free for 12 months.

High levels of invasiveness and relative inefficacy are major concerns and limitations of standard treatments that provide the impetus for further developing neurostimulation as a treatment for epilepsy. Sensible approaches for DBS in refractory epilepsy are: a) to target crucial 'pacemaker' central nervous systems structures (such as the thalamus or the subthalamic nucleus) or b) to interfere with the area of ictal onset itself. Our study aimed at evaluating the efficacy of DBS in the medial temporal lobe after the ictal onset zone had been identified in this region.

Animal studies have shown abortive effects on epileptic activity when electrical fields were applied to hippocampal slices [45]. In vivo studies in rats showed that electrical stimuli applied following a kindling stimulus ('quenching') can delay the development of the kindling process [25, 52]. Bragin *et al.* and Velisek *et al.* found that repeated stimulation of the hippocampal perforant path in the kainate rat model significantly reduced seizures [9, 46]. In humans, preliminary short-term AH-DBS showed promising results with significant reduction of interictal epileptiform activity and seizure frequency [45]. Half of the patients treated with AH-DBS in this study had a reduction of seizure frequency of >50% allowing tapering of one or more AEDs. None of the patients reported side effects or showed changes in bedside neurological and neuropsychological testing. Results of formal neuropsychological testing comparing pre- and post-DBS results will be published shortly.

The mechanism of action (MOA) of DBS in reducing seizures remains unclarified. Some support the hypothesis that actual stimulation is not necessary to achieve efficacy and claim that efficacy is based on the lesion provoked by the insertion of the electrode ('microthalamotomy' effect) [19]. Furthermore, prolonged seizure control in patients who underwent invasive recording with conventional electrodes has been described [22]. Blinded randomisation of patient to ''on'' and ''off'' stimulation paradigms following implantation during follow-up ≥6 months may clarify this issue and may also simultaneously clarify the potential effect of sham stimulation due to an implanted device. DBS may also act through local inhibition induced by current applied to nuclei that are involved in propagating, sustaining or triggering of epileptic activity in a specific CNS structure ('reversible functional lesion'). Apart from this 'local' inhibition, the MOA of DBS may be based on the effect on projections leaving from the area of stimulation to other central nervous structures. This may be the most likely hypothesis when crucial structures in epileptogenic networks are involved. However, considering that the medial temporal lobe structures are also potentially involved in these networks it may be that targeting the ictal focus may also affect the epileptogenic network.

General conclusion

Patients with refractory epilepsy present a particular challenge to new therapies. In this population, VNS has demonstrated to be an efficacious and safe treatment. The efficacy of VNS in less severely affected populations remains to be evaluated. Nevertheless, sufficient evidence now exists to rank vagus nerve stimulation for epilepsy as effective based upon preponderance of Class I evidence. The current consensus on efficacy is that 1/3 of patients have a considerable improvement in seizure control with a reduction in seizure frequency of at least 50%, 1/3 of patients experience a worthwhile reduction of seizure frequency between 30 and 50%. In the remaining 1/3 of the patients there is little or no effect. VNS seems equally efficient for children. The degree of improvement in seizure control from VNS remains comparable to new antiepileptic drugs. Patients appear willing to undergo surgery for improvements in this range in order to avoid the usual undesirable effects of antiepileptic medication. Contrary to treatment with AEDs, efficacy has a tendency to improve with longer duration of treatment up to 18 months postoperatively. Analysis of larger patient groups and insight in the mode of action may help to identify patients with epileptic seizures or syndromes that respond better to VNS and guide the search for optimal stimulation parameters. Further improvement of clinical efficacy may result from this.

Deep brain stimulation for epilepsy is beyond the stage of proof-of-concept but still needs thorough evaluation in confirmatory pilot studies before it can be offered to a larger patient population. The most adequate

targets and stimulation parameters need to be identified. In a recent study, amygdalohippocampal DBS significantly reduced seizure frequency during long-term follow-up without clinically relevant side effects. For patients who are less suitable candidates for epilepsy surgery, DBS may become a valuable alternative. Randomized and controlled studies in larger patient series are mandatory to identify the potential treatment population and optimal stimulation paradigms.

References

1. Agostini E, Chinnock JE, Daly MD, Murray JG (1957) Functional and histological studies of the vagus nerve and its branches to the heart, lungs and abdominal viscera in the cat. J Physiol 135: 182–205
2. Ben-Menachem E, Hellstrom K, Verstappen D (2002) Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients Neurol 24(59): S44–S47
3. Ben-Menachem E, Hellstrom K, Waldton C, Augustinsson LE (1999) Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. Neurol 52: 1265–1267
4. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, Tarver WB, Wernicke JF (1994) Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. Epilepsia 35: 616–626
5. Boon P, De Reuck J, Calliauw L, Hoksbergen I, Achten E, Thiery E, Caemaert J, De Somer A, Decoo D (1994) Clinical and neurophysiological correlations in patients with refractory partial seizures and intracranial structural lesions. Acta Neurochir (Wien) 128: 68–83
6. Boon P, Vandekerckhove T, Achten E, Thiery E, Goossens L, Vonck K, D'Have M, Van Hoey G, Vanrumste B, Legros B, Defreyne L, De Reuck J (1999) Epilepsy surgery in Belgium, the experience in Ghent. Acta Neurol Belg 99: 256–265
7. Boon P, Vonck K, de Reuck J, Caemaert J (2002) Vagus nerve stimulation for refractory epilepsy. Seizure 11: 448–455
8. Boon P, Vonck K, Vandekerckhove T, D'Havé M, Nieuwenhuis L, Michielsen G, Vanbelleghem H, Goethals I, Caemaert J, Calliauw L, De Reuck J (1999) Vagus nerve stimulation for medically refractory epilepsy; efficacy and cost-benefit analysis. Acta Neurochir (Wien) 141: 447–453
9. Bragin A, Wilson CL, Engel J (2002) Increased after discharge threshold during kindling in epileptic rats. Experimental Brain Research 144: 30–37
10. Chkhenkeli SA, Chkhenkeli IS (1997) Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. Stereotact Funct Neurosurg 69: 221–224
11. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
12. Foley JO, DuBois F (1937) Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory and motor fibres. J Comp Neurol 67: 49–97
13. Hech C, Helmers SL, De Giorgio CM (2002) Vagus nerve stimulation therapy, epilepsy, and device parameters. Neurology 59: 531–537
14. Gates JR (1992) Candidacy for corpus callosum section. In: Luders HO (ed) Epilepsy surgery. Raven Press, New York
15. George R, Salinsky M, Kuzniecky R, Rosenfeld W, Bergen D, Tarver WB, Wernicke JF (1994) Vagus nerve stimulation for treatment of partial seizures: 3. Long-term follow-up on first 67 patients exiting a controlled study. Epilepsia 35: 637–643
16. George R, Sonnen A, Upton A *et al* (1995) The vagus nerve stimulation study group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurol 45: 224–230
17. Hammond EJ, Uthman BM, Reid SA, Wilder BJ (1992) Electrophysiological studies of cervical vagus nerve stimulation in humans: I. Evoked potentials. Epilepsia 33: 1021–1028
18. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation therapy for partial onset seizures. A randomized, active control trial. Neurol 51: 48–55
19. Hodaie M, Wennberg RA, Dostrovsky J, Lozano A (2002) Chronic anterior thalamic stimulation for intractable epilepsy. Epilepsia 43: 603–608
20. Hornig GW, Murphy JV, Schallert G, Tilton C (1997) Left vagus nerve stimulation in children with refractory epilepsy: an update. South Med J 90: 484–488
21. Juul-Jensen P, Foldsprang A (1983) Natural history of epileptic seizures. Epilepsia 24: 297–312
22. Katariwala NM, Bakay RAE, Pennel PB, Olson LD, Henry TR, Epstein CM (2001) Remission of intractable epilepsy following implantation of intracranial electrodes. Neurol 57: 1505–1507
23. Krahl SE, Browning RA, Smith DC (1994) Possible mechanisms of the seizure attenuating effects of vagus nerve stimulation. Soc Neurosci Abstr 20: 1453 (abstract)
24. Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 3(342): 314–319
25. Lian J, Bikson M, Sciortino C, Stacey WC, Durand DM (2003) Local suppression of epileptiform activity by electrical stimulation in rat hippocampus in vitro. J Physiol 547: 427–434
26. Lozano AM, Hamani C (2004) The future of deep brain stimulation. J Clin Neurophysiol 21: 68–69
27. Lundgren J, Amark P, Blennow G, Stromblad LG, Wallstedt L (1998) Vagus nerve stimulation in 16 children with refractory epilepsy. Epilepsia 39: 809–813
28. Majoie HJ, Berfelo MW, Aldenkamp AP, Renier WO, Kessels AG (2005) Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. Seizure 14: 10–18
29. Moriarty GL, Gates JR, Dunn ME, Frost MD, Gregory R, Kispert DB, Penovich PE, Ritter FJ, Spiegel RH (1996) Functional cortical mapping with subdural electrode arrays in brain tumor resection. J Epilepsy 9: 119–127
30. Murphy JV, the pediatric VNS study group (1999) Left vagal nerve stimulation in children with medically refractory epilepsy. Pediatrics 134: 563–566
31. Naritoku DK, Terry WJ, Helfert RH (1995) Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. Epilepsy Res 22: 53–62
32. Paintal AS (1973) Vagal sensory receptors and their reflex effects. Phys Rev 53: 159–227
33. Rajna P, Lona C (1989) Sensory stimulation for inhibition of epileptic seizures. Epilepsia 30: 168–174
34. Ramsay RE, Uthman BM, Augustinsson LE, Upton AR, Naritoku D, Willis J, Treig T, Barolat G, Wernicke JF (1994) Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side-effects and tolerability. Epilepsia 35: 627–636
35. Salinsky MC, Uthman BM, Ristanovic RK, Wernicke JF, Tarver WB (1996) Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open extension trial. Arch Neurol 53: 1176–1180

36. Saper CB, Kibbe MR, Hurley KM, Spencer S, Holmes HR, Leahy KM, Needleman P (1990) Brain natriuretic peptide-like immunoreactive innervation of the cardiovascular and cerebrovascular systems in the rat. Circ Res 67: 1345–1354
37. Siegel AM, Cascino GD, Meyer FB, McClelland RL, So EL, Marsh WR, Scheithauer BW, Sharbrough FW (2004) Resective reoperation for failed epilepsy surgery: seizure outcome in 64 patients. Neurol 28(63): 2298–2302
38. Spencer SS, Berg AT, Vickrey BG, Sperling MR, Bazil CW, Shinnar S, Langfitt JT, Walczak TS, Pacia SV, Ebrahimi N, Frobish D, Multicenter Study of Epilepsy Surgery (2003) Initial outcomes in the Multicenter Study of Epilepsy Surgery. Neurol 23(61): 1680–1685
39. Spencer SS, Guimaraes P, Katz A, Kim J, Spencer D (1992) Morphological patterns of seizures recorded intracranially. Epilepsia 33: 537–545
40. Sperling MR, O'Connor MF, Saykin AJ, Plummer C (1996) Temporal lobectomy for refractory epilepsy. JAMA 276: 470–475
41. Upton AR, Cooper IS, Springman M, Amin I (1985) Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. Int J Neurol 19–20: 223–230
42. Van Ness PC (1992) Surgical outcome for neocortical (extrahippocampal) focal epilepsy. In: Luders HO (ed) Epilepsy surgery. Raven Press, New York
43. van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Raftopoulos C (2005) Deep EEG recordings of the mammillary body in epilepsy patients. Epilepsia 46: 781–785
44. Velasco M, Velasco F, Velasco A, Boleaga B, Jimenez F, Brito F, Marquez I (2000) Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41: 158–169
45. Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, Marquez I (2000) Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41: 158–169
46. Velisek L, Veliskova J, Stanton PK (2002) Low frequency stimulation of the kindling focus delays basolateral amygdala kindling in immature rats. Neurosci Lett 326: 61–63
47. Vonck K, Boon P, Achten E, De Reuck J, Caemaert J (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 52: 556–565
48. Vonck K, Boon P, D'Havé M, Vandekerckhove T, O'Connor S, De Reuck J (1999) Long-term results of vagus nerve stimulation in refractory epilepsy. Seizure 8: 328–334
49. Vonck K, Thadani V, Gilbert K, Dedeurwaerdere S, De Groote L, De Herdt V, Goossens L, Gossiaux F, Achten E, Thiery E, Vingerhoets G, Van Roost D, Caemaert J, De Reuck J, Roberts D, Williamson P, Boon P (2004) Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. J Clin Neurophysiol 21: 283–289
50. Walker BR, Easton A, Gale K (1999) Regulation of limbic motor seizures by GABA and Glutamate transmission in Nucleus Tractus Solitarius. Epilepsia 40: 1051–1057
51. Ward AA Jr (1983) Perspectives for surgical therapy of epilepsy. In: Ward AA Jr, Penry JK, Purpura DP (eds) Epilepsy ARNMD. Raven Press, New York, pp 371–390
52. Weiss SRB, Li XL, Rosen JB, Li H, Heynen T, Post RM (1995) Quenching: inhibition of development and expression of amygdala kindled seizures with low frequency stimulation. Neuroreport 4: 2171–2176
53. Wright GD, McLellan DL, Brice JG (1984) A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatry 47: 769–774

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Vagus nerve stimulation: indications and limitations

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Summary

Vagus nerve stimulation (VNS) is an established treatment for selected patients with medically refractory seizures. Recent studies suggest that VNS could be potentially useful in the treatment of resistant depressive disorder. Although a surgical procedure is required in order to implant the VNS device, the possibility of a long-term benefit largely free of severe side effects could give VNS a privileged place in the management of resistant depression. In addition, VNS appears to affect pain perception in depressed adults; a possible role of VNS in the treatment of severe refractory headache, intractable chronic migraine and cluster headache has also been suggested. VNS is currently investigated in clinical studies, as a potential treatment for essential tremor, cognitive deficits in Alzheimer's disease, anxiety disorders, and bulimia. Finally, other studies explore the potential use of VNS in the treatment of resistant obesity, addictions, sleep disorders, narcolepsy, coma and memory and learning deficits.

Keywords: Neuromodulation; vagus nerve stimulation; VNS; epilepsy; refractory seizures; depression.

The vagus nerve stimulation (VNS) system

In humans, vagus nerve stimulation (VNS) is applied to the left vagus nerve in the cervical area using the NeuroCybernetic Prosthesis (NCP, Cyberonics, Inc., Houston, TX, U.S.A.) system. This equipment consists of three parts: 1) the implantable, multiprogrammable bipolar NCP pulse generator, which is similar to a cardiac pacemaker in size and shape, 2) two helical electrodes, which are wrapped around the vagus nerve and are linked to the pulse generator by a bipolar lead [12], and 3) a programming wand linked to a computer programming software, which allows non-invasive programming, functional assessment (device diagnostics), and data retrieval. The pulse generator is implanted in a subcutaneous pocket in the left chest wall just below the clavicle, whereas the electrodes are attached to the vagus nerve, made accessible by an incision in the neck (Fig. 1). Through a subcutaneous tunnel, the electrodes are linked to the pulse generator. The system delivers electrical impulses at frequencies between 1 and 30 Hz, at 0.25–3.5 mA, with a pulse width varying from 130 to 1000 μs at variable on-off times.

VNS in epilepsy

The first clinical application of VNS in humans was intended for the treatment of medically refractory seizures. Since 1988, when the first pilot studies were done [3, 4], VNS has been used in more than 16,000 patients for the treatment of epilepsy. In 1997, the US Food and Drug Administration approved the NCP system for the management of medically refractory partial-onset seizures for which surgery is not recommended or has failed [5, 7]. Two large, well-designed multicenter trials involved over 300 patients with medically refractory epilepsy suffering from at least 6 partial-onset seizures/month. These studies demonstrated that VNS, as an adjunct to optimal antiepileptic medication, reduces seizure frequency by approximately 25% after 3 months of treatment, and the benefit appears to be maintained or increase over time [41]. Adverse effects were mild and consisted primarily of hoarseness of voice during the ''on'' periods of stimulation. VNS may result in a reduction of tonic and tonic-clonic seizures as well. Data from the VNS Trial indicate that approximately 30% of the patients experience a greater than 75% reduction in seizure frequency and over 50% of the patients experience a greater than 50% reduction in seizure frequency. The difference in outcomes between the patients with partial-onset seizures and those with generalized tonic-clonic seizures or Lennox-Gastaut syndrome was not found to be statistically significant. The improvement of quality of life in these patients is significant [19, 24].

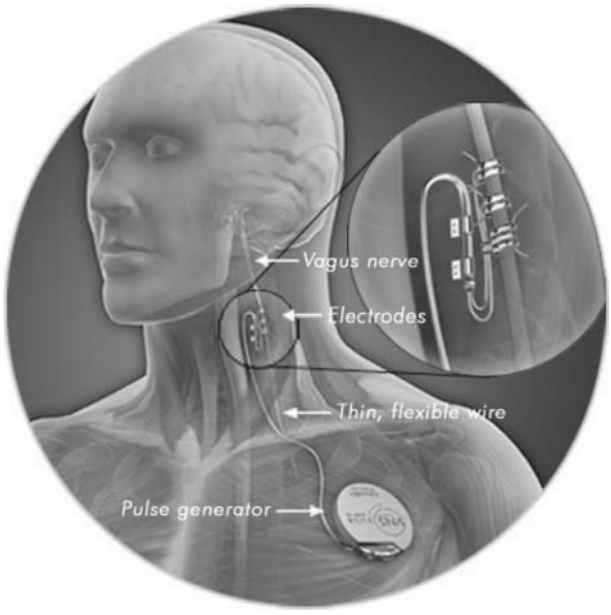

Fig. 1. The implanted VNS NCP system *in situ*

The original Food and Drug Administration (FDA) approval of the use of VNS for epilepsy was limited to patients over the age of 12. Since that time, there has been interest in extending the use of VNS in younger patients. Several studies have reported results that support the safety of the use of VNS in children with refractory seizures [1, 25]. Sixty children were treated as part of double blind clinical trials conducted to support the FDA application [23]. At 18 months, the median reduction in seizure frequency was 50%, similar to that achieved in adults. Adverse events were also similar to those reported in adults [24]. A second series included 19 children, with follow-up periods extending up to 30 months. Overall, 50% of patients had a 50% reduction in seizure frequency [14, 15]. In another series of 38 patients with an age range from 11 months to 16 years, 29% had a greater than 90% reduction in seizure frequency, while 39% had 50–90% reduction [28]. There are additional studies that support the safety and efficacy of VNS in adults and children with partial onset seizures refractory to medical therapy [17, 31]. There are, however, two major limitations of VNS: a) stimulation does not eliminate seizures completely, and b) it is not possible to predict which patients will respond. Therefore, many authors suggest that VNS should be used mainly in patients with refractory seizures who are not candidates for resective surgical treatment, i.e. patients with bilateral or unresectable foci or no identified structural abnormality.

Neuroanatomical basis of VNS action in epilepsy

The precise mechanism by which VNS suppresses seizures is not known. However, the electrical stimuli applied at the vagus nerve must influence the state of excitability of the brain. This effect is mediated by the vagus nerve, which consists of approximately 80% afferent nerve fibres. The cell bodies of the afferent cells are located in the nodose ganglion and project primarily to the nucleus of tractus solitarius (NTS). Input from the vagus nerve influences projections to the nucleus of the solitary tract. There are widespread anatomical connections of the nucleus of the solitary tract in the central nervous system (CNS) (Figs. 2, 3) that could explain the widespread influence of VNS [18, 20].

Neurons of this nucleus project to numerous areas in the forebrain and brainstem, and indirectly to the locus ceruleus and via diffuse connections to the cortex. Important structures, thought to mediate antiepileptic effects and receiving projections from the NTS, include the amygdala and the thalamus. There is a substantial projection through the parabrachial nucleus and thalamus to the insula and other rostral parts of the cerebrum (Fig. 3). In addition, efferent pathways project to the reticular formation, basal forebrain, amygdala, hippocampus, hypothalamus, dorsal raphe, cerebellum, and spinal cord [5, 32, 34]. The cell bodies of the efferent fibres are located in the nucleus ambiguous and the dorsal motor nucleus of the vagus nerve. They provide in-

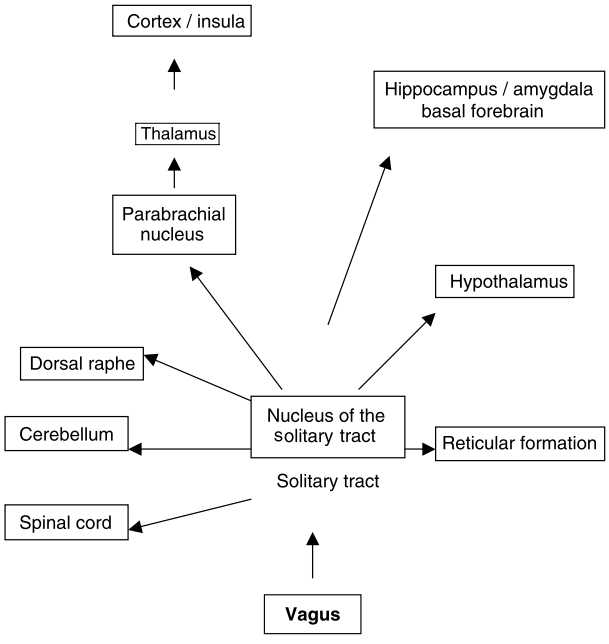

Fig. 2. Possible connections of the vagus nerve and the nucleus of the solitary tract

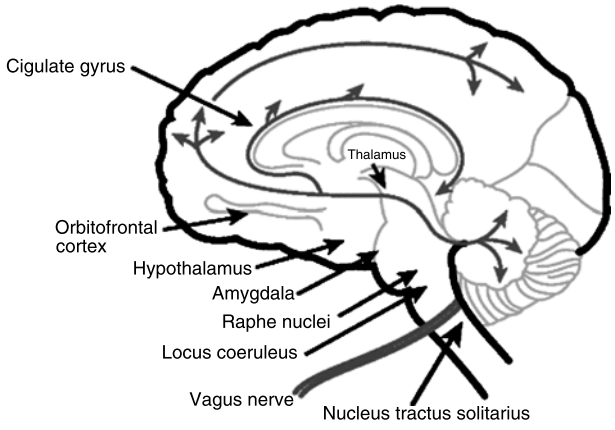

Fig. 3. Anatomical illustration of vagal nerve projections

nervation to the heart, aorta, lungs, gastrointestinal tract, and voluntary striated muscles of the larynx and pharynx [12, 42]. The heart rate is mostly influenced by the right vagal nerve [39]. The formation of the different parts of the vagal system, i.e. the afferent and efferent parts with their respective brainstem nuclei (NTS, nucleus ambiguous, and dorsal nucleus of vagus nerve) and the asymmetric distribution of functions, with the right vagus nerve being preferentially involved in the chronotropic regulation of the heart, has been explained in an evolution-based concept, the polyvagal theory [29].

VNS in depression

Depression is one of the most severe diseases with respect to global impact on quality of life, morbidity, and mortality. According to a World Health Organization study, unipolar major depression will rank at the second place of the leading causes of disability-adjusted life years worldwide in 2020, just behind ischaemic heart disease [26]. The hypothesis that VNS could be effective in treating depression and the interest in its use for this purpose was initially based on the following observations: a) reports of improved mood and cognition among epilepsy patients treated with VNS [8, 9, 12], b) drugs used to treat epilepsy, including carbamazepine, gabapentin, lamotrigine, and valproate, are also used to treat mood disorders [10, 12], c) Positron emission tomography studies show that VNS affects the metabolism and function of limbic structures in a way compatible with the effect of antidepressant medication, d) neurochemical studies in animals and humans reveal that VNS alters the concentrations of monoamines in the CNS, and e) the vagus nerve is anatomically linked to brain structures related to mood disorders [11, 12, 33]. Activation of the left vagus nerve has been shown to induce widespread bilateral effects in brain areas implicated in depression, including the inferior temporal structures (amygdala) and the prefrontal cortex [12].

A well-tolerated, efficacious long-term treatment in medically resistant depression is not yet available; VNS could offer a valuable treatment option because it has minimal side effects as it has been documented by its use in the treatment of epilepsy [3]. The first implantation of a VNS system for the treatment of resistant depression was performed in 1998 at the Medical University of South Carolina. In 2001, VNS was approved for a CE mark (indicating compliance with safety and environmental regulations) in the member countries of the European Union for treatment of adults with treatment-resistant or treatment-intolerant chronic or recurrent depression, including unipolar and bipolar depression [3, 11, 35, 37, 38]. The interest in VNS increased considerably after the publication of the results of an open-label, multicenter pilot study on its use as a potential treatment of relatively drug-resistant major depressive episodes. Patients with a DSM-IV diagnosis of major depressive disorder or bipolar I or II disorder were included [16]. The results of these investigations at 1-year follow-up were promising [21, 23, 33]. In a follow-up study, patients were assessed at 9 months after the 3-month assessment. During this period, changes in psychotropic medication and VNS parameters were allowed. The response rate (defined as at least 50% reduction in baseline Hamilton rating score) was 40%; the remission rate (Hamilton rating score less than 10) increased from 17% after the acute-phase study to 29% [21]. The most common side effects at 1-year post implantation were voice alteration (21%), dyspnoea (7%) and neck pain (7%) [21]. The effects of VNS on cognitive functions were assessed with a neurocognitive test battery, before, and 10 weeks after, the start of VNS; no deterioration in any of the neurocognitive measures was detected. Motor speed (finger tapping), performance of the digit symbols test, verbal fluency, logical reasoning, working memory and response inhibition improved [36].

Other applications of VNS

A pilot study investigated whether VNS can improve the cognitive function in Alzheimer's disease. The preliminary results are promising. The researchers reported that, after six months of VNS therapy, 7 of 10 patients had a median improvement of 2.5 points in cognitive function, assessed by the Alzheimer's Disease

Assessment Scale [40]. Three of the responders were on concurrent cholinesterase inhibitor therapy. Randomised, controlled clinical trials with sufficient numbers of patients and longer-term outcomes are needed before any conclusions can be reached concerning the effectiveness and safety of VNS in patients with Alzheimer's disease [40]. The efficacy of VNS in essential tremor has been studied in 9 patients. Four weeks after VNS implantation, the patients' tremor was assessed using a masked videorecorder. The evaluators found no improvement in upper extremity tremor. Therefore, VNS did not seem to have any appreciable treatment effect in essential tremor [13]. On the basis of the observed analgesic effects of VNS in patients with depression, VNS was implanted in patients with severe refractory chronic cluster and migraine headaches [22]. Of the five patients treated, one had an excellent result and became able to return to work while two other patients experienced a significant improvement in their headache [22].

Surgical complications

Similarly to any surgical procedure, there is a possibility of operative and postoperative complications. Left vocal cord paralysis with postoperative hoarseness can rarely occur, presumably due to injury to the efferent motor fibers of the vagus nerve. Migration of the pulse generator under the skin can also occur. Lead failure from tension on the electrode wire develops in less than 5% of patients after several years; this may be more common in children who grow rapidly. A rare pulse generator malfunction resulted in continuous high-intensity VNS for 4 hours and caused permanent paralysis of the vocal cord in one patient. Another patient developed paralysis of the left diaphragm 4 months after stimulation; this was directly associated to output current and also, to whether the head was turned to the left during stimulation.

Adverse effects of VNS

Adverse effects occur only during the ''ON'' phase of VNS. When unacceptable side effects occur, one can turn off the stimulator using a magnet. During stimulation, all patients experience some type of sensory alteration in the throat and neck. This is usually not painful, and the patient quickly gets used to the stimulation. Hoarseness is another common symptom, and occurs as a result of stimulation or injury of efferent fibers to the laryngeal muscles. Other symptoms that occur with high-intensity stimulation include cough, dyspnea, dyspepsia, vomiting, and insomnia [20]. Adverse effects have a negligible impact on the quality of life of treated patients, are reported to be mild, and tend to diminish over time. Surprisingly, in humans, VNS has no clinically significant effect on heart rate and visceral or respiratory function [30]. Unlike antiepileptic drugs, VNS has not been associated with adverse effects such as depression, fatigue, dizziness, insomnia, confusion, cognitive impairment, weight gain or sexual dysfunction.

Discussion

VNS is an effective, safe, and well-tolerated treatment in patients with long-standing, refractory partial-onset seizures; it may also be beneficial in other types of seizures. However, data indicate that the full effect of VNS may be delayed for as long as a year and that patients continue to improve during that time. In particular, 73% of patients maintained the clinical benefit, while 47% of patients with minimal or no benefit at 3 months, achieved clinical benefit at 12 months [6]. In addition, 57% of patients realized some degree of clinical benefit after 24 months of VNS therapy [6]. It should be pointed out, however, that, few patients with medically resistant epilepsy become seizure-free. Patients with epilepsy undergoing VNS therapy experienced significant quality of life (QOL) benefits that were sustained in the long-term [1]. Compared with other treatment modalities, VNS is cost-effective, if maintenance therapy is achieved, because this leads to a reduction in the cost of medications and hospitalisations. However, in the treatment of drug-refractory epilepsy, a seizure-free state is rarely achieved, and VNS is mostly combined with antiepileptic drugs maintenance therapy [11]. Problems arising during the implantation procedure are rare and manageable. VNS may not be recommended to patients with cardiac conduction disorders or sleep apnoea [38]. Furthermore, the safety and efficacy of VNS have not been established in patients with the following history: depression with schizophrenia, schizoaffective disorder, delusional disorder, depression with a rapid cycling bipolar character, cardiac arrhythmias, dysautonomias, previous brain surgery, respiratory diseases including dyspnoea and asthma, ulcers (gastric, duodenal, or other), vasovagal syncope, neurological diseases other than epilepsy or depression, presence of only one intact vagus nerve, other concurrent forms of brain stimulation, preexisting hoarseness, and pregnancy or nursing [6].

Vagus nerve stimulation as a treatment of medically resistant depression is a new development. The results of

the first American multicenter open-label add-on study with 30 patients showed that 40% of the patients achieved at least 50% symptom reduction after 10 weeks of VNS [33]. This study was subsequently extended to include 30 additional patients [36]. The two-year results of peer-reviewed study of VNS in treatment-resistant depression have been published recently [27]. Based on last observation carried forward analyses, response rate was 42% and remission rate was 22% after two years of VNS therapy (in patients who had received a mean of 15.7 unsuccessful clinical treatments in the current depressive episode). At two years, 81% of the participants were still receiving VNS therapy [27]. Short-term and long-term benefits were seen in more than one-third of treatment-resistant patients. Benefits seen at one year were largely sustained for two years [27]. An open-label European multicenter study is being conducted. At present, the preliminary results of VNS suggest that there is efficacy in the acute and long-term treatment of medically resistant depression. Technical issues need to be investigated, such as how to tailor each patient's individual treatment with respect to stimulation frequency, intensity, and duration. In a recent report, the threshold of eliciting a response in the vagus nerve by VNS was found to be age-dependent, with higher thresholds in young patients [18]. The identification of predictive factors for response to VNS is important. The open-label American multicenter study showed that the following variables are significant: receiving ECT ever in lifetime, response to most recent ECT, and number of unsuccessful antidepressant medication trials in a current major depressive episode [2]. The long-term results of these initial patients further confirm the significant relationship between VNS therapy and long-term improvement in depression. In patients with depression, VNS provides a new option when first-line treatments are unable to provide relief [27, 33]. Quality-of-life benefits may be experienced by nonresponders and responders. After 9 months of therapy, both responders and non-responders reported significant long-term improvements in vitality, emotional and mental health, and social function [6]. It appears that VNS is most effective in patients with moderate but not extreme resistance to conventional antidepressant treatments [36].

In conclusion, the clinical benefit of VNS in patients with epilepsy improves over time and is sustained in the long-term. Preliminary data suggest a sustained antidepressant effect in moderately resistant major depression. If these findings are confirmed by additional studies, VNS could become a key treatment in depression. Further insights into the mechanisms of its action in epilepsy, depression, and other neuropsychiatric disorders are expected. However, implantation of a VNS system is an invasive method and it needs a clear indication every time is applied.

References

1. Amar AP, Levy ML, McComb JG, Apuzzo MLJ (2001) Vagus nerve stimulation for control of intractable seizures in childhood. Pediatr Neurosurg 34: 218–223
2. American Psychiatric Association Task Force on ECT (2001) The practice of electroconvulsive therapy, 2nd edn. American Psychiatric Publishing, Washington
3. Ben-Menachem E (2001) Vagus nerve stimulation, side effects, and long-term safety. Clin Neurophysiol 18: 415–418
4. Borckard JJ, Kozel FA, Anderson B, Walker A, George MS (2005) Pain Res Manag 10: 9–14
5. Cechetto DF (1987) Central representation of visceral function. Fed Proc 46: 17–23
6. Cyberonics Inc. (2005) Depression Physician's Manual. Houston, Texas
7. DeGiorgio CM, Thompson J, Lewis P, Arrambide S, Naritoku D, Handforth A, Labar D, Mullin P, Heck C; VNS U.S. Study Group (2000) Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 41: 1195–1200
8. Dunner DL (2001) Acute and maintenance treatment of chronic depression. J Clin Psychiatry 62 Suppl 6: 10–16
9. Elger H, Hoppe C, Falkai P, Rush AJ, Elger CE (2000) Vagus nerve stimulation in association with mood improvements in epilepsy patients. Epilepsy Res 42: 203–210
10. George MS, Nahas Z, Bohning DE, Lomarev M, Denslow S, Osenbach R, Ballenger JC (2000) Vagus nerve stimulation: a new form of therapeutic brain stimulation. CNS Spectrums 5: 2–11
11. George M, Sackeim HA, Marangell LB, Husain MM, Nahas Z, Lisanby SH, Ballenger JC, Rush AJ (2000) Vagus nerve stimulation: a potential therapy for resistant depression? Psychiatr Clin North Am 23: 757–783
12. George M, Sackeim HA, Rush AJ, Marangell LB, Nahas Z, Husain MM, Lisanby S, Burt T, Goldman J, Ballenger JC (2000) Vagus nerve stimulation: a new tool for brain research and therapy. Biol Psychiatry 47: 287–295
13. Handforth A, Ondo WG, Tatter S (2003) Vagus nerve stimulation for essential tremor: a pilot efficacy and safety trial. Neurology 61: 1401–1405
14. Hornig G, Murphy JV, Schallert G, Tilton C (1997) Left vagus nerve stimulation in children with refractory epilepsy. South Med J 90: 484–488
15. Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D (2000) Vagus nerve stimulation treatment for Lennox-Gestaut syndrome. J Child Neurol 15: 509–512
16. Kellner CH, Fink M (2002) The efficacy of ECT and "treatment resistance." J ECT 18: 1–2
17. Kirse DJ, Werle AH, Murphy JV, Eyen TP, Bruegger DE, Hornig GW, Torkelson RD (2002) Vagus nerve stimulator implantation in children. Arch Otolaryngol Head Neck Surg 128: 1263–1230
18. Koo B (2001) EEG changes with vagus nerve stimulation. J Clin Neurophysiol 18: 434–441
19. Labar D, Murphy J, Tecoma E (1999) Vagus nerve stimulation for medication-resistant generalized epilepsy. VNS Study Group E-04. Neurology 52: 1510–1512
20. Luders HO, Comair YG (2001) Epilepsy surgery, 2nd edn. Lippincott Williams & Wilkins, New York, NY

21. Marangell LB, Rush AJ, George MS, Sackeim HA, Johnson CR, Husain MM, Nahas Z, Lisanby SH (2002) Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. Biol Psychiatry 51: 280–287
22. Mauskop A (2005) Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalgia 25: 82–86
23. McCall WV (2001) Electro convulsive therapy in the era of modern psychopharmacology. Int J Neuropsychopharmacol 4: 315–324
24. Morris GL 3rd, Mueller WM (1999) Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Vagus Stimulation Study Group E101-105. Neurology 53: 1727–1735
25. Murphy JV (1999) Left vagal nerve stimulation in children with medically refractory epilepsy. J Pediatr 134: 563–567
26. Murray CJL, Lopez AD (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 349:1436–1442
27. Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, Martinez JM, George MS (2005) Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 66: 1097–1104
28. Patwardhan RV, Stong B, Bebin EM, Mathisen J, Grabb PA (2000) Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. Neurosurgery 47: 1353–1358
29. Porges SW (1999) Orienting in a defensive world: mammalian modifications of our evolutionary heritage: a polyvagal theory. Psychophysiology 32: 301–318
30. Ramsay RE, Uthman BM, Augustinsson LE, Upton AR, Naritoku D, Willis J, Treig T, Barolat G, Wernicke JF (1994) Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. Epilepsia 35: 627–636
31. Renfroe JB, Wheless JW (2002) Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy. Neurology 59 Suppl 4: S26–S30
32. Ricardo JA, Koh ET (1978) Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala and other forebrain structures in the rat. Brain Res 153: 1–26
33. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, Nahas Z, Haines S, Simpson RK Jr, Goodman R (2000) Vagus nerve stimulation (VNS) for treatment-resistant depression: a multicenter study. Biol Psychiatry 47: 276–286
34. Rutecki P (1990) Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia 31 Suppl 2: S1–S6
35. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J (2001) Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 285: 1299–1307
36. Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S, Simpson RK Jr, Goodman RR (2001) Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology 25: 713–728
37. Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000) A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 57: 425–434
38. Schachter SC (2002) Vagus nerve stimulation: where are we? Curr Opin Neurol 15: 201–206
39. Sitdikov FG, Gil'mutdinova RI, Minnakhmetov RR, Zefirov TL (2000) Effects of vagus nerves on functional parameters of rat heart in postnatal ontogeny. Bull Exp Biol Med 130: 620–623
40. Sjogren MJ, Hellstrom PT, Jonsson MA, Runnerstam M, Silander HC, Ben-Menachem E (2002) Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: a pilot study. J Clin Psychiatry 63: 972–980
41. TEC Assessment (1998) Chronic vagus nerve stimulation for the treatment of seizures
42. Vonck K, Van Laere K, Dedeurwaerdere S, Caemaert J, De Reuck J, Boon P (2001) The mechanism of action of vagus nerve stimulation for refractory epilepsy: the current status. J Clin Neurophysiol 18: 394–401

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Vagus nerve stimulation for intractable epilepsy: outcome in two series combining 90 patients

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Summary

Vagus nerve stimulation (VNS) is the most widely used non-pharmacological treatment for medically intractable epilepsy and has been in clinical use for over a decade. It is indicated in patients who are refractory to medical treatment or who experience intolerable side effects, and who are not candidates for resective surgery. VNS used in the acute setting can both abort seizures and have an acute prophylactic effect. This effect increases over time in chronic treatment to a maximum at around 18 months. The evidence base supporting the efficacy of VNS is strong, but its exact mechanism of action remains unknown. A vagus nerve stimulator consists of two electrodes embedded in a silastic helix that is wrapped around the cervical vagus nerve. The stimulator is always implanted on the left vagus nerve in order to reduce the likelihood of adverse cardiac effects. The electrodes are connected to an implantable pulse generator (IPG) which is positioned subcutaneously either below the clavicle or in the axilla. The IPG is programmed by computer via a wand placed on the skin over it. In addition, extra pulses of stimulation triggered by a hand-held magnet may help to prevent or abort seizures. VNS is essentially a palliative treatment and the number of patients who become seizure free is very small. A significant reduction in the frequency and severity of seizures can be expected in about one third of patients and efficacy tends to improve with time. Vagus nerve stimulation is well tolerated and has few significant side effects. We describe our experience on the use of VNS on drug-resistant epilepsy in 90 patients treated in two departments (in Athens, Greece and Newcastle, England).

Keywords: Neuromodulation; VNS; vagus nerve stimulation; refractory seizures; epilepsy.

Introduction

Approximately 70% of epilepsy patients have their seizures controlled with a single anti-epileptic drug and a further 10% are controlled with polypharmacy. Patients are considered to be refractory to medical therapy if seizures cannot be brought under control within two years and treatment with at least two antiepileptic ''first line'' drugs such as phenytoin, carbamazepine, valproic and phenobarbital. A number of options exist for such patients. If the seizure disorder is related to a structural abnormality within the brain, resection of the epileptogenic zone should be considered where possible. In cases where a resectable epileptogenic zone is not identified, other surgical options should be considered: these include callosotomy, subpial transection and VNS. VNS can be used in all forms of epilepsy, including mixed seizure disorders. Before VNS implantation is considered, a thorough evaluation must be undertaken of the patient and his/her epilepsy. The presence of disabling epileptic seizures of at least two years' duration and the failure of multiple antiepileptic drugs to control seizures should be confirmed by an epileptologist. Magnetic resonance imaging (MRI) and ictal electroencephalogram (EEG) with videotelemetry are essential to characterise the seizure types precisely, to exclude pseudoseizures, and when possible to diagnose an overall epilepsy syndrome for each patient. It is of particular importance to exclude the presence of a resectable epileptogenic zone.

Experimental and clinical evidence

Alteration in EEG activity in response to vagus nerve stimulation in animals was first reported in 1938 [1]. In 1985 Zabara proposed that VNS might desynchronise cerebral electrical activity, and thereby attenuate seizures [20]. Subsequent animal studies revealed that specific amplitudes and frequencies of vagus nerve stimulation could desynchronise EEG activity in a manner that may disrupt a seizure. In several animal models of epilepsy

VNS was found both to terminate seizures acutely and to have a prophylactic effect against subsequent seizures [10, 18]. A significant proportion of vagal afferents project to the nucleus of the tractus solitarius. The nucleus of the tractus solitarius contains both GABAergic and glycinergic neurones which in turn have extensive projections to spinal and bulbar motor neurones, the reticular formation and the parabrachial nuclei. The reticular formation and the parabrachial nuclei have diffuse projections, both direct and indirect, to the cerebral cortex, through which it is likely that VNS moderates cortical electrophysiology. It has been suggested that slow hyperpolarisation may be one of the mechanisms that underlie the seizure-reducing effects of VNS, reducing activity in neurones involved in propagation of seizure activity [13]. Animal studies have also demonstrated equal anticonvulsant activity for right, left and bilateral VNS, but greater cardiac slowing with right-sided stimulation [12, 15, 21].

Based on evidence of safety and efficacy in animals, trials of VNS in patients with epilepsy were initiated in 1988 [14]. These trials used the Neuro Cybernetic Prosthesis (NCP) system (Cyberonics, Houston, Texas) to deliver intermittent electrical stimulation to the left cervical vagus nerve. The results of multiple trials, including two multi-centre double-blinded randomised controlled studies on patients with medically intractable partial seizures, have demonstrated that VNS is a safe and effective technique for improving seizure control, with reports of 23–31% of patients experiencing a 50% or greater reduction in seizure frequency [5, 17]. The US Food and Drug Administration granted approval for VNS as an adjunctive treatment for refractory partial onset seizures in July 1997. A number of retrospective clinical series have examined the efficacy of VNS in the treatment of generalised epilepsy and suggested that it is similar to that in partial epilepsy (30–60% of patients achieving a 50% or greater reduction in seizure frequency) [6, 7]. Several case series, including some in children, have reported VNS safety and efficacy in the paediatric population to be comparable with that in adult patients [9, 11].

Operative technique

In order to implant the NCP system, the patient is positioned supine with the neck slightly extended and turned 20–30° to the right. A transverse cervical incision is made, centred midway down the anterior border of the sternomastoid muscle. The platysma is divided or split, and dissection is continued deep to the anterior border of sternomastoid. The carotid sheath is defined and opened, exposing the common carotid artery and the internal jugular vein. The vagus nerve usually lies posteriorly in the groove between the artery and the vein but occasionally it can lie anteriorly and so extreme care must be taken on opening the carotid sheath, and also in distinguishing the vagus from other superficial nerves such as the ansa cervicalis. The vagus nerve is dissected free from the surrounding tissue and gently elevated with vessel loops. It is advisable to expose at least a 3 cm length of nerve, as this greatly facilitates electrode placement.

An incision approximately 6 cm long is then made 2–3 cm below and parallel to the left clavicle (some surgeons prefer an anterior axillary incision, especially in young female patients). A subcutaneous pocket is fashioned inferiorly by blunt and sharp dissection until its size is adequate for the diameter of the IPG. At this stage it is best to tunnel the bipolar lead between the cervical and infraclavicular incisions. If this is done after the electrodes have been placed around the vagus nerve, tissue manipulation during tunnelling may lead to their being inadvertently dislodged. The electrodes are attached in turn to the nerve, starting with the inferior anchor helix, by pulling the attached sutures apart with fine forceps and placing the midpoint of the helix over the nerve. The forceps are then used to coil the remainder of each helix around the nerve, being careful not to damage the embedded electrode. The nerve is then placed back in its normal anatomical position and the bipolar lead is looped in a gentle curve and sutured through a silicone retainer to adjacent soft tissue in order to avoid transmission of tension to the vagus nerve during neck movements. A second loop is made superficially and sutured to the fascia of sternomastoid. The distal terminals of the tunnelled bipolar leads are connected to the IPG. The system is then tested with the telemetry wand (covered by a sterile plastic sheath) to confirm a good electrical connection and the initial programming may be done at this time. The IPG is placed in the subcutaneous pocket with the excess lead coils positioned posteriorly (in order to minimise the possibility of damage when the incision is reopened to change the battery). The two incisions are closed.

The majority of patients are able to go home on the day of surgery. The NCP system can be activated immediately. Low settings are used at first in order to minimise side effects and to allow tolerance to develop. The system is usually programmed initially for intermittent stimulation of 30 sec on-time and 5 min off; signal frequency of 30 Hz; pulse width of 500 ms; output current

0.25 mA. The patient returns at intervals of 1–2 weeks when the current is raised in 0.25 mA increments to 1.5–2 mA. If the response is poor, it may be improved by increasing the 'duty cycle' – the percentage of time that the stimulator is 'on' – or by using a more rapidly cycling setting (e.g. 14 sec on, 1.5 min off). A magnet may be supplied to selected patients, which will produce extra stimulation, usually for 30 sec to 1 min and at a higher current. This may be used during an aura, or may attenuate a seizure once it starts; where seizures occur at a certain time of day it may also be useful. Battery life is estimated at about 56 months but is obviously dependant on the parameters used. Replacement of the IPG is straightforward but requires reopening of the chest wall incision [19].

Adverse effects of VNS therapy

Adverse effects of VNS therapy are principally mediated through the efferent fibres and include voice alteration, dyspnoea, cough and throat discomfort. These symptoms are usually readily reduced to tolerable levels by modulation of the IPG settings [5]. Aspiration secondary to impaired swallowing during vagus stimulation has been reported in children [9]. Cognitive functions, including alertness, co-ordination and memory may actually be improved by chronic vagus stimulation [2]. Surgical complications are uncommon. They include infection (which may necessitate removal of the device), vocal cord paralysis or lower facial muscle paresis [5]. Lead breakage is extremely uncommon.

VNS series in Athens, Greece

Twenty patients over the age of 12 years received a VNS implant between 1997 and 2005 in the Neurosurgical Department, University of Athens, Evangelismos General Hospital (Athens, Greece). All suffered from intractable epilepsy. All, except three, had abnormal EEGs. Four patients presented as Lennox-Gastaut syndrome, two as nocturnal frontal lobe epilepsy, and one as typical Bourneville disease. Seven patients suffered from cryptogenic partial epilepsy with secondary generalisation. Four patients suffered from symptomatic partial epilepsy; of those, one had a congenital stroke in the territory of the middle cerebral artery, one post-encephalitic gliosis, and two had extensive heterotopias. Another patient had post encephalitic seizures; his brain MRI, however, was normal. Finally, the last patient in this series had partial complex seizures with secondary generalisation probably of temporal origin; however, he refused to undergo a presurgical evaluation. In all patients, the autonomic nervous system was evaluated for potential side effects of VNS with ECG, and clinical examination. Changes in cardiac rhythm during the Valsalva test, after deep breathing and on standing position were studied during presurgical evaluation. This assessment was repeated six months after implantation in order to reveal any influence of VNS on autonomic function. No abnormalities were found [16]. Postoperatively, all patients recorded their seizures in a diary, including all the seizures that were suppressed by the use of the magnet. Follow up time ranges from six months to nine years.

Four patients have remained virtually seizure-free following a period of adjustment of the stimulation parameters. The reduction in seizure frequency remains higher than 95%. Only sporadic minor seizures were reported mainly in the presence of other provocative factors like sleep deprivation, dose omission, concomitant treatment, strong emotional states etc. These patients have experienced an enormous change in their lives. The first patient (PV-female) suffered from Lennox-Gastaut syndrome. Because of the frequent seizures she used to go to the bathroom only escorted by her mother. Now, she is able to go alone to a special school and she learns to play tennis. The second patient (LK-male) suffered from cryptogenic multifocal partial epilepsy. Since the VNS treatment, he is able to work a few hours every day in a special environment. The third patient (IM-male) had a major congenital damage in the right parietal-occipital area. He has remained seizure free only under certain parameters (on = 30 sec, off = 5 min, I = 0.75 mA). Any change of the parameters resulted in reappearance of the seizures. The fourth patient (VM-female) had extensive heterotopias in both hemispheres. This patient suffered from multifocal complex partial seizures. Another patient (GT-male) remained initially seizure-free following VNS implantation. He suffered from extremely resistant cryptogenic neocortical temporal epilepsy since childhood. Prior to NCP implantation, he had refused to undergo a presurgical evaluation for partial temporal lobe resection. Following VNS, however, he developed schizophrenia-like psychosis with forced EEG normalization [4]. He was hospitalized in a psychiatric clinic and received aloperidol with a rapid clinical improvement. However, because of the psychosis his family demanded the removal of the NCP; this was actually done six months after the implantation.

A major impact of VNS was documented in patients with Lennox-Gastaut syndrome. In addition to the one

Table 1. *Patients with intractable epilepsy treated by VNS (University of Athens, Greece)*

Patient	Age (years)	Seizures or syndromic classification	MRI findings	Results (percentage of reduction in seizure frequency)
PV/female	34	Lennox Gastaut	no abnormal findings	>95%, virtually seizure-free
PE/male	30	Lennox Gastaut	no abnormal findings	75–80%
DF/female	31	Lennox Gastaut	mild cortical atrophy	75%
DM/male	19	Lennox Gastaut	mild cortical atrophy	60%
LK/male	33	cryptogenic multifocal partial epilepsy with S.G.	no abnormal findings	>95%, virtually seizure-free
MS/male	26	symptomatic partial epilepsy	congenital (R) MCA ischemia	60%
GT/male	39	partial complex seizures with S.G. probably of temporal origin	no abnormal findings	>95%, initially virtually seizure-free. Later, the NCP removed because of psychosis
AK/female	51	cryptogenic partial complex seizures with S.G.	no abnormal findings	<25%
VS/male	29	cryptogenic partial complex seizures with S.G.	no abnormal findings	50%
AV/female	47	symptomatic partial epilepsy following neonatal meningitis	post encephalitic gliosis	60%
MT/female	22	cryptogenic partial complex seizures with S.G	no abnormal findings	55–60%
RP/female	45	cryptogenic partial complex seizures with rare S.G	ischemic foci bilaterally	<25–55%
EM/female	19	cryptogenic partial complex seizures with S.G	mild atrophy, enlargement of ventricles	60%
IM/male	35	symptomatic partial complex seizures with S.G.	occipital-parietal-temporal heterotopia	>95%, virtually seizure-free
VM/female	46	cryptogenic partial complex seizures with S.G	no abnormal findings	70%
VM/female	22	symptomatic partial complex seizures with S.G.	extensive bilateral heterotopias	>95%, virtually seizure-free
MG/male	22	nocturnal frontal lobe epilepsy	no abnormal findings	0%
KT/male	23	nocturnal frontal lobe epilepsy	no abnormal findings	0%
VA/male	28	post encephalitic seizures	no abnormal findings	55%
PM/male	27	bourneville disease	characteristics of B.D.	<25%

SG Secondary generalization; *(R) MCA* right middle cerebral artery; *BD* Bourneville Disease; *NCP* Neuro Cybernetic Prosthesis.

who remains seizure-free, the decrease in seizure frequency in the other patients was 60, 75, and higher than 75%, respectively. The caregivers of all the patients with Lennox-Gastaut syndrome are satisfied and they want to keep this treatment active. Four other patients reported a remarkable seizure reduction by 50–75%. Most of the patients described that many of the recorded seizures were shorter and of reduced severity; patients and carers described them as ''milder''. Seven patients had a decrease in seizure frequency less than 50%; four of them had essentially no influence on either seizure severity or seizure frequency (<25%). They asked for the NCP removal. Remarkably, two of them are patients suffering from nocturnal frontal lobe epilepsy. No patient experienced an increase in seizure frequency.

Most of the patients suffered from mild discomfort over the sternocleidomastoid muscle and the majority from cough during periods of increasing the electrical stimulation; these symptoms subsided without reducing the amplitude of the current except in cases of maximum tolerated amplitude. Eleven patients presented with changes in voice pitch and/or throat paraesthesia when the generator was on. One patient had diarrhoea, without any obvious microbial cause; this subsided after a decrease in current amplitude. One patient had a toothache at the low back teeth area on the left side which subsided when the stimulation was switched off.

VNS series in Newcastle, England

Seventy patients have undergone VNS implantation in Newcastle General Hospital (Newcastle-Upon-Tyne, United Kingdom) between 1996 and 2005. Age at diagnosis of seizure disorder ranged from three months to forty years and age at surgery ranged from two years to sixty-three years. Seizure frequency ranged from seven per month up to almost continuous seizure activity. Two patients had previous surgery for epilepsy (one a right frontal lobectomy and one a resection of the atrophic right parietal lobe). The commonest seizure type was generalised tonic-clonic seizures; complex partial, simple partial, myoclonic and absence seizures were also represented. Many patients had mixed seizure disorders. All patients had a thorough work-up including MRI and EEG. Some patients also underwent single photon emission computed tomography (SPECT) and one patient had corticography. Three quarters of the patients in the series improved with VNS. The duration and intensity of seizures was generally reduced, as well as the overall reduction in seizure frequency. Some degree of hoarseness

was almost universal but significant complications have been extremely rare (one post-operative aspiration with no long term consequences, one late (>2 years) infection, and one patient with significant discomfort at the insertion site of the IPG). All patients in the series remain on anti-epileptic medication. Battery changes have been necessary in a small number of cases but obviously this number will increase, as battery life is finite.

Conclusions

Vagus nerve stimulation is an important therapeutic option for patients with intractable epilepsy who are not suitable for other types of epilepsy surgery, or refuse to undergo a resection surgery. The procedure is well tolerated and in our population no significant complications were referred from our patients except a unique case with psychosis and force normalisation probably due to VNS. According to our results concerning the influence of VNS on seizure frequency a small proportion of patients around 20% could have a remarkable reduction of seizures or remain actually seizure free. All our patients with Lennox-Gastaut syndrome had a seizure reduction of more than 60%. A percentage of 35% had no influence on seizure frequency. Remarkably, no influence of VNS was found on two patients suffering from nocturnal frontal lobe epilepsy. The small number of patients does not permit conclusions on more specific of the characteristics of the patients who responded to VNS treatment. We do not have conclusive results concerning the influence of VNS on seizure severity, except the impression of caregivers and the patients that the seizures were shorter in duration and milder in 60–70% of our patients. No patient discontinued the anti-epileptic drugs and our data are not sufficient to conclude whether the efficacy of VNS treatment improves over time as many authors suggested. There is not, yet, reliable method of predicting which patients will respond to VNS therapy. If more precise indications for VNS therapy could be determined then results may well improve in the future.

References

1. Bailey P, Bremer F (1938) A sensory cortical representation of the vagus nerve. J Neurophysiol 1: 405–412
2. Clark KB, Naritoku DK, Smith DC, Browning RA, Jensen RA (1999) Enhanced recognition memory following vagus nerve stimulation in human subjects. Nat Neurosci 2: 94–98
3. Espinosa J, Aiello MT, Naritoku DK (1999) Revision and removal of stimulating electrodes following long-term therapy with the vagus nerve stimulator. Surg Neurol 51: 659–664
4. Gatzonis SD, Stamboulis E, Siafakas A, Angelopoulos E, Georgaculias N, Singounas E, Jenkins (2000) Acute psychosis and EEG normalization after vagus nerve stimulation. J Neurol Neurosurg Psychiatry 69: 278–279
5. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51: 48–55
6. Labar D, Murphy J, Tecoma E (1999) Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 Study Group. Neurology 52: 1510–1512
7. Labar D, Nikolov B, Tarver B, Fraser R (1998) Vagus nerve stimulation for symptomatic generalized epilepsy: a pilot study. Epilepsia 39: 201–205
8. Lundgren J, Amark P, Blennow G, Stromblad LG, Wallstedt L (1998) Vagus nerve stimulation in 16 children with refractory epilepsy. Epilepsia 39: 809–813
9. Lundgren J, Ekberg O, Olsson R (1998) Aspiration: a potential complication to vagus nerve stimulation. Epilepsia 39: 998–1000
10. McLachlan RS (1993) Suppression of interictal spikes and seizures by stimulation of the vagus nerve. Epilepsia 34: 918–923
11. Murphy JV (1999) Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. J Pediatr 134: 563–566
12. Naritoku DK, Morales A, Pencek TL, Winkler D (1992) Chronic vagus nerve stimulation increases the latency of the thalamocortical somatosensory evoked potential. Pacing Clin Electrophysiol 15: 1572–1578
13. Parent A, Carpenter M (1996) Carpenter's human neuroanatomy, 9th edn. Williams & Wilkins, Baltimore, p 1011
14. Penry JK, Dean JC (1990) Prevention of intractable partial seizures by intermittent stimulation in humans: preliminary results. Epilepsia 31 Suppl 2: S40–S43
15. Rutecki P (1990) Anatomical, physiological and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia 31 Suppl 2: S1–S6
16. Stabulis E, Catsaros N, Gatzonis S, Siafakas A, Georgaculias N, Sakas D (2005) Cardiac vagal tests and vagus nerve stimulation in epilepsy. Clin Auton Res 15: 54–56
17. The Vagus Nerve Stimulation Study Group (1995) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizure. Neurology 45: 224–230
18. Woodbury JW, Woodbury DM (1991) Vagal stimulation reduces the severity of maximal electroshock seizures in intact rats: use of a cuff electrode for stimulating and recording. Pacing Clin Electrophysiol 14: 94–107
19. Yoshor D, Barbaro N (2003) Palliative Surgery for Epilepsy: Corpus Callosotomy and Vagus Nerve Stimulation. In: Batjer H, Loftus C (eds) Textbook of neurological surgery: principles and practices. Lippincott Williams & Wilkins, Baltimore, pp 2748–2754
20. Zabara L (1985) Peripheral control of hypersynchronous discharge in epilepsy. Electoencephalogr Clin Neurophysiol 61: 162
21. Zabara J (1992) Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia 33: 1005–1012

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Electrical stimulation and gene-based neuromodulation for control of medically-refractory epilepsy

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Summary

The failure of available antiepileptic medications to adequately control seizures in a substantial number of patients underscores the need to develop novel epilepsy therapies. Recent advancements in technology and the success of neuromodulation in treating a variety of neurological disorders have spurred interest in exploring promising therapeutic alternatives, such as electrical stimulation and gene-based synaptic control. A variety of different stimulation approaches to seizure control targeting structures in the central or peripheral nervous system have been investigated. Most studies have been based on uncontrolled observations and empirical stimulation protocols. Today the vagus nerve stimulator is the only FDA approved adjunctive treatment for epilepsy that utilizes electrical stimulation. Other potential strategies including direct stimulation of the epileptogenic cortex and deep brain stimulation of various targets are currently under investigation. Chronically implanted devices for electrical stimulation have a variety of limitations. First, they are susceptible to malfunction and infection. Second, most systems require battery replacement. Finally, electrical stimulation is incapable of manipulating neuronal function in a transmitter specific fashion. Gene delivery to epileptogenic targets or targets implicated in regulating seizure threshold has been investigated as an alternative means of neuromodulation in animal models. In summary, positive preliminary results and the lack of alternative treatment options provide the impetus for further exploration of electrical stimulation and gene-based therapies in pharmacoresistant epilepsy. Various specific targets and approaches to modulating their activity have been investigated in human studies.

Keywords: Neuromodulation; gene therapy; epilepsy; seizures; electrical stimulation; review.

Abbreviations

AAV Adeno-associated virus, *AdLC* adenoviral vector expressing LC, *AEDs* antiepileptic drugs, *ANT* anterior nucleus of thalamus, *BFNC* benign familial neonatal convulsions, *BPS* bursts of pulse stimulation, *CM* centromedian (nucleus of thalamus), *CNS* central nervous system, *CT* computed tomography, *DBS* deep brain stimulation, *EEG* electroencephalogram, *FDA* food & drug administration, *GPi* globus pallidus internus, *HSV* herpes simplex virus, *Kir* inwardly rectifying potassium channels, *LC* light chain, *MIE* medically intractable epilepsy, *MRI* magnetic resonance imaging, *SNr* substantia nigra, pars reticulate, *STN* subthalamic nucleus, *rTMS* repetitive transcranial magnetic stimulation, *TMS* transcranial magnetic stimulation, *TNS* trigeminal nerve stimulation, *VNS* vagus nerve stimulation.

Introduction

Epilepsy, characterized by the repeated occurrence of unprovoked seizures, is one of the most common neurological disorders with an estimated prevalence of 5–8 per 1000 population in developed countries. A large epidemiologic study in the United States (Rochester, MN) showed an age-adjusted epilepsy prevalence of 6.8 per 1000 population, and a cumulative incidence through age 74 of 3.1% [17, 18]. Epilepsy exacts an enormous toll on patients and their families, while the loss of employment potential and cost of medical care has a substantial impact on society. Despite many decades of research, new antiepileptic drugs (AEDs), and advances in surgical therapy, a large number of people with epilepsy suffer from incompletely controlled seizures or the side effects of drugs or surgical treatment [27]. For these medically refractory patients, current approaches to treatment will, at best, lessen but not prevent the occurrence of seizures. Recent studies have indicated that approximately two thirds of patients with newly diagnosed epilepsy will experience good seizure control with the first or second AED administered [21, 22]. Almost one out of three patients, however, will have difficult-to-control epilepsy with frequent, disruptive seizures and undesirable medication-related side effects. Medically intractable epilepsy (MIE) is often a chronic, lifelong problem associated with a poor quality of life, constant

feelings of anxiety and lack of control, comorbid depression and AED-related adverse effects (such as cognitive impairment, sexual dysfunction, weight gain etc.).

Some patients with MIE may be good candidates for epilepsy surgery targeting the epileptogenic tissue. However, resection or destruction of the seizure focus is not an option for many people with MIE, either because of difficulties localizing the focus or because of proximity to eloquent brain areas and unacceptable surgical risks [36]. Thus, current surgical options can not be applied to a substantial number of patients. Moreover, nondestructive options have inherent advantages over approaches that require resection of brain tissue.

The goal of new therapies is to provide effective control of seizures without impacting the person's neuropsychological function and/or quality of life. Electrical neurostimulation and gene-based targeting have been proposed as potential new therapeutic strategies for the treatment of patients with MIE. Recent successes of brain stimulation for movement disorders have encouraged consideration of brain stimulation therapy for epilepsy. Several strategies have been investigated in human and animal models exploring the potential of electrical stimulation targeting structures in the central and/or peripheral nervous system. Similarly, the development of advanced generation systems for gene delivery to mature neurons has created the potential to treat epilepsy by altering the expression of proteins within the circuits that underlie refractory epilepsy. Because neither gene delivery nor stimulation is destructive, the approaches can be contemplated as means of treating seizure foci within eloquent neural structures.

Within the central nervous system two basic approaches have been implemented, namely direct or indirect targeting of epileptogenic areas. The first approach relies on careful identification of the epileptogenic tissue (cortex or hippocampus). This is usually accomplished by the means of a presurgical invasive evaluation utilizing intracranial subdural grid or depth electrodes. In the course of the invasive evaluation, intracranial recordings have guided direct cortical or hippocampal stimulation, employed as a potential treatment in small series of patients with MIE. The second approach aims at presumed seizure-gating networks. Potential target structures (such as the cerebellum or various deep brain nuclei) are believed to play a central, regulatory role in the epileptogenic network. Thus, electrical stimulation is used for control of distant epileptogenic cortex. Finally, stimulation of extracranial targets residing in the peripheral nervous system (stimulation of the vagus and trigeminal cranial nerves) has been employed as a means of modulating cortical excitability. Despite significant advances in the field of neuromodulation for pain and movement disorders, epilepsy neuromodulation faces a number of challenges including appropriate selection of favorable candidates, optimal stimulation parameters and target sites, evaluation of long-term effects of neural stimulation on tissue reorganization, plasticity and epileptogenicity, development of reliable algorithms for seizure detection and prediction and validation of long-term safety and efficacy with well-designed randomized, controlled trials. It is hoped that better understanding of the pathophysiology of epilepsy and the mechanisms of action of targeted electrical stimulation/neuromodulation will lead to further advancements in this field.

Electrical stimulation of the nervous system

Electrical stimulation in the nervous system can be classified in two main categories: a) electrical stimulation of the central nervous system (CNS), and b) electrical stimulation of the peripheral nervous system (PNS). The former, i.e. CNS stimulation can be further classified into: a) *direct stimulation* targeted to the presumed epileptogenic tissue such as the cortex or hippocampus and amygdala, and b) indirect stimulation targeted to any of the following structures: cerebellum, thalamus (anterior or centromedian), basal ganglia, subthalamic nucleus and caudate. PNS can be further classified into: a) vagus nerve stimulation and b) trigeminal nerve stimulation. All these methods and approaches are described below.

Direct CNS targeting of presumed epileptogenic zone

Cortex

Chronic implantation of subdural and/or depth electrodes is often required in a subgroup of epilepsy surgery candidates in order to better localize the region(s) of seizure onset and/or map eloquent cortex (Fig. 1). In the course of such invasive evaluations direct electrical stimulation of the cortex is routinely performed. Standard cortical stimulation parameters for the purposes of presurgical mapping consist of constant current pulses with a pulse width of 0.3 msec delivered in 50–60 Hz trains lasting for 3–8 sec [34]. A constant-current biphasic square wave, bipolar stimulator is typically used. Stimulation involves a pair of two electrodes

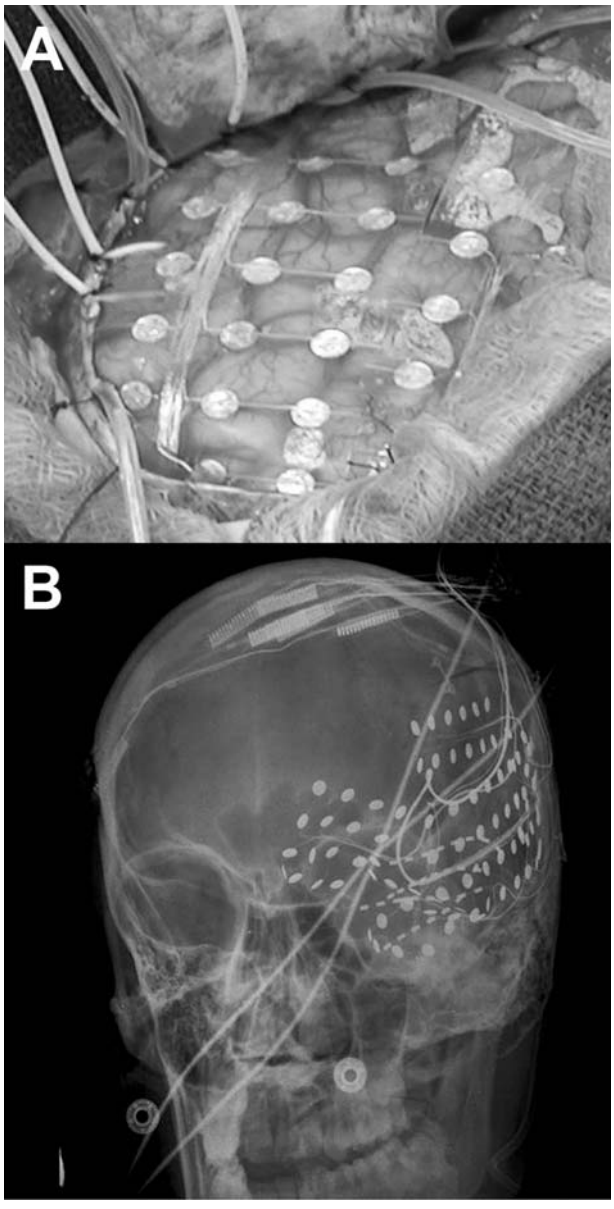

Fig. 1. (A, B) Subdural grid electrodes: intraoperative picture following placement of a combination of subdural and depth electrodes in a patient with suspected temporal lobe epilepsy. The subdural array consists of a ''grid'' of electrodes placed directly on the cortex during craniotomy

and begins at a low intensity (1 mA) with increasing current at 0.5–1 mA increments to a maximum of 15 mA or until a functional response and/or afterdischarges are obtained. Afterdischarges can take the form of single discharges, brief self-limited bursts or sustained evolving electrographic activity resembling electrographic seizures. To monitor for afterdischarges and/or electrically-provoked seizure activity electrocorticography (ECoG) is necessary during cortical stimulation.

In this setting of extraoperative cortical mapping, Lesser *et al.* reported that additional brief bursts of pulse stimulation (BPS) were effective in aborting stimulation-induced afterdischarges [23]. The pulse trains of BPS were briefer than standard cortical stimulation, lasting for 0.3–2 sec (median = 0.5 sec). Otherwise, the pulses of BPS had the same intensity and stimulus characteristics as the preceding pulses used for cortical localization purposes. Furthermore, BPS pulses were delivered through the same electrodes that had just been used for standard direct cortical stimulation. This series consisted of 17 patients implanted with subdural electrodes. The effect of BPS in stopping afterdischarges appeared to be limited to the first few seconds following BPS. When BPS were administered 115 of a total of 226 afterdischarges were aborted within 2 sec (compared with only 21 out of a total of 475 afterdischarges, which resolved within 2 sec in the absence of BPS) [23]. The same group performed a follow-up study in 7 patients implanted with subdural electrodes to explore optimal BPS stimulation parameters. The investigators reported that BPS was more likely to terminate an afterdischarge when applied: (1) during the negative phase of the afterdischarge waveform; (2) earlier rather than later in the course of the afterdischarge; (3) to afterdischarges that do not start immediately after the end of standard cortical stimulation; (4) to afterdischarges that have a continuous rhythmic pattern; and (5) to afterdischarges occurring at the stimulated electrode pair (primary site) as opposed to secondary sites (electrodes that had received standard cortical stimulation) [33].

Although afterdischarges cannot be equated with spontaneous epileptiform activity these observations have kindled interest in applying direct cortical stimulation to counteract spontaneous seizures. Experience from afterdischarge studies indicates that BPS may be more effective, when stimulation is delivered early, at the onset of a discharge, which is still localized [25]. Accordingly, for the purposes of clinical application, closed loop automated delivery systems would need to be developed and validated. Osorio *et al.* have presented data from 4 patients with implanted subdural electrodes, connected to a device capable of implementing an automated seizure detection algorithm for control of stimulation delivery (contingent or closed-loop stimulation). Studies were performed after completion of the presurgical invasive evaluation and before planned removal of the implanted intracranial electrodes. High frequency (100–500 Hz) electrical stimulation was delivered directly to the epileptogenic tissue and in close

temporal proximity to the onset of seizures. While this in-hospital ultra-short term trial (average duration of 57 hours), did not demonstrate anti-epileptic activity, it did demonstrate that closed-loop delivery of electrical stimulation is a viable option for patients implanted with invasive electrodes [37].

The feasibility and safety of responsive stimulation is currently undergoing evaluation at selected academic institutions as part of a randomized, double blind, active control study (Responsive Neurostimulator System – NeuroPace Inc., Mountain View, CA). Approximately 80 adults with focal pharmacoresistant epilepsy will be recruited in this study and monitored for at least 2 years following implantation. The neurostimulator device is implanted in the skull and connected to two cortical strip or depth leads, which target the presumed location of the epileptogenic focus. Optimal placement of these electrodes has been determined by previous evaluation for epilepsy surgery including placement of intracranial electrodes, if necessary, to determine the likely sites of seizure onset [29].

Hippocampus and amygdala

Epilepsy arising from the mesial temporal lobe structures is by far the most common substrate of focal epilepsy. The amygdala and hippocampus are commonly involved in the initial phases of EEG discharges of seizures arising from the temporal lobe. Patients with intractable seizures and unilateral mesial temporal lobe epilepsy are excellent candidates for surgical treatment. However, surgical resection is not recommended in patients with bilateral independent temporal foci or when eloquent cortex is found to overlap with the presumed epileptogenic zone.

Experimental evidence in animals indicates that prolonged low frequency stimulation (1 Hz applied for 10–15 min) can inhibit the development and expression of amygdala-kindled seizures; a procedure referred to as ''quenching'' [59]. Similar parameters are known to induce long term depression of synaptic responses, when applied to synaptic hippocampal pathways *in vitro*. In animal models of amygdala kindling, an increase in afterdischarge and seizure thresholds has been observed, when low-frequency stimulation is applied both during and after completion of the kindling process.

Velasco *et al.* first reported that subacute unilateral electrical stimulation of the hippocampus decreased interictal and ictal activity during a 2–3 week period. In this study, 10 patients were implanted with bilateral depth hippocampal electrodes ($n = 2$) or unilateral subdural basotemporal electrodes ($n = 8$) as part of a standard preoperative invasive evaluation. Stimulation was performed after completion of ictal video-EEG recordings, which allowed for an accurate determination of the seizure onset zone. Based on these recordings, all 10 patients were felt to be good candidates for standard anterior temporal lobectomies, which were performed at the end of the 2–3 weeks of amygdalo-hippocampal stimulation. Stimulation was continuous (interrupted only for 1 hour/day). Applied stimulation parameters (130 Hz, 450 μsec pulse width, and 200–400 μA intensity), were somewhat arbitrary. Stimulation contacts were located at the hippocampal formation in 7 patients, at the parahippocampal gyrus in 2, and at the white matter lateral to hippocampus in 1 patient. The authors reported that all patients experienced clinical seizures during the first 6 days of amygdalo-hippocampal stimulation. However, subsequent clinical seizures were completely abolished in the 7 patients with electrode contacts at the hippocampal formation [52]. The short period of observation and duration of seizure freedom (<2 weeks) limit the conclusions that can be drawn from this study.

Based on these observations, Vonck *et al.* proposed the use of commercially available standard DBS electrodes for the purposes of diagnostic recording as well as short- and long-term therapeutic stimulation of the amygdalo-hippocampal region. Two quadripolar DBS electrodes were implanted in each hemisphere through two occipital burr holes in 3 MIE patients with normal brain MRI (nonlesional), whose scalp video-EEG evaluations suggested mesial temporal lobe epilepsy. The most anterior electrode was placed in the amygdala; the second electrode aimed at the anterior part of the hippocampus. This strategy yielded good-quality invasive EEG recordings, which allowed for the identification of a unilateral mesial temporal seizure onset zone in all 3 patients. After completion of diagnostic recordings, chronic unilateral stimulation of the amygdalo-hippocampal epileptogenic region was performed. Initial stimulation parameters were similar to those used by Velasco (continuous stimulation interrupted for 1 hour/day, 130 Hz frequency, 450 μsec pulse width). Interictal spike counts before and after the initiation of stimulation were empirically utilized to assess adequacy of stimulation parameters. Two patients had >50% reduction in interictal spike activity without changing the initial stimulation settings. In the third patient >50% spike count reduction was accomplished after increasing stimulation frequency to 200 Hz. During a follow-up period of

3–6 months all 3 patients were reported to have a greater than 50% reduction of seizure frequency (range 50–93%). While none were seizure free, no adverse events were reported [55].

Thus, initial limited trials of mesial temporal lobe stimulation suggest the potential for a therapeutic reduction in epileptic activity. The data available, at present, suggests that this effect would not be curative. Thus, the benefits of reduced seizure frequency and severity on quality of life need to be carefully weighed against the costs and risks associated with this approach. Further, this data has evolved out of the convenient utilization of recording electrodes that play a role in current therapeutic protocols. There is little data to providing a mechanistic understanding for the basis of this therapeutic effect. Investigation of the underlying pathophysiology, as well as larger trials, may provide a means for optimizing this approach.

Indirect targeting of presumed epileptogenic zone

Cerebellum

The sole output of the cerebellar cortex is inhibitory, mediated by the axons of the large GABA-ergic Purkinje cells. Based on this fact, stimulation of the cerebellar cortex was postulated to inhibit the targets of cerebellar efferents. Attempts to apply this principle to animal models of epilepsy have had mixed results. Nonetheless, this theory led Irving Cooper to attempt cerebellar stimulation as a means for the treatment of MIE. This effort marked the first trial of epilepsy treatment using electrical stimulation of the human brain. In 1973, Cooper's group reported ''a marked improvement in seizure control'' in 6 out of 7 patients with intractable seizures following chronic subdural stimulation of the superomedial cerebellum [10]. Subsequent uncontrolled studies by Cooper and other investigators reported benefit in the majority of stimulated patients. Unfortunately, these results were not replicated in the two controlled double-blind studies conducted by Van Buren in the U.S. ($n = 5$) and Wright in the U.K. ($n = 12$ patients). No significant reduction of seizure frequency was observed after cerebellar stimulation for 10 and 6 months, respectively [48, 60].

The history of cerebellar stimulation underscores the need for well designed, blinded, placebo-controlled studies in the budding field of neuromodulation for epilepsy. At present, this technique is not considered to be an effective therapy for epilepsy, although the small number of patients in the controlled trial limits definite conclusions.

Recently Velasco *et al.* reopened the subject with their report of a pilot double-blind, controlled study in 5 patients with intractable motor seizures. Four-contact pad electrodes were placed bilaterally on the superomedial aspects of the cerebellum. Following Cooper's example, low-frequency (10 Hz) stimulation was delivered at a fixed pulse width of 0.45 msec and intensity of 3.8 mA; voltage output was adjusted based on electrode impedance to deliver a predetermined amount of charge density. Intermittent stimulation with alternating 4 min on and off intervals was applied throughout the day. This approach yielded significant reductions in the frequency of generalized tonic–clonic seizures in stimulated patients at 3 and 6 months, as compared to pre-stimulation baseline [49].

Thalamus

The thalamus constitutes the major route and relay station for afferents to the cortex. Physiological activity in various thalamic nuclei is capable of influencing extensive cortical areas. Furthermore, thalamocortical pathways are believed to play a central role in the synchronization and propagation of seizures. Naturally, this centrally-located, fairly circumscribed structure is an attractive target for deep brain stimulation (DBS). So far, human studies have explored the therapeutic potential of electrical stimulation of the centromedian and anterior nuclei in patients with pharmacoresistant epilepsy.

Anterior thalamus

The anterior thalamic nuclei (ANT, also referred to as anterior nucleus of the thalamus) constitute a group of first order relay nuclei, which receive afferents from lower brain centers (mamillary bodies and fornix) and forward messages to the neocortex (primarily cingulate). This anatomical arrangement makes ANT an integral component of the limbic system and attractive target for electrical neuromodulation. Several animal studies by Mirski *et al.* implicated the posterior hypothalamus, ANT and mamillothalamic tract in the pathogenesis and expression of experimental generalized seizures. In rats, high-frequency (100 Hz) stimulation of the posterior hypothalamus was found to increase the threshold for the first clonic and first tonic chemically-induced seizure (following administration of pentylenetetrazole) [32].

The first human study of ANT stimulation was conducted by Cooper and Upton, who reported a significant

decrease in seizure frequency in 4 out of 6 patients with pharmacoresistant focal epilepsy [47]. One patient remained seizure-free during two years of follow-up. However, details of stimulation were not provided. In another case series, all 5 patients with intractable focal or generalized epilepsy had decreased seizure frequency in the range of 24–89% (mean 54%, compared to a 1–3-month baseline) following bilateral implantation of DBS electrodes in the ANT [19]. Surgery was performed under the guidance of intraoperative microelectrode recordings. Interestingly, improved seizure control was observed immediately after implantation, although high-frequency (100 Hz) stimulation did not start until 4 weeks later. Furthermore, cessation of stimulation after a period of 7 months or longer did not result in increased seizure frequency. These unexpected observations sug-

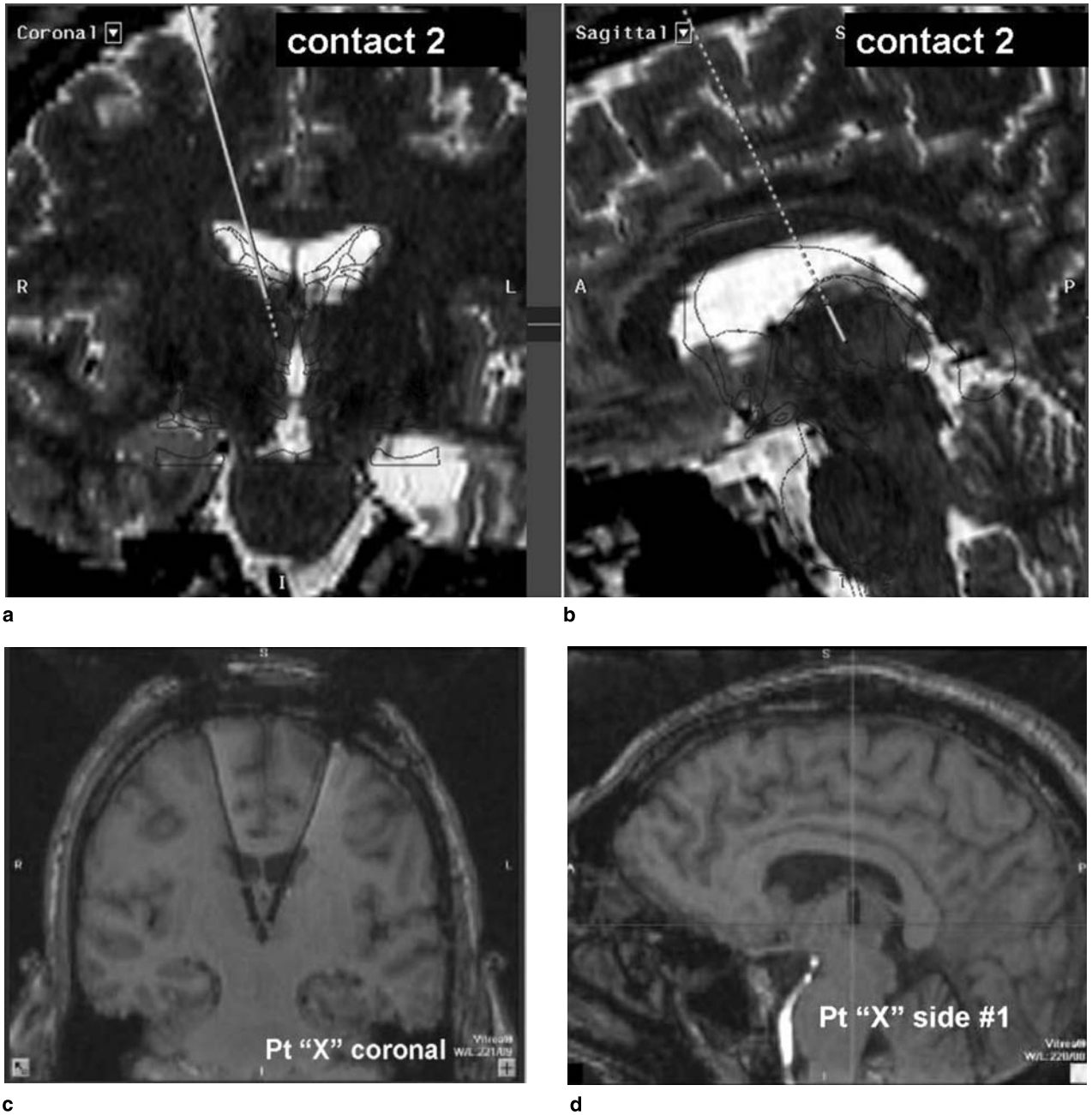

Fig. 2. Thalamic anterior nucleus deep brain stimulation: (a) Coronal T2 MRI images of trajectory planning for placement of ANT DBS. (b) Sagittal T2 MRI images of trajectory and target planning for placement of ANT DBS. (c) Postoperative coronal T1 MRI revealing location of ANT DBS. (d) Postoperative sagittal T1 MRI revealing location of ANT DBS

gest the possibility of an initial lesioning (''microthalamotomy'') effect. Hence, the contribution/effects of stimulation *per se* remain questionable.

In a subsequent similar study of high-frequency, bilateral ANT stimulation, 4 out of 5 patients experienced deterioration of seizure control after discontinuation of stimulation, a finding that argues against the lesioning hypothesis. In this study, chronic intermittent ANT stimulation resulted in significant improvement with respect to severity of seizures in 4 out of 5 patients (on the grounds of significant reduction of incapacitating secondarily generalized tonic–clonic seizures and complex partial seizures associated with falls). Only one patient showed a significant reduction in total seizure frequency as compared to the pre-implantation baseline.

The safety and efficacy of bilateral DBS targeting the anterior nuclei of the thalamus is currently investigated as part of a multicenter, randomized, double-blind, placebo-controlled study. Approximately 150 adults with pharmacoresistant epilepsy will be recruited and monitored for at least 13 months following implantation. The stimulation device, DBS electrodes and implantation procedure are similar to those of routine movement disorder surgery (Medtronic – Minneapolis, MN). Stimulation will be open-loop (continuous and not modified in response to patient's EEG or seizure activity). Figure 2a and b demonstrate the use of Framelink (Sofamore Danek, USA) software to plan bilateral anterior thalamic nucleus DBS implantation. Figure 2c and d depict postoperative MRIs on a patient implanted with bilateral ANT DBS electrodes in place. The results of this trial are not yet available, but promise to provide a definitive assessment of the utility of ANT DBS for MIE.

Centromedian thalamus

The centromedian nucleus of the thalamus (CM) is part of the intralaminar nucleus, a higher order relay station involved in reticulocortical and corticortical communication. As such the CM plays a central role in wakefulness, attention and regulation of cortical excitability. The group of Velasco has published several reports on the clinical and electrophysiologic effects of electrical stimulation of the CM nucleus in patients with MIE. Acute unilateral stimulation of CM produced frequency-dependent responses on scalp EEG which were not associated with any clinical/behavioral changes. Low-frequency (3–6 Hz) electrical stimulation elicited electrocortical incremental responses with a bilateral scalp distribution maximum at the ipsilateral hemisphere, whereas high-frequency (60 Hz) stimulation resulted in desynchronization of scalp EEG and very slow electronegative DC (direct current) shifts [53]. These observations support the impact of CM thalamocortical projections in regulating cortical function.

The Velasco group was the first to report on the beneficial effects of CM stimulation in 5 patients with MIE and (secondarily) generalized motor seizures. Seizure frequency was evaluated at baseline and 3 months post-implantation. Bilateral depth electrodes were stereotactically placed through frontal burr holes, tunneled away from the scalp incision and externalized on the anterior chest wall for the 3-month period of observation. Intermittent (2-hour daily) high-frequency (60–100 Hz) stimulation alternating from right to left side led to reductions of generalized tonic–clonic seizures by 80–100% and complex partial seizures by 60–100% [51]. Because of economic constraints only two patients had the electrodes connected to an internalized system after completion of this preliminary study.

In a subsequent study, the same authors examined the effects of chronic electrical stimulation of the CM in 13 patients with MIE (ages 4–31 years), followed for a period of at least 12 months post-implantation (range 12–94, mean = 41.2 months). Bilateral electrode placement was guided by ventriculography and confirmed with electrophysiological studies (scalp EEG responses evoked with low versus high-frequency stimulation) and MRI. Electrodes were connected to internal pulse generators. Stimulation of 4–6 V was delivered continuously, at high-frequency (60 Hz), alternating between the right and left side (delivered in 1 min bursts with a 4 min off interval preceding stimulation of the alternate side). The authors observed a 90% reduction in the frequency of generalized tonic–clonic and atypical absence seizures. In contrast, no significant decrease was seen in patients with complex partial seizures. Because all of the patients with Lennox-Gastaut syndrome (LGS) responded to chronic stimulation, the authors concluded that LGS is a clear indication for bilateral CM DBS. On the other hand focal epilepsies arising from the temporal lobes were not significantly improved [50].

In contrast to these findings, a placebo-controlled pilot study of bilateral CM stimulation in 7 patients with MIE (ages 16–41 years) failed to show significant benefit. This small study utilized a 9-month double-blind, cross-over protocol. Baseline seizure calendars were collected prospectively for several months prior to implantation of internal pulse generators. Bilateral

electrode placement was guided by CT/MRI stereotactic measurements and was confirmed by postoperative CT scans. Stimulators remained off for the first 1–2 months after implantation and prior to randomization. During the first 3 months following randomization (phase 1), stimulators were active in 4 and off in the remaining 3 patients. This was followed by a 3-month washout period of no stimulation (phase 2; off period). During phase 3, patients – who had not received stimulation in phase 1 – were crossed over to stimulation. The remaining patients remained in the off mode during phase 3. At 9 months post-randomization (phase 4), all patients were changed to open label stimulation. Intermittent stimulation parameters were chosen to imitate the parameters initially used by the Velasco group (high-frequency, 65 Hz, 90 μsec pulses, of 0.5–10 V administered in trains 1 min on and 4 min off for 2 hours/day). This study showed that bilateral CM stimulation was safe and well-tolerated. Overall there was an approximate 30% reduction in the mean frequency of tonic–clonic seizures with the stimulator on, as compared to an 8% decrease with stimulator turned off. Only one patient experienced a sustained >50% reduction of generalized seizure frequency during the 9-month period of double-blind observation. During the open-label segment, 3 of 6 patients reported generalized seizure frequency decrease that exceeded 50% with continuous 24-hour/day CM stimulation (follow-up ranging from 3 to 13 months) [13]. However, several factors, including small study size, cross-over design, potential for long-lasting carry-over effects following transient discontinuation of stimulation, lack of knowledge with respect to optimal stimulation parameters and patient selection preclude definitive conclusions regarding efficacy.

Basal ganglia

The basal ganglia constitute a richly interconnected set of forebrain nuclei, which are integrated into several networks exerting influence over multiple cortical regions. Over the past decade DBS of the subthalamic nucleus (STN) and the globus pallidus internus (GPi) has evolved into a well established therapy for the treatment of Parkinson's disease and other movement disorders. At the same time, experimental evidence has emerged to suggest that the basal ganglia play a role in the modulation of seizure control. The pioneering work of Karen Gale's group showed that inhibition of neurons in the substantia nigra pars reticulata (SNr), the main output nucleus of the basal ganglia, can suppress several types of seizures in various animal models [14]. This data led investigators to postulate the existence of an endogenous ''nigral control of epilepsy system''. In an attempt to test the application of this theory, both the STN and caudate nucleus have been targeted in human studies.

Subthalamic nucleus (STN)

Benabid *et al.* presented their first case report of STN stimulation for epilepsy in 2002. A 5-year old girl with MIE secondary to a focal left centroparietal cortical dysplasia experienced significant and sustained reduction in the number and severity of seizures during 30 months of chronic left unilateral high frequency STN stimulation [5]. The same group reported an additional four cases of MIE treated with bilateral high-frequency stimulation and followed up for a period ranging from 10 to 30 months using the techniques established in parkinsonian patients. Four out of these five patients showed ''a clear reduction of seizure frequency'' [8]. Consistent with Gale's theory, the authors observed that the best responses were obtained with targeting of the inferior part of the STN, in a region that is closer to the SNr and differs from the usual STN target in Parkinson's disease. Our group at the Cleveland Clinic Foundation reported another four patients with intractable focal epilepsy treated with chronic bilateral STN stimulation and followed up for a period ranging from 8–18 months. In this group, two patients experienced a significant decrease in seizure frequency and severity. No effect was observed in the other two cases [35]. The preliminary results of these two small case series have not yet been followed by larger double-blind, controlled studies.

Caudate

Experience with caudate stimulation for the treatment of MIE in humans is very limited. Sÿramka *et al.* from Slovakia, and Chkhenkeli *et al.* from the Republic of Georgia have presented positive results in uncontrolled case series. Chkhenkeli reported a series of 23 patients with implanted neurostimulators and 15 with externalized depth electrodes targeting in the ventral caudate nucleus. Low-frequency stimulation in the range of 4–6 Hz resulted in a reduction of neocortical and mesial temporal interictal epileptiform discharges [9]. In contrast, high frequency (50–100 Hz) stimulation was associated with ''provocation or augmentation'' of interictal epileptiform activity in the ipsilateral hippocampus and

amygdala. The authors reported no serious complications and no clinical seizures as a result of therapeutic stimulation. Of note, these reports lack information regarding patients' spontaneous clinical seizures before and after caudate stimulation.

Electrical stimulation of the peripheral nervous system

Vagus nerve

Vagus nerve projects diffusely to the thalamus, amygdala and forebrain as well as to other cortical areas through the nucleus tractus solitarius (NTS) and medullary reticular formation, respectively. It is postulated that the vagus nerve modulates cortical excitability and exerts an influence on the generation and propagation of seizures [56]. Experiments by Walker *et al.* have provided evidence that decreased excitation or increased inhibition in NTS reduces susceptibility to limbic motor seizures in animals [57]. Bailey *et al.* were the first to provide evidence that vagus nerve stimulation can produce EEG desynchronization in cats [3]. More recently, in 1985, Zabara proposed and demonstrated the use of vagus nerve stimulation (VNS) as a means of controlling experimental seizures in canines [62].

The vagus nerve is a mixed cranial nerve made of predominantly sensory fibers (approximately 80%). Motor fibers innervate the larynx and provide parasympathetic cholinergic supply to the heart, lungs and abdominal vis-

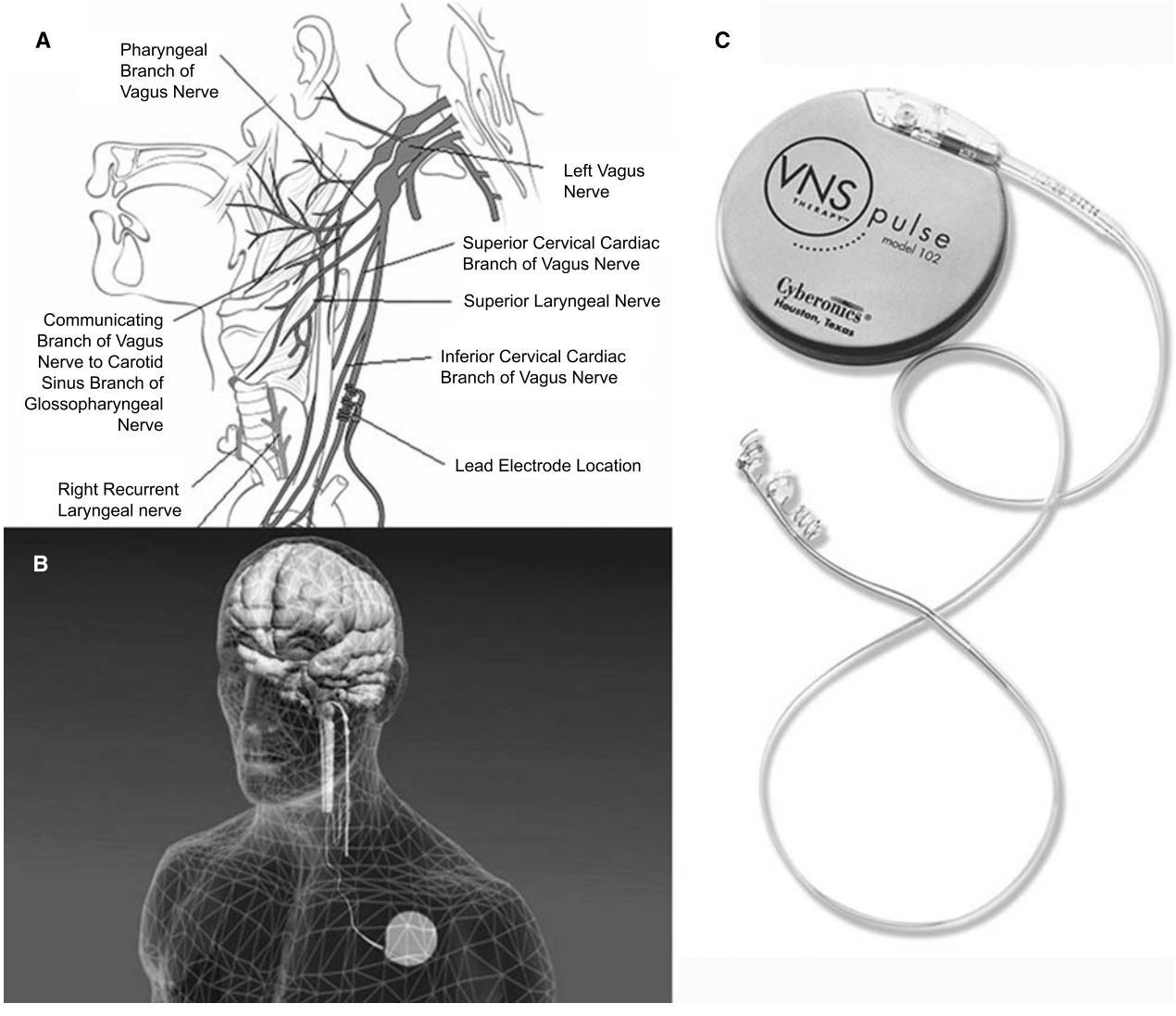

Fig. 3. Vagal nerve stimulator: (A) Anatomical diagram depicting manufacturer recommended implant location. (B) Illustration of IPG and electrode in situ. (C) Model 102 IPG with attached VNS electrode

cera. The right vagus nerve innervates the sinoatrial node of the heart while the left innervates the atrioventricular node. Stimulation of the right vagus nerve has been shown to produce more cardiac slowing in a dog model as compared to the left side, and hence the left vagus nerve is the usual target of stimulation in humans [40].

The VNS Therapy System (Cyberonics, Houston, TX) is based on a pulse generator, which is similar to a cardiac pacemaker in shape and size. The generator is implanted on the anterior chest and attached to two helical electrodes, which are wrapped around the cervical portion of the left vagus nerve (Fig. 3). It is the first battery-powered, programmable, transcutaneously controlled neurostimulator approved for the treatment of MIE on the basis of efficacy and safety data from two prospective, randomized controlled studies. These studies led to the introduction of VNS in the U.S. in 1997 as adjunctive therapy ''in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications''. Efficacy of VNS has been assessed in several trials; the initial pilot study by Penry and Dean used high frequency (47–145 Hz) whereas the more recent ones utilized low frequency (1–30 Hz) stimulation. As some patients can sense when the VNS device is active, placebo-controlled studies are not feasible. The two large double-blinded randomized controlled trials, involved randomization of more than 300 patients to receive 3 months of ''high dose'' (frequency = 20–50 Hz; pulse width = 500 μs; 0.25–3.50 mA; 30 sec on, 5 min off) versus ''low dose'' (0.25–0.35 Hz; 130 μs; 0.25–3.50 mA; 30 sec on, 180 min off) stimulation. During this period antiseizure medications remained unchanged. Compared with 3-month pre-VNS baselines, significantly greater seizure rate reductions were observed in the high (−24 to −28%) than in the low (−6 to −15%) intensity stimulation groups. About 30–40% of the high dose group and 15–20% of the low dose group had a 50% or greater reduction of seizure frequency [16].

These results of VNS are broadly comparable to those seen in the trials of new antiepileptic medications (AEDs) for patients with refractory complex partial seizures. The median reduction in seizure frequency at 12 months after completion of the initial double blind study was 45%, compared with 28% directly after completion of the study. This finding supports the notion of a sustained therapeutic benefit over longer follow-up periods [41]. Unlike AEDs, VNS is devoid of drug-drug interactions and drug-related adverse CNS effects (including fatigue, dizziness, cognitive impairment, weight gain or sexual dysfunction).

VNS is usually contraindicated in patients with a history of previous cervical vagotomy or previous left neck surgery. The most frequent stimulation-related side effects are hoarseness, cough, and throat pain. They occur during the period of stimulation and tend to diminish with time. Stimulation-related side effects can be alleviated by changing stimulation settings (reducing stimulation intensity and/or pulse width). Early and uncommon complications include vocal cord paralysis, Horner's syndrome, lower facial paresis and bradycardia/asystolic cardiac arrest. Delayed effects include shortness of breath, persistent cough, hoarseness or paresthesia, worsening of obstructive sleep apnea, or worsening of swallowing difficulties. The potential for mechanical complications (such as lead fracture or generator malfunction) as well as wound infections constitute inherent risks associated with implantable devices such as VNS. Finally, studies have indicated that the risk of sudden unexpected death in epilepsy (SUDEP) is not higher in patients receiving VNS compared to the baseline risk of patients with MIE [2]. VNS is currently FDA-approved solely for use in adults with pharmacoresistant focal epilepsy. However, encouraging preliminary results have been obtained by studying off-label applications in children as well as patients with generalized epilepsy syndromes. Predicting which patients will respond to VNS prior to implantation remains problematic.

Trigeminal nerve

In 1976, Maksimow first reported that manual stimulation of trigeminal nerve by exerting a strong pressure on the infraorbital branches interrupted ''grand mal seizures'' in 29 of the 50 epileptic patients, when performed at the beginning of seizure, but not when stimulated during the convulsion [26]. In 2000, Fanselow *et al.* demonstrated a reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered electrical trigeminal nerve stimulation (TNS) [12]. The advantages claimed over vagal nerve stimulation are the potential to stimulate the nerve bilaterally for presumed better effect, minimal invasiveness and the lack of potential cardiovascular/abdominal visceral side effects. DeGiorgio *et al.* initiated a pilot study of infra-orbital TNS for epilepsy based on Fanselow's animal study and reported 39–76% seizure reduction in two patients without any side effects or intolerance [11]. However, further clinical trials are needed to confirm efficacy and address possible placebo effects.

Transcranial magnetic stimulation

The noninvasive technique of transcranial magnetic stimulation (TMS) was first introduced by Barker *et al.* for the purpose of stimulating a region of cerebral cortex using a rapidly cycling magnetic field [4]. Stimulation is achieved by either single or paired pulse sequences or by repetitive transcranial magnetic stimulation (rTMS). During rTMS regularly repeated magnetic pulses (with a frequency up to 60 Hz) are delivered to a single scalp site for several seconds. TMS requires a high electrical current, which is produced by a pulse generator for very brief periods (in the order of 1 msec), and is passed through a coil placed on the scalp. The rapidly changing current creates a strong and focal magnetic field, which unlike transcranial electric stimulation is unimpeded and undistorted by the intervening scalp or skull. The rapidly alternating magnetic field induces electrical currents intracranially, which can be focused to smaller regions of interest by placing on the scalp two TMS coils in a "figure of eight" fashion. Commercially available TMS devices produce 1.5–2.5 Tesla at the coil surface and are capable of activating cortical neurons at a depth of 1.5–2.0 cm beneath the scalp. Repetitive TMS is thought to have both excitatory and inhibitory effects on the cortex depending on frequency and intensity of stimulation. It is thought that lower frequencies result in activation of cortical interneurons, whereas higher frequencies produce stimulation of cortical motoneurons. In general, low frequency rTMS (trains of $\sim$1 Hz) cause a decrease in motor cortex excitability, whereas higher frequencies (trains of 2–20 Hz) appear to have mostly facilitatory effects on the cortex.

It is beyond the scope of this chapter to discuss in detail, but three basic principles emerge from most rTMS studies. First, the effects of rTMS are largely cortical and not spinal in origin, although descending volleys can modulate subcortical and spinal structures. Second, the effects of rTMS on cortical excitability are not limited to motor cortex, but are applicable to different cortical areas involved in a variety of (eloquent) functions. Finally, the duration of rTMS effects can be long lasting, from 5–60 min to as long as 72 hours. It seems logical to assume that low frequency rTMS can be utilized to modulate hyperexcitable cortex, as is the case in epilepsy or dystonia for example.

Safety of clinical application

The electric currents induced by TMS in the brain are comparable to those used in peripheral nerve stimulation with maximum induced charge of $0.8\,C/cm^2$. The total charge per phase is much lower than that used for electroconvulsive therapy (by four or more orders). Single pulse TMS has little detectable effect on heart rate, arterial blood pressure, EEG, cognitive or motor test performance, and cerebral blood flow studies [7]. When applied ipsilaterally to an epileptogenic focus, TMS stimuli (single, paired or quadruple) did not induce any seizures or cause any observable adverse effects in a study of 21 patients with MIE, who had intracranial electrodes implanted as part of their invasive presurgical evaluation [43]. Repetitive TMS bears quite different safety risks depending on the frequency and effects of stimulation on cortical excitability. rTMS is more likely to induce seizures, when compared to single pulse TMS. The risk of seizure induction is usually associated with high stimulus intensities, long train durations and/or short intertrain intervals [38, 58]. Although high-frequency rTMS may result in temporary disruption of neuropsychological processes such as language, there have been no descriptions of long-lasting effects on cognitive, motor or sensory function.

Treatment of epilepsy

As discussed, low frequency trains of rTMS are known to produce a relatively long-lasting suppression of cortical excitability, and may have the potential of alleviating seizures in individuals with epilepsy. Akamatsu *et al.* examined this hypothesis by studying the effects of low-frequency rTMS in experimentally induced seizures. They demonstrated that 1000 TMS pulses given at a frequency of 0.5 Hz increased the latency for development of pentylenetetrazol-induced seizures in rats [1]. The first open pilot study was performed by Tergau *et al.* on nine patients with pharmacoresistant temporal and extratemporal focal epilepsy. Seizure frequency during the 4 weeks before and after low-frequency rTMS was assessed. Repetitive TMS was given for five days at a frequency of 0.33 Hz (two trains of 500 pulses per day delivered at 100% motor threshold intensity). Antiepileptic drugs were kept constant throughout the period of follow up. The investigators reported a significant reduction of seizure frequency by approximately 44% during the post-intervention period [45]. All patients appeared to tolerate the treatment well. Seizure frequency again reached baseline level after 6–8 weeks. Similarly, Menkes and Gruenthal reported positive results with low-frequency rTMS in a single case of MIE secondary to focal cortical dysplasia. In

this study, biweekly 0.5 Hz rTMS was administered for 4 weeks at 5% below motor threshold. Seizure frequency and interictal spikes were observed to decrease by 70 and 77%, respectively [31].

Nonetheless, these positive effects of 0.3–0.5 Hz rTMS on seizure frequency have yet to be replicated in blinded randomized trials. In the only blinded controlled study, Theodore *et al.*, compared the effects of 1 Hz rTMS (given for 15 min twice daily) to placebo stimulation in a group of 24 patients with focal epilepsy. The investigators only observed a trend toward a short term reduction of seizure frequency, which did not reach statistical significance [46]. These negative findings may be attributable to the choice of rTMS parameters (for example frequency of rTMS was higher in this study) and the characteristics of the patients' epilepsy (some patients had deeply-situated mesial temporal foci, which may be inaccessible by TMS). Hence, there exists a need for further randomized trials using realistic sham stimulation protocols aimed at examining different rTMS parameter combinations (frequency and intensity of stimulation, number and frequency of applications, train duration etc.) in larger and more homogenous groups of individuals with epilepsy. In summary, rTMS has been shown to be safe in human volunteers and patients with epilepsy. The effects of rTMS vary with the frequency of stimulation, and can be utilized for both diagnostic and clinical purposes. Low frequency rTMS may in fact have the potential to alleviate seizures, but a clear role in the treatment of MIE remains to be established.

Gene-targeting

An increasing appreciation for the genetic causes of epilepsy [30, 54, 42] has led to an interest in the application of gene transfer as a means of therapy. Further, the mechanism of epilepsy can be viewed as an imbalance in the excitatory and inhibitory neurotransmission. Thus, means of altering the genetic underpinnings of epileptogenesis and the expression of proteins capable of synaptic modulation may lead to new therapies, prevention, and even cures for some syndromes. Viral vector mediated gene delivery can affect the stable production of proteins within neurons, hence providing a vehicle for these therapies. Neuroactive peptides, adenosine, genes encoding voltage- and ligand-gated ion channels of neurons and genes encoding proteins involved in synaptic transmission are agents that can be delivered by gene therapy with potential utility in epilepsy treatment [28, 30, 42, 54, 61]. Several vector systems have been used for gene transfer in vivo. Vectors constructed with adenovirus, HSV, AAV, and lentivirus can effectively transduce neurons, suggesting that these vectors may be applied to the treatment of neurological disorders [54]. To date, most work in the nervous system has been performed with adenoviruses because of their high infective efficiency. One major disadvantage of adenoviral vectors is the limited time course of expression due to cytolytic or noncytolytic mechanisms. AAV is a parvovirus that has not been linked to any human pathological processes [6]. Vectors derived from AAV contain only 4% of the wild-type genome, and consequently have no cytotoxic side effects and a minimal capacity to provoke an immune response. rAAV vectors can infect a broad range of cells in multiple species, including both dividing and non-dividing cells. With the evolution of this technology, the production of therapeutic transgenes by viral vectors could be targeted to specific cell and tissue types and controlled by using specific and inducible/repressible promotor systems.

Neuropeptides and epilepsy

Most therapeutic strategies for epilepsy have focused on the modulation of signaling mediated by the excitatory and inhibitory neurotransmitters, glutamate and γ-aminobutyric acid (GABA). However, the preferential release of neuropeptides under conditions of increased neuronal activity, particularly during seizures, has encouraged investigation of their role in seizure modulation [54]. Substance P and corticotropin releasing factor (CRF) play a ''pro-epileptic'' role, while others like neuropeptide Y, galanin, somatostatin, and dynorphin play an ''anti-epileptic role'' [28, 39]. A comparison of dynorphin A, galanin, neuropeptide Y (NPY) and somatostatin in a model of self-sustaining status epilepticus demonstrated that all these neuropeptides possessed significant anti-seizure activity. However, their anticonvulsant profiles followed different patterns. Somatostatin and NPY induced strong, but transient suppression of spikes and seizures, while seizure suppression by dynorphin and galanin was more profound and irreversible [28]. Galanin and NPY have been shown to antagonize excitatory glutamatergic neurotransmission in the hippocampus [39, 24]. Compelling evidence supports an anticonvulsant role for these peptides in various experimental models of seizures, following both exogenous application and endogenous release [54, 28]. Neuroprotection against excitotoxic cell death and seizure-induced

neurogenesis are two novel aspects of peptide action in the CNS that are relevant to epilepsy research [54, 15].

Vectors for neuropeptide gene delivery

These findings led to the hypothesis that overexpression of Galanin and NPY in specific brain areas may be an effective strategy for inhibition of seizures and epileptogenesis. Attenuation of seizures and neuronal death by AAV vectors that mediate galanin expression and secretion has recently been reported [24, 15]. In one study, an AAV vector was engineered to carry a fibronectin sequence together with the galanin gene [15]. AAV-mediated delivery of this secretory signal, along with the coding sequence for the active galanin peptide, significantly attenuated in vivo focal seizure sensitivity in rat inferior collicular cortex and prevented hippocampal hilar cell loss secondary to kainate-induced seizures. By using a rAAV vector under the control of a doxycycline sensitive promoter, control of transgene expression was achieved. The threshold for seizure generation returned to baseline within 1 week of turning off vector mediated gene expression. This study demonstrates the feasibility of both controllable and long-term seizure attenuation using a gene-therapy vector. In another study, Lin *et al.* constructed a rAAV vector, in which the galanin gene was driven by a neuron-specific promoter [24]. The study showed long-lasting ($\leq$2.5 months) functional overexpression of galanin, specifically in hilar interneurons and their terminal projection fields, thus demonstrating that the peptide can be produced and transported along axons (even at a long distance from its site of synthesis). Lin *et al.* reported that restricted galanin overexpression results in powerful inhibition of seizures induced by intrahippocampal injection of kainic acid and detected by EEG analysis.

Richichi *et al.* studied the effect of long-lasting AAV mediated hippocampal NPY expression on acute kainate induced seizures and kindling epileptogenesis [39]. The authors used vectors with different serotypes to optimize neuronal gene expression. The rAAV serotype 2 (rAAV2) vector increased neuropeptide Y expression in hilar interneurons only, whereas the chimeric serotypes 1 and 2 vector caused far more widespread expression including the mossy fibers, pyramidal cells, and subiculum. EEG seizures induced by intrahippocampal injection of kainate were reduced by 50–75% depending on the spread of NPY expression, and seizure onset was markedly delayed. In rats injected with chimeric serotypes 1 and 2 vector, status epilepticus was abolished, and kindling acquisition was significantly delayed. The experimental findings in rodent models of seizures suggest that targeted gene transfer may provide a basis for development of new gene therapies for MIE.

Ion channel gene transfer

Phenytoin and several other commonly used antiseizure medications are thought to inhibit seizures by stabilizing the voltage-dependent sodium channel in its inactivated state, thereby limiting sustained repetitive firing of a neuron. Benign familial neonatal convulsions (BFNC), an autosomal dominant epilepsy of infancy, is caused by mutations in the KCNQ2 or the KCNQ3 potassium channel genes [42]. Studies of ion channels in epilepsy focus on genes encoding voltage- and ligand-gated ion channels of neurons. These proteins form another attractive target for epilepsy gene therapy. Because a relatively minor reduction of K^+ current may produce epilepsy [42], perhaps a gene that only modestly enhances that current could effectively inhibit seizures. The family of inwardly rectifying potassium (Kir) channels plays an important role in the generation of action potentials in excitable cells. In the central nervous system, the Kir gene (electrical silencing gene) contributes to stabilizing the resting potential close to the reversal potential of K^+. These channels therefore act to inhibit depolarization to the threshold for triggering action potentials. Johns *et al.* demonstrated that infection of superior cervical ganglion neurons by an adenoviral vector harboring the Kir2.1 gene suppressed neuron excitability, but did not affect normal electrical activity after induction of Kir2.1 gene expression [20]. Vector mediated Kir gene expression could therefore regulate overactive neuronal populations providing a means to treat MIE.

Synaptic inhibition through gene transfer

Seizures occur when brain cells in the area of a brief electrical disturbance send uncontrolled coordinated synaptic output to surrounding neural structures [30]. Therefore, the neuronal expression of a protein that inhibits synaptic transmission provides an ideal strategy for the treatment of seizures by interrupting abnormal synchronization of brain cells. Clostridial toxin light chain (LC) inhibits synaptic transmission by digesting synaptobrevin, a critical component of the vesicle-docking protein complex responsible for neurotransmitter release [44]. Yang *et al.* applied an adenoviral vector expressing

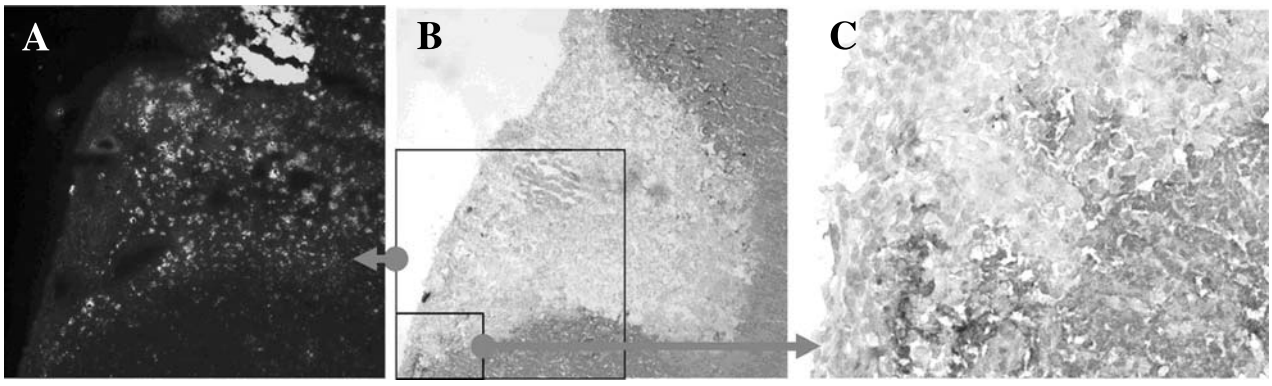

Fig. 4. Transgene expression and the digestion of synaptobrevin: (A) GFP expression at the area of cannula and surface of brain spread from injection area in the tissue of AdLC animal; (B) immunohistochemical staining using an antibody against synaptobrevin/VAMP-1; (C) LC expression area showed decreased synaptobrevin expression

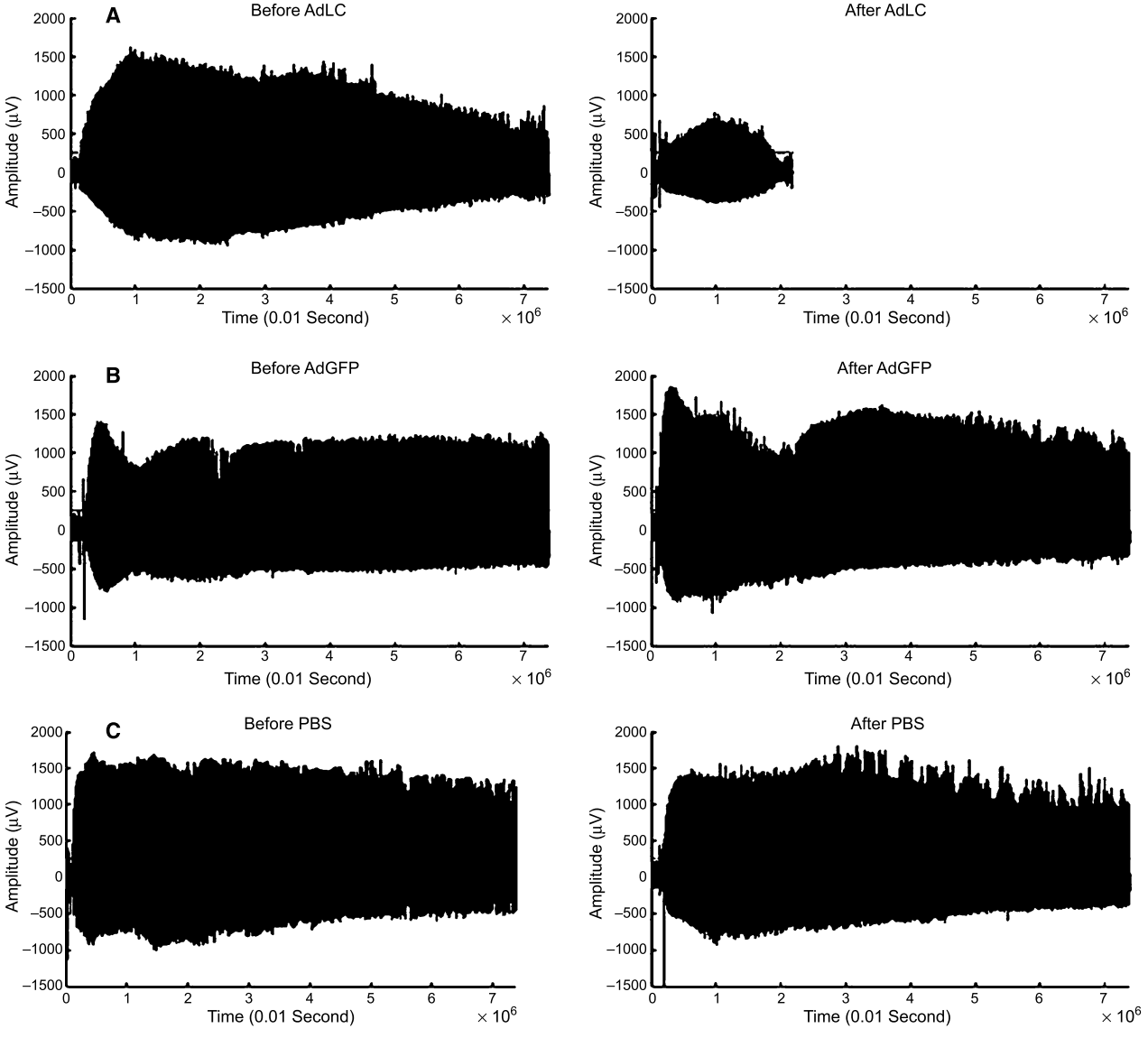

Fig. 5. AdLC inhibits seizures following penicillin injection. Spiking induced by penicillin injection before and ten days after AdLC (A), AdGFP (B), and PBS (C) administration. Spike amplitude (Y-axis) is plotted as a function of time course after the induction of seizures (X-axis)

LC (AdLC) to eloquent cortex to a penicillin-induced epilepsy rat model. Light chain expression depleted synaptobrevin levels in the rat cortex (Fig. 4). AdLC administration significantly suppressed EEG frequency, amplitude and duration in epileptic rats (Fig. 5). In addition to suppressing epileptiform discharges and seizures as measured by EEG, AdLC also improved seizure grade and prolonged the latency to seizure onset as documented by clinical observation of seizure manifestations [61]. LC expression did not induce any detectable motor function changes in a variety of validated assays including the BBB scale, rotarod and grip strength assays. Thus, LC gene delivery to epileptic foci represents a novel option for the treatment of medically refractory epilepsy, especially for foci located in eloquent cortex.

Concluding remarks

Advances in technology and the success of neuromodulation in treating a variety of neurological disorders have spurred interest in exploring promising therapeutic alternatives, such as electrical stimulation and gene-based targeting for the treatment of MIE. Despite several positive reports in humans along with experimental observations in animal models, the technique of electrical stimulation for the treatment of epilepsy is still in its infancy. Furthermore, very little is known about its mechanisms of action and its short and long-term effects. Likewise, the promising results of viral vector mediated cerebral gene delivery have prompted the development of clinical trials for the application of this approach. However, these trials are still in the planning stages, and anti-epileptic gene transfer has not yet been performed on humans.

The history of electrical stimulation indicates that results from well-designed, randomized, placebo-controlled studies are essential. Except for VNS, none of the other brain-stimulation therapies has been proven effective in controlled trials. Small controlled studies have failed to show benefit from stimulation of the cerebellum or the centromedian nucleus of the thalamus. At the time of this report, results of larger, ongoing, multicenter trials are eagerly awaited. The distinct advantage of neurostimulation is that, unlike lesioning and resection, it is a reversible approach that carries minimal risk for persistent loss of neurological function. In addition, electrical stimulation has the benefit of nonpharmacologic action, and is therefore devoid of drug-drug interactions and drug-related adverse CNS effects. On the other hand, chronic electrical stimulation may theoretically lead to kindling or long-term changes in tissue plasticity and/or epileptogenicity. Ideally electrical stimulation should lead to complete control of epileptic seizures akin to successful resective surgery for epilepsy. VNS, however, like most antiepileptic medications, provides only a palliative treatment option in patients with MIE. As the field of neuromodulation advances, it is important to continually weigh the risks and costs associated with surgical intervention, electrode implantation and hardware failures against the long-term benefits of seizure control and improvement in patients' quality of life.

The data presented demonstrate that stimulation of a wide variety of targets has been investigated for efficacy in epilepsy. However, only limited work has been done in animal models or in a focused fashion. Consequently, little is known about the optimal parameters of stimulation, determination of appropriate target sites and selection of favorable candidates. The number of possible combinations of stimulus waveform, frequency, pulse width, intensity and duration of stimulation, and electrode configurations seems bewildering and calls for further experimental validation. Because current stimulation protocols are determined empirically, it is not yet clear whether or how to best customize stimulation to individual patients. To date, most reports have examined the potential of ''blind'' intermittent or continuous neurostimulation that constitutes the delivery of current at predetermined settings independent of the patient's physiological state. New ''intelligent'' stimulators are in development; these devices would be programmed to either respond to or anticipate the onset of seizures and deliver stimulation at the optimal time point. It is hoped that new insights into the mechanisms of electrical stimulation and greater understanding of epilepsy will provide answers to these questions. To that end, continued animal studies and systematic exploration using computer models is warranted.

Gene transfer promises to provide a means for neuromodulation through the delivery or inhibition of select proteins and peptides. To the extent that this approach will specifically alter synaptic function broadly or within specific systems (neuropeptide specific gene transfer), it constitutes an alternative approach to electrical stimulation. This approach will enable a device-free alternative, hence, avoiding the problems of implanted devices including infection, malfunction, MRI safety, and battery life. However, this technology carries its own specific risks including the potential for inflammatory response and inefficient control of gene expression. We

anticipate that the continued evolution of this technology will provide solutions to these risks. While clinical trials of this approach are likely to occur in the next five years, solid proof of efficacy is unlikely to be available in the near future.

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References

1. Akamatsu N, Fueta Y, Endo Y, Matsunaga K, Uozumi T, Tsuji S (2001) Decreased susceptibility to pentylenetetrazol-induced seizures after low-frequency transcranial magnetic stimulation in rats. Neurosci Lett 310: 153–156
2. Annegers JF, Coan SP, Hauser WA, Leestma J, Duffell W, Tarver B (1998) Epilepsy, vagal nerve stimulation by the NCP system, mortality, and sudden, unexpected, unexplained death. Epilepsia 39: 206–212
3. Bailey P, Bremer F (1938) A sensory cortical representation of the vagus nerve. J Neurophysiol 1: 405–412
4. Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. Lancet 1: 1106–1107
5. Benabid AL, Minotti L, Koudsie A, de Saint MA, Hirsch E (2002) Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luysi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. Neurosurgery 50: 1385–1391
6. Berns KI, Hauswirth WW (1979) Adeno-associated viruses. Adv Virus Res 25: 407–449
7. Bridgers SL (1991) The safety of transcranial magnetic stimulation reconsidered: evidence regarding cognitive and other cerebral effects. Electroencephalogr Clin Neurophysiol Suppl 43: 170–179
8. Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 4 Suppl 3: S83–S93
9. Chkhenkeli SA, Chkhenkeli IS (1997) Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. Stereotact Funct Neurosurg 69: 221–224
10. Cooper IS, Amin I, Gilman S (1973) The effect of chronic cerebellar stimulation upon epilepsy in man. Trans Am Neurol Assoc 98: 192–196
11. DeGiorgio CM, Shewmon DA, Whitehurst T (2003) Trigeminal nerve stimulation for epilepsy. Neurology 61: 421–422
12. Fanselow EE, Reid AP, Nicolelis MA (2000) Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation. J Neurosci 20: 8160–8168
13. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
14. Gale K, Iadarola MJ (1980) Seizure protection and increased nerve-terminal GABA: delayed effects of GABA transaminase inhibition. Science 208: 288–291
15. Haberman RP, Samulski RJ, McCown TJ (2003) Attenuation of seizures and neuronal death by adeno-associated virus vector galanin expression and secretion. Nat Med 9: 1076–1080
16. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL III, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51: 48–55
17. Hauser WA, Annegers JF, Kurland LT (1993) Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia 34: 453–468
18. Hauser WA, Annegers JF, Kurland LT (1991) Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. Epilepsia 32: 429–445
19. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
20. Johns DC, Marx R, Mains RE, O'Rourke B, Marban E (1999) Inducible genetic suppression of neuronal excitability. J Neurosci 19: 1691–1697
21. Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 342: 314–319
22. Kwan P, Brodie MJ (2001) Effectiveness of first antiepileptic drug. Epilepsia 42: 1255–1260
23. Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, Cysyk B, Krauss G, Gordon B (1999) Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. Neurology 53: 2073–2081
24. Lin EJ, Richichi C, Young D, Baer K, Vezzani A, During MJ (2003) Recombinant AAV-mediated expression of galanin in rat hippocampus suppresses seizure development. Eur J Neurosci 18: 2087–2092
25. Loddenkemper T, Lüders HO (2004) Mechanisms and efficacy of deep brain stimulation in epilepsy. In: Rosenow F, Lüders HO (eds) Presurgical assessment of the epilepsy with clinical neurophysiology and functional imaging, vol. 3. Elsevier, Amsterdam, pp 539–570
26. Maksimow K (1976) Interruption of grand mal epileptic seizures by the trigeminal nerve stimulation. Neurol Neurochir Pol 10: 205–208
27. Mattson RH, Cramer JA, Collins JF, Smith DB, Delgado-Escueta AV, Browne TR, Williamson PD, Treiman DM, McNamara JO, McCutchen CB (1985) Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures. N Engl J Med 313: 145–151
28. Mazarati A, Wasterlain CG (2002) Anticonvulsant effects of four neuropeptides in the rat hippocampus during self-sustaining status epilepticus. Neurosci Lett 331: 123–127
29. McKhann GM (2004) Novel surgical treatments for epilepsy. Curr Neurol Neurosci Rep 4: 335–339
30. McNamara JO (1999) Emerging insights into the genesis of epilepsy. Nature 399: A15–A22
31. Menkes DL, Gruenthal M (2000) Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. Epilepsia 41: 240–242
32. Mirski MA, Fisher RS (1994) Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. Epilepsia 35: 1309–1316
33. Motamedi GK, Lesser RP, Miglioretti DL, Mizuno-Matsumoto Y, Gordon B, Webber WR, Jackson DC, Sepkuty JP, Crone NE (2002) Optimizing parameters for terminating cortical afterdischarges with pulse stimulation. Epilepsia 43: 836–846
34. Nair DR, Matsumoto R, Lüders HO, Burgess R, Bingaman W (2004) Direct cortical electrical stimulation in the treatment of epilepsy. In: Lüders HO (ed) Deep brain stimulation and epilepsy. Martin Dunitz, London, pp 275–284

35. Neme S, Montgomery EB Jr, Rezai A, Wilson K, Lüders HO (2004) Subthalamic nucleus stimulation in patients with intractable epilepsy: the Cleveland experience. In: Lüders HO (ed) Deep brain stimulation and epilepsy. Martin Dunitz, London, pp 349–355
36. Nilsen KE, Cock HR (2004) Focal treatment for refractory epilepsy: hope for the future? Brain Res Brain Res Rev 44: 141–153
37. Osorio I, Frei MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB (2005) Automated seizure abatement in humans using electrical stimulation. Ann Neurol 57: 258–268
38. Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, Valls-Sole J, Brasil-Neto JP, Wassermann EM, Cohen LG (1993) Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalogr Clin Neurophysiol 89: 120–130
39. Richichi C, Lin EJ, Stefanin D, Colella D, Ravizza T, Grignaschi G, Veglianese P, Sperk G, During MJ, Vezzani A (2004) Anticonvulsant and antiepileptogenic effects mediated by adeno-associated virus vector neuropeptide Y expression in the rat hippocampus. J Neurosci 24: 3051–3059
40. Rutecki P (1990) Anatomical, physiological, and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia 31 Suppl 2: S1–S6
41. Salinsky MC, Uthman BM, Ristanovic RK, Wernicke JF, Tarver WB (1996) Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. Arch Neurol 53: 1176–1180
42. Schroeder BC, Kubisch C, Stein V, Jentsch TJ (1998) Moderate loss of function of cyclic-AMP-modulated KCNQ2/KCNQ3 K^+ channels causes epilepsy. Nature 396: 687–690
43. Schulze-Bonhage A, Scheufler K, Zentner J, Elger CE (1999) Safety of single and repetitive focal transcranial magnetic stimuli as assessed by intracranial EEG recordings in patients with partial epilepsy. J Neurol 246: 914–919
44. Sudhof TC (1995) The synaptic vesicle cycle: a cascade of protein-protein interactions. Nature 375: 645–653
45. Tergau F, Naumann U, Paulus W, Steinhoff BJ (1999) Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. Lancet 353: 2209
46. Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer P, Werhahn K, Kelley KR, Cohen L (2002) Transcranial magnetic stimulation for the treatment of seizures: a controlled study. Neurology 59: 560–562
47. Upton AR, Amin I, Garnett S, Springman M, Nahmias C, Cooper IS (1987) Evoked metabolic responses in the limbic-striate system produced by stimulation of anterior thalamic nucleus in man. Pacing Clin Electrophysiol 10: 217–225
48. Van Buren JM, Wood JH, Oakley J, Hambrecht F (1978) Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg 48: 407–416
49. Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, Davis R (2005) Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 46: 1071–1081
50. Velasco F, Velasco M, Jimenez F, Velasco AL, Brito F, Rise M, Carrillo-Ruiz JD (2000a) Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery 47: 295–304
51. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28: 421–430
52. Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, Marquez I (2000b) Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41: 158–169
53. Velasco M, Velasco F, Velasco AL, Brito F, Jimenez F, Marquez I, Rojas B (1997) Electrocortical and behavioral responses produced by acute electrical stimulation of the human centromedian thalamic nucleus. Electroencephalogr Clin Neurophysiol 102: 461–471
54. Vezzani A (2004) Gene therapy in epilepsy. Epilepsy Curr 4: 87–90
55. Vonck K, Boon P, Achten E, De RJ, Caemaert J (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 52: 556–565
56. Vonck K, Van LK, Dedeurwaerdere S, Caemaert J, De RJ, Boon P (2001) The mechanism of action of vagus nerve stimulation for refractory epilepsy: the current status. J Clin Neurophysiol 18: 394–401
57. Walker BR, Easton A, Gale K (1999) Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. Epilepsia 40: 1051–1057
58. Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, Hallett M (1996) Use and safety of a new repetitive transcranial magnetic stimulator. Electroencephalogr Clin Neurophysiol 101: 412–417
59. Weiss SR, Li XL, Rosen JB, Li H, Heynen T, Post RM (1995) Quenching: inhibition of development and expression of amygdala kindled seizures with low frequency stimulation. Neuroreport 6: 2171–2176
60. Wright GD, McLellan DL, Brice JG (1984) A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatry 47: 769–774
61. Yang J, Teng Q, Garrity-Moses M, Federici T, Najm I, Chabardes S, Moffitt M, Boulis NM (2005) Gene therapy of epilepsy by adenovirus-mediated tetanus toxin light chain gene transfer. Mol Ther 11 Suppl 1: S168 (Abstract)
62. Zabara J (1992) Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia 33: 1005–1012

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Rationale, mechanisms of efficacy, anatomical targets and future prospects of electrical deep brain stimulation for epilepsy

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Summary

Electrical stimulation of deep brain structures is a promising new technology for the treatment of medically intractable seizures. Performed *in vitro* and on animal models of epilepsy, electrical stimulation has shown to reduce seizure frequency. Preliminary results on humans are encouraging. However, such improvements emerge despite a lack of understanding of the precise mechanisms underlying electrical stimulation either delivered directly on the epileptogenic zone (direct control) or through an anatomical relay of cortico-subcortical networks (remote control). Anatomical targets such as the thalamus (centromedian nucleus, anterior thalamus, mamillary body and mamillothalamic tracts), the subthalamic nucleus, the caudate nucleus and direct stimulation of the hippocampal formation have been successfully investigated. Although randomized controlled studies are still missing, deep brain stimulation is a promising treatment option for a subgroup of carefully selected patients with intractable epilepsy who are not candidates for resective surgery. The effectiveness, the optimal anatomic targets, the ideal stimulation parameters and devices, as well as patient selection criteria are still to be defined.

Keywords: Deep brain stimulation; electrode; epilepsy; anterior thalamus; centromedian nucleus; subthalamic nucleus; caudate nucleus; hippocampus.

Introduction

Despite considerable advances in pharmacological therapy for epilepsy, 25–30% of medically treated epileptic patients still continue to have seizures and will be considered as pharmacoresistant [25]. Resective surgery has shown its efficacy in the control of intractable seizures if presurgical evaluation clearly demonstrates a focal epileptogenic zone that can be removed without causing unacceptable neurological deficit. However, up to 50% of focal epileptic cases are unsuitable for surgery either because of the involvement of eloquent areas or the bilateral or multifocal nature of the ictal onset or because they show an unsatisfactory response to surgical treatment [32]. Moreover, some patients may not have access to surgical therapy because of the limitation of human or technical resources or the high technical complexity and cost.

Electrical stimulation of the brain has been proposed as an additional option to resective surgery. The first trial of epilepsy treatment by brain stimulation was made by Cooper *et al.* in 1973 [13] who reported reduction of seizure frequency by cerebellar subdural stimulation. Since the 1980s, other preliminary studies have suggested some effect on seizure frequency by stimulation of several targets among deep brain structures including the anterior thalamus [23, 26, 29], the centromedian thalamic nucleus [20, 53–59, 61, 63], the caudate nucleus [11, 12], the mamillary body [45, 51] the STN [1, 34, 46] and more recently the amygdalohippocampal complex [59, 61, 63]. Moreover, well-controlled studies demonstrated that seizures can be influenced in human by vagus nerve stimulation (VNS) [3, 24]. Finally, recent studies focused on direct stimulation of the epileptic focus have shown a decrease of the interictal epileptic activity as well as the seizure frequency [44, 69].

Although electrical stimulation of the brain needs further large, controlled and completed clinical trials to be definitely validated as a therapy for intractable epilepsy, it is an attractive and promising new technology.

Rationale

Bikson *et al.* [6] documented in vitro the effect of electrical stimulation on the rat hippocampal slice where epileptiform synchronous discharges were produced by addition of the convulsive drug, picrotoxin, to the bath-

ing medium. They applied current gradients across the slice and observed a current shift in the extracellular recording, concurrent with elimination of the epileptiform discharges. These observations support the concept of depolarization block as a mechanism of inhibition of electrical stimulation, likely associated with the release of extracellular potassium during neural stimulation.

Only limited studies have been conducted on electrical stimulation in animal models of epilepsies. Subthalamic nucleus deep brain stimulation has been shown to be of benefit in the Genetic Epilepsy Rats from Strasbourg (GAERS) or kainic acid induced limbic rat model of epilepsy [2, 9, 49, 63]. Vagus nerve stimulation has also shown to be effective on epileptogenic activity in pentylenetetrazol (PTZ) and strychnine induced generalized seizures in dogs and rats [68, 70] while it showed no reduction in spike and wave discharges in GAERS [16]. Direct stimulation of hippocampus was evaluated by Bragin *et al.* [8] in the kainic acid rat model of partial seizures. Stimulation significantly reduced the numbers of epileptiform interictal spikes during the period of stimulation, but did not affect the number of ictal events. Brain metabolic activation induced by stimulation of the anterior nucleus of the thalamus was studied by Mirski and Ferrendelli [40] for PTZ induced seizures on guinea pig. Administration of PTZ produced increased glucose uptake in the posterior thalamus, anterior thalamus, and the mammillothalamic tract. Sectioning of the mammillothalamic tract increased the threshold for producing seizures [41]. Subsequently, the same group investigated high-frequency electrical stimulation of the mammillary bodies. As with mammillothalamic tract lesions, the threshold for producing seizures in rats increased significantly. Similar beneficial results were obtained by stimulating the anterior nucleus, the target of the mammillothalamic tract and the hippocampal output via the fornix [42]. Bilateral anterior thalamic nucleus lesions and high-frequency stimulation were shown protective against pilocarpine-induced seizures and status epilepticus in rats [23]. Bertram *et al.* [4] have studied in two rat models of limbic seizures the electrophysiological and anatomical effect of limbic epilepsy on the medial thalamus and suggested that this thalamic region was part of the neural circuitry of limbic epilepsy and may play a significant role in seizure modulation.

Weiss *et al.* [66] reported that low-frequency stimulation (1 Hz) applied after high-frequency kindling stimulation (60 Hz) of the amygdala inhibited development of amygdala-triggered seizures and afterdischarges (quenching effect) in rat. Quenching was associated with a long-lasting increase in the after discharge threshold. The same phenomenon was also observed by hippocampal stimulation [67].

The extrapolation of these animal findings to the human disorders remains to be determined, but human trials have proceeded.

Mechanisms of efficacy

Despite increasing use in clinical practice, the mechanism by which electrical stimulation may control epileptic activity remains poorly understood. The extent to which stimulation will activate or inhibit neurons at various distances from the stimulating electrode is unclear. Moreover, effects of electrical stimulation are known to change with frequency and duration of stimulation. Therefore, stimulation at a particular site may inhibit seizures at some settings and provoke seizures with others. Generally, theories about the effect of electrical stimulation center around two hypotheses: 1) the neurochemical hypothesis, by which stimulation is hypothesized to cause preferential release of inhibitory neurotransmitters; and 2) the electrical hypothesis, by which stimulation is presumed to inactivate neurons in the vicinity of the electrode by depolarization block and subsequent failure of the sodium channels.

At the level of cortico-subcortical networks, several circuits involving cortical and basal ganglia structures have been shown to play an important role in the control of epileptogenicity. According to this concept, electrical stimulation of one of the anatomical relay of these networks may be seen as a remote control of epilepsy generation and/or propagation in opposition to the alternative approach consisting on specifically targeting the area of presumed epileptogenic focus with electrical stimulation, which can be considered as a direct control.

Remote control

Nigral control of epilepsy system (Fig. 1)

Based on previous work of Gale and Iadarola [22, 27], activation of the dorsal midbrain anticonvulsant zone (DMAZ), located ventral to the superior colliculi, leads to suppression of cortical epileptogenicity. The substantia nigra pars reticulata (SNpr), through its GABA-ergic inhibitory output, results in DMAZ inactivation. During resting conditions, activity of the SNpr is sustained by the tonic excitatory output from the subthalamic nucleus (STN). Disinhibition of the DMAZ is achieved by elec-

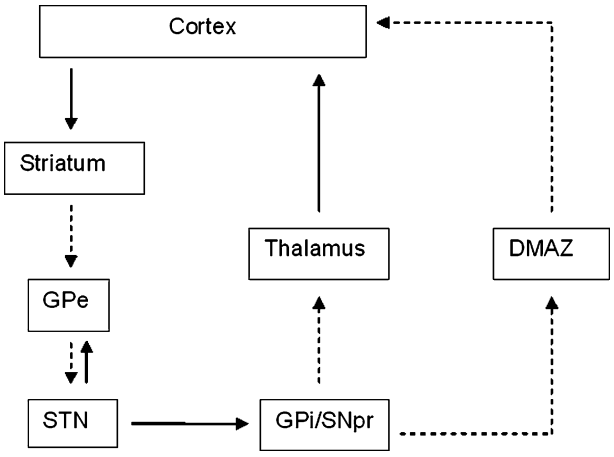

Fig. 1. Nigral control of epilepsy system (——► activation pathways; - - - - ► inhibition pathways)

trically induced inhibition of the STN and/or activation of the pallido-subthalamic GABA-ergic inhibitory pathway [34]. This hypothesis has been sustained by evidences that STN high frequency DBS induces a decrease of seizure frequency in the GAERS model of epilepsy [2, 9, 62] and by SPECT studies performed on 2 patients with frontal lobe epilepsy showing STN DBS induced hyperperfusion of frontal areas connected with basal ganglia [46]. Importance of these different pathways involved in the control of epileptic seizures, as well as long-term outcome remain to be investigated.

The limbic circuit (Fig. 2)

The anterior thalamic nuclei (AN) are part of the limbic system, which goes from the hippocampus via the fornix to the mammillary bodies, then to the anterior thalamus, the cingulate gyrus, and finally – via the cingulum bundle – to the entorhinal cortex and back to the hippocampus. The role of AN in the pathogenesis of seizure generalization is based on the finding that low-frequency electrical stimulation of AN leads to the generation of recruiting rhythms and synchronizes the pattern of EEG activity whereas high-frequency stimulation has been shown to result in EEG desynchronization and leads to decrease the cortex sensitivity to seizures [47]: these findings are supported by the observation of increased metabolic activity in AN during seizures and that lesioning or high frequency stimulation of the AN can reduce epileptic activity in rat model of epilepsy [40, 42]. Based on previous anatomy and physiology reports, Bertram *et al.* [4, 5] have suggested that the DM nucleus, located posterior and inferior to the AN may also act as a physiological synchronizer in seizure processes that takes widespread hyperexcitability in the limbic system.

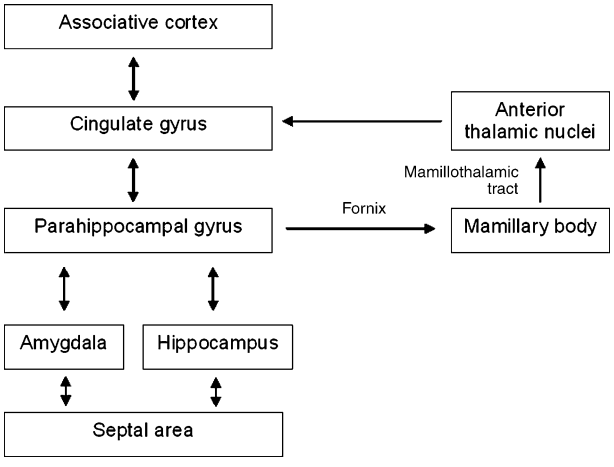

Fig. 2. Limbic circuit

The non-specific reticulo-thalamo-cortical system (Fig. 3)

The centromedian thalamic nucleus (CM) is an intralaminar nucleus that represents a thalamic relay of a reticulo-cortical system that participates crucially in wakefulness and attentive processes [43] as well as in regulation of cortical excitability in genetic generalized epileptic seizures in cats [28]. More recent experimental studies *in vivo* and computational modeling focused on absence seizures and Lennox-Gastaut syndrome showed that spike-wave (SW) complexes are progressively built up (i.e. not suddenly generalized) in intracortical synaptic networks [37, 38] with subsequent excitation of thalamic reticular neurons. Moreover, it was found that in humans, stimulation of the CM regions produced either synchronizing or desynchronizing electrocortical responses, depending on the frequency of stimulation. Low-frequency (6 pulses/second) stimulation produced synchronizing recruiting-like responses whereas high-frequency (60 pulses/second) stimulation produced EEG

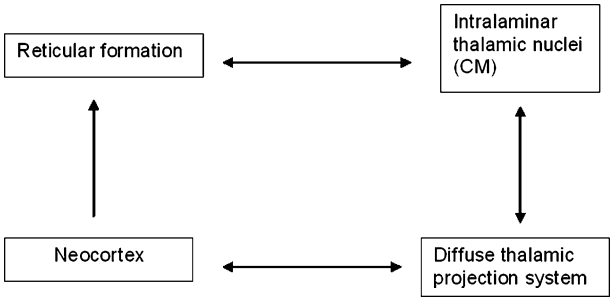

Fig. 3. Non-specific reticulo-thalamo-cortical system

desynchronization and negative direct currents (DC) shifts, suggesting that low- and high-frequency stimulation induce deactivation or activation of thalamic neurons that in turn presumably produce similar effects on cerebral cortex excitability [59].

Direct control

High-frequency electrical stimulation in either mesial temporal structures (amygdalo-hippocampal complex) or in neocortex (epileptogenic zone) has been reported to produce long-term depression of cortical responsiveness as well as inhibition of kindling in either cellular cultures [33], animal [67] or human [30, 44, 62, 64]. The mechanisms by which electrical stimulation leads to reduced epileptogenicity is thought to be obtained through an inhibitory action of the stimulation on the targeted tissue, possibly located in specific cortical layers or cerebral pathways, [67]. This inhibitory hypothesis is supported by Velasco *et al.* study [61] in which SPECT studies showed hippocampal hypoperfusion induced by electrical stimulation of hippocampus in human and autoradiographic studies performed on removed specimens where increased hippocampal benzodiazepine receptor binding was observed. However, other mechanisms may be involved as addressed by Yamamoto *et al.* [69] who observed that low-frequency stimulation (0.9 Hz) could have an inhibitory effect on epileptogenic focus in mesial temporal lobe epilepsy. Therefore, additional studies of this modality of stimulation may be worthwhile.

Anatomical targets

Stereotactically implanted DBS electrodes to treat movement disorders is a safe procedure that has been associated with a low rate of complications, such as hemorrhage and infection, or morbidity [6, 35]. For the treatment of epilepsy, electrodes are typically placed bilaterally into the anterior principal nucleus of the thalamus, the centromedian nucleus, or the subthalamic nucleus or at focus. MRI targeting, recording of extracellular unit activity, and electroencephalographic monitoring of stimulation effects are used to monitor the accuracy of electrode placement. Electrodes are connected by extension leads to a subcutaneous, battery-powered, programmable stimulator on the chest wall. Typical settings for stimulation are 1–10 V, 60–450 μs pulses in trains of 100–165 Hz, running either continuously or 1 min ''on'' and 5 min ''off''. Some physicians use bipolar and others use referential stimulation. The settings can be reprogrammed and stimulus trains turned ''on'' or ''off'' with a paddle held close to the chest.

Remote control

Thalamus stimulation

Centromedian nucleus (CM)

The largest experience with implantation of thalamic DBS electrodes is in the CM, primarily through the work of Velasco and coworkers. They published a pilot study of CM stimulation in 1987 [56] where stimulation was delivered via externalized electrodes for 2 hours per day for up to 3 months. Stimulation was with 0.8–2 mA bipolar 100 μs pulses at frequencies of 60–100 Hz, for 1 min of every 5 min. Patients had generalized and partial seizures. Seizures frequencies improved by 60–100%. The same group published the largest series of CM stimulation in 2001 [62]. In this study, 49 patients were treated with bilateral CM stimulation at 2.5–5 V, 200–450 μs, 60–130 Hz for 1 min of every 5 min. Efficacy was claimed for generalized tonic-clonic seizures, tonic seizures, and atypical absences, but could not be clearly demonstrated for most partial seizures. Simultaneous recordings from the scalp and DBS electrodes suggested that CM participates in the onset of generalized tonico-clonic convulsions (GTCC) and typical absences, while it may play a role in the propagation of secondary GTCC. However, the exact role of the CM related to the epileptic genesis and spread remains unclear as well as the mechanisms of action of CM stimulation, although EEG desynchronization observed during high frequency CM stimulation suggests that CM stimulation lowers the excitability of cortical areas.

The only published controlled trial of CM stimulation for epilepsy was done by Fisher *et al.* in 1992 [20]. Seven patients with intractable partial or generalized onset seizures were implanted with bilateral CM electrodes. Stimulus parameters consisted of 90 μs pulses at a rate of 65 Hz, with voltage of 2–5 V, ''on'' for 1 min of every 5 min. During stimulation, the patients experienced a mean 30% reduction in the number of seizures. However, it was not statistically significant because of the small number of patients. Thus, there is still controversy about efficacy of CM stimulation.

Anterior thalamus

In the seventies, pioneering studies performed by Cooper *et al.* showed that stimulation of the anterior

thalamus could suppress seizures in pharmacologically intractable epileptic patients [13, 14]. Upton *et al.* [49] reported improvement in four of six patients with intractable partial seizures after stimulation of the anterior nucleus of the thalamus. Because information was lacking about the degree of improvement and precise categorization of epilepsy, several groups interested in stimulation for epilepsy began to design a controlled trial to evaluate safety and efficacy of thalamic stimulation [19]. Pilot studies [26] were then done with 14 patients whose ages ranged from 19 to 44 years. 11/14 subjects had partial seizures and 3/14 had generalized tonic-clonic seizures. Seizure onset was thought to be bilateral temporal in five, frontal in four, and multifocal in five patients. Stimulation parameters differed according to different institutions. Analysis was done at 3, 6, and 12 months after implantation. Overall seizures reduction was observed in more than 50% of cases at 12 months. Considering only the 9 patients who had frontal or temporal seizure foci, decrease in seizure frequency was 77.8% at 3 months and 66.7% at 6 and 12 months. Five patients had seizures that produced falls, and four of them had significant improvement. Some of the patients seemed to improve before stimulation, raising the issue of either a micro-lesion effect of implantation, or a regression to the mean or even a placebo effect. In this protocol, none of the 14 patients in the pilot trial experienced any serious adverse events. Currently, a multicenter randomized, controlled trial of anterior thalamic stimulation, sponsored by Medtronic (Minneapolis, MN) is being done. This trial includes approximately 120 patients with partial seizures, with or without secondary generalization, and at least six seizures per month. After implantation, the stimulator will be turned off (placebo) or activated at 5 V (active stimulation), 90 μs pulses at 145 Hz, ''on'' for 1 min and ''off'' for 5 min and the blinded phase will continue for 3 months.

Recently, Raftopoulos *et al.* [45] have observed improvement of seizure frequency in 3 patients (1 with hypothalamic hamartoma and the 2 others with seizures originating at least partially from mesiotemporal structures) with high-frequency stimulation of the mamillary bodies and mamillothalamic tracts, without memory disturbances [17].

Subthalamic nucleus (STN) stimulation

Based on the success in animal models (GAERS) supporting the evidence of a subcortical network that influences the cortical excitability (nigral control of epilepsy system) in epilepsy and the safety of stimulation for movement disorders, STN stimulation was performed in patients with uncontrolled seizures. Two pioneering studies, one from Grenoble and another from Cleveland groups, reported results of STN stimulation with intractable epilepsy and considered unsuitable for resective surgery. Chabardès *et al.* [10] observed an average improvement in seizure frequency up to 80%, with three of the five involved patients showing a good response. The second series, by Loddenkemper *et al.* [34], reported substantial improvement in two of the five patients treated with continuous STN stimulation at 100 Hz and stimulus duration of 60 μs.

Caudate nucleus stimulation

Chkhenkeli [11, 12] reported a series of 57 patients treated with bilateral implantation of electrodes into the head of the caudate nucleus. Unlike experience with thalamic, subthalamic, or hippocampal stimulation, caudate stimulation seemed superior in decreasing seizures when delivered at low frequencies of 4–8 Hz. The degree of improvement was not quantified and seizure types not categorized, but qualitative reports suggest improvements. Caudate nucleus stimulation for epilepsy has not been tested in controlled studies.

Direct control

Hippocampal stimulation

Recently, Velasco *et al.* [60] described the concept of direct stimulation of hippocampus to control seizures. They included 10 patients being evaluated for possible mesial temporal epilepsy. These patients had implantation of depth electrodes into hippocampus or the parahippocampal gyrus via a posterior approach. After standard recording, stimulation was delivered at high frequency and low intensity (130 Hz, 0.2–0.4 mA) for up to 3 weeks. The authors reported improvement over time in interictal spike frequency as well as in seizure frequency in patients with implanted hippocampal stimulating electrodes. This paradigm was used in 15 additional patients, five of them receiving sham stimulation. Active stimulation improved interictal spiking and seizures in stimulated patients, while no improvement was noticed in patients with sham stimulation. As the electrodes used in this study were not suitable for long-term stimulation, Vonck *et al.* [64]

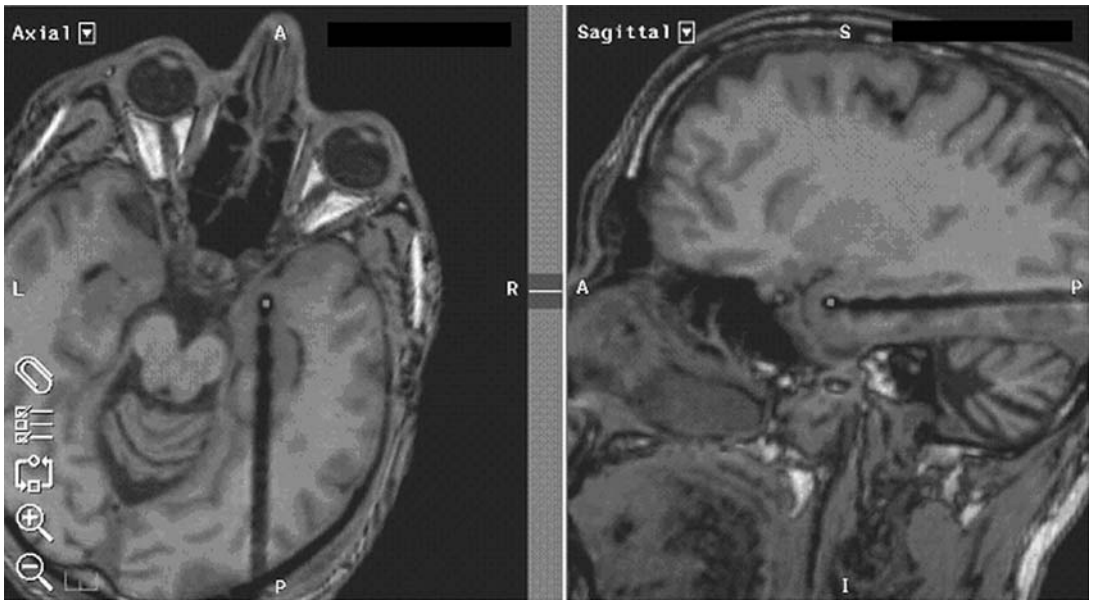

Fig. 4. Postoperative T1-weighted MRI with an implanted electrode for AHCS

evaluated the efficacy of long-term recording and stimulation through DBS quadripolar electrodes (Activa 3387, Medtronic). Electrodes were placed in the amygdala and hippocampus of three patients with intractable seizures and stimulation was performed chronically through implantable device for 3–6 months. Stimulation was done with frequencies of 130 Hz, pulse width up to 450 μs, and amplitude up to 3 V. All three patients had a significant reduction in seizure frequency (greater than 50%) and two improved enough for tapering of antiepileptic medications. Experience with an increased number of patients has also been reported by the same group [52].

Our own experience with amygdalo-hippocampal complex stimulation (AHCS) is based on 5 patients with intractable epilepsy (4 females and 1 male, age 32–47) in which either unilateral right (2 patients) or left (3 patients) AHCS was indicated (Fig. 4). In all the cases, either a strictly unilateral or bilateral with one dominant side epileptogenic zone was identified in the mesial temporal lobe. One patient with bitemporal epilepsy had depth electrodes recording. All the candidates were unsuitable for resective surgery because their normal interictal speech or visuo-spatial memory function was associated with severe postictal dysfunction and correlated with the absence of clearly identifiable hippocampal sclerosis. Follow-up is ongoing from 5 months to 3 years and results show a significant decrease (50–95%) of seizure frequency in all the patients. No stimulation-induced side effects were noticed.

Future prospects

Open-loop and closed-loop systems

Deep brain stimulation is a promising treatment option in medically refractory epilepsy cases. However, it must still be considered as experimental and further investigations regarding indications, selection of targets, electrode placement, stimulation paradigms, long-term outcome and side effects are needed. Increasing knowledge about the mechanism of deep brain stimulation has been helpful in designing ideal stimulation waveforms and to define the optimal stimulus duration (continuous versus intermittent) and stimulation frequency depending on which neuronal element is stimulated [31, 36]. Furthermore, improvements in signal processing tools and detection devices for epileptogenicity have led to a better localization of the epileptogenic zone. Consequently, seizure control or interruption by electrical stimulation at the epileptogenic zone can be accomplished according to two stimulation concepts, namely open-loop and closed-loop systems. Applied to electrical stimulation for the control of epilepsy, closed loop is defined as the delivery of electrical current to a target, exclusively in response to a specific cue or command (seizure detection by a defined algorithm), compared to open-loop in which electrical current is delivered independently of time of occurrence of seizures (Fig. 5). It has previously been shown that such closed-loop systems can effectively interrupt after discharges elicited by cortical stimulation

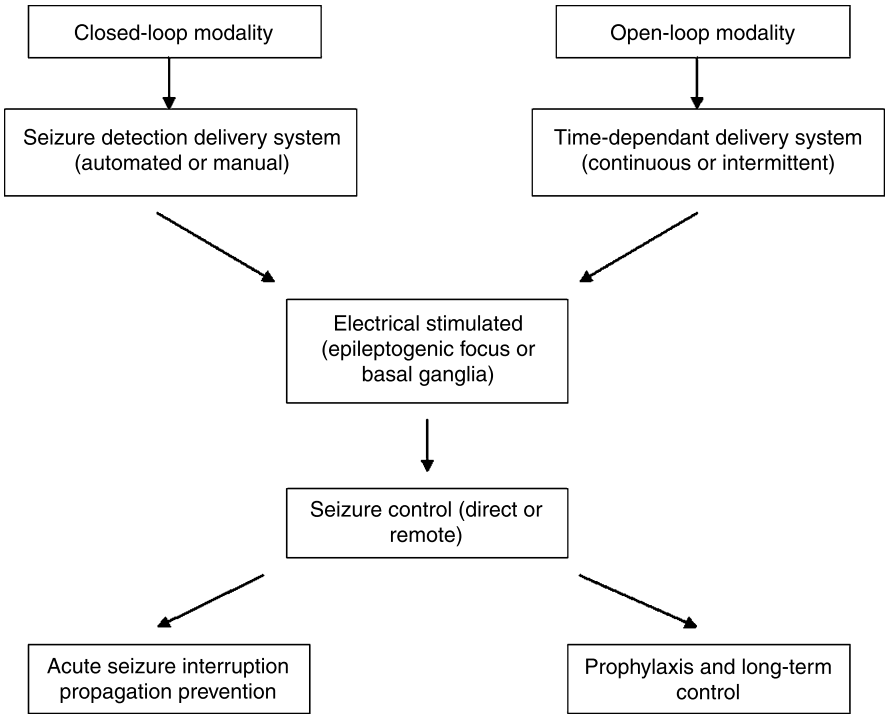

Fig. 5. The open- and closed-loop stimulation modalities

[33]. Recently, a pilot study has investigated the feasibility, safety, tolerability and efficacy of high-frequency electrical stimulation through such closed-loop systems directly on epileptogenic tissue or remotely through connected structures with promising results on human [44]. Both paradigms – closed- and open-loop stimulation – may therefore be used as complementary treatment methods with different indications. Open-loop stimulation could be used in the prophylaxis and long-term reduction of seizure frequency. Closed-loop stimulation could be effective in acute seizure interruption, preventing further seizure propagation and secondary generalization.

Repetitive transcranial magnetic stimulation

According to the Faraday's law of electromagnetism, a change in the strength of a magnetic field through a given area of conducting material induces an electrical current. In transcranial magnetic stimulation (TMS), the stimulator creates a rapidly changing magnetic field and the brain serves as the adjacent conducting material in which the current is generated. The development of repetitive cortical transcranial magnetic stimulation (rTMS) has brought a new insight in the treatment of epileptic disorders. Low frequency rTMS (defined as <1 Hz) has been shown to reduce (whereas high frequency rTCMS enhances) the cortical excitability [70]. Consequently, rTMS has been proposed as a therapeutic tool in reducing seizure frequency. Tergau *et al.* [48] administered rTMS in nine medically intractable epileptic patients. They found a significant decrease in seizure frequency up to 6 weeks after discontinuation of rTMS. There is increasing evidence that repetitive cortical transcranial magnetic stimulation produces antiepileptic effects, especially in patients with well-localized epileptogenic cortical malformations [21, 30, 39]. We can postulate that the evidence obtained from rTMS as applied for focal superficial epilepsy could be used as predictor of response to chronic cortical stimulation through implanted devices (epidural or subdural chronic focal cortical stimulation); this remains to be shown. Moreover, improvement of stimulators and magnetic field focus could allow targeting and stimulation of deeper brain structures by rTMS.

New targets

A refined comprehension of the physiopathology of the seizure onset and propagation at cortico-subcortical levels may result in exploration of new stimulation targets like the GPe, the SNpr, or even additional subcortical structures such as, the cerebellar peduncles, the pontine reticular formation, the hypothalamus, and midbrain [27]. These structures have been demonstrated to be involved in different animal seizure models, suggesting that other deep brain stimulation targets may be

effective in some epilepsies that are not regulated by the nigral control of epilepsy system.

Conclusion

Deep brain stimulation is a promising treatment option for a subgroup of carefully selected patients with intractable epilepsy who are not candidates for resective surgery. As several distinct neuronal networks seem to be involved in the control of epileptogenicity, electrical stimulation delivered at different relays of these networks may, at least theoretically, show efficacy on seizure control. The complex physiopathology of seizure onset and propagation justifies further electrophysiologic and clinical research for the understanding of the precise correlations existing between clinical manifestations, epileptogenic brain pathologies, and networks involved in the control of epileptogenicity. Furthermore, a refined comprehension of the mechanisms of action of deep brain simulation at cortico-subcortical levels will certainly be helpful for the refinement of patient selection criteria, anatomical targets and ideal stimulation parameters.

At this point in time, DBS for the treatment of epilepsy should be considered as innovative therapy. The indications and results are yet not fully validated and the therapeutic objective should remain palliative. However, with more extensive trials, DBS in epilepsy will definitively become part of the neurosurgical armamentarium.

References

1. Benabid AL, Minotti L, Koudsie A, De Saint Martin A, Hirsch E (2002) Antiepileptic effect of high-frequency stimulation of the subthalamic nucleus (corpus luysi) in a case of medically intractable epilepsy caused by focal dysplasia: a 30-month follow-up: technical case report. Neurosurgery 50(6): 1385–1391
2. Benazzouz A, Vercueil L, Bressand K, Piallat B, Marescaux C, Benabid AL (1998) Role du noyau subthalamique dans le contrôle nigral des épilepsies: étude par lésion et stimulation à haute fréquence dans un modèle animal d'épilepsie généralisée. In: Libey J (ed) Epilepsies partielles graves de l'enfant: strategies diagnostiques et traitements chirurgicaux. Eurotext: 305–310
3. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, Tarver WB, Wernicke JF (1994) Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. Epilepsia 35: 616–626
4. Bertram EH, Mangan PS, Zhang D, Scott CA, Williamson JM (2001) The midline thalamus: alterations and a potential role in limbic epilepsy. Epilepsia 42: 967–978
5. Bertram EH, Zhang DX, Mangan P, Fountain N, Rempe D (1998) Functional anatomy of limbic epilepsy: a proposal for central synchronization of a diffusely hyperexcitable network. Epilepsy Res 32(1–2): 194–205
6. Bikson M, Lian J, Hahn PJ, Stacey WC, Sciortino C, Durand DM (2001) Suppression of epileptiform activity by high frequency sinusoidal fields in rat hippocampal slices. J Physiol 531: 181–191
7. Binder DK, Rau GM, Starr PA (2005) Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. Neurosurgery 56(4): 722–732
8. Bragin A, Wilson CL, Engel J Jr (2002) Rate of interictal events and spontaneous seizures in epileptic rats after electrical stimulation of hippocampus and its afferents. Epilepsia 43 Suppl 5: 81–85
9. Bressand K, Dematteis M, Ming Gao D, Vercueil L, Louis Benabid A, Benazzouz A (2002) Superior colliculus firing changes after lesion or electrical stimulation of the subthalamic nucleus in the rat. Brain Res 943(1): 93–100
10. Chabardès S, Kahane P, Minotti, Koudsie A, Hirsch E, Benabid AL (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 4 Suppl 3: S83–S93
11. Chkhenkeli SA, Chkhenkeli IS (1997) Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. Stereotact Funct Neurosurg 69(1–4 Pt 2): 221–224
12. Chkhenkeli SA, Sramka M, Lortkipanidze GS, Rakviashvili TN, Bregvadze ESh, Magalashvili GE, Gagoshidze TSh, Chkhenkeli IS (2004) Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clin Neurol Neurosurg 106(4): 318–329
13. Cooper IS, Amin I, Gilman S (1973) The effect of chronic cerebellar stimulation upon epilepsy in man. Trans Am Neurol Assoc 98: 192–196
14. Cooper IS, Upton AR, Amin I (1980) Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. Appl Neurophysiol 43: 244–258
15. Cooper IS, Upton AR (1985) Therapeutic implications of modulation of metabolism and functional activity of cerebral cortex by chronic stimulation of cerebellum and thalamus. Biol Psychiatry 20: 811–813
16. Dedeurwaerdere S, Vonck K, Claeys P, Van Hese P, D'Have M, Grisar T, Naritoku D, Boon P (2004) Acute vagus nerve stimulation does not suppress spike and wave discharges in genetic absence epilepsy rats from Strasbourg. Epilepsy Res 59(2–3): 191–198
17. Duprez TP, Serieh BA, Raftopoulos C (2005) Absence of memory dysfunction after bilateral mammillary body and mammillothalamic tract electrode implantation: preliminary experience in three patients. AJNR 26(1): 195–197
18. Dybdal D, Gale K (2000) Postural and anticonvulsant effects of inhibition of the rat subthalamic nucleus. J Neurosci 20: 6728–6733
19. Fisher R (2004) Anterior thalamic nucleus stimulation: issues in study design. In: Lüders H (ed) Deep brain stimulation and epilepsy. Martin Dunitz, Inc., London
20. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
21. Fregni F, Thome-Souza S, Bermpohl F, Marcolin MA, Herzog A, Pascual-Leone A, Valente KD (2005) Antiepileptic effects of repetitive transcranial magnetic stimulation in patients with cortical malformations: an EEG and clinical study. Stereotact Funct Neurosurg 83(2–3): 57–62
22. Gale K, Iadarola MJ (1980) Seizure protection and increased nerve-terminal GABA: delayed effects of GABA transaminase inhibition. Science 208: 288–291

23. Hamani C, Ewerton FI, Bonilha SM, Ballester G, Mello LE, Lozano AM (2004) Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery 54(1): 191–195
24. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology 51: 48–55
25. Hauser WA, Hesdorffer DC (1990) Incidence and prevalence. In: Hauser WA, Hesdorffer DC (eds) Epilepsy: frequency, causes and consequences. Demos, New York
26. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43(6): 603–608
27. Iadarola MJ, Gale K (1982) Substantia nigra: site of anticonvulsant activity mediated by gamma-aminobutyric acid. Science 218: 1237–1240
28. Jasper HH, Naquet R, King LE (1955) Thalamocortical recruiting responses in sensory receiving areas in the cat. Electroencephalogr Clin Neurophysiol 7: 99–114
29. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45(4): 346–354
30. Kinoshita M, Ikeda A, Begum T, Yamamoto J, Hitomi T, Shibasaki H (2005) Low-frequency repetitive transcranial magnetic stimulation for seizure suppression in patients with extratemporal lobe epilepsy-A pilot study. Seizure 14(6): 387–392
31. Kuncel AM, Grill WM (2004) Selection of stimulus parameters for deep brain stimulation. Clin Neurophysiol 115(11): 2431–2441
32. Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 342(5): 314–319
33. Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, Cysyk B, Krauss G, Gordon B (1999) Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. Neurology 53: 2073–2081
34. Loddenkemper T, Pan A, Neme S (2001) Deep brain stimulation in epilepsy. J Clin Neurophysiol 18: 514–532
35. Lyons KE, Wilkinson SB, Overman J, Pahwa R (2004) Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. Neurology 63(4): 612–616
36. McIntyre CC, Savasta M, Walter BL, Vitek JL (2004) How does deep brain stimulation work? Present understanding and future questions. J Clin Neurophysiol 21(1): 40–50
37. Meeren H, Pijn JP, Van Luijtelaar E, Coenen A, Lopes da Silva F (2002) Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. J Neurosci 22: 1480–1495
38. Meeren H, van Luijtelaar G, Lopes da Silva F, Coenen A (2005) Evolving concepts on the pathophysiology of absence seizures: the cortical focus theory. Arch Neurol 62(3): 371–376
39. Menkes DL, Gruenthal M (2000) Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. Epilepsia 41(2): 240–242
40. Mirski MA, Ferrendelli JA (1986) Selective metabolic activation of the mammillary bodies and their connections during ethosuximide-induced suppression of pentylenetetrazol seizures. Epilepsia 27: 194–203
41. Mirski MA, Fisher RS (1994) Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. Epilepsia 35: 1309–1316
42. Mirski MA, Rossell LA, Terry JB, Fisher RS (1997) Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 28: 89–100
43. Moruzzi G, Magoun HW (1949) Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol 1: 459–473
44. Osorio I, Frei MG, Manly BF, Sunderam S, Bhavaraju NC, Wilkinson SB (2001) An introduction to contingent (closed-loop) brain electrical stimulation for seizure blockage, to ultra-short-term clinical trials, and to multidimensional statistical analysis of therapeutic efficacy. J Clin Neurophysiol 18(6): 533–544
45. Raftopoulos C, van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Ivanoiu A, Grandin C (2004) Preliminary results of deep brain stimulation of the mammillary bodies and mammillothalamic tracts in chronic refractory epilepsy. Acta Neurochir (Wien) 146: 885
46. Shon YM, Lee KJ, Kin HJ, Chung YA, Ahn KJ, Kim YI, Yang DW, Kim BS (2005) Effect of chronic deep brain stimulation of the subthalamic nucleus for frontal lobe epilepsy: subtraction SPECT Analysis. Stereotact Funct Neurosurg 83(2–3): 84–90
47. Steriade M (1997) The thalamus, vol. 1. Elsevier Science Publishing, Amsterdam
48. Tergau F, Naumann U, Paulus W, Steinhoff BJ (1999) Low-frequency repetitive transcranial magnetic stimulation improves intractable epilepsy. Lancet 353(9171): 2209
49. Upton AR, Amin I, Garnett S (1987) Evoked metabolic responses in the limbic-striate system produced by stimulation of anterior thalamic nucleus in man. Pacing Clin Electrophysiol 10: 217–225
50. Usui N, Maesawa S, Kajita Y, Endo O, Takebayashi S, Yoshida J (2005) Suppression of secondary generalization of limbic seizures by stimulation of subthalamic nucleus in rats. Neurosurg 102(6): 1122–1129
51. Van Rijckevorsel K, Abu Serieh B, de Tourtchaninoff M, Raftopoulos C (2005) Deep EEG recordings of the mammillary body in epilepsy patients. Epilepsia 46(5): 781–785
52. Van Roost D, Boon P, Vonck K, Caemaert J, Claeys P, Achten E (2004) Amygdalohippocampal deep brain stimulation for refractory temporal lobe epilepsy. Acta Neurochir (Wien) 146: 885
53. Velasco F, Velasco M, Jimenez F, Velasco AL, Brito F, Rise M, Carrillo-Ruiz JD (2000) Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery 47(2): 295–304
54. Velasco F, Velasco M, Jimenez F, Velasco AL, Marquez I (2001) Stimulation of the central median thalamic nucleus for epilepsy. Stereotact Funct Neurosurg 77(1–4): 228–232
55. Velasco F, Velasco M, Marquez I, Velasco G (1993) Role of the centromedian thalamic nucleus in the genesis, propagation and arrest of epileptic activity. An electrophysiological study in man. Acta Neurochir Suppl 58: 201–204
56. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28(4): 421–430
57. Velasco F, Velasco M, Velasco AL, Jimenez F (1993) Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity. Epilepsia 34: 1052–1064
58. Velasco F, Velasco M, Velasco AL, Jimenez F, Marquez I, Rise M (1995) Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. Epilepsia 36(1): 63–71
59. Velasco M, Velasco F, Velasco AL, Brito F, Jimenez F, Marquez I, Rojas B (1997) Electrocortical and behavioral responses produced by acute electrical stimulation of the human centromedian thalamic nucleus. Electroencephalogr Clin Neurophysiol 102(6): 461–471

60. Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, Marquez I (2000) Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia 41: 158–169
61. Velasco M, Velasco F, Velasco AL, Jimenez F, Brito F, Marquez I (2000) Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control. Arch Med Res 31(3): 304–315
62. Velasco M, Velasco F, Velasco AL (2001) Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. J Clin Neurophysiol 18(6): 495–513
63. Vercueil L, Benazzouz A, Deransart C, Bressand K, Marescaux C, Depaulis A, Benabid AL (1998) High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions. Epilepsy Res 31: 39–46
64. Vonck K, Boon P, Achten E, De Reuck J, Caemaert J (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 52: 556–565
65. Vonck K, Dedeurwaerdere S, De Groote L, Thadani V, Claeys P, Gossiaux F, Van Roost D, Boon P (2005) Generator replacement in epilepsy patients treated with vagus nerve stimulation. Seizure 14(2): 89–99
66. Weiss SR, Li XL, Rosen JB, Li H, Heynen T, Post RM (1995) Quenching: inhibition of development and expression of amygdala kindled seizures with low frequency stimulation. Neuroreport 6(16): 2171–2176
67. Weiss SR, Eidsath A, Li XL, Heynen T, Post RM (1998) Quenching revisited: low level direct current inhibits amygdala-kindled seizures. Exp Neurol 154(1): 185–192
68. Woodbury D, Woodbury J (1990) Effects of vagal stimulation on experimentally induced seizures in rats. Epilepsia 31 Suppl 2: 7–19
69. Yamamoto J, Ikeda A, Satow T, Takeshita K, Takayama M, Matsuhashi M, Matsumoto R, Ohara S, Mikuni N, Takahashi J, Miyamoto S, Taki W, Hashimoto N, Rothwell JC, Shibasaki H (2002) Low-frequency electric cortical stimulation has an inhibitory effect on epileptic focus in mesial temporal lobe epilepsy. Epilepsia 43(5): 491–495
70. Zabara J (1992) Inhibition of experimental seizures in canines by repetitive stimulation. Epilepsia 33: 1005–1012
71. Ziemann U, Steinhoff B, Tergau F, Paulus W (1998) Transcranial magnetic stimulation: its current role in epilepsy research. Epilepsy Res 30: 11–30

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Anatomical and physiological basis and mechanism of action of neurostimulation for epilepsy

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Summary

Neurostimulation is an emerging treatment for neurological diseases. Different types of neurostimulation exist mainly depending of the part of the nervous system that is being affected and the way this stimulation is being administered. Vagus nerve stimulation (VNS) is a neurophysiological treatment for patients with medically or surgically refractory epilepsy. Over 30,000 patients have been treated with VNS. No clear predictive factors for responders have been identified. To date, the precise mechanism of action remains to be elucidated. Better insight in the mechanism of action may identify seizure types or syndromes that respond better to VNS and may guide the search for optimal stimulation parameters and finally improve clinical efficacy.

Deep brain stimulation (DBS) has been used extensively as a treatment for movement disorders. Several new indications such as obsessive compulsive behaviour and cluster headache are being investigated with promising results. The vast progress in biotechnology along with the experience in other neurological diseases in the past ten years has led to a renewed interest in intracerebral stimulation for epilepsy. Epilepsy centers around the world have recently reinitiated trials with deep brain stimulation in different intracerebral structures such as the thalamus, the hippocampus and the subthalamic nucleus.

Keywords: Neuromodulation; neurostimulation; mechanism of action; refractory epilepsy; deep brain stimulation; vagus nerve stimulation; VNS; DBS.

Introduction

Neurostimulation is an emerging treatment for neurological diseases. Electrical pulses are administered directly to or in the neighbourhood of nervous tissue in order to manipulate a pathological substrate and to achieve a symptomatic or even curative therapeutic effect. Different types of neurostimulation exist mainly depending of the part of the nervous system that is being affected and the way this stimulation is being administered (Fig. 1).

Electrical stimulation of the tenth cranial nerve or *vagus nerve stimulation (VNS)* is an extracranial form of stimulation that was developed in the eighties and is currently routinely available in epilepsy centers around the world. Through an implanted device and electrode, electrical pulses are administered to the afferent fibers of the left vagus nerve in the neck. It is indicated in patients with refractory epilepsy who are unsuitable candidates for epilepsy surgery or who have had insufficient benefit from such a treatment [1]. As stimulation is applied to that part of the vagus nerve that passes through the neck, direct intracerebral manipulation is unnecessary.

Another form of extracranial neurostimulation consists of *transcranial magnetic stimulation (TMS)*. A coil that transmits magnetic fields is held over the scalp and allows a non-invasive evaluation of separate excitatory and inhibitory functions of the cerebral cortex. In addition, repetitive TMS (rTMS) can modulate the excitability of cortical networks [2]. This therapeutic form of TMS is currently being investigated as a treatment option for refractory epilepsy [11] but it has not been widely used unlike VNS.

Intracerebral neurostimulation requires accessing the intracranial nervous system as stimulation electrodes are inserted into intracerebral targets for '*deep brain stimulation' (DBS)* or placed over the cortical convexity for '*cortical stimulation'(CS)*. These modalities of neurostimulation are not novel for neurological indications. Some have been extensively used e.g. for movement disorders and pain. Moreover, several new indications such as obsessive-compulsive behaviour and cluster headache are being investigated with promising results. In the past,

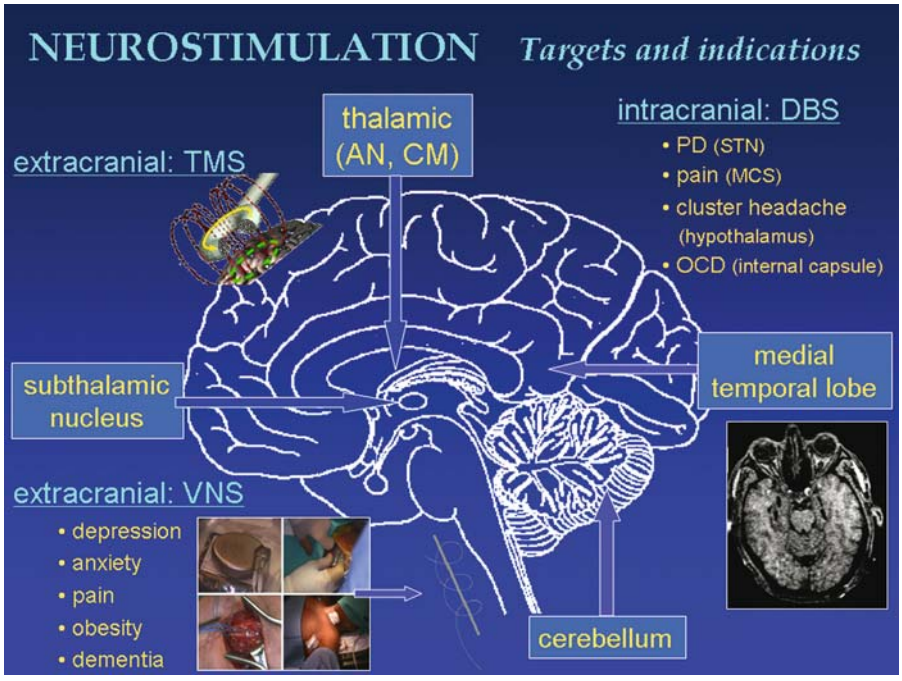

Fig. 1. Overview of neurostimulation modalities

DBS and CS of different brain structures such as the cerebellum, the locus coeruleus and the thalamus have already been performed. This was done mostly in patients with spasticity or psychiatric disorders who also had epilepsy but the technique was not fully explored or developed into an efficacious treatment option. The vast progress in biotechnology along with the experience in other neurological diseases in the past ten years has led to a renewed interest in intracerebral stimulation for epilepsy. A few epilepsy centers around the world have recently reinitiated trials of deep brain stimulation in different intracerebral structures such as the thalamus and the subthalamic nucleus.

VNS on one hand and TMS, DBS and CS on the other hand are currently at different levels of availability and clinical applicability. VNS is widely available and used around the world with over 40,000 patients currently being treated. Therapeutic TMS protocols for epilepsy have been developed in centers with a large experience in diagnostic TMS. At this time, TMS is not a routinely available treatment in epilepsy centers. DBS is under investigation in experimental trials in some specialised centers with large experience in refractory epilepsy and functional neurosurgery [16]. Apart from a group of patients who carry implanted devices from the earlier era of neurostimulation for epilepsy, the more recent studies report results in no more than 100 patients worldwide. CS is considered a therapeutic neurostimulation option for specific types of epilepsy e.g. neocortical epilepsy on theoretical grounds but is currently unexplored in humans.

Vagus nerve stimulation

Clinical efficacy

Jacob Zabara and Joan Lockard were the first to publish abstracts in Epilepsia in 1985 and 1986 on the animal experiments that showed a reduction in seizure frequency and/or severity when vagal afferents were stimulated in dogs and monkeys, respectively. The first descriptions of the implantable VNS Therapy™ system for electrical stimulation of the vagus nerve in humans was published in the literature in the early ninetees [12]. At the same time, initial results from two single-blinded pilot clinical trials (phase-1 trials EO1 and EO2) in a small group of patients with refractory complex partial seizures who were implanted, since November 1988 in three epilepsy centers, in the U.S.A. were reported. In 9/14 patients, treated for 3–22 months a reduction in seizure frequency of at least 50% was observed. One of the patients was seizure-free for more than 7 months. Some patients reported less severe seizures with briefer ictal and postictal periods. Complex partial seizures, simple partial seizures as well as secondary generalized seizures were affected. Already in these early reports, improved alertness unrelated to seizure control was noticed. Several patients reported abortion of seizures

with manual activation of stimulation via the magnet, a feature that allows external activation of the device in case of an aura or ongoing seizure. On the other hand, it was noticed that the reduction in frequency, duration and intensity of seizures lagged by 4–8 weeks the initiation of treatment. These are initial indications for a combined anti-seizure and anti-epileptic effect of VNS. The potential mechanisms of action, described at that time, included desynchronization of neuronal discharge, release of inhibitory neurotransmitters, stimulation of inhibitory pathways or increase in the electrical threshold for seizures.

In 1993, Uthman *et al.* [13] reported on the long-term results from the EO1 and EO2 studies. Fourteen patients had, by then, been treated for 14–35 months. There was a mean reduction in seizure frequency of 46%. Five patients had a seizure reduction of at least 50%, of whom 2 experienced long-term seizure freedom. In none of the patients, VNS induced seizure exacerbation. It appeared that three types of responses to vagal stimulation occurred: rapid-sustained, gradual and non-response. In the meantime, two prospective multicenter ($n = 17$) double-blind randomised studies (EO3 and EO5) were started including patients from centers in the U.S.A. ($n = 12$), Canada ($n = 1$) as well as Europe ($n = 4$). In these two studies, patients over the age of 12 with partial seizures were randomised to a HIGH or LOW stimulation paradigm. The parameters in the HIGH stimulation group (output: gradual increase up to 3.5 mA, 30 Hz, 500 μs, 30 s on, 5 min off) were those believed to be efficacious based on animal data and the initial human pilot studies. Because patients can feel stimulation, the LOW stimulation parameters (output: single increase to point of patient perception, no further increase, 1 Hz, 130 μs, 30 s on, 3 hours off) were chosen to provide some sensation to the patient in order to protect the blinding of the study. LOW stimulation parameters were believed to be less efficacious and the patients in this group represented an active control group rather than a true placebo group. The results of EO3 in 113 patients were promising with a decrease in seizures' frequency of 24% in the HIGH stimulation group versus 6% in the LOW stimulation group after 3 months of treatment. The number of patients was insufficient to achieve Food and Drug Administration (FDA) approval leading to the EO5 study in the U.S.A. which included 198 patients. Ninety-four patients in the HIGH stimulation group had a 28% decrease in seizure frequency versus 15% in patients in the LOW stimulation group [5].

The controlled EO3 and EO5 studies had their primary efficacy end-point after 12 weeks of VNS. Prospective long-term follow-up studies are available assessing efficacy and tolerability from the end of the controlled studies to 1 and 3 years later. In these studies, patients who ended the controlled trials were offered enrolment in a long-term prospective efficacy and safety study. Patients belonging to the LOW stimulation groups were crossed-over to HIGH stimulation parameters. In all published reports on these long-term results increased efficacy with longer treatment was found [3, 15, 17]. In open extended trials, the mean reduction in seizure frequency increased up to 35% at one year and 44% at two years at which time the improved seizure control reached a plateau. In Sweden, long-term follow-up in the largest patient series ($n = 67$) in one center not belonging to the sponsored clinical trials at that time, reported similar efficacy rates with a mean decrease in seizure frequency of 44% in patients treated up to 5 years.

Mechanism of action

As for many antiepileptic treatments, clinical application of VNS preceded the elucidation of its mechanism of action (MOA). Following a limited number of animal experiments in dogs and monkeys, investigating safety and efficacy, the first human trial was performed. Since then, progress has been made on the identification of structural and functional pathways that are involved in the seizure-suppressing effect of VNS.

The tenth cranial nerve afferents have numerous projections within the central nervous system; signals generated in vagal afferents have the potential to affect the entire organism [2]. An overview of the main structures in the brainstem and cerebral hemispheres that receive vagal input is given in Fig. 2. Relatively few specific functions of the vagus nerve have been well characterised. The vagus nerve is often considered protective, defensive, relaxing. This primary function is exemplified by the lateral line system in fish, the early precedent of the autonomic nervous system. The control of homeostatic functions by the central nervous system in these earlier life forms was limited to the escape and the avoidance of perturbing stimuli or suboptimal conditions. Its complex anatomical distribution has earned the vagus nerve its name, as vagus is the Latin word for wanderer. These two facts together inspired researchers to suggest the name 'great wandering protector'.

Crucial questions with regards to the MOA of VNS occur at different levels. Vagus nerve stimulation aims at inducing action potentials within the different types of *fibers* that constitute the nerve (Fig. 3). The question remains, what fibers are responsible and/or necessary

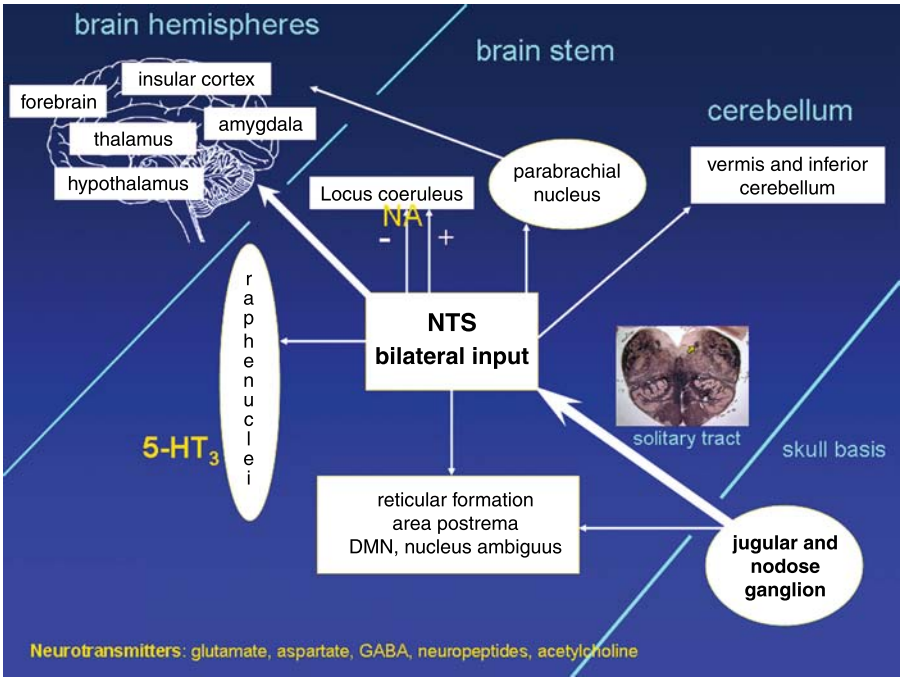

Fig. 2. Overview of the main structures in the brainstem, cerebellum and cerebral hemispheres receiving vagal afferent input. *NA* Noradrenaline, *5-HT3* serotonine, *NTS* nucleus of the solitary tract, *DMN* dorsal motor nucleus

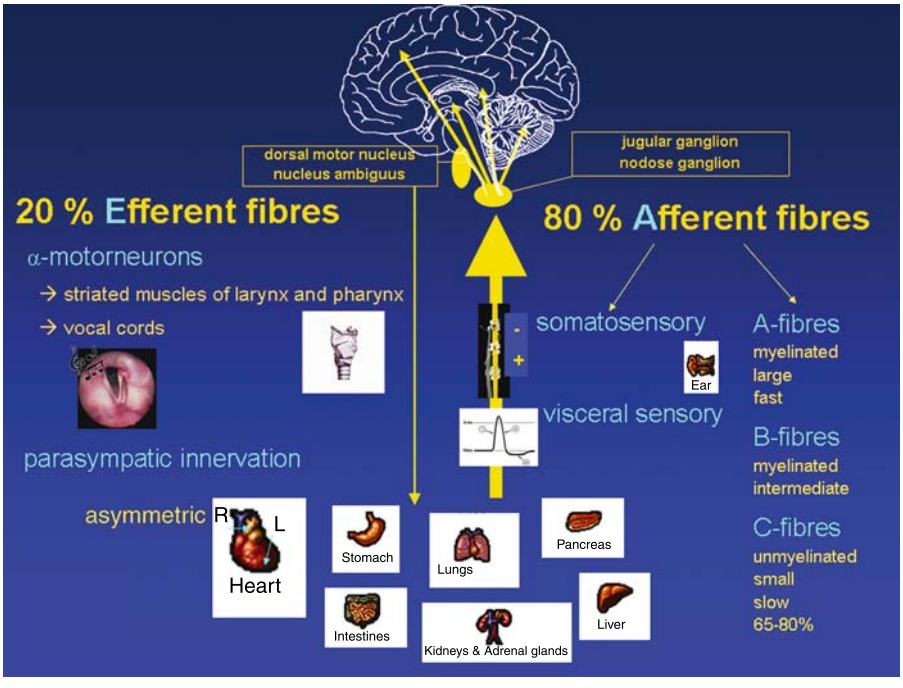

Fig. 3. Overview of the main afferent and efferent vagal fibers

for VNS seizure-suppressing effect. Unidirectional stimulation, activating afferent vagal fibers is preferred as epilepsy is considered a disease with cortical origin and efferent stimulation may cause side effects. It is unknown whether stimulation of efferent fibers is also involved in the MOA of VNS e.g. through parasympathic effects on heart function. Stimulation of vagal nerve fibers aims at influencing synaptic transmission at a distance. The next step is to identify *central nervous system structures* located on the anatomical pathways from the cervical part of the vagus nerve up to the cortex, that play a functional role in the MOA of VNS. This may involve central gateway or pacemaker function structures such as the thalamus or it may involve more specific targets involved in the pathophysiology of epilepsy such as the limbic system or a combination of

both. A third issue concerns the identification of the potential involvement of specific *neurotransmitters*. The intracranial effect of VNS may be based on local or regional GABA increases or glutamate and aspartate decreases or may involve other neurotransmitters that have been shown in the past to have a seizure threshold regulating role such as serotonine and norepinephrine.

When the efficacy of a given treatment in epilepsy is considered a certain hierarchical profile of the treatment can be distinguished. A treatment can have pure *anti-seizure* effects meaning that it can abort seizures. To confirm such an effect the treatment is most often administered during an animal experiment in which the animals are injected with a proconvulsant compound followed by the administration of the treatment under investigation. It has been shown in animal experiments as well as in clinical use in humans that VNS exerts such an effect. However, in the clinical trials with VNS, many patients did not regularly self-trigger the device at the time of a seizure and still showed good response to VNS. Moreover, VNS is administered in an intermittent way and it appears that seizures occurring during the VNS off-time are also affected. This intermittent way of stimulation is insufficient to explain the reduction of seizures on the basis of abortive effects alone and suggests a true preventative or so-called *anti-epileptic* effect of VNS. Antiepileptic efficacy implicates that a treatment can prevent seizures, as the main characteristic of the disease, namely the unexpected recurrence of seizures is prevented from happening. For some antiepileptic drugs this effect is supposed to exist but as these treatments are administered on a daily basis resulting into steady state blood levels of the active compound, their effects may also be based on a continued antiseizure effect. For VNS, a unique situation (based on the fact that intermittent stimulation is safe and spares the battery), occurs with regard to investigating a true antiepileptic effect. The fact that VNS influences seizures at a time when stimulation is in the off-mode has also been shown in many animal and human experiments and suggests VNS-induced 'long-term' changes. The precise nature of these changes remains to be identified.

Since 1985, Zabara had reported that at the termination of stimulation, there is a prolonged silent period of no seizure activity, which outlasts the stimulation period by approximately a time factor of four [18]. Stimulation for one minute could produce seizure suppression for five minutes. Seizure control extended well beyond the end of the stimulation period. Also sequential stimulation periods were additive in their effectiveness. In experiments by Lockard *et al.* [7], intermittent VNS during 2–6 weeks in monkeys with focal seizures and secondary generalization induced a reduction in seizure frequency or synchronization of the interseizure interval, an effect that lasted during follow-up baseline periods without stimulation for at least 2 weeks. McLachlan *et al.* [8] found that interictal spike frequency was significantly decreased or abolished after 20 s of VNS in rats. Spikes remained low or abolished for a variable duration, usually around 60 s to 3 min after the end of stimulation. VNS pretreatment during 1 and 60 min, prior to seizure triggering stimulation, significantly reduced the duration of behavioural seizures and afterdischarges in amygdala kindled rats. Takaya *et al.* [10] investigated the sustained anticonvulsant effect of VNS in awake and freely moving animals. In this study, VNS was discontinued before induction of PTZ-seizures that were significantly shortened in duration, providing direct evidence that VNS-induced anticonvulsant effects are not limited to the duration of stimulation. Moreover, the repetition of stimuli increased the VNS efficacy suggesting that efficacy of intermittent stimulation improves with long-term use. In patients treated for 6–25 months, acute 30 s stimulation trains reduced interictal epileptiform discharges for 60–210 s. Zagon *et al.* [19] found that VNS-induced slow hyperpolarization in the parietal cortex of the rat outlasted a 20 s VNS train by 15 s.

The ultimate goal of an anti-epileptic treatment is the cure of epilepsy. This implies that the treatment reverses the development of a pathological process that may have evolved over a long period of time. Such an *antiepileptogenic* treatment is clearly protective and may even be used for other neuroprotective purposes. The fact that seizures reoccur after the end of battery life of VNS is a strong argument against VNS having such an effect. However, as progress in the development of more relevant animal models for epilepsy is made, the antiepileptogenic potential of neurostimulation, in general, is being explored and promising results have been reported, e.g. in the kindling model.

Conclusion

From a clinical point of view, it is concluded that VNS is an efficacious and safe treatment for patients with refractory epilepsy. VNS appears to be a broad-spectrum treatment; identification of responders on the basis of either type of epilepsy or of specific patient characteristics proves difficult. Large patient groups have been examined; however, identifying predictive

factors for response may demand more complex investigations such as CBF studies or alternative means to externally stimulate vagal afferents. Optimising stimulation parameters and individual titration on the basis of routine neurophysiological monitoring is probably a more promising path towards increased clinical efficacy. VNS is a safe treatment and lacks the typical cognitive side effects associated with many other antiepileptic treatments. Moreover, many patients enjoy a positive effect of VNS on mood, alertness and memory. In contrast to many pharmacological compounds, treatment tolerance does not develop in VNS. In contrast, efficacy tends to increase with the longer duration of treatment.

Extensive research has been directed towards investigating the antiepileptic and potential antiepileptogenic properties of VNS and the identification of involved fibers, intracranial structures and neurotransmitter systems. Animal experiments and research in humans comprise *electrophysiological* studies (EEG, EMG, EP), *functional anatomic brain imaging* studies (PET, SPECT, fMRI, c-fos, densitometry), *neuropsychological and behavioural* studies. Also, from the extensive clinical experience with VNS in humans interesting clues on the MOA of VNS have arisen. It has become clear that effective stimulation in humans is primarily mediated by afferent vagal A- and B-fibers. Unilateral stimulation influences both cerebral hemispheres. Crucial brainstem and cerebral structures have been identified and include the locus coeruleus, the nucleus of the solitary tract, the thalamus and limbic regions. Neurotransmitters may involve not only the major inhibitory neurotransmitter GABA but also serotoninergic and adrenergic systems. The MOA of VNS in epilepsy seems to be based on a combined mechanism of acute abortion (antiseizure effect) resulting in immediate interference with a seizure, acute prophylaxis (antiepileptic effect) which allows the treatment to be administered in an intermittent way and chronic prophylaxis (chronic antiepileptic effect) as reflected by the increased efficacy after prolonged stimulation. Clues in favour of a true antiepileptogenic effect have been deduced from preliminary animal studies but have not been confirmed in clinical practice because, following battery depletion, seizures recur.

The basis for the combined acute and more chronic effects of VNS most likely involves recruitment of different neuronal pathways and networks. The more chronic effects are thought to be a reflection of modulatory changes in subcortical site-specific synapses which can influence larger cortical areas. In the complex human brain, these neuromodulatory processes require time to build up. Once installed, certain antiepileptic neural networks may be more easily recruited, e.g. by changing the stimulation parameters, that may be titrated to the individual needs of each patient. This raises hope for potential anti-epileptogenic properties of VNS, by using long-term optimized stimulation parameters, which may affect and potentially reverse pathological processes that have been installed over a long period of time. However, from a clinical point of view, VNS cannot be considered yet a curative treatment.

Deep brain stimulation

The earliest reports on intracranial neurostimulation involved stimulation of cerebellar structures. In most instances electrical current was administered through electrodes bilaterally placed on the superior medial cerebellar cortex, representing a form of cortical stimulation (CS) [4]. Intermittent (1–8 min on, 1–8 min off) high-frequency (150–200 Hz) cerebellar stimulation was initially investigated in the treatment of spasticity due to cerebral palsy or stroke in several hundreds of patients with implantation times of up to 20 years. In a report on 51 patients with functioning devices, 50% had a marked reduction in spasticity and 69% a moderate to marked reduction in athetoid movements [4]. Speech improved in 60%, hand coordination in 61% and drooling in 53%. Some of these patients also had refractory seizures. Cerebellar CS resulted into seizure freedom in 60% and significant seizure reductions in another 20%. Some patients remained seizure-free after stimulation had ceased due to non-functioning of the implanted devices. Despite these promising results, in epilepsy two controlled studies in small patient groups ($n = 5$ and $n = 12$) did not show significant effects and cerebellar stimulation for epilepsy was abandoned. There is however still substantial evidence for a seizure-controlling effect of the cerebellum that justifies to further explore this treatment modality.

The selection of other targets for DBS in recent pilot trials in humans has resulted from the progress in the identification of epileptogenic networks that play an important role in the pathophysiology of epilepsy [9]. Although the cortex plays an essential role in seizure origin, increasing evidence shows that subcortical structures may be involved in the clinical expression, propagation, control and sometimes initiation of seizures. Consequently, several subcortical nuclei such as the subthalamic nucleus and the caudate nucleus have been targeted in pilot trials in humans for different types of

epilepsy. There seems to be a general consensus that the thalamocortical interactions are essential in the development of a large number of seizures and the propagation of most of them. Within the thalamus, ascending projections from the reticular formation and other brainstem cell groups impinge on pathways radiating to numerous forebrain structures including those of the neocortex, basal ganglia and limbic system. At the same time, neural inputs from diverse telencephalic regions converge on thalamic nuclei from which projections descend onto brainstem neurons. Some thalamic nuclei, referred to as specific nuclei, maintain strong and direct synaptic relations with the sensorimotor or the association cortex. Other thalamic nuclei project more diffusely to wide regions of the cortex and are called nonspecific nuclei e.g. reticular nuclei, anterior nuclei and intralaminar nuclei such as the centromedian nucleus of Luys. The thalamus has also been proposed as one of the major important structures on the central nervous pathways involved in the MOA of VNS. Large patient series have been treated with DBS in the centromedian nucleus and pilot trials investigating the efficacy and safety of the anterior nucleus are currently undertaken.

Few controlled studies investigating DBS are available. Blinded crossing-over between periods during which stimulation is either on or off reflects the necessary design for evaluating the true efficacy of DBS protocols. However, the most optimal design of such protocols may be difficult to develop. It has become clear, especially from the experience with VNS, but also from other studies, that increased efficacy may be observed after longer duration of stimulation, possibly on the basis of neuromodulatory changes that take time to develop. It is unknown however, how long these developments take exactly or whether there are individual or age-related differences and to what extent permanent protective changes can be achieved. Consequently, crossover after 3 months may be too short a time to evaluate fully expressed efficacy, especially using a stimulation protocol of e.g. only several hours/day. The choice of targeting the *amygdalohippocampal region* in a pilot trial in humans at Ghent University Hospital was based on several considerations. For further elaboration on this specific target we refer to the chapters in this book by Van Roost *et al.* and Boon *et al.*

Mechanism of action

The development of neurostimulation therapy for neurological conditions is stimulated by two major concerns related to standard available treatments. First, there is a general tendency to find treatments that are minimally invasive and least harmful to the patient. Secondly, the refractory character of certain neurological diseases and the inability to treat them with currently available means provides an impetus to search for novel treatments. VNS is less invasive than DBS as it does not require opening of the skull, which is generally associated with increased risk. Some refractory pathologies in the brain have led the search to effective treatments that are sometimes very invasive; this invasiveness however, is balanced by the refractoriness of the pathology and/or the high success rate of the treatment. Most often lesioning or resection of brain tissue is involved in such treatments. The increasing insight into basic mechanisms underlying normal and pathological neurological functioning, combined with the rapidly evolving progress in the biomedical devices with miniaturized technology and electronics, has led to the idea that similar effects to lesioning could be reached by neurostimulation. In the meantime, neurostimulation has proven to be effective in several neurological conditions but its true mechanism(s) of action remain unknown.

Reports in the literature support the hypothesis that actual stimulation is not necessary and claim that treatment efficacy is based on the lesion provoked by the insertion of the electrode. This observation was described following electrode insertion in the anterior nucleus of the thalamus and referred to as 'microthalamotomy'. Also reports have described prolonged seizure control in patients who underwent invasive recording with conventional electrodes. In many epilepsy centers, a time interval occurs between the invasive recordings and consequent resective procedures. Following the results of invasive recordings, a resective procedure may not be feasible. Seizure frequency following the removal of the implanted electrodes is evaluated without further immediate interventions. It may be that when is targeted the anterior thalamic nucleus, lesions are more effective in such a confined area compared to the amygdalohippcampal region. It is possible that essential pathways could be accidentally or coincidentally lesioned during medial temporal lobe targeting. This seems an unlikely hypothesis in a series of treated patients. In a SPECT study by Velasco *et al.*, in 6 patients who underwent 3 weeks of hippocampal stimulation using subdural strips, the postimplantation SPECT (before stimulation) shows similar findings to the preimplantation images [14]. The images, after 3 weeks of DBS, show clear hippocampal hypoperfusion comparable to images taken after anterior temporal lobectomy.

The implantation-related lesion might provoke earlier signs of hypoperfusion in the lesioned region. Moreover, in contrast to the findings by Hodaie *et al.* [6] seizures did not decrease until several days after initiation of stimulation, a finding confirmed in our series of amygdalohippocampal stimulation. It is possible that the lesioning hypothesis holds true for some targets but is not applicable to others. Blinded randomization of patients to ''on'' and ''off'' stimulation paradigms following implantation for substantial periods of time (e.g. 6 months) may clarify not only this but also the potential effect of sham stimulation of an implanted device.

A second hypothesis is that DBS acts through local inhibition by the applied current to a certain structure, the so-called 'reversible functional lesion'. In the case of targeting crucial structures in a network, nuclei that are involved in propagation, sustainment or triggering of epileptic activity are inhibited. In the case of targeting an ictal focus, a similar mechanism may act suggesting that applied current inhibits overexcitable tissue. Apart from 'local' inhibition, the mechanism of action of DBS may be based on the effect on projections from the area of stimulation to other central nervous structures. This may be the most likely hypothesis whenever crucial structures in epileptogenic networks are involved. However, considering that medial temporal lobe structures are also potentially involved in these networks, targeting the ictal focus may also affect the epileptogenic network. When projections from one structure to another are involved, antiepileptic mechanisms may operate through either the activation of inhibitory projections or the inhibition of (over) excitatory projections.

References

1. Ben-Menachem E (2002) Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurol 1: 477–482
2. Berthoud H, Neuhuber WL (2000) Functional and chemical anatomy of the afferent vagal system. Auton Neurosci 85: 1–17
3. Boon P, Vonck K, Van Walleghem P, D'Have M, Goossens L, Vandekerckhove T, Caemaert J, De Reuck J (2001) Programmed and magnet-induced vagus nerve stimulation for refractory epilepsy. J Clin Neurophysiol 18: 402–407
4. Davis R (2000) Cerebellar stimulation for cerebral palsy spasticity, function and seizures. Arch Med Research 31: 290–299
5. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation therapy for partial onset seizures. A randomized, active control trial. Neurology 51: 48–55
6. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
7. Lockard JS, Congdon WC (1986) Effects of vagal stimulation on seizure rate in monkey model. Epilepsia 27: 626
8. McLachlan RS (1993) Suppression of interictal spikes and seizures by stimulation of the vagus nerve. Epilepsia 34: 918–923
9. Proctor M, Gale K (1999) Basal ganglia and brain stem anatomy and physiology. In: Engel J, Pedley TA (eds) Epilepsy, the comprehensive CBD rom. Lippincot Williams and Wilkins, Baltimore
10. Takaya M, Terry WJ, Naritoku DK (1996) Vagus nerve stimulation induces a sustained anticonvulsant effect. Epilepsia 37: 1111–1116
11. Tassinari CA, Cincotta M, Zaccara G, Michelucci R (2003) Transcranial magnetic stimulation and epilepsy. Clin Neurophysiol 114: 777–798
12. Terry R, Tarver WB, Zabara J (1990) An implantable neurocybernetic prosthesis system. Epilepsia 31: S33–S37
13. Uthman BM, Wilder BJ, Penry JK, Dean C, Ramsay RE, Reid SA, Hammond EJ, Tarver WB, Wernicke JF (1993) Treatment of epilepsy by stimulation of the vagus nerve. Neurology 43: 1338–1345
14. Velasco AL, Velasco M, Velasco F, Menes D, Gordon F, Rocha L, Briones M, Marquez (2000) Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report. Arch Med Res 31: 316–328
15. Vonck K, Boon P, D'Havé M, Vandekerckhove T, O'Connor S, De Reuck J (1999) Long-term results of vagus nerve stimulation in refractory epilepsy. Seizure 8: 328–334
16. Vonck K, Boon P, Achten E, De Reuck J, Caemaert J (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 52: 556–565
17. Vonck K, Thadani V, Gilbert K, Dedeurwaerdere S, De Groote L, De Herdt V, Goossens L, Gossiaux F, Achten E, Thiery E, Vingerhoets G, Van Roost D, Caemaert J, De Reuck J, Roberts D, Williamson P, Boon P (2004) Vagus nerve stimulation, a transatlantic experience. J Clin Neurophysiol 21: 283–289
18. Zabara J (1985) Time course of seizure control to brief repetitive stimuli. Epilepsia 26: 518
19. Zagon A, Kemeny AA (2001) Slow hyperpolarization in cortical neurons: a possible mechanism behind vagus nerve stimulation therapy for refractory epilepsy? Epilepsia 41: 1382–1389

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The role of neuromodulation of the hippocampus in the treatment of intractable complex partial seizures of the temporal lobe

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Summary

We present the results of chronic electrical stimulation of the hippocampus (ESH) in 9 patients with complex partial seizures and at least 18 months follow-up. The magnetic resonance imaging (MRI) scan was normal in 5 while in 4 patients it showed hippocampal sclerosis. The seizure frequency ranged from 10 to 50 seizures per month. All patients were submitted to implantation of diagnostic 8-contact bilateral hippocampal depth electrodes to determine the location of epileptic foci. Once the focus was located, the diagnostic electrodes were replaced by deep brain stimulation (DBS) electrodes. Following DBS, all patients improved. With respect to outcome, patients were divided in two groups, one seizure-free (5 patients) and the other with residual seizures (4 patients). Both groups shared similar clinical features. However, the patients who were seizure free had normal MRI scan while those who had residual seizures were being stimulated on a sclerotic hippocampus. We conclude that electrical stimulation of the epileptic hippocampal formation can control mesial temporal seizures. Best results are obtained if we stimulate a hippocampus which does not show sclerosis in the MRI. In these cases, seizures are stopped and the recent memory tests improve even in patients with bilateral foci. This result is of extreme importance to patients who have either intractable seizures and normal MRI or bilateral epileptogenic foci, are excluded as candidates for temporal lobectomy and are left with no other alternative.

Keywords: Neuromodulation; hippocampus; complex partial seizures; deep brain stimulation; DBS; epilepsy.

Introduction

Mesial temporal lobe epilepsy (MTLE) is a challenge for epileptologists because of the high number of patients who are drug-resistant. In our Epilepsy Surgery Clinic at the General Hospital of Mexico, the main cause for patient referral is MTLE. Up to 70% of patients referred for surgery have complex partial seizures arising from the hippocampal formation. This experience is shared by other epilepsy surgery clinics [19, 20]. Even though anterior temporal lobectomy offers good results [2, 6, 9, 10, 13], there is a big number of patients in whom it is not possible to recommend it. This category of patients includes those: a) who have bilateral hippocampal foci and in whom bilateral temporal lobectomy is contra-indicated because of the expected loss of short term memory [11] or b) patients in whom the epileptic focus is located in an eloquent area, i.e. in the anterior and middle left hippocampus.

Neuromodulation is a procedure that has been used in epilepsy, and various targets have been stimulated. These include centromedian thalamic stimulation [12, 13], cerebellar stimulation [3, 5] and vagal nerve stimulation [8, 1]. Nevertheless, with regard to complex partial seizures originating in the hippocampal formation, the benefits have been limited. In 2000, Velasco *et al.* proposed the stimulation of the hippocampus in order to control MTLE and they published a study of 10 patients who had diagnostic hippocampal electrodes inserted and in whom subacute hippocampal stimulation was performed before submitting them to temporal lobectomy [13]. This study showed that there is indeed a seizure improvement. In 7 patients, in whom subacute electrical stimulation was performed, the seizures disappeared on day 6 and the interictal spikes were reduced significantly after day 13 of subacute stimulation. During this preliminary work, we studied a few basic mechanisms underlying the beneficial therapeutic effect of hippocampal stimulation on seizures [13–16]. Several tests were performed and provided the following findings: increased threshold and decreased duration of the afterdischarges induced by acute hippocampal stimulation, depression of the paired pulse hippocampal recovery cycles, SPECT hypoperfusion and autoradiographic increase of the

Table 1. *Clinical characterization of 9 selected patients with mesial temporal lobe epilepsy*

KG	Age [Yr]	Sex	ONSET [Yr]	FREQ [Sz/mo]	Sz type I	Sz type II	MRI	AED
67	27	M	3	25	CXP	SGTC	normal	CBZ, VA
71	40	M	16	35	CXP	none	LHS	CBZ, GBP
101	29	F	12	27	CXP	none	normal	PHT
102	27	F	16	50	CXP	SGTC	LHS	VA, PRI, CLN
106	43	M	6	22	CXP	SGTC	LHS	VA, LMT
109	20	M	13	25	CXP	SGTC	normal	CBZ
111	24	F	13	30	CXP	SGTC	normal	CBZ, TPM
112	14	M	11	25	CXP	SGTC	LHS	CBZ, PHT
115	38	M	10	19	CXP	SGTC	normal	OXC, PHT

Yr Year, *Sz/mo* seizures per month, Sz type I is the most frequent type and type II is less frequent type, *CXP* complex partial seizures, *SGTC* secondary generalized tonic clonic seizures, *LHS* left hippocampal sclerosis, *AED* antiepileptic drugs, *CBZ* carbamazepine, *VA* valproate, *PHT* phenytoin, *PRI* primidone, *CLN* clonazepam, *OXC* oxcarbazepine.

benzodiazepine receptor binding in the stimulated hippocampal tissue [4]. Such studies suggest that the antiepileptic effect of hippocampal stimulation is due to an inhibitory mechanism.

In 2002, Velasco *et al.* reported the first case of chronic bilateral hippocampal stimulation in a 23-year-old patient with MTLE and normal MRI, in whom depth electrode recordings showed bilateral hippocampal foci. The seizures disappeared completely and the patient showed a neuropsychological improvement in the memory tasks. Currently, his follow up is 6 years and 5 months long. On the second year the batteries were depleted and he started having seizures again; as soon as the batteries were replaced, the seizures stopped and have not reappeared.

In this chapter, we present the results of chronic electrical stimulation of the hippocampus (ESH) in 9 patients with drug-resistant MTLE and at least 18 months follow-up.

Patients and methods

The protocol was approved by the Scientific and Ethical Committees of the General Hospital of Mexico. Nine patients with MTLE were selected for this study (Table 1), 6 males and 3 females, with an age range from 14 to 43 years (average 29). All had complex partial seizures; secondary tonic clonic generalization was documented in 7 patients. Five patients had normal MRI scan and 4 had hippocampal sclerosis. All patients received 2 antiepileptic drugs either at toxic blood levels or within the therapeutic range. Nevertheless, they continued having seizures. The seizure frequency ranged from 10 to 50 seizures per month (average 28). The evaluation of patients included a clinical history with special emphasis on the seizure types, compliance to antiepileptic medication with adequate blood levels, 4 serial EEGs, MRI, neuropsychological examination and psychiatric evaluation. Patients were trained to keep a seizure calendar which they handed to us on a monthly basis. All patients were submitted to implantation of diagnostic 8-contact bilateral hippocampal depth electrodes to determine where the epileptic foci were located (SD 8P, Ad Tech Medical Instrument Co., Racine, WI, USA).

Once the focus was located, the diagnostic electrodes were replaced by permanent 4-contact electrodes (3789 DBS and IPG by Medtronic, Inc., Minneapolis, MN) and connected to the DBS system, either bilateral (in case of bilateral foci) or unilateral. All patients were stimulated choosing the two contacts that covered the area where the epileptic focus was localized, i.e. either the anterior hippocampus or the amygdalo-hippocampal junction. Figure 1 shows the stimulated contacts and their localization.

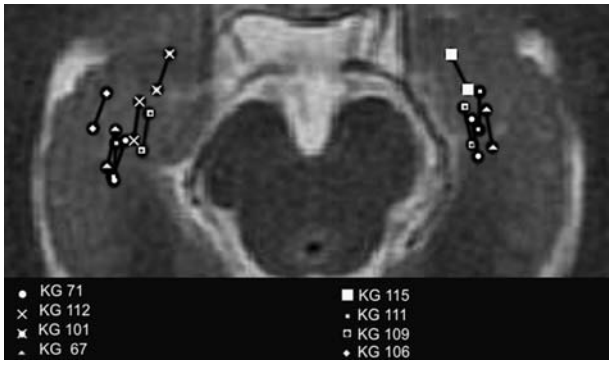

Fig. 1. Diagram showing the position of the stimulated contacts for ESH. Note that all contacts are either in the amygdalo-hippocampal junction or anterior and middle hippocampus

In an aleatory manner, 4 patients underwent one month OFF period before starting ESH and 5 started immediately after the DBS system was implanted. The parameters for ESH were as follows: daily stimulation sessions with 1 min trains of Lilly pulses with an interstimulus interval of 4 min. Such trains consist of a 130 Hz frequency, with individual pulses of 450 μs in duration and amplitude of 400–600 μA. In the patients with bilateral electrodes, the stimulation has the same characteristics but is alternated between the right and left hippocampus.

Results

The long-term follow-up period ranged from 18 months to six and a half years. For statistical reasons, the whole group was analyzed on month 18. We divided the analysis in 3-month periods; we have the average of 3 months before the stimulation started and 6 periods of 3 months each comprising the 18 months of chronic stimulation. Between the baseline period and the chronic stimulation, there is one month OFF period which was

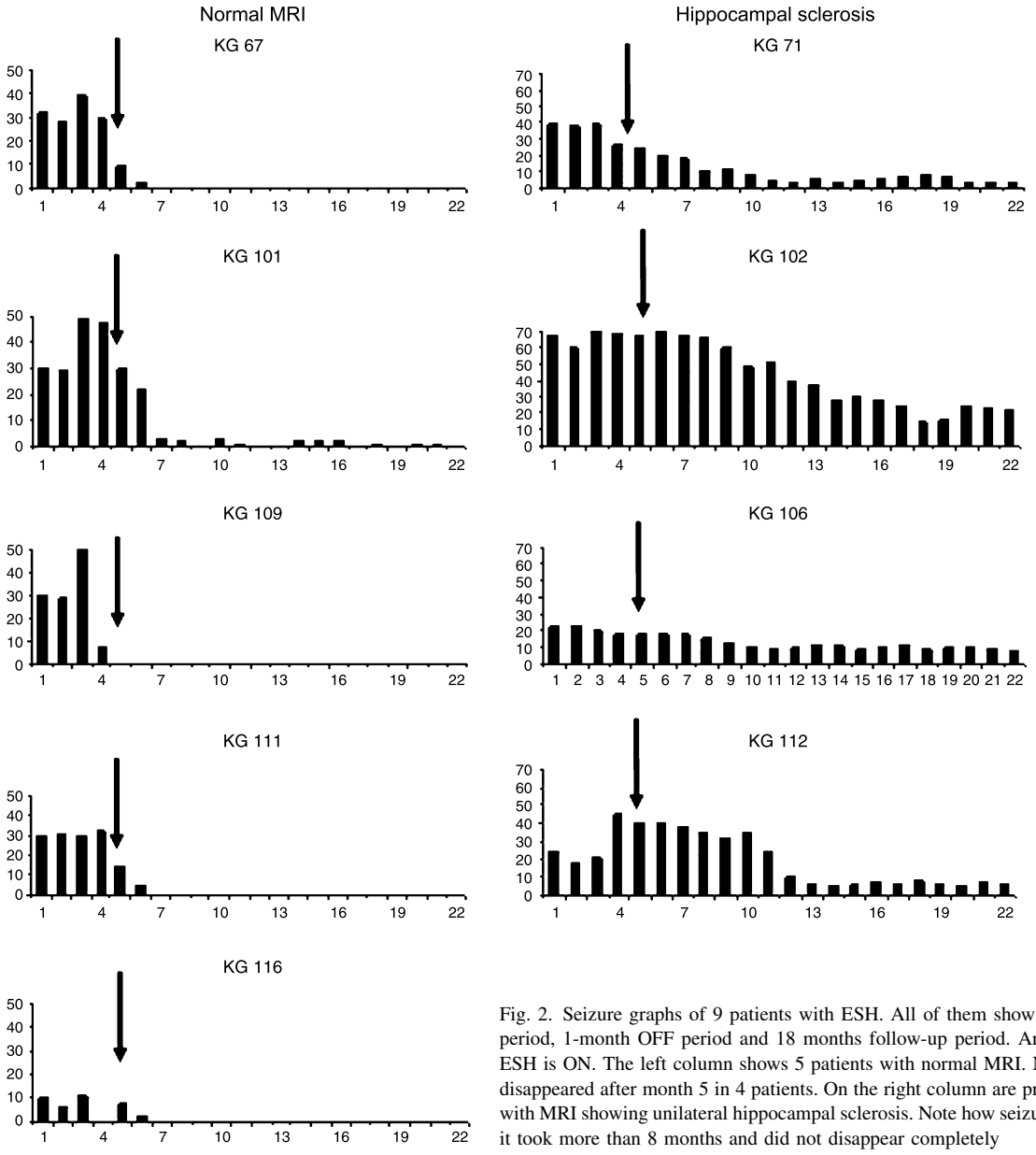

Fig. 2. Seizure graphs of 9 patients with ESH. All of them show 3-month baseline period, 1-month OFF period and 18 months follow-up period. Arrow shows where ESH is ON. The left column shows 5 patients with normal MRI. Note how seizures disappeared after month 5 in 4 patients. On the right column are presented 4 patients with MRI showing unilateral hippocampal sclerosis. Note how seizures decreased but, it took more than 8 months and did not disappear completely

analyzed separately. The duration of the OFF period was limited to one month.

When we counted at month 18, all patients had improved; it was evident, however, that the patients' outcome could be divided in two groups, one was seizure-free (5 patients) and the other had residual seizures (30% average for the 4 patients) (Fig. 2). Both groups shared similar clinical features. The only consistent difference was that the patients who were seizure free had normal MRI scans compared to those who had residual seizures and were being stimulated on a sclerotic hippocampus.

Normal MRI group

Five patients had normal MRI scans. The monthly seizure average frequency for the 3-month basal period was 26.8 seizures. During the OFF period, the seizures average frequency was 29.3. By the end of the first 3-month stimulation period, the seizure average frequency had decreased to 6.4 seizures and by the end of the last three months the seizure average frequency was 0.13. The difference is highly significant from the beginning of the stimulation period ($p < 0.001$ by month 3 and $p < 0.0001$ by month 18). Four patients are seizure-free and one of them has occasional seizures (1 per 3 months).

Hippocampal sclerosis group

Four patients had unilateral hippocampal sclerosis on MRI scan. The monthly seizure average frequency for the 3-month basal period was 36.8. During the OFF period, the seizures average frequency was 44. By the end of the first 3-month stimulation period, the seizure average frequency remained the same as during the baseline period (36.6 seizures) and by the end of the last 3 months the seizure average frequency was 10.5. A significant difference between the baseline period and the improvement of chronic stimulation started being evident after 6 months of stimulation. Although the difference is highly significant after month 6 ($p < 0.0001$) the patients did not become seizure-free and persisted with a seizure average frequency of 10.5 in 3 months.

The neuropsychological evaluation revealed a significant improvement in the tests of patients who were seizure free. In the patients who had residual seizures, the tests continued showing poor performance, mainly in recent memory. There were no undesirable effects. Only one patient (KG 115) had skin erosion in the neck which required antibiotic therapy and afterwards plastic surgery to correct it.

Conclusion

Electrical stimulation of the epileptic hippocampal formation is an efficient method for controlling mesial temporal seizures. Best results are obtained if we stimulate a hippocampus which does not show sclerosis in the MRI. In these cases, seizures are terminated and the recent memory tests improve even in patients with bilateral foci. This result is of extreme importance because these patients who have either intractable seizures and normal MRI or bilateral epileptogenic foci are the ones who are excluded as candidates for temporal lobectomy and are left with no other alternative.

References

1. Amar AP, Apuzzo MLJ, Liu CY (2004) Vagus nerve stimulation therapy alter failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation n therapy patient outcome registry. Neurosurgery 55: 1086–1093
2. Cahan LD, Sutherling W, McCullough MA, Rausch R, Engel J, Crandall PH (1984) Review of the 20-year UCLA experience with surgery of epilepsy. Cleve Clin J Med 51: 313–323
3. Cooper IS, Amin I, Ricklan M (1976) Chronic cerebellar stimulation in epilepsy: clinical and anatomical studies. Arch Neurol 33: 559–570
4. Cuellar-Herrera M, Velasco M, Velasco F, Velasco AL, Jiménez F, Orozco S, Briones M, Rocha L (2004) Evaluation of GABA system and cell damage in parahippocampus of patients with temporal lobe epilepsy showing antiepileptic effects alter subacute electrical stimulation. Epilepsia 45: 459–466
5. Davis R, Emmans SE (1992) Cerebellar stimulation for seizure control 17 year study. Stereotact Funct Neurosurg 58: 200–208
6. Engel J Jr (1987) Outcome with respect to epileptic seizures. In: Engel J Jr (ed) Surgical treatment of the epilepsies. Raven Press, New York, pp 553–569
7. Frost M, Gates J, Helmers SL *et al* (2001) Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. Epilepsia 42: 1148–1152
8. Morris G, Mueller W (1999) Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Neurology 53: 1731–1735
9. Primrose DC, Ojeman GA (1961) Outcome of resective surgery for temporal lobe epilepsy. In: Lüders H (ed) Epilepsy surgery. Raven Press, New York, pp 601–618
10. Radhakrishnan K, So EL, Silbert PL, Jack CR Jr, Cascino GD, Sharborough FW, O'Brien PC (1998) Predictors of outcome of anterior temporal lobectomy for intractable epilepsy. Neurology 51: 465–471
11. Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal Lesions. J Neurol Psychiatry 20: 11–21
12. Velasco F, Velasco M, Velasco AL, Jimenez F (1993) Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity. Epilepsia 34: 1052–1064
13. Velasco F, Velasco M, Jiménez F *et al* (2000) Predictors in the treatment of difficult to control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery 47: 295–305
14. Velasco AL, Boleaga B, Brito F, Jiménez F, Gordillo JL, Velasco F, Velasco M (2000) Absolute and relative predictor values of some non-invasive and invasive studies for the outcome of anterior temporal lobectomy. Arch Med Res 31: 62–74
15. Velasco AL, Velasco M, Velasco F, Ménes D, Gordon F, Rocha L, Briones M, Márquez I (2000) Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures. Arch Med Res 31: 316–328
16. Velasco M, Velasco F, Velasco AL (2001) Centromedian thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. Clin Neurophysiol 18: 1–15
17. Velasco F, Velasco M, Velasco AL, Ménez D, Rocha L (2001) Electrical stimulation for epilepsy 1. Stimulation of hippocampal foci. Stereotact Funct Neurosurg 77: 223–227
18. Velasco F, Carrillo-Ruiz JD, Brito F *et al* (2005) Double blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 46: 1–11
19. Wieser HG, Engel J Jr, Williamson PD, Babb TL, Gloor P (1993) Surgically remediable temporal lobe síndromes. In: Engel J Jr (ed) Surgical treatment of the epilepsies. Raven Press, New York, pp 49–63
20. Williamson PD, Wiesser HG, Delgado Escueta AV (1993) Clinical characteristics of partial seizures. In: Engel J Jr (ed) Surgical treatment of the epilepsies. Raven Press, New York, pp 387–397

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Neurosurgical aspects of temporal deep brain stimulation for epilepsy

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Summary

Deep brain stimulation (DBS), which mimics the effect of ablative surgery in movement disorders, is considered by analogy as potentially useful in the epileptic temporal lobe as an alternative to resection. It could be applied to patients in whom resective surgery is less beneficial, e.g. cases without memory impairment or with bilateral hippocampal involvement. In patients who undergo invasive presurgical analysis, the necessary intrahippocampal leads can serve for the application of DBS, provided that they are suited for chronic use. The hippocampus, in which the focus of epilepsy is detected, is stimulated continuously using high-frequency square-wave pulses. The reduction of interictal spike activity during a period of acute stimulation is the criterion for deciding whether the leads will be connected to an internal pulse generator. We are conducting a pilot study, with 16 patients enrolled so far, ten of whom have been followed up for more than one year. Some theoretical considerations are dedicated to hippocampal DBS.

Keywords: Neuromodulation; intractable seizures; epilepsy; deep brain stimulation; DBS; temporal lobe.

Introduction

In temporal lobe epilepsy, resective surgery achieves short-term cure (seizure freedom according to Engel's class IA) in up to 85% of cases and long-term cure in 57–66% of cases [13, 18, 27]. Seizure-free state has also been achieved in 65% of the patients with temporal lobe epilepsy two years after gamma knife surgery [15]. Resective surgery may, on the other hand, entail the risk of visual field defects as well as cognitive impairment that is proportional either to the extent of existing residual function in the afflicted hippocampus before surgery or to the extent of collateral brain damage after surgery [8, 9]. Hence, resective surgery, in spite of its noteworthy results, does not offer the hoped-for solution in about one third of the patients who are considered good candidates on the basis of extensive presurgical assessment. Moreover, resective surgery is eventually considered inappropriate in a great number of patients with medically intractable temporal lobe epilepsy because either the focus is not confined to one temporal lobe or serious cognitive impairment is likely to occur after surgery. For these reasons, neuromodulation by means of electrical stimulation is currently considered as an alternative therapy.

History

Various targets of neuromodulation have been used in the treatment of epilepsy: the cerebellar cortex [4], the caudate nucleus [2, 16], the locus coeruleus [5], the centromedian thalamic nucleus [6, 23, 24], the anterior thalamic nucleus [10, 19], the subthalamic nucleus [1], and the vagus nerve [14]. Electrical stimulation of the aforementioned targets – which are not the foci of epilepsy – aims at the activation of a postulated anticonvulsant control system in the brain, that restores the imbalance between excitatory and inhibitory processes which led to the epileptic seizures [3]. It has become clear that deep brain stimulation (DBS) may exert either excitatory or inhibitory effects on neuronal circuitry, depending on stimulation frequency, polarity, proximity to the neurons, and function of these neurons. By switching the electric current off, DBS is basically reversible, especially as to its side effects. This has promoted the exploration of new targets and applications. In movement disorders, high-frequency DBS mimics the effects of ablative surgery. By analogy with this type of action and supported by experiments on animal models of epilepsy, hippocampal DBS was first applied to a hippocampus, in which the focus of epilepsy was located, prior to its resection [22]. Subacute and chronic (3–4 months)

hippocampal stimulation was found to terminate clinical seizures, to significantly decrease the number of interictal spikes, and to have no undesirable effects on short-term memory [22]. The next step is to study whether the clinical use of chronic hippocampal DBS may serve as an alternative to hippocampal resection, in those patients who are not the ideal candidates for resection or in those who prefer a less invasive treatment.

Method

Placing an electrode into the hippocampus is a procedure that is well-known for diagnostic purposes, namely for depth EEG recording. Electrodes are inserted by means of a stereotactic device, using either a lateral orthogonal [12], a frontodorsal [21] or a posteroanterior approach [11, 17].

We adopted the latter approach. Patients in whom intrahippocampal depth recordings are indicated may become good candidates for intrahippocampal DBS, and patients who seem to be candidates for chronic intrahippocampal DBS deserve prior depth analysis. Therefore we use leads that are labeled for chronic DBS (model 3387, Medtronic, Minneapolis, MN, USA) to perform both the depth recordings and stimulation, hence eliminating the need to exchange the diagnostic leads against therapeutic ones. These are catheter-like, 1.27-mm-thick polyurethane electrodes that carry four cylindric platinum-iridium contacts of 1.5 mm length each, distributed in line over the distance 10.5 mm of the lead. The very flexible lead is rendered stiffer by an internal stylet, which is removed after the insertion of the lead into the brain parenchyma. Because the operational length of the lead (10.5 mm) is quite limited as compared to the length of the hippocampus (≈43 mm), two of these leads are inserted in each temporal lobe, one in the basal amygdala and the other in the hippocampal head (Fig. 1).

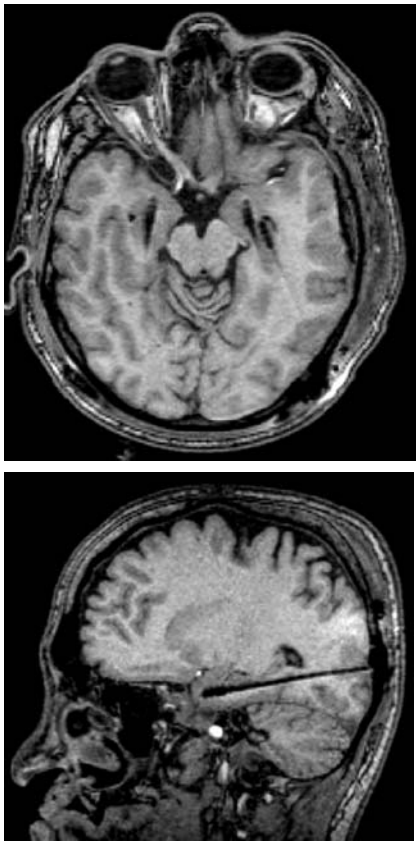

Fig. 1. Axial and sagittal MR imaging after stereotactic insertion of DBS leads bilaterally in amygdala and caput hippocampi. An additional subdural grid electrode has been placed over the left temporal lobe

Under local anesthesia, the Leksell stereotactic frame (G-frame, Elekta AB, Stockholm, Sweden) is fixed onto the patient's head, that is completely shaved prior to the procedure. MR imaging (1.5 Tesla, Magnetom Avanto, Siemens, Erlangen, Germany) is done in stereotactic conditions. Usually 176 sagittal slices of 1.2 mm thickness are acquired in a 3D-T1-MPRAGE sequence. These data are transferred to the planning desk (FrameLink 4, StealthStation, Medtronic, Minneapolis, USA), where images are reformatted and registered to the frame's coordinate system. Targeting is done by direct visualisation of the hippocampal head and the basal portion of the amygdala. The hippocampal head is targeted halfway the surface of the cerebral peduncle and the uncal recess of the temporal ventricular horn. The entry points for the electrodes in amygdala and hippocampus are chosen a little apart at the occipital or parietooccipital bone, in a way that the trajectories run postero-anteriorly, and at the same time, slightly latero-medially. The trajectories are adjusted as to not crossing sulci, but they are allowed to cross the temporal horn of the lateral ventricle. It is also avoided to realize trajectories that "ideally" run through the hippocampi starting from their slender tails, because this may interfere with the hippocampal function – at both the affected and the healthy side – and rarely cause global amnesia [20]. For the surgical procedure proper, the patient is brought under general anesthesia and in a prone position. Prophylactic antibiotics are administered (cefazoline 2×2 g i.v. on the operation day and cefuroxim 1.5 g q 8 hrs for the next 7 days). The trajectory through the brain is paved by the insertion of a 1-mm-thick straight probe, prior to the placement of the DBS lead. The latter is then fixed at the level of the burr hole by means of acrylic cement, and connected to a percutaneous extension lead. If required, subdural strip or grid electrodes are implanted in a separate procedure one or two days after the stereotactic procedure.

The position of the leads is always verified by MR imaging. For the sake of safety and according to the newest recommendations of Medtronic, the specific absorption rate (SAR) of the MRI should not exceed 0.1 W/kg. All electrode contacts are connected with the monitoring system (128-channel digital video-EEG, Beehive, Grass-Telefactor, West Warwick, RI, USA). Antiepileptic drugs are gradually tapered until habitual seizures are recorded. The finding of a unilateral or bilateral, focal or regional medial temporal lobe seizure onset is the criterion for offering to the patient the choice to undergo continuous amygdalohippocampal DBS. Acute DBS is delivered using an external pulse generator (DualScreen, model 3628, Medtronic, Minneapolis, MN, USA) and constitutes a trial. Electric stimulation consists of biphasic square-wave pulses, with a pulse width of 450 μs and a frequency of 130 Hz. The anteriormost and the third contact of each electrode serve as cathodes, the other contacts as anodes. The stimulation output is defined by keeping it subthreshold to the occurrence of stimulation artefacts recorded from the hippocampal electrode when the amygdalar electrode is activated with 0.1 V increments. Once defined, this stimulation output is delivered to both the amygdalar and the hippocampal electrodes. The interictal spike activity in the stimulated area serves as a surrogate parameter for ictal activity. After continuous delivery for 23 hours per day, DBS is interrupted every morning at about the same time for one hour, during which the leads are disconnected from the pulse generator and reconnected with the video-EEG equipment [25]. If the number of interictal spikes is found to be reduced by more than 50% during seven consecutive days, it is decided to convert acute DBS into chronic DBS. Chronic DBS is delivered by one programmable internal pulse generator

(or exceptionally two) with 2×4 output contacts (Kinetra, model 7428, Medtronic, Minneapolis, MN, USA). The pulse generator is implanted under general anesthesia in an abdominal subcutaneous pouch and connected with the intracerebral electrodes by means of 95-cm-long extension wires. Patients are followed up at regular 2-week intervals. Seizure frequency and side-effects of amygdalohippocampal DBS are monitored. Extensive neuropsychological assessment is scheduled 6 months after implantation.

Pilot study

Within the frame of a pilot study, that is supported by the company Medtronic, we included up to now 16 patients for acute amygdalohippocampal DBS. Out of these 16 patients, two did not meet the criteria for chronic implantation and one preferred selective amygdalohippocampectomy over chronic DBS. Out of the 13 patients who received chronic DBS, ten were followed up for at least one year. Their results in terms of seizure reduction are discussed in the chapter "Clinical experience with vagus nerve stimulation and deep brain stimulation in epilepsy" in this book. In the 13 patients who had chronic DBS, the following adverse events were observed: a small asymptomatic bleeding at the electrode entry point in one patient and around an amygdalar contact (which disappeared after one week) in another patient. Three late subcutaneous infections occurred and resulted in the temporary removal and replacement of extension lead and internal pulse generator.

Theoretical considerations

Electric current may exert a modulatory action on neuronal processing through a) the applied electric field, b) the release of substances, c) the modification of synaptic connections, or d) the modification of cellular

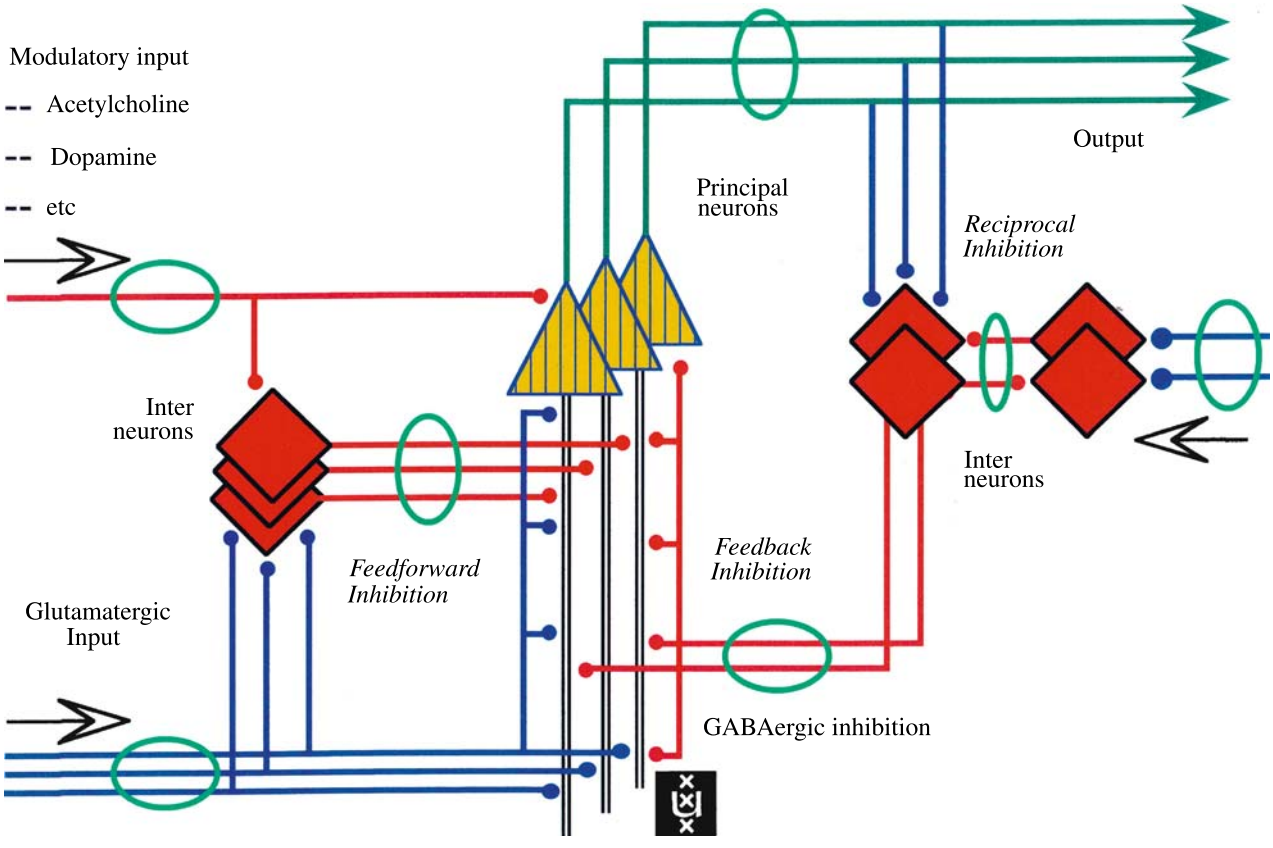

Fig. 2. Schematic hippocampus-like circuit (according to Wierenga CJ and Wadman WJ [26]). The sites where functional stimulation can exert distinct modulatory effects on circuit signal transfer by changing the synaptic efficacy are indicated by ovals around the fibers. The principal neurons (triangles) will ultimately generate the output signals of the circuit, but they can also be activated antidromically. Their main input consists of glutaminergic excitatory fibres (dark) and a variety of e.g. cholinergic and dopaminergic modulations. Local interneurons (diamonds) can exert GABAergic inhibitory influences (light fibres) on the principal neurons, either in a feedforward or in a feedback organization, through collaterals of the output fibres or external glutaminergic input. The variety of possible modifications is increased by reciprocal inhibition between subtypes of local interneurons and the complicated spatial projections of the various input pathways on the dendrite trees of the principal neurons. As yet, the optimal adequate stimulus to modify a synaptic connection is not known, but it is clear that by the simultaneous influences on different fibre bundles, the number of possibilities to modify circuits becomes staggering high

properties. DBS, in its clinical application, is delivered as a macrostimulation, that reaches and influences a multitude of neuronal and glial cells, fibres and synapses, each of which may have a facilitating or inhibitory action on the circuitry. Hence, DBS, in general and in the amygdalohippocampal complex in particular, produces a large combination of microeffects; however, only the average result of these effects can be observed so far, in an empirical manner. It is not even known whether each hippocampus which is subjected to DBS is influenced the same way, due to the variability in electrode locations, and the variability in neuronal reorganization in the afflicted hippocampus. The delivery of microstimulation could offer, at least theoretically, the possibility of more selective interfering with hippocampal processing, as depicted in Fig. 2. Refinements of this type may constitute a perspective for the future.

References

1. Benabid AL, Koudsie A, Benazzouz A, Vercueil L, Fraix V, Chabardes S, Lebas JF, Pollak P (2001) Deep brain stimulation of the corpus luysi (subthalamic nucleus) and other targets in Parkinson's disease. Extension to new indications such as dystonia and epilepsy. J Neurol 248 Suppl 3: 37–47
2. Chkhenkeli SA, Chkhenkeli IS (1997) Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy. Stereotact Funct Neurosurg 69: 221–224
3. Chkhenkeli SA, Šramka M, Lortkipanidze GS, Rakviashvili TN, Bregvadze ES, Magalashvili GE, Gagoshidze TS, Chkhenkeli IS (2004) Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clin Neurol Neurosurg 106: 318–329
4. Cooper IS, Upton AR (1978) Effects of cerebellar stimulation on epilepsy, the EEG and cerebral palsy in man. Electroencephalogr Clin Neurophysiol Suppl 34: 349–354
5. Feinstein B, Gleason CA, Libet B (1989) Stimulation of locus coeruleus in man. Preliminary trials for spasticity and epilepsy. Stereotact Funct Neurosurg 52: 26–41
6. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
7. Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD (2005) Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy. A Technical Note. Stereotact Funct Neurosurg 83: 153–158
8. Gleissner U, Helmstaedter C, Schramm J, Elger CE (2002) Memory outcome after selective amygdalohippocampectomy: a study in 140 patients with temporal lobe epilepsy. Epilepsia 43: 87–95
9. Helmstaedter C, Van Roost D, Clusmann H, Urbach H, Elger CE, Schramm J (2004) Collateral brain damage, a potential source of cognitive impairment after selective surgery for control of mesial temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 75: 323–326
10. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
11. Lunsford LD, Latchaw RE, Vries JK (1983) Stereotactic implantation of deep brain electrodes using computed tomography. Neurosurgery 13: 280–286
12. Musolino A, Tournoux P, Missir O, Talairach J (1990) Methodology of ''in vivo'' anatomical study and stereo-electroencephalographic exploration in brain surgery for epilepsy. J Neuroradiol 17: 67–102
13. Paglioli E, Palmini A, Paglioli E, da Costa JC, Portuguez M, Martinez JV, Calcagnotto ME, Hoefel JR, Raupp S, Barbosa-Coutinho L (2004) Survival analysis of the surgical outcome of temporal lobe epilepsy due to hippocampal sclerosis. Epilepsia 45: 1383–1391
14. Penry JK, Dean JC (1990) Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. Epilepsia 31 Suppl: 40–43
15. Régis J, Rey M, Bartolomei F, Vladyka V, Liscak R, Schrottner O, Pendl G (2004) Gamma knife surgery in mesial temporal lobe epilepsy: a prospective multicenter study. Epilepsia 45: 504–515
16. Šramka M, Fritz G, Gajdosova D, Nadvornik P (1980) Central stimulation treatment of epilepsy. Acta Neurochir Suppl 30: 183–187
17. Spencer DD, McCarthy G, Luby ML, Spencer SS (1994) MRI stereotactic placement of intracranial electrodes. In: Shorvon SD, Fish DR, Andermann F, Bydder GM, Stefan H (eds) Magnetic resonance scanning and epilepsy. Plenum Press, New York, pp 149–153
18. Tellez-Zenteno JF, Dhar R, Wiebe S (2005) Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 128: 1188–1198
19. Upton AR, Cooper IS, Springman M, Amin I (1985–86) Suppression of seizures and psychosis of limbic system origin by chronic stimulation of anterior nucleus of the thalamus. Int J Neurol 19–20: 223–230
20. Van Roost D, Solymosi L, Schramm J, van Oosterwyck B, Elger CE (1998) Depth electrode implantation in the length axis of the hippocampus for the presurgical evaluation of medial temporal lobe epilepsy: a computed tomography-based stereotactic insertion technique and its accuracy. Neurosurgery 43: 819–827
21. van Veelen CWM, Debets RMC, van Huffelen AC, van Emde Boas W, Binnie CD, Storm van Leeuwen W, Velis DN, van Dieren A (1990) Combined use of subdural and intracerebral electrodes in preoperative evaluation of epilepsy. Neurosurgery 26: 93–101
22. Velasco AL, Velasco M, Velasco F, Menes D, Gordon F, Rocha L, Briones M, Márquez I (2000) Subacute and chronic electrical stimulation of the hippocampus on intractable temporal lobe seizures: preliminary report. Arch Med Res 31: 316–328
23. Velasco F, Velasco M, Jiménez F, Velasco AL, Brito F, Rise M, Carrillo-Ruiz JD (2000) Predictors in the treatment of difficult-to-control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery 47: 295–304
24. Velasco F, Velasco M, Velasco AL, Jiménez F, Márquez I, Rise M (1995) Electrical stimulation of the centromedian thalamic nucleus in control of seizures: long-term studies. Epilepsia 36: 63–71
25. Vonck K, Boon P, Achten E, De Reuck J, Caemaert J (2002) Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol 52: 556–565
26. Wierenga CJ, Wadman WJ (2003) Functional relation between interneuron input and population activity in the rat hippocampal cornu ammonis 1 area. Neuroscience 118: 1129–1139
27. Wieser HG, Ortega M, Friedman A, Yonekawa Y (2003) Long-term seizure outcomes following amygdalohippocampectomy. J Neurosurg 98: 751–763

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Deep brain stimulation for treatment of the epilepsies: the centromedian thalamic target

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Summary

Electrical stimulation (ES) of the thalamic centromedian nucleus (CMN) has been proposed as a minimally invasive alternative for the treatment of difficult-to-control seizures of multifocal origin and seizures that are generalized from the onset. ES intends to interfere with seizure propagation in a non-specific manner through the thalamic system. By adopting a frontal parasagittal approach and based on anterior–posterior (AC–PC) commissure intersection, deep brain stimulation (DBS) electrodes are stereotactically inserted. Electrophysiologic confirmation of electrodes position is accomplished by eliciting cortical recruiting responses and direct current (DC) shifts by low- and high-frequency stimulation through the electrodes. Cycling mode of bipolar stimulation has been used at 60–130 Hz, 0.45 msec, 2.5–3.5 V, 1 min ON in one side 4 min OFF, 1 min ON in the other side and 4 min OFF forward and back for 24 h. ES of CMN significantly decreases generalized seizures of cortical origin and focal motor seizures. Best results are obtained in non-focal generalized tonic clonic seizures and atypical absences of the Lennox-Gastaut syndrome. Experience has indicated that the most effective target for seizure control is the thalamic parvocellular centromedian subnucleus.

Keywords: Neuromodulation; deep brain stimulation; centromedian nucleus; thalamus; seizure control; multifocal epilepsy; Lennox-Gastaut syndrome.

Introduction

The non-specific thalamic system [2, 6, 11] that includes the intralaminar, paralaminar, and midline thalamic nuclei [4] has been implicated in the initiation and propagation of epileptic attacks [7, 14]. The thalamic centromedian nucleus (CMN) is part of the non-specific thalamic system; it represents the largest intralaminar nucleus located immediately above the AC–PC line at the level of the posterior commisure (PC) (Fig. 1) and therefore seems an accessible target from the stereotactic point of view. Electrical stimulation (ES) of CMN intends to interfere with seizure propagation and to become a minimally invasive therapeutic alternative for patients who are not candidates for the standard resective or ablative procedures. This includes patients who have seizures originating from the onset in: a) multiple cortical foci, b) bilateral symmetric foci, c) eloquent areas, or d) seizures without any evidence of focal origin.

Patients and methods

We have used the centromedian thalamic nucleus electrical stimulation (CMES) to treat 22 patients with multiple epileptic foci (bilateral temporal lobe foci: 16, bilateral supplementary motor cortex foci: 6), five with epilepsia partialis continua and 26 patients with Lennox-Gastaut syndrome [10]. All patients had a seizure history for more than 2 years (from 2 to 21 years) and had been treated with multiple anticonvulsive regimes with appropriate drugs at or even above therapeutic ranges; this was confirmed by anticonvulsive drugs blood levels. In the pre-operative period, anticonvulsants were adjusted to optimal therapeutic levels, repeated electroencephalogram (EEG) studies were performed, and magnetic resonance imaging (MRI) studies were done to determine the etiology precisely. During this period, the patients and more often their relatives were trained to keep a chart of the seizures, specifying seizure type and medication intake. The study protocol was approved by the Scientific and Ethical Committees of our Institution and the patients or their caregivers signed written consent forms. We studied 15 patients in a double-blind, randomized protocol in which stimulators were turned OFF for 3 months, beginning 6 months after the commencement of CMES in one-half of the patients and after 9 months in the other half of the patients [9] as determined by lottery numbers. The surgical procedure was performed under general anesthesia and by means of a frontal parasagittal approach; electrodes were stereotactically guided in order to place the tetrapolar electrode tip in the z coordinate at the plane of the AC–PC line and the y coordinate touching the posterior commissure anterior border. The distance to the middle line i.e. the x coordinate is 8–10 mm at an angle of 45–60° with relation to the AC–PC line. With these coordinates, three of the four electrode contacts are placed in the parvocellular CM sub nucleus, which has been found to be the most effective target for seizure control in our patients (Fig. 1) [9]. In the past, electrophysiological confirmation of electrode position was

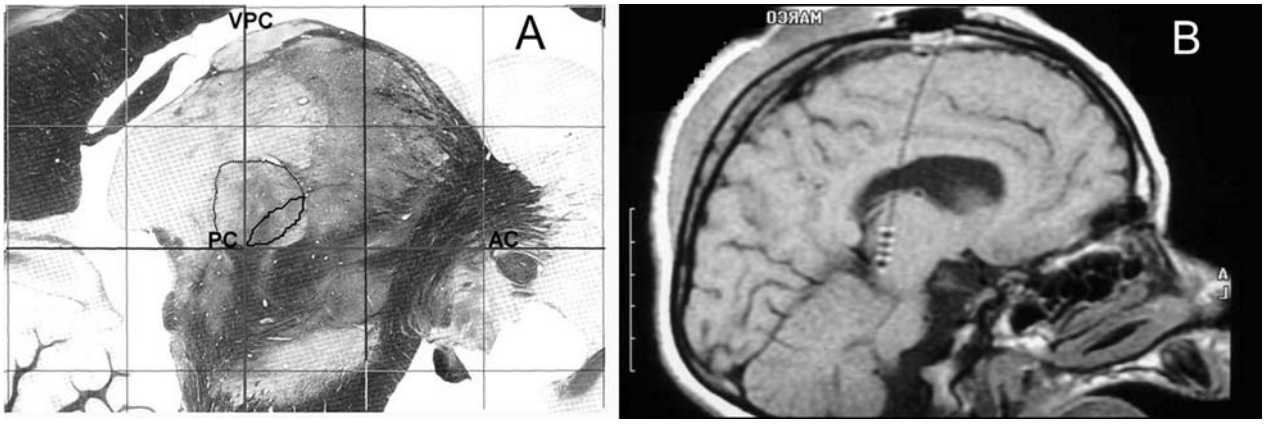

Fig. 1. Stereotaxic placing of CM electrodes. (A) Stereotaxic diagram modified from Schaltenbrand and Bailey showing optimal stereotaxic target. CM localization is accomplished by air ventriculography. This method demonstrates anterior (*AC*) and posterior (*PC*) commissures of the third ventricle. Two lines are drawn, AC–PC line and vertical line perpendicular to PC (*VPC*). Target point for the electrode tip was at a distance of 10 mm from the midline and the intersection of AC–PC line with VPC. CM delineated by continuous line, optimal target delineated by discontinuous line. (B) Sagittal MRI showing right CM electrode implanted in patient KCMM12. Note the coronal burr hole through which the electrode is introduced. The electrode has four contacts, two of which are chosen for CMES

made through externalized electrodes during the post-operative period. With the patient awake and unrestrained, we confirm the electrode position intraoperatively, as recently described [3]. To confirm electrode position, we obtain intra-operative recordings with the patient being operated on under local anesthesia [3] or under general anesthesia that can be reverted at the moment of stimulation and recording. It is important to avoid benzodiazepines or long-lasting barbiturates as anesthetics and to add muscle relaxants as necessary to maintain the patient immobilized for recording.

Low-frequency bipolar stimulation (6–10 Hz) of the electrode's adjacent contacts is used to evoke EEG recruiting responses [13]. These potentials, characteristic of the non-specific thalamic system [2, 6, 12],

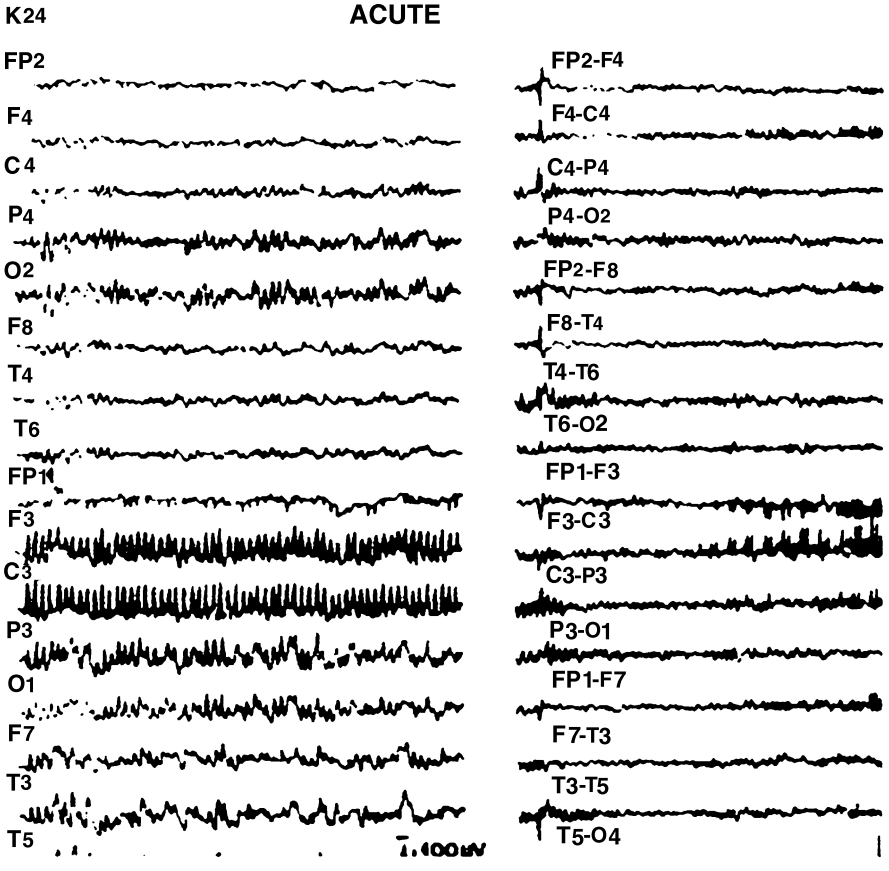

Fig. 2. Recruiting responses obtained by unilateral left side stimulation of CM in acute (trans-operative) and chronic (through totally implanted systems) (modified from Velasco *et al.* [9])

are long-latency (32 msec), monophasic, negative, waxing and waning, bilateral electrocortical responses more prominent in the frontal and parasagittal leads [10, 13]. In CMN, they are elicited only when the parvocellular subnucleus is stimulated. Stimulation of the dorsomedially placed magnocellular subnucleus induces biphasic positive, negative potentials of the augmenting-response type, while posterior basal area stimulation induces primary, short-latency responses recorded in the parietal leads (Fig. 2). With the electrodes temporarily externalized, a post-operative MRI is performed and electrode positions are verified on the anatomic atlas using image fusion techniques.

Chronic stimulation parameters are set at 130 Hz, 0.45 msec at a voltage of approximately 60%, necessary to obtain recruiting responses. A cycling stimulation mode is used, alternating right and left 1-min stimulation periods with 4-min intervals during 24 h [9]. Patients are followed up at the Out-patient Clinic every 3 months during the first year and every 6 months thereafter. The patients' relatives are asked to continue keeping a seizure diary and medication intake chart. We have learned that seizure improvement usually begins during the first month ON stimulation, but becomes maximal at 3–6 months. Improvement remains fairly stable and seldom requires adjustment of stimulation parameters. Should an increase in seizure frequency occur in 2 consecutive months, careful revision of the stimulation system including impedance, plain X-ray films to detect fracture, dislocation, or migration of DBS electrodes, repetition of recruiting response tests, and setting the pulse generator at appropriate parameters while recording the EEG is conducted.

Results

All patients recuperated well from the surgical procedure and post-operative MRI studies did not show brain swelling or hemorrhage. The results in seizure control were variable. Prior to using intra-operative verification of electrode position through recruiting responses and before realizing that the most efficient site to stimulate for seizure control was restricted to the parvocellular sub nucleus [8]. Over the last 5 years, patients in whom stereotactic position of electrode contacts is found at a distance more than 2 mm from the intended target in any direction or in whom we fail to obtain electrophysiological confirmation, are returned to the operating room. The electrodes are then replaced because we are convinced that these predictors are essential for obtaining a good outcome. To date, we have treated patients with seizures originating in multiple clinical and EEG foci, patients with seizures originating from the primary motor cortex, and patients with seizures without evidence of focal origin, such as the Lennox-Gastaut syndrome. The results in these categories of patients are described below.

Multifocal seizures (n = 22)

All cases have been followed for more than 26 months (average, 41.9 months) and the decrease in seizure frequency ranged from 23 to 96%. The residual persisting clinical seizures are mainly partial complex or brief tonic episodes and rarely generalized tonic clonic seizures. EEG studies used to show focal spikes and bilateral synchronous discharges in the majority of patients; they

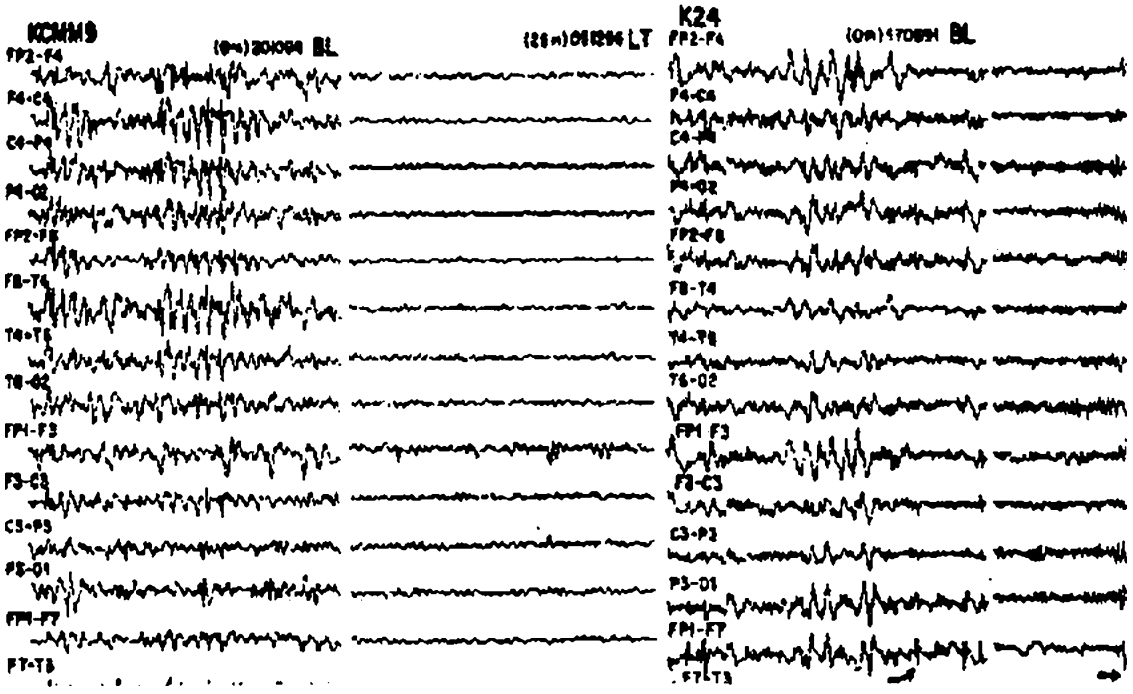

Fig. 3. Effect of chronic CM stimulation on EEG. Right side: pre- and post-operative in Lennox-Gastaut syndrome showing a 2.5-cps spike and wave pattern. Left side: pre- and post-operative recordings in a case with focal spikes and secondary synchronous discharges (from Velasco *et al.* [9])

changed to show mainly focal spikes with no generalized discharges (Fig. 3).

Focal motor seizures (epilepsia partialis continua) (n = 5)

All patients were children between 4 and 7 years of age. The effect on secondary generalization of seizures was immediate; focal motor seizures decreased in all patients, and only one patient has remained in chronic stimulation. Unfortunately, at this age group placement of neurostimulation systems is often complicated with skin erosions that occur repeatedly over electrodes, connectors, cables, and pulse generators. Consequently, taking into account the DBS systems currently available, we consider these patients as poor candidates for neurostimulation with the currently available stimulation systems.

Lennox-Gastaut syndrome (n = 26)

This group of patients was the most severely affected, presenting with a seizure frequency ranging from 53 to thousands of seizures per month; sometimes the seizures were impossible to count, despite the levels of the anticonvulsant drugs. All patients had a deteriorated mental condition; thus, neuropsychologic performance could be evaluated only by means of ability scales. EEG showed the typical 2.0–2.5 spike and wave EEG pattern (Fig. 4). In Table 1, we analyze the clinical status, imaging findings, and the outcome in a group of 13 patients followed-up for an average period of 18 months; these patients showed a seizure reduction ranging from 53 to 100%. For the first 2 years, the patients were maintained on a fixed dose of anticonvulsant drugs that provided the best control in the pre-operative period; thereafter, anticonvulsant medication was adjusted and two of these patients are seizure-

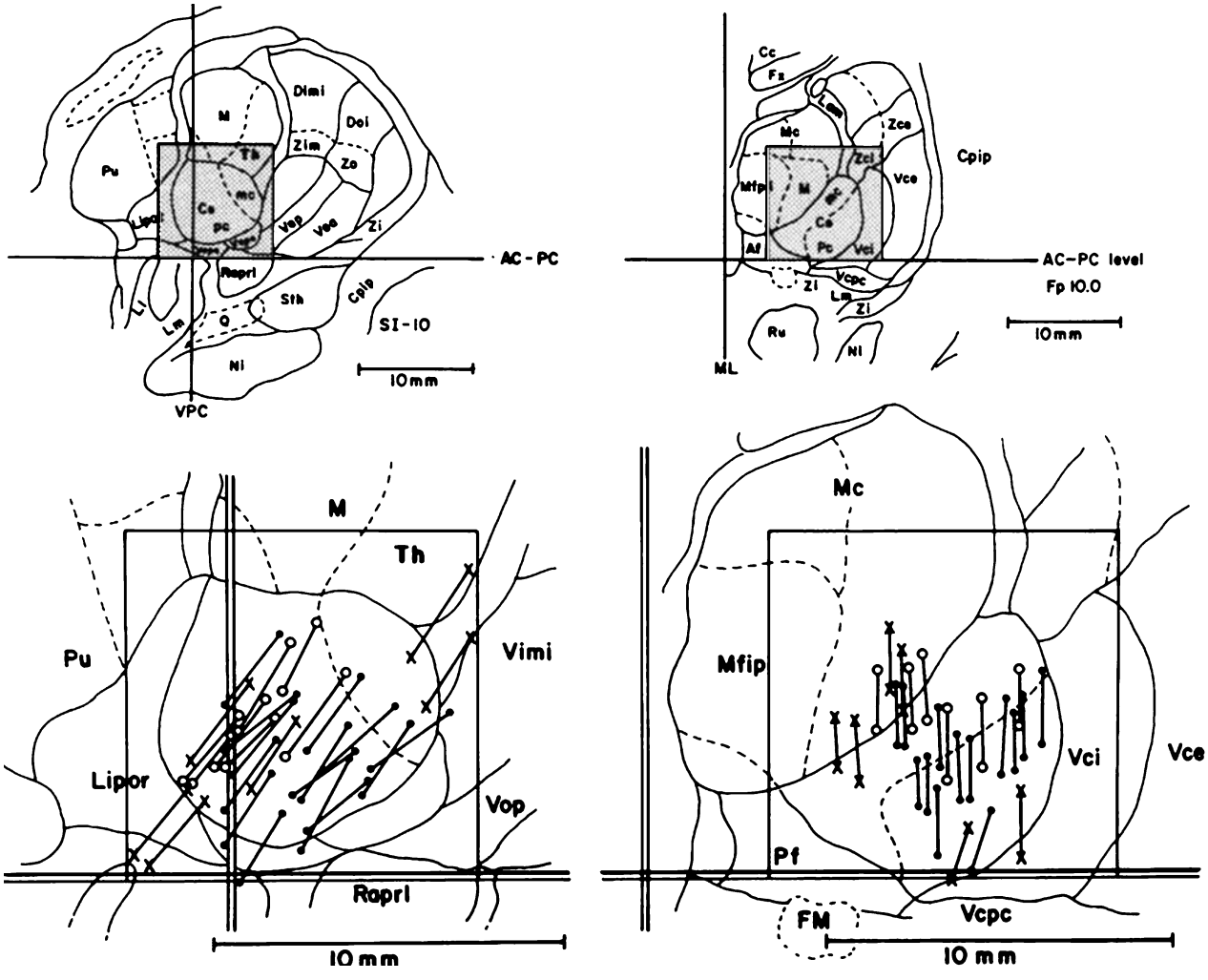

Fig. 4. Placement of contacts used for bipolar CM stimulation on sagittal (*left*) and frontal (*right*) sections of Schaltrenbrand and Wahren atlas (from Velasco *et al.* [9])

Table 1. *Clinical characterization of 10 selected patients with Lennox-Gastaut syndrome*

INIT	Age (years)	MRI	EEG SK-W	Seizure type		sz/month before CMES	Final improvement (%)
				GTC	AA		
GA	8	N	Y	Y	Y	3119	100
MAM	7	RF DYSG	Y	Y	Y	4300/NC st	100
AMP	9	BITEMP	Y	Y	Y	3780/NC st	95
MS	13	L ATR	Y	Y	Y	3030	95
MAPR	11	N	Y	Y	Y	1200	95
JM	21	N	Y	Y	Y	787	91
JS	21	TbSc	Y	Y	Y	2576	89
IM	22	N	Y	Y	Y	18	87
LC	19	N	Y	Y	Y	56	79
EGV	10	N	Y	Y	Y	50/Cst	70
DC	4	TbSc	Y	N	Y	150	58
JR	13	N	Y	Y	Y	35	53
LVAP	13	CB INF	Y	N	Y	50	30

GTC Generalized tonic clonic; *AA* atypical absences; *CXP* complex partial seizures; *AED* antiepileptic drug; *SK-W* slow spike wave complexes; *N* normal; *RF DYSG* right fontal dysgenesia; *BITEMP* bitemporal encephalomalasia; *L ATR* left hemispheric atrophy; *TbSc* tuberous sclerosis, *CB INF* cerebral infarct. *sz/month before CMES* Calculated by averaging the 3 months baseline immediately before starting CMES; *4300/NCs* 4300 plus several non-convulsive status per year; *50/Cst* 50 seizures plus several convulsive statuses per year. Patient improvement at 18 months. Note that no patient who had convulsive or non-convulsive status had another one after CMES (MAM, MAP, and EGV).

free and OFF medication. Concomitant with seizure improvement, patients experienced improvement in neuropsychologic performance, with 73% (19 of 26) re-incorporated into school or work.

Although the best results have been obtained in Lennox-Gastaut syndrome, there were several cases in this group who showed only mild improvement. On the other hand, although the frequency of focal seizures decreased less with CMN stimulation, there were cases presenting with an improvement in seizure frequency of up to 96% in the long term.

To determine the role they play in the degree of improvement the precise electrode placement in different CMN areas and the electrophysiologic confirmation by means of the recruiting response, we analyzed these variables against efficacy in seizure control. Figure 4 shows placement of the electrode contact for chronic stimulation: filled dots represent electrodes through which typical cortical recruiting responses were induced; empty dots represent electrodes that induced augmenting (positive–negative) responses, and X those electrodes that did not induce long-latency, diffuse responses. Typical recruiting responses were induced mainly by contacts placed in parvocellular CMN. Table 2 correlates stereotactic placement and electrophysiologic confirmation with the long-term outcome of Lennox-Gastaut patients (presented in Table 1); C indicates correct and I, incorrect placement or electrophysiologic confirmation. We note that imprecise placement or lack of electrophysiologic confirmation correspond in general with poor outcome.

Table 2. *Stereotactic placement, electrophysiologic predictors, and seizure relief obtained after 18 months of CMES are shown*

Patient initials	Stereotactic placement		Electrophysiologic		Final improvement (%)
	RCM	LCM	RCM	LCM	
GA	I	C	I	C	100
MAM	C	C	C	C	100
AMP	C	I	C	C	95
MS	C	C	C	C	95
MAP	C	C	C	C	95
JM	C	C	C	C	91
JS	C	C	C	C	89
EM	C	C	C	C	87
LC	C	C	I	I	79
EGV	C	C	C	I	70
DC	C	I	C	C	58
JR	C	I	I	I	53
LVA	I	C	I	I	30

C Correct and *I* incorrect placement for stereotaxic placement and localization of neurophysiologic responses (see text for details).

Conclusions

Electrical stimulation of the thalamic CMN is efficient in controlling various types of seizures. Best results have been seen in Lennox-Gastaut syndrome, in which improvement is often spectacular. In these cases, improvement compares favorably with that in corpus callosotomy [5] and vagus nerve stimulation [1]. Focal seizures improve in the long term, but secondary generalization improves within days to months from the commencement of stimulation. In focal seizures, therefore,

CMN stimulation appears to interfere mainly with seizure propagation. Correct stereotactic placement and electrophysiologic confirmation are essential for obtaining a satisfactory outcome.

References

1. Frost M, Gates J, Helmers SL, Wheless JW, Levisohn P, Tardo C, Conry JA (2001) Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. Epilepsia 42: 1148–1152
2. Jasper HH (1949) Diffuse projection systems. The integrative action of the thalamic reticular system. Electroencephalogr Clin Neurophysiol 1: 405–420
3. Litt B, Cranston S (2004) EEG and true anterior thalamic nucleus. In: Lúders HO (ed) Deep brain stimulation for epilepsy. Taylor and Francis, London, pp 171–185
4. Nauta WJH, Witlock DG (1964) Anatomical analysis of the non-specific thalamic projection system. In: Delefresnaye JF (ed) Brain mechanisms and consciousness. Charles C Thomas, Springfield IL, USA, pp 81–115
5. Rossi GF, Colicchio G, Marchese E, Pompucci A (1996) Callosotomy for severe epilepsies with generalized seizures: outcome and prognostic factors. Acta Neurochir (Wien) 138: 221–227
6. Skinner JE, Lindsley DB (1973) The non-specific mediothalamic-frontocortical system: its influence in electrocortical activity and behavior. In: Pribam KH, Luria AR (eds) Psychophysiology of frontal lobes. Academic Press, New York, pp 185–236
7. Velasco F, Velasco M, Márquez I, Velasco G (1993) Role of centromedian thalamic nucleus in the genesis, propagation and arrest of epileptic activity: an electrophysiological study in man. Acta Neurochir Suppl 58: 201–205
8. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28: 421–430
9. Velasco F, Velasco M, Jiménez F, Velasco AL, Brito F, Rise M, Carrillo-Ruiz JD (2000) Predictors in the treatment of difficult to control seizures by electrical stimulation of the centromedian thalamic nucleus. Neurosurgery 47: 295–305
10. Velasco F, Velasco M, Jiménez F, Velasco AL, Rojas B, Pérez ML (2002) Centromedian nucleus stimulation for epilepsy: clinical, electroencephalographic and behavioral observations. Thalamus Related Systems 1: 387–398
11. Velasco F, Velasco M, Jiménez F, Velasco AL, Salin-Pascual R (2005) Neurobiological background for performing surgical intervention in the inferior thalamic peduncle treatment of major depression disorders. Neurosurgery 57: 439–446
12. Velasco M, Lindsley DM (1965) Role of orbitofrontal cortex in regulation of thalamo cortical electrical activity. Science 149: 1375–1377
13. Velasco M, Velasco F, Velasco AL, Brito F, Jiménez F, Márquez I, Rojas B (1996) Electrocortical and behavioral responses by acute electrical stimulation of the human centromedian thalamic nucleus. Electroencephal Clin Neurophysiol 102: 461–471

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Anterior thalamic nucleus stimulation for epilepsy

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Summary

One option for treatment of medically refractory debilitating epilepsy is stimulation of the anterior thalamic nucleus, which projects via the cingulate gyrus to limbic structures and neocortex. In this chapter we describe the technique for anterior thalamic deep brain stimulation and report outcomes of early series of patients. The prospective double-blind randomized Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial will evaluate the efficacy of this technique for epilepsy treatment.

Keywords: Neuromodulation; thalamus; anterior thalamic nucleus; stimulation; epilepsy; SANTE trial.

Introduction

Seizures are episodes of disturbed brain function that cause changes in attention and/or behavior due to abnormal electrical excitation in the brain. Seizures as a clinical entity were described in Indian, Chinese and Mesopotamian literature about 3000 years ago. Later, Hippocrates postulated that the convulsions were due to abnormal brain activity. Epilepsy, defined as two or more seizures, afflicts nearly 3% of the population at some point in their lifetime, though only one-tenth of this number has epilepsy that is active. The consequences of uncontrolled epilepsy are vast [23] and range from physical injury such as contusions, fractures, lacerations and burns to psychosocial disorders resulting from depression, social withdrawal, embarrassment, decreased independence and limited employment opportunities. Mortality rates are four to seven times greater than in the general population and sudden death can result directly from seizures, or occur as an indirect consequence of severe depression and suicide [23]. Of the 0.3% of the population that are active epileptics, two-thirds are controlled by medical therapy, and one-third are refractory even after 18 months of aggressive therapy with two standard anti-epileptic agents. A percentage of the medically refractory patients will have seizures arising from a focal area that is not in eloquent cortex and thus be candidates for surgical resection of their seizure focus. The remainder of these active epileptics are possibly candidates for alternative surgical therapy, such as stimulation. This chapter reviews the development of one type of stimulation, that of the anterior nucleus of the thalamus, for the treatment of epilepsy.

Rationale behind treatment

Dr. Irving Cooper was among the prolific leaders in treatment of seizures by stimulation. His early work performing anterior choroidal artery ligation and cryogenic thalamotomy had the rationale of treating seizures by lesioning of high-traffic pathways [21]. Cooper *et al.* also stimulated the cerebellum [6], which earlier work by Cooke and Snider had suggested should inhibit seizures [5].

Subsequent central nervous system targets have included the caudate, posterior hypothalamus, centromedian [9] and anterior thalamic nuclei, subthalamic nucleus [4], ictal cortex, and hippocampus [26]. The trigeminal [7] and vagal nerves have also been targeted with stimulation, with the latter being among the more common modalities for medically refractory seizure therapy, since it has demonstrated efficacy and few side effects [1].

In 1937, James W. Papez decribed a ''Proposed Mechanism of Emotion'' linking the hippocampus via the fornix to the mammillary bodies, anterior nucleus of the thalamus and cingulate cortex [20]. Atrophy, MRI signal change or sclerosis of structures within this Cicuit of Papez have been noted in mesial temporal sclerosis and

other forms of epilepsy [18]. The hippocampus in particular, is noted to be sclerotic in some forms of epilepsy.

Stimulation of deep brain nuclei has a complex mechanism with ranging effect; it is postulated to result in inhibition at a cellular level [16]. Subthalamic nucleus stimulation may mediate its effects via glutamate or dopamine release in the substantia nigra pars reticulata [2, 3, 8, 15, 24]. Whereas low frequency stimulation drives or synchronizes cortical activity, high frequency stimulation blocks epileptiform activity in the cortex. Subthalamic nucleus stimulation can raise or lower the seizure threshold depending on its frequency [14].

Stimulation of targets within the Circuit of Papez is hypothesized to result in direct anterograde cortical stimulation. The anterior thalamic nucleus is an ideal target for stimulation because it is a relatively small target with projections via the cingulate gyrus to limbic structures that ultimately affect wide regions of neocortex.

Rodent studies are consistent with a potential beneficial effect for anterior thalamic nucleus stimulation to treat epilepsy. High frequency (100 Hz) stimulation of the anterior nucleus in rats administered pentylentetrazol raised the clonic seizure threshold relative to naïve rats or those stimulated in adjacent regions of the brain [17]. Low frequency (8 Hz) stimulation, interestingly, was proconvulsant and caused behavioral arrest [17].

Seizures induced by pilocarpine were seen after a prolonged latency in rats undergoing anterior nuclear stimulation and eliminated by bilateral anterior nuclear thalamotomy. Unilateral stimulation or lesioning affected neither seizure propensity nor latency [19].

Surgical technique

Candidates for stimulation of the anterior thalamic nucleus are those with partial onset epilepsy who are refractory despite twelve to eighteen months of therapy with at least two therapeutically dosed anti-epileptic agents. Patients should either have failed or not be candidates for focal cortical resection of the epileptogenic focus and/or vagal nerve stimulation.

Patients are administered general endotracheal anesthesia prior to placement of the Leksell frame under sterile conditions. The frame is positioned with four pins after temporary fixation with ear bars. Its tilt is parallel to the lateral canthal-external auditory meatal line, which is itself approximately parallel to the anterior commisure–posterior commisure (AC–PC) line. After attachment of the magnetic resonance imaging (MRI) localizer, a 1.5 Tesla MRI is obtained with both fast spin echo inversion recovery and standard T2 images.

Targeting is performed via three methods. Indirect localization according to the Schaltenbrand atlas [22] is performed by first identifying the AC–PC line on the sagittal image. Axial images parallel to, and coronal images perpendicular to the AC–PC line are then obtained. The coordinates of AC and PC are obtained to calculate the midcommisural point. The anterior thalamic nucleus is located 5 mm lateral and 12 mm above the midcommisural point according to the Schaltenbrand atlas [22].

Since the anterior nucleus of the thalamus is readily visible in the floor of the lateral ventricle on MRI, direct localization is a second method for target localization. Coordinates are calculated relative to the center of the frame.

The third method of localization enables simulation of the trajectory from entry point to target by Medtronic Stealth navigation (Medtronic Inc., Minneapolis, MN). The MR image is downloaded into the Stealth station computer, The AC, PC and midline points are marked, and the anterior thalamic nucleus target is calculated. Inputting the entry point at or anterior to the coronal suture plots the trajectory, as well as the anterior-posterior and lateral arc coordinates for the Leksell frame.

After Mayfield fixation and sterile preparation of the unshaved head, an incision is made overlying the coronal suture and burrholes are placed. The dura and pia are sharply incised and cauterized, and after final check of the actual trajectory with the Stealth system to confirm avoidance of critical structures, a guiding cannula is inserted into the brain under direct fluoroscopic and Leksell frame guidance. The deep brain stimulation lead is advanced through the cannula to target and the cannula and lead stylet are carefully removed. We have used the Model 3387 Medtronic stimulator leads with electrodes 1.5 mm apart, as the target is relatively larger than other DBS targets. The lead is secured to a burrhole cap and the skin incision is closed. The Leksell frame is removed and the head, neck, and infraclavicular regions are sterilized in preparation for internal pulse generator placement. The scalp incision is then reopened for connection of the lead to an extension wire that is tunneled subcutaneously to an internal pulse generator placed via a separate incision in an infraclavicular pocket.

After reversal and recovery from anesthesia, postoperative MRI images are obtained to confirm appropriate lead placement (Fig. 1), and the patient is discharged to home two days later. Stimulators, which have variable frequency, pulse width and pulse amplitude, are turned

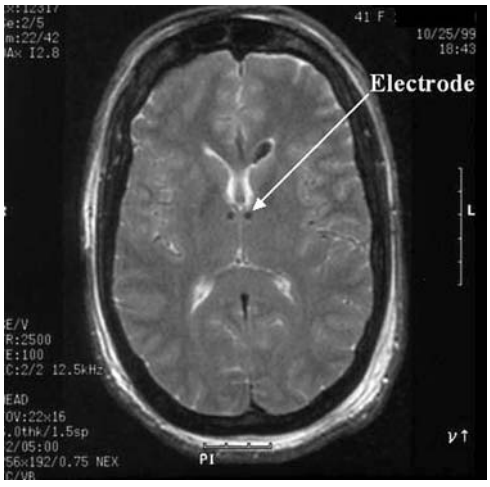

Fig. 1. A T2-weighted axial magnetic resonance image demonstrating lead placement for anterior thalamic nucleus stimulation

on approximately ten to fourteen days postoperatively. For initial stimulation the frequency is set at 130 Hz and the pulse width at 60 μs. There are four contacts on the deep brain stimulation lead; the contact inducing the optimal clinical effect at minimal voltage and with the fewest side effects is identified. Generally multiple outpatient visits are necessary to optimize the stimulation parameters.

Results of anterior thalamic nucleus stimulation in epilepsy patients

The first series of five epilepsy patients undergoing anterior thalamic nucleus deep brain stimulation [11] revealed that seizure frequency was decreased by 54% at a mean of 15 months follow-up, with two patients having greater than a 75% reduction in seizure frequency. Implantation of the stimulators appeared to confer the greater portion of benefit, however, as there was no significant difference between when the stimulators were on or off [11].

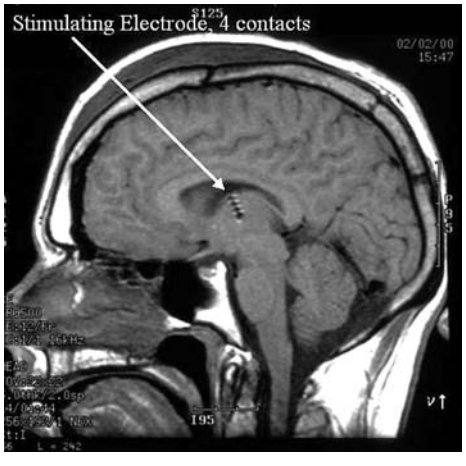

Fig. 2. A sagittal magnetic resonance image demonstrating lead placement for anterior thalamic nucleus stimulation

A second multicenter series of five patients undergoing anterior thalamic nucleus DBS for epilepsy revealed that four demonstrated decreased secondary generalization of seizures and decreased incidence of falling. One patient demonstrated decreased seizure frequency [12].

SANTE trial

Evaluating the efficacy of a clinical treatment modality requires a clinical trial. The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial began in December 2003 to test whether bilateral stimulation of the anterior nucleus of the thalamus can safely and effectively reduce seizure frequency in patients with epilepsy [25]. Ten to twenty sites in the United States and Canada will enroll approximately 125 patients in the prospective, randomized, double-blind study. Trial candidates are adults with partial-onset seizures with/without secondary generalization experiencing an average of six or more seizures per month for whom at least three antiepileptic drugs have proven ineffective. They will continue to receive their epilepsy medications while participating in the trial. Patients may have had vagal nerve stimulators, but their generator must be explanted at the time of DBS generator placement.

All patients will be implanted and monitored for up to two years following DBS implantation, with long-term follow-up until the device is approved or the study is stopped. Patients in the active group, who will receive neurostimulation at a voltage of 5, pulsewidth of 90 μs and frequency of 145 Hz, will be monitored for a reduction in seizure rates compared to the control group, who will not receive neurostimulation (voltage zero, pulsewidth 90 μs, frequency 145 Hz) during the double-blind phase. After the double-blind phase, all patients will receive neurostimulation. A battery of neuropsychological tests will be performed in all patients participating in the trial at various time points throughout the duration of the two years.

Closed-loop systems

Early results of open-loop systems, in which seizure detection triggers stimulation [13], suggest that a closed-loop system, in which the ictal activity is first detected and then squelched by an implanted device, may ulti-

mately be a possibility. Recently, high-frequency stimulation was performed in eight patients with a closed-loop system, in which stimulation was delivered either to the epileptogenic cortex ($n = 4$) or via the anterior thalamic nucleus ($n = 4$) after automated seizure detection. Three of the four patients in which stimulation was to the cortex and two of four with stimulation to the anterior thalamic nucleus responded with decreased seizures [19].

A clinical trial recruiting 80 patients at thirteen medical centers began in February of 2004 to evaluate the efficacy of the implantable Responsive Neurostimulator (RNS) Neuropace (Mountain View, California) for treatment of medically refractory seizures.

Conclusion

Eradification of epilepsy remains an elusive goal. Deep brain stimulation may ultimately contribute to decreasing the morbidity and mortality of this disease. The anterior nucleus of the thalamus appears to be a promising target for such stimulation.

References

1. The Vagus Nerve Stimulation Study Group (1995) A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology 45: 224–230
2. Benazzouz A, Hallett M (2000) Mechanism of action of deep brain stimulation. Neurology 55: S13–S16
3. Breit S, Schulz JB, Benabid AL (2004) Deep brain stimulation. Cell Tissue Res 318: 275–288
4. Chabardes S, Kahane P, Minotti L, Koudsie A, Hirsch E, Benabid AL (2002) Deep brain stimulation in epilepsy with particular reference to the subthalamic nucleus. Epileptic Disord 4 Suppl 3: S83–S93
5. Cooke PM, Snider RS (1955) Some cerebellar influences on electrically-induced cerebral seizures. Epilepsia 4: 19–28
6. Cooper IS, Amin I, Gilman S (1973) The effect of chronic cerebellar stimulation upon epilepsy in man. Trans Am Neurol Assoc 98: 192–196
7. DeGiorgio CM, Shewmon DA, Whitehurst T (2003) Trigeminal nerve stimulation for epilepsy. Neurology 61: 421–422
8. Dinner DS, Neme S, Nair D, *et al* (2002) EEG and evoked potential recording from the subthalamic nucleus for deep brain stimulation of intractable epilepsy. Clin Neurophysiol 113: 1391–1402
9. Fisher RS, Uematsu S, Krauss GL, *et al* (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
10. Hamani C, Ewerton FI, Bonilha SM, *et al* (2004) Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery 54: 191–195
11. Hodaie M, Wennberg RA, Dostrovsky JO, *et al* (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
12. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45: 346–354
13. Kossoff EH, Ritzl EK, Politsky JM, Politsky JM, Murro AM, Smith JR, Duckrow RB, Spencer DD, Bergey GK (2004) Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. Epilepsia 45: 1560–1567
14. Lado FA, Velisek L, Moshe SL (2003) The effect of electrical stimulation of the subthalamic nucleus on seizures is frequency dependent. Epilepsia 44: 157–164
15. Lee KH, Chang SY, Roberts DW, Kim U (2004) Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J Neurosurg 101: 511–517
16. Lee KH, Roberts DW, Kim U (2003) Effect of high-frequency stimulation of the subthalamic nucleus on subthalamic neurons: an intracellular study. Stereotact Funct Neurosurg 80: 32–36
17. Mirski MA, Rossell LA, Terry JB, Fisher RS (1997) Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 28: 89–100
18. Oikawa H, Sasaki M, Tamakawa Y, Kamei A (2001) The circuit of Papez in mesial temporal sclerosis: MRI. Neuroradiology 43: 205–210
19. Osorio I, Frei MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB (2005) Automated seizure abatement in humans using electrical stimulation. Ann Neurol 57: 258–268
20. Papez JW (1937) A proposed mechanism of emotion. Arch Neur and Psych 38: 725–743
21. Rosenow J, Das K, Rovit RL, Couldwell WT (2002) Irving S Cooper and his role in intracranial stimulation for movement disorders and epilepsy. Stereotact Funct Neurosurg 78: 95–112
22. Schaltenbrand G, Warren W (1977) Atlas for stereotaxy of the human brain. Thieme, Stuttgart
23. Sperling MR (2004) The consequences of uncontrolled epilepsy. CNS Spectr 9: 98–101, 106–109
24. Tai CH, Boraud T, Bezard E, Bioulac B, Gross C, Benazzouz A (2003) Electrophysiological and metabolic evidence that high-frequency stimulation of the subthalamic nucleus bridles neuronal activity in the subthalamic nucleus and the substantia nigra reticulata. Faseb J 17: 1820–1830
25. Theodore WH, Fisher RS (2004) Brain stimulation for epilepsy. Lancet Neurol 3: 111–118
26. Vonck K, Boon P, Goossens L, Dedeurwaerdere S, Claeys P, Gossiaux F, Van Hese P, De Smedt T, Raedt R, Achten E, Deblaere K, Thieleman A, Vandemaele P, Thiery E, Vingerhoets G, Miatton M, Caemaert J, Van Roost D, Baert E, Michielsen G, Dewaele F, Van Laere K, Thadani V, Robertson D, Williamson P (2003) Neurostimulation for refractory epilepsy. Acta Neurol Belg 103: 213–217

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Cerebellar and thalamic stimulation treatment for epilepsy

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Summary

The present chapter describes the most important available experimental and clinical evidence on the role of electrical stimulation of the cerebellum or the thalamus in the control of epilepsy. Cerebellum serves as an integrator of sensory information and regulator of motor coordinating and training. The sole output of the cerebellum is inhibitory Purkinje cell projections to deep cerebellar nuclei in the brainstem. Cerebellar stimulation in animal models of epilepsy has given mixed results. Nevertheless, more than 130 epileptic patients have been subjected to cerebellar stimulation and the results from uncontrolled studies have been encouraging. The anterior thalamic nucleus (ATN) is part of the Papez circuit, a group of limbic structures with demonstrated role in epilepsy. The centromedian thalamic nucleus (CMN) is considered part of the thalamic reticular system. Stimulation of either of these nuclei in experimental animals has been associated with considerable antiepileptic effects. On the basis of the research evidence, numerous studies have been done on humans, which gave promising results. Currently, a multicenter trial on stimulation of the ATN, the SANTE trial is in progress in the USA. On the basis of the reported studies, the authors aim to provide insights into how the electrical stimulation of the above structures exerts an antiepileptic effect and also provide suggestions regarding the future progress in this field.

Keywords: Neuromodulation; thalamus; cerebellum; deep brain stimulation; DBS; epilepsy; refractory seizures.

Introduction

The cerebellum [11], because of its GABA-ergic Purkinje cells output and relay input into motor cortex and hippocampus, and the nonspecific thalamus [71, 73, 75] because of its widespread influence on cortical function, both have been investigated as targets for brain stimulation in the treatment of epilepsy in a number of experimental animal studies and human clinical trials.

Cerebellar stimulation for epilepsy

More than one half of human brain neurons form the cerebellum; the structure serves as a unique integrator of inputs from second order sensory nuclei in brainstem (via mossy fiber inputs) and motor training information from olivary nuclei (via climbing fiber inputs) [15]. The cerebellum regulates motor coordination and training and recently has been shown to support learning and memory processing [23]. The sole output of the cerebellum is inhibitory Purkinje cell projections to deep cerebellar nuclei in brainstem. Cerebellar pathways subsequently project to widespread frontal lobe and subcortical structures. The Purkinje cell inhibitory output and widespread cortical projections support the possible role of cerebellar stimulation to reduce epileptogenic activity (Fig. 1).

Cooper *et al.* first developed electrical cerebellar stimulation for the treatment of generalized and partial seizure disorders in humans in 1973 [12]. Human trials were based on animal studies by Cooke and Snider [10] and other investigators [64] showing that anterior cerebellar stimulation shortens trains of hippocampal epileptiform activity induced by electroshock. These studies followed the earlier work by Walker [76] showing that cerebellar stimulation could increase the amplitude and fast activity in the cerebral EEG in animals and the important work by Moruzzi [52] showing that decerebrate posturing in cats was decreased by high-frequency electrical stimulation of the anterior cerebellum and increased by low-frequency stimulation. Studies of the influence of cerebellar electrical stimulation on animal models of epilepsy are conflicting, however, and suggest a variable influence on seizures.

Animal models of epilepsy

Early workers found a positive benefit of cerebellar stimulation in animal models of epilepsies. Anterior cer-

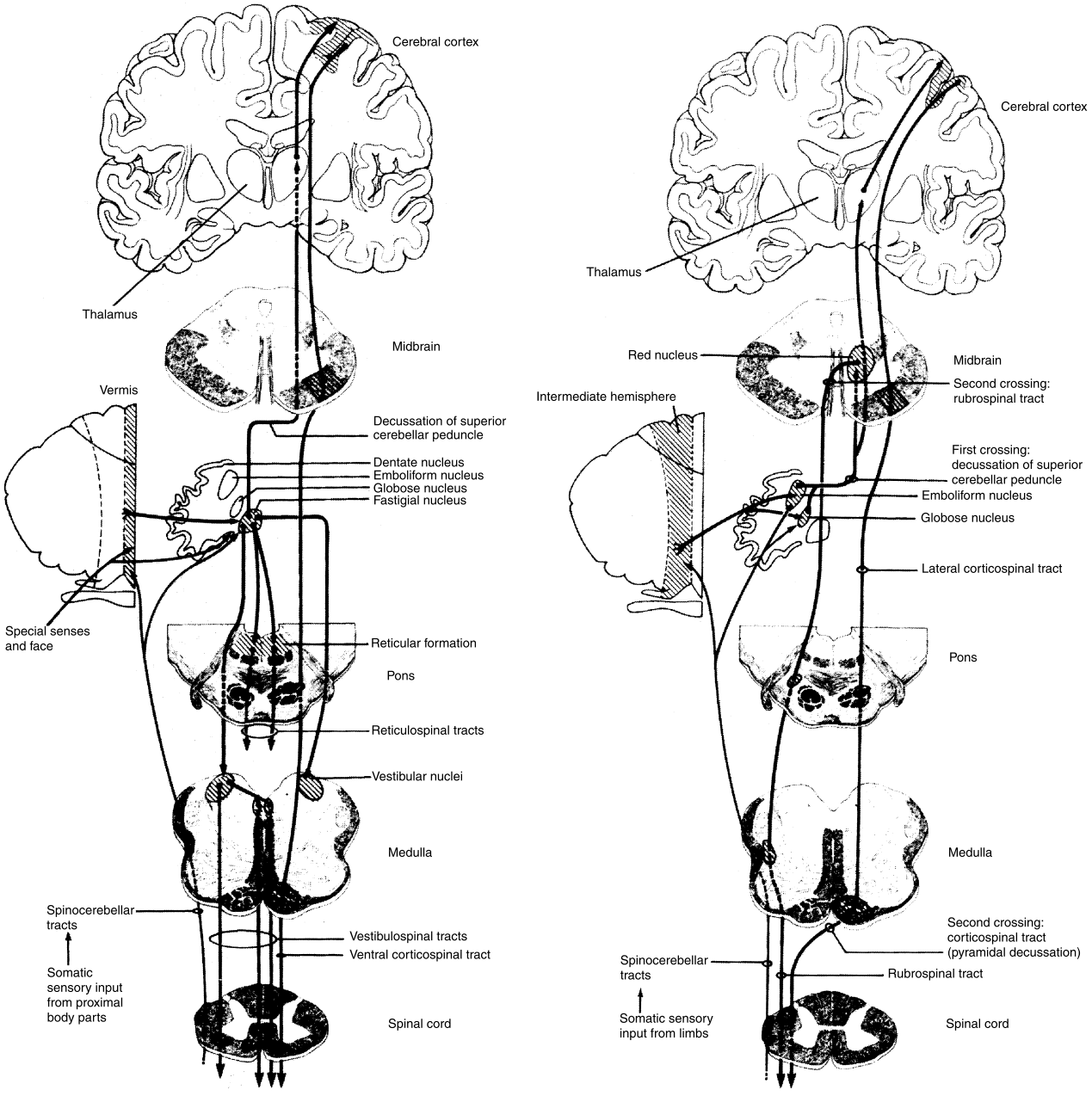

Fig. 1. Ascending and descending motor pathways between cortex and cerebellar vermis (*left panel*) and cerebellar intermediate zone (*right panel*). Permission from Kandel

ebellar stimulation has been reported to arrest seizures induced by focal cerebral electrical stimulation in cats [10], to reduce variably frontal lobe cobalt-induced seizures [24], and to reduce temporarily cobalt-induced spiking in cats [53]. Stimulation of deep nuclei or of the hemispheric cerebellum can inhibit focal penicillin-induced spikes, with pyramus and right paramedian stimulation being most effective [35]. Vermal cortical and fastigial nuclear stimulation at high frequencies (100 Hz) was effective in reducing the number of epileptiform spikes in the feline generalized penicillin model. Outcome of dentate nucleus stimulation was more variable [31]. Cerebellar hemisphere stimulation in rabbits blocked or reduced pentylenetetrazol-induced ictal activity, but only within a very narrow rage of stimulation parameters; biphasic stimulation at 10 Hz, 1.3- to 1.5-ms pulse duration, and 4.0 V amplitudes were most effective. Other indirect evidence suggests that the cerebellum may modulate the genesis of partial seizures. Penicillin-induced hippocampal afterdischarges were as-

sociated with the increase of Purkinje cell activity that lasted many seconds after the afterdischarges [50]. Ablation of the vermis and of the intermediate zones increased spike frequency in cats with the penicillin-induced focal epilepsy of the sensorimotor cortex [35]. The seizure-suppressing effect of cerebellar stimulation on amygdaloid afterdischarges was blocked by bilateral fastigial nuclear lesions [50]. Godlevskii *et al.* [28] recently showed that paleocerebellar (uvula and nodulus) stimulation at low frequencies (10–12 Hz) produced increased cortical spiking in penicillin-treated rats; high frequency stimulation (100–300 Hz) interfered with spiking. Intrinsic burst rhythms in cerebellum originate in olivary nuclei, internuclei (unipolar brush cells and Golgi cells) and Purkinje cells [63]. It is unclear whether low and high frequency stimulation may have differential effects on parallel fibers in the molecular layer or Purkinje cell and granular layers that contain interneurons.

Several studies in animal models of the epilepsies have shown no benefit from cerebellar stimulation. In other studies, only the motor manifestations of seizures were inhibited. In a series of experiments by Meyers *et al.* [45], acute and chronic anterior cerebellar stimulation did not influence electrographic or clinical manifestations of any of four different seizure models in cats: enflurane, pentylenetrazol, penicillin, and chloralose. Prolonged high-frequency simulation of the vermis with increasing voltages reduced spike bursts [67]. This was also associated with behavioral and electrographic arousal. Cerebellum removal, cerebellar hemisphere stimulation, or low-frequency stimulation of the culmen were ineffective. Cerebellar stimulation to block electrically induced seizure activity was ineffective [65]. Removal of the cerebellum can decrease tonic hindlimb extension induced by pentylentetrazol, although this could reflect an action on limb tone [56]. Ramier *et al.* [57] found stimulation to have variable influences on focal cobalt-induced seizure frequency; seizures were often prolonged, and spiking increased.

Effects of stimulation in monkeys are also mixed. Stimulation of fastigial and dentate nuclei in monkeys did not alter discharges from cobalt-induced foci [30]. Superficial cerebellar stimulation did not alter focal seizures in monkeys [33]. Fastigiobulbar stimulation in hippocampal cobalt-induced epilepsy resulted in desynchronization and interruption of spiking; however, stimulation only affected the clonic phase of seizures, and dentatothalamic stimulation was excitatory [3]. Lockard *et al.* [44] used stimulation parameters similar to those for human trial (10-Hz, 1-ms pulses, 10 min on, 10 min off, and 2-mA current) in an alumina-gel monkey model and found an inverse relationship between clinical seizures and EEG interictal cerebellar stimulation. Seizures increased three times the baseline rates in monkeys, but 9 of 12 monkeys had granulation tissue abscesses at stimulation sites. Rubio *et al.* [62] performed superior left cerebellar stimulation in kindled rats. Stimulation initially facilitated the development of kindling, but later prevented secondary generalized seizures. Ipsilateral, left amgydalar afterdischarge thresholds during electrical stimulation decreased between 1 and 8 trials and then increased between 11 and 18 trials: after 18 trials, control animals had the longest duration afterdischarge train. Stimulation caused ''light hypertonicity'' of the arms, head tremor and ataxic gait. They concluded that electrode injury caused reductions in afterdischarge duration and that stimulation initially interfered with dentate and interpositus nucleus efferents.

In 1980, Laxer *et al.* [43] summarized the available animal findings; electrical stimulation of the vermis or of the intermediate cortex has resulted in improvement of generalized seizure activity and of focal limbic seizures in some animal models. Stimulation of the cerebellar hemisphere has produced only a minimal effect on focal seizure of the limbic system. Direct stimulation of the fastigial nucleus is more effective for limbic seizures, but for generalized seizures, stimulation of the medial cerebellar nuclei proves more effective. Cerebellectomy decreases motor manifestations of seizures. The benefits of cerebellar stimulation are not clear or uniform among various animal models and experimental paradigms. A clear understanding of the underlying physiology of cerebellar stimulation has been lacking. A further complication in the studies has been the considerable intrinsic variability of epileptiform activity in the animal models of the epilepsies; changes cannot easily be ascribed to the effects of stimulation [25].

Human studies

The physiological effects of stimulation of the intermediate zones and vermis of the spinocerebellum and the mesial portion of the lateral hemispheres in man are poorly understood. The spinocerebellum appears to regulate body tone and indirectly regulates motor output via information from cortical and peripheral sensorimotor afferents. Efferent connections from the intermediate zone to the red nuclei magnocellular areas and from the vermis to the reticular formation may modulate cerebral excitation. Stimulation of the overlying cerebel-

lar cortex, for example, has facilitated fastigial nucleus evoked excitatory postsynaptic potentials (EPSPs) in the medullary reticular formation [36] and may block cortical somatosensory evoked potential (SEP) responses [11, 37]. An increase in Purkinje cell inhibitory output, however, does not appear to explain stimulation effects on epilepsy; single-unit recordings demonstrate a decrease in the firing rate of Purkinje cells both near and distant from stimulating electrodes [24]. Repetitive stimulation completely suppresses spontaneous Purkinje cell activity during the period of stimulation [53]. Surface folial stimulation inhibits Purkinje cell activity for 80–500 ms following single-pulse shocks [35].

After several years of experience with animal work and uncontrolled clinical trials, Cooper recommended a protocol for chronically stimulating the surface of the intermediate zone and vermis of the anterior cerebellum by fully implanted electrodes. His protocol used four or eight electrodes, stimulation settings of 10 Hz, a several-minute on and off cycle, and current intensity just below meningeal irritation, approximately 2.5 mA [11]. He later recommended adjusting the minimal charge densities to alter spinal cord reflexes and cortical SEPs. Cooper recommended broad selection criteria and included patients with multifocal epileptiform discharges on the EEG, IQ above 80, absence of a mass lesion, and either generalized or partial seizures. Many of the series of cerebellar stimulation for epilepsy are difficult to interpret because of variations in patient selection, treatment protocols and the unsystematic, collection of outcome data. Cooper reported a 50% or greater reduction of seizures in 18 out of 34 patients (53%) treated with chronic anterior cerebellar stimulation, including dramatic seizure reduction in some patients. Overall, in the published literature, a total of 132 patients are reported with cerebellar stimulation for treatment of epilepsy: 92 (70%) had reductions in seizures. In many of these series, there was little description of seizure types, basic clinical information, and follow-up data. Some patients had only temporary stimulation; some had stimulators no longer delivering current (Table 1).

The largest nonrandomized stimulation treatment series are those of Davis and Emmons [17]. In 1992, Davis and colleagues reported on implanting cerebellar stimulators in 338 patients, delivering charge densities of 0.9–2.5 $\mu C/Cm^2$/phase at 10–180 pulses per second to bilateral electrode pads on the superiomedial cerebellar cortex. Although the indication was spasticity in 90%, 33 patients also had epilepsy, and 6 of these patients had only epilepsy (19–21). Overall 27 patients (84%) demonstrated a seizure reduction. Patients continued to use chronic cerebellar stimulation for an average of 13.9 years, with a range of 9–17 years. An argument has been made by Davis and Emmons [17] and by Bidzinski *et al.* [5] for a ''carry-over'' benefit of stimulation after as little as 10–12 day of temporary stimulation. The mech-

Table 1. *Summary of human cerebellar stimulation studies for treatment of epilepsy. A total of 115 patients received cerebellar stimulation in uncontrolled studies; 17 patients received stimulation in controlled studies*

Year	*Uncontrolled studies*	Number of patients	Seizure outcome			
			Seizure free	Seizures reduced	No change	Seizures increased
1973	Cooper	34		18	16	
1977	Gilman	6		5	1	
1977	Fenton	1		1		
1977	Dow	3		1	2	
1979	Levy	6		3	3	
1981	Bidzinski*	14	5	8	1	
1984	Heath	8	4	4		
1984	Madrazo	3		3		
1984	Amin	2		2		
1987	Klun	6	3	3		
1991	Davis*	32	19	8	4	1
Total	11	115	31	56	27	1
	Controlled studies					
1978	Van Buren	5		1	4	
1984	Wright	9		1	8	
2005	Velasco	3		3		
Total	3	17		5	12	

* Follow-up includes patients with remote (>1 year stimulation).

anisms for such an effect are unknown and variability in seizure patterns may have accounted for some effects in uncontrolled series. Two double-blind, controlled studies emulated Cooper's recommended protocol of anterior cerebellar stimulation. Neither reported significant seizure reduction during chronic stimulation. Wright *et al.* [77] treated 12 patients who had partial and generalized seizure in a cross-over study. All patients had generalized epileptiform discharges, and some patients had focal discharges. Nine patients had complete data collected, and only one had reduced seizures during the treatment period. Surprisingly, 11 of the patients felt as if their epilepsy had improved during the trial; however, they described benefits from both stimulation and placebo phases of treatment [77]. Van Buren *et al.* [68] performed an influential pilot study in which he compared baseline prestimulation seizure frequency and seizure frequencies during on and off stimulation periods in 5 patients. Seizure frequencies were unchanged during the stimulation on treatment and pretreatment baseline periods. This study was criticized because patients' seizures significantly increased during stimulation off periods compared to pretreatment baseline and stimulation on treatment phases. It is unclear from the data whether this was due to a "rebound effect" or to other uncontrolled experimental effects. There also were some possible calculation errors in the statistical analysis.

Velasco *et al.* [69] noted that implantable programmable pulse generators were not available in previous cerebellar trials and replicated Van Buren's randomized pilot study. Five patients had stimulation electrodes placed over superomedial cerebellum with programmable stimulators. In an initial blinded study period, 3 patients were randomized to receive cerebellar stimulation; 2 patients received sham stimulation. The patients averaged between 8 and 22 motor seizures per month at baseline. These were predominantly tonic clonic or tonic seizures; 2 patients also had drop attacks and one had myoclonic and atypical absence seizures. Cerebellar stimulation was adjusted to obtain charge density of 2 microcoulomb/cm^2/phase at a pulse frequency of 10 per second, on 5 min off for 4 min with one minute train duration alternating between left and right cerebellar electrodes. Patients subsequently had open stimulation. During the 3 month treatment period, seizures frequencies were reduced by 72% for the three patients with actual (non-sham) stimulation (baseline: mean 6.2 seizure per month versus treatment: 1.7 seizures/month). The two patients with sham stimulation did not improve: (baseline: mean 4.6 seizures per month versus sham-treatment: mean 3.7 seizures per month). Tonic clonic seizures were markedly reduced during cerebellar stimulation ($p = 0.023$), however, the ANOVA analysis was unlikely to be valid for the small pilot group. During open stimulation, patients had additional reductions in seizures over 6–9 months of treatment. Electrodes became displaced in 3 of the 5 patients and were moved back over the superior cerebellum in a second surgery.

Chronic cerebellar stimulation appears to be generally safe and well tolerated in these previous trials, although it has been shown that morphological changes may occur adjacent to the stimulation electrodes. Riklan *et al.* [58] performed a battery of psychological tests in 13 patients and detected no cognitive changes during chronic stimulation. Davis reports that none of his 62 patients who had stimulation treatment for spasticity alone developed seizures during stimulation. In a literature review of 676 patients treated with cerebellar stimulation (90% for spasticity), Davis noted one reported postoperative death. Morphological changes due to stimulation were detected in three patients at autopsy [60]. Changes included loss of Purkinje's cells and climbing fibers within 2 mm from stimulating electrodes. It appears that an important factor in both safety and possible efficacy is the maintenance of stimulation charge densities in the range of 1–5 $\mu C/cm^2$/phase [8, 18, 19].

An important role for cerebellum in learning and working memory has been shown recently. D'Angelo *et al.* [15], for example, demonstrated with fMRI that the cerebellum is activated by tasks requiring verbal working memory and that transcranial magnetic stimulation of cerbellum transiently interferes with performance in a verbal discrimination task. It is unclear whether transcranial magnetic stimulation interferes with larger regions of cerebellum than electrical stimulation of the antero-superior cerebellum. Riklan *et al.* previously showed antero-superior cerebellar stimulation improved, rather than decreased, motor performance in neuropsychological tests [59].

Results from some animal studies and from uncontrolled human trials of chronic cerebellar stimulation treatment for epilepsy are encouraging; however, these results have not been confirmed in controlled studies. Nevertheless, only 17 patients have been tested in controlled studies of cerebellar stimulation for epilepsy. A variety of clinical issues remain unsettled, including which seizure types might be best treated, which stimulation parameters are optimal, and what the physiological rationales for this treatment are. It has not been established that superior cerebellar stimulation facilitates

rather than blocks Purkinje cell output to dentate nuclei and other cerebellar nuclei. Moreover, it is unclear how activation of deep cerebellar nuclei might mediate epilepsy or whether superficial cerebellar stimulation might alter intrinsic rhythms originating in olivary nuclei, internuclei (unipolar brush cells and Golgi cells) and Purkinje cells [63].

Thalamic stimulation for epilepsy

The widespread inputs from thalamus to cortex have provided a rationale for thalamic stimulation therapy for epilepsy. Thalamocortical projections arise from specific thalamic nuclei such as ventral posterolateral, ventral posteromedial and lateral geniculate nuclei, and from non-specific nuclei such as reticular, anterior, and intralaminar nuclei. Projections from specific thalami nuclei are highly organized topographically and project to middle cortical layers, while nonspecific thalamic connections are diffusely organized and project widely upon superficial cortical layers [40]. The thalamus is the origin of both normal and pathologic rhythmic oscillations which can be recorded on the electroencephalogram (EEG), such as normal sleep spindles and generalized spike and wave discharges [38]. Stimulation of non-specific thalamic nuclei can block epileptiform activity in experimentally induced convulsions [42], though generalized ictal activity can also be triggered [61], depending on stimulation frequencies and current. The thalamus also synchronizes seizure activity which begins in limbic [4] and subcortical areas [47] and may cause focal seizure activity to become generalized. During spike-wave seizures, synchronized activity of gamma-aminobutyric acid (GABAergic) neurons in the reticular nucleus of the thalamus causes inhibitory postsynaptic potentials (IPSPs) in thalamocortical neurons, which correspond to the slow wave component on the EEG [7]. These influences support a rationale for stimulating the thalamus to treat intractable epilepsy.

Centromedian nucleus stimulation

The centromedian (CM) nucleus is an intralaminar nucleus and is considered part of the thalamic reticular system. While the majority of the intralaminar neurons project to the basal ganglia, some project directly to the cerebral cortex [39]. In 1941, Dempsey and Morison found that stimulation of the thalamus resulted in diffuse electroencephalographic changes [22]. In particular, low frequency stimulation (8–12 Hz) of the intralaminar nuclei in cats generated a long-latency, surface negative potential that waxed and waned in amplitude over wide cortical areas, termed the recruiting response. In rabbits, different frequencies of stimulation elicited different EEG responses [51]: low frequency (3 Hz) stimulation of the medial thalamus produced cortical EEG synchronization in the form of the recruiting response, but stimulation at a frequency of 200 Hz resulted in EEG desynchronization. Moreover, Jasper and Droogleever-Fortuyn demonstrated that bilateral cortical spike-and-slow-wave complexes on the EEG appeared to result from stimulation of the intralaminar thalamic nucleus in cats at rates close to 3 Hz [38]. These complexes largely resembled the pattern seen in human absence epilepsy. This phenomenon seemed to occur at a critical level of drowsiness preceding full arousal, and stimulation of the reticular activating system blocked such spike-and-wave discharges [55]. In addition, inactivation of the feline midline thalamus by potassium chloride injections appeared to suppress penicillin-induced generalized spike-and-wave discharges [2], and electrical stimulation of the medial thalamus blocked epileptiform activity in experimentally induced convulsions [42].

In addition to the preclinical animal studies mentioned above, the large size of the CM nucleus and its location on either side of the third ventricle prompted Velasco and his colleagues in Mexico city to try CM stimulation for treatment of intractable epilepsy in 1984 [74]. These authors initiated a pilot trial of bilateral CM stimulation in five patients with primary generalized or multifocal intractable epilepsy [71]. They delivered electrical stimulation for 1 min every 5 min, for two hours per day via electrodes externalized to the chest, and followed the patients for 3 months. The stimulation appeared to result in 80–100% reduction in generalized seizures, and 60–100% reduction in other seizure types.

The same authors conducted another uncontrolled trial of bilateral CM thalamic stimulation in 23 patients with multiple intractable seizure types [72]. They used a stimulation frequency of 60 Hz, pulse width of 1 msec and a voltage of 8–15 V. They delivered electrical stimulation for two hours per day for three months. One patient became seizure free, and approximately 50% of the patients experienced 50% reduction in seizure frequency. The most substantial decrease in seizure frequency was noted in patients with generalized tonic-clonic and partial motor seizures. The same group published their accumulated experience of CM stimulation in 49 patients [70]. These patients had seizures with multifocal onset in the frontal and temporal lobes, as well as Lennox-

Gastaut syndrome. Stimulation was delivered for 1 min every 5 min at a frequency of 60–130 Hz, voltage of 2.5–5.0 V, and pulse width of 0.21–0.45 msec. Patients with generalized tonic-clonic, atonic, and atypical absence seizures appeared to benefit most from the stimulation, as opposed to those with complex partial seizures or focal temporal spikes. Of note, the electrodes were externalized, and the authors were able to record from the CM nucleus, which appeared to play an important role in seizure propagation.

The promising results of these uncontrolled trials prompted a placebo-controlled trial of bilateral CM stimulation in patients with intractable epilepsy at Johns Hopkins University [26]. Seven patients were randomized in a double blind cross-over design to three-month blocks of either stimulation or no stimulation, separated by a three-month block of washout. Pulse width was 90 μsec and stimulation was delivered at 65 Hz for one min every five min. Voltage was set at half the sensory threshold (2–5 V). A 30% reduction of seizure frequency occurred when the stimulator was on. However, due to the small sample size, this was not statistically significant. The authors argued that carry-over effect from the stimulation-on segment to the stimulation-off segment might have played a role. In addition, the data of one patient was excluded from the analysis because considerable benefit from the first three-month stimulation segment precluded crossing over to the other treatment arm.

More recently, stimulation of the centromedian nucleus in 11 patients at frequencies ranging between 20 and 130 Hz appeared to result in desynchronization of the EEG and suppress focal motor seizures [9]. In these patients, depth electrode recordings again confirmed the role of the centromedian nucleus in spread of epileptic activity. A large controlled trial to assess the efficacy of CM thalamic stimulation against intractable epilepsy may still be needed in view of the promising results of the uncontrolled trials. However, the modest improvement of patients with CM stimulation in the small controlled trial by Fisher *et al.* [26] prompted search for new stimulation targets.

Anterior nucleus stimulation

The anterior thalamic nucleus (ATN) is part of the Papez circuit, a group of limbic structures with demonstrated roles in memory and cognition as well as epilepsy. The ATN receives projections from the mammillary bodies through the mammillothalamic tract, and projects to the cingulate gyrus, as well as the amygdala, hippocampus, orbito-frontal cortex, and caudate nuclei. Its connectivity with the caudate creates a strio-limbic interface necessary for both motor and mental behavior [13]. Lesions of the anterior thalamic nucleus are associated with symptoms that resemble those of frontal lobe dysfunction. These include severe perseverative behavior, apathy, anterograde memory deficits, and executive function loss [27]. The rationale of anterior thalamic stimulation for treatment of epilepsy emanates, in part, from its connectivity with cortical and limbic structures.

Numerous experiments have demonstrated the role of the ATN in propagation of generalized seizures. Mirski and Ferrendelli originally demonstrated that a threshold convulsant stimulus resulted in selective metabolic activation of the mammillary bodies, the mammillothalamic tracts, and the anterior thalamic nuclei in guinea pigs [46]. Subsequently, they found that lesioning the mammillothalamic tract in these animals inhibited the occurrence of pentelenetetrazole (PTZ) induced seizures [46], demonstrating the essential role of these structures in mediating the convulsive action of PTZ. Moreover, high frequency (100 Hz) stimulation of the mammillothalamic tract [48] or ATN in rats resulted in increasing the threshold of PTZ-induced seizures [49]. In contrast, low frequency stimulation (8 Hz) appeared to be proconvulsant. Bilateral stimulation of the ATN prolonged the latency to the occurrence of pilocarpine-induced status epilepticus in rats, and animals with bilateral anterior nucleus resection had no seizures at all [32].

Irving Cooper and his collaborators were the first to stimulate the anterior thalamic nucleus in patients with intractable epilepsy. They reported seizure reduction of more than 60% in five of six patients [14]. They used a stimulation frequency of 100 Hz and a voltage of 5 V. They also reported that the risk of chronic thalamic stimulation was low [13]. Subsequently, Upton *et al.* employed ATN stimulation in six patients, of whom four showed statistically significant improvement. They reported that one of these patients became seizure free for at least two years. Sussman and colleagues used ATN stimulation in five patients with intractable epilepsy and followed them for 1–2 years. They reported improvement in three of them [29, 66]. These authors used parameters similar to those employed by Cooper *et al.* in that they initiated the stimulation with 100 Hz square waves at 4 V, and increased the voltage incrementally to an average of 5–6 V.

Given these results, it was felt that a controlled trial of anterior thalamic stimulation was needed, but many questions about safety and optimal stimulation para-

meters were unanswered. Recently, two open label studies demonstrated the safety and efficacy of ATN stimulation in controlling seizures [34, 41], paving the road for a randomized trial. In one of these trials [34], five patients, aged 15–45 years, with a variety of partial and generalized seizures underwent insertion of bilateral anterior thalamic stimulators. The following stimulation parameters were used: 100 Hz, 10 V, and 90 μsec pulse width. The mere insertion of the stimulator, i.e. prior to stimulation, resulted in >50% reduction in seizure frequency. All seizure types appeared to benefit equally from the insertion. When the stimulation was turned on, no further improvement in seizure frequency was noted. The authors argued that the initial benefit might have been due to injuring the anterior thalamic nucleus by electrode insertion, the so-called micro-thalamotomy effect, or to a placebo effect.

In the other open label trial [41], five patients, aged 24–47 years, with temporal, frontal, or multifocal partial seizure onsets were enrolled. Again, the authors used voltages ranging between 1 and 10 V, a frequency of 100 Hz, and a pulse width of 90 μsec. Whereas only one patient had a statistically significant reduction in seizure frequency, four of the five patients experienced a significant decrease in the frequency of ''serious seizures'', defined by the authors as generalized seizures or complex partial seizures associated with falls. The procedure was reported to be well tolerated by all patients.

Currently, a multicenter randomized controlled trial, called SANTE (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy), is underway [54]. Enrolled patients have medically refractory partial onset epilepsy, with or without secondary generalization. Stimulation is performed at a frequency of 145 Hz with a 90-μsec pulse width. A three-month blinded phase during which patients are randomized to active stimulation with a voltage of 5 V, or sham treatment (0 V) is followed by open-label stimulation. The double blind design of the study allows no preliminary results to be available at this point.

References

1. Anderson P, Eccles JC, Voorhoeve PE (1964) Postsynapatic inhibition of cerebellar Purkinje cells. J Neurophysiol 27: 1138–1153
2. Avoli M, Gloor P (1981) The effects of transient functional depression of the thalamus on spindles and on bilateral synchronous epileptic discharges of feline generalized penicillin epilepsy. Epilepsia 22: 443–452
3. Babb TL, Mitchell AG, Crandal PH (1974) Fastigiobulbar and dentate-thalamic influences on hippocampal cobalt epilepsy in the cat. Electroencephalogr Clin Neurophysiol 36: 141–154
4. Bertram EH, Zhang DX, Mangan P, Fountain N, Rempe D (1998) Functional anatomy of limbic epilepsy: a proposal for central synchronization of a diffusely hyperexcitable network. Epilepsy Res 32: 194–205
5. Bidzinski J, Bacia T, Ostrowski K (1981) Effects of cerebellar cortex electrostimulation on the frequency of seizures in drug-resistant epilepsy. Neurol Neurochir Pol 31: 605–609
6. Bloedel JR, Roberts WJ (1969) Functional relationships among neurons of the cerebellar cortex in the absence of anesthesia. J Neurophysiol 32: 75–84
7. Blumenfeld H (2005) Cellular and network mechanisms of spike-wave seizures. Epilepsia 46 Suppl 9: 21–33
8. Brown W, Babb T, Soper HV, Lieb JP, Ottino CA, Crandall PH (1977) Tissue reactions to long-term electrical stimulation of the cerebellum in monkeys. J Neurosurg 47: 366–379
9. Chkhenkeli SA, Sramka M, Lortkipanidze GS, Rakviashvili TN, Bregvadze E, Magalashvili GE, Gagoshidze T, Chkhenkeli IS (2004) Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clin Neurol Neurosurg 106: 318–329
10. Cooke PM, Snider RS (1955) Some cerebellar influences on electrically induced cerebral seizures. Epilepsia 4: 19–28
11. Cooper IS, Amin I, Upton A, Riklan M, Watkins S, McLellan L (1977) Safety and efficacy of chronic stimulation. Neurosurgery 1: 203–205
12. Cooper IS, Riklan M, Amin I, Cullinan T (1978) A longer term follow up study of cerebellar stimulation for the control of epilepsy. In: Cooper IS (ed) Cerebellar stimulation in man. Raven Press, New York, NY, pp 19–38
13. Cooper IS, Upton AR (1985) Therapeutic implications of modulation of metabolism and functional activity of cerebral cortex by chronic stimulation of cerebellum and thalamus. Biol Psychiatry 20: 811–813
14. Cooper IS, Upton ARM, Garnett S, Amin I, Springman M (1983) Chronic stimulation of anterior nucleus of thalamus for limbic system seizures. Presented at Meeting of American Society for Stereotactic and Functional Neurosurgery, Durham, NC
15. D'Angelo E, Rossi P, Gall D, Prestori F, Nieus T, Maffei A, Sola E (2005) Long-term potentiation of synaptic transmission at the mossy fiber-granule cell relay of cerebellum. Prog Brain Res 148: 69–80
16. Dauth GW (1974) Cerebellar cortical stimulation effect on EEG activity in seizure afterdischarges in anesthetized cats. In: Cooper IS (ed) The cerebellum, epilepsy and behavior. Plenum Press, New York
17. Davis R, Emmons SE (1992) Cerebellar stimulation for seizure control: 17-year study. Sterotact Functional Neurosurg 58: 200–208
18. Davis R, Emmons SE (1988) Safety and efficacy of cerebellar stimulation for seizure control. Boll Lega It Epil 64: 105–115
19. Davis R, Engle H, Kudzma J, Gray E, Ryan T, Dusnak A (1982) Update of chronic cerebellar stimulation for spasticity and epilepsy. Appl Neurophysiol 45: 44–50
20. Davis R, Gray E, Engle H, Dusnak A (1983) Reduction of intractable seizures using cerebellat stimulation. Appl Neurophysiol 46: 57–61
21. Davis R, Gray E, Engle H, Dusnak A (1984) The reduction of seizures in cerebral palsy and epileptic patients using chronic cerebellar stimulation. Acta Neurochir Suppl 33: 161–167
22. Dempsey EW, Morison RS (1941) The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. Am J Physiol 135: 293–300
23. Desmond JE, Chen SH, Shieh PB (2005) Cerebellar transcranial magnetic stimulation impairs verbal working memory. Ann Neurol 58: 553–560
24. Dow RS, Fernadez-Guardiola A, Manni E (1962) The influence of the cerebellum on experimental epilepsy. Electroencephalogr Clin Neurophysical 14: 383–398

25. Ebner TJ, Bantli H, Bloedel JR (1980) Effects of cerebellar stimulation on unitary activity within a chronic epileptic focus in a primate. Elecroencephalogr Clin Neurophysiol 49: 585–599
26. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33: 841–851
27. Ghika-Schmid F, Bogousslavsky J (2000) The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. Ann Neurol 48: 220–227
28. Godlevskii LS, Stepanenko KI, Lobasyuk BA, Sarakhan EV, Bobkova LM (2004) The effects of electrical stimulation of the paleocerebellar cortex on penicillin-induced convulsive activity in rats. Neurosci Behav Physiol 34: 797–802
29. Goldman HW, Sussman NM, Callanan M, Bergen J, Jackel RA, Kaplan L, Cooper IS, Harner RN (1988) Anterior thalamic stimulation for medically intractable epilepsy. Part I: Implantation and stimulation. Epilepsia 29: 677
30. Grimm RJ, Frazee JG, Bell CC, Kawasaki T, Dow RS (1970) Quantitative studies in cobalt model epilepsy: the effect of cerebellar stimulation. Int J Neurol 7: 113–140
31. Hablitz JJ, Wray DV (1977) Modulation of the cerebellar electrical and unit activity by low-frequency stimulation of caudate nucleus in chronic cats. Exp Neurol 55: 289–294
32. Hamani C, Ewerton FI, Bonilha SM, Ballester G, Mello LE, Lozano AM (2004) Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery 54: 191–195, discussion 195–197
33. Hemmy DC, Larson SJ, Sances A Jr (1977) The effect of cerebellar stimulation of focal seizure activity and spasticity in monkeys. J Neurosurg 46: 648–653
34. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
35. Hutton JT, Frost JD, Foster J (1972) The influence of the cerebellum in cat penicillin epilepsy. Epilipsia 13: 401–408
36. Ito M, Udo M, Mano N, Kawai N (1970) Synaptic action of the fastigiobulbar impulses upon neurons in the medulary reticular formation and vesibular nuclei. Exp Brain Res11: 29–47
37. Iwata NK, Hanajima R, Furubayashi T, Terao Y, Uesugi H, Shiio Y, Enomoto H, Mochizuki H, Kanazawa I, Ugawa Y (2004) Facilitatory effect on the motor cortex by electrical stimulation over the cerebellum in humans. Exp Brain Res 159: 418–424
38. Jasper HH, Droogleever-Fortuyn J (1947) Experimental studies on the functional anatomy of petit mal epilepsy. Res Publ Ass Nerv Dis 26: 272–298
39. Jones EG, Leavitt RY (1974) Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. J Comp Neurol 154: 349–377
40. Jones EG (1998) Viewpoint: the core and matrix of thalamic organization. Neuroscience 85: 331–345
41. Kerrigan JF, Litt B, Fisher RS, Cranstoun S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45: 346–354
42. Krauss GL, Fisher RS (1993) Cerebellar and thalamic stimulation for epilepsy. Adv Neurol 63: 231–245
43. Laxer KD, Robertson LT, Julien RM, Dow RS (1980) The relationship between cerebellar function and epileptic discharges. In: Glaser GH, Penry JK, Woodbury D (eds) Anti-epileptic drugs: mechanisms of action. Raven Press, New York, pp 415–427
44. Lockard JS, Ojmann GA, Congdon WC, DuCharme LL (1979) Cerebellar stimulation in alumina-gel monkey model: inverse relationship between clinical seizures and EG interictal burts. Epilepsia 20: 223–234
45. Meyers RR, Burchiel KK, Stockard JJ, Bickford RG (1975) Effects of acute and chronic paleocerebellar stimulation on experimental models of epilepsy in the cat: studies with enflurane, pentylenetetrazol, penicillin and choralose. Epilepsia 16: 257–267
46. Mirski MA, Ferrendelli JA (1984) Interruption of the mammillothalamic tract prevents seizures in guinea pigs. Science 226: 72–74
47. Mirski MA, Ferrendelli JA (1986) Anterior thalamic mediation of generalized pentylenetetrazol seizures. Brain Res 399: 212–223
48. Mirski MA, Fisher RS (1994) Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. Epilepsia 35: 1309–1316
49. Mirski MA, Rossell LA, Terry JB, Fisher RS (1997) Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res 28: 89–100
50. Mitra J, Snider RS (1975) Effects of hippocampal after discharges on purkinje cell activity. Epilepsia 16: 235–243
51. Monnier M, Kalberer M, Krupp P (1960) Functional antagonism between diffuse reticular and intralaminary recruiting projections in the medial thalamus. Exp Neurol 2: 271–289
52. Moruzzi G (1950) Problems in cerebellar physiology. Charles C Thomas, Springfield, IL
53. Mutani R, Bergamini L, Doriguzzi T (1969) Experimental evidence for the existence of an extra-rhinencephalic epileptogenic focus. Part 2. Effects of the paleocerebellar stimulation. Epilepsia 10: 351–362
54. Oommen J, Morrell M, Fisher RS (2005) Experimental electrical stimulation therapy for epilepsy. Curr Treat Options Neurol 7: 261–271
55. Pollen DA, Perot P, Reid KH (1963) Experimental bilateral wave and spike from thalamic stimulation in relation to level of arousal. Electroencephalogr Clin Neurophysiol 15: 1017–1028
56. Raines A, Anderson RJ (1976) Effects of acute cerebellectomy on maximal electroshock seizures and anticonvulsant efficacy of diazepam in the rat. Epilepsia 17: 177–182
57. Ramier GR, Grimm RJ, Dow RS (1976) Effects of cerebellar stimulation cobalt induced epilepsy in the cat. Electroencephalogr Clin Neurophysiol 23: 456–462
58. Riklan M, Cullinan T, Shulman M, Cooper IS (1976) A psychometric study of chroni cerebellar stimulation in man. Biol Psychiatry 11: 543–574
59. Riklan M, Halgin L, Shulman M, Cullinan T, Cooper IS (1978) Behavioral alterations following acute, shorter-term and longer-term cerebellar stimulation in humans. In: Cooper IS (ed) Cerebellar stimulation in man. Raven Press, New York, NY, pp 161–184
60. Robertson LT, Dow RS, Cooper IS, Levy LF (1979) Morphological changes associated with chronic cerebellar stimulation in the human. J Neurosurg 51: 510–520
61. Rokyta R, Mares P (1976) Influence of thalamic stimulation on cortical epileptogenic focus. Experientia 32: 71–72
62. Rubio C, Custodio V, Juarez F, Paz C (2004) Stimulation of the superior cerebellar peduncle during the development of amygdaloid kindling in rats. Brain Res 1010: 151–155
63. Simpson JI, Hulscher HC, Sabel-Goedknegt E, Ruigrok TJ (2005) Between in and out: linking morphology and physiology of cerebellar cortical interneurons. Prog Brain Res 148: 329–340
64. Snider R (1973) Cerebellar modifications in cerebral areas. In: Cooper IS, Riklan M (eds) The cerebellum, epilepsy, and behavior. Plenum, New York
65. Strain GM, Van Meter WG, Brockman WH (1978) Elevation of seizure thresholds: a comparison of cerebellar stimulation, Phenobarbital and diphe nylhdantoin. Epilepsia 19: 493–504

66. Sussman NM, Goldman HW, Jackel RA, Kaplan L, Callanan M, Bergen J, Harner RN (1988) Anterior thalamic stimulation for medically intractable epilepsy. Part II: Preliminary clinical results. Epilepsia 29: 677
67. Testa G, Pellegrini A, Giaretta D (1979) Effects of electrical stimulation and removal of cerebellar structures in an experimental model of generalized epilepsy. Epilepsia 20: 447–454
68. Van Buren JM, Wood JH, Oakley J, Hambrecht F (1978) Preliminary evaluation cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. J Neurosurg 48: 407–416
69. Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, Davis R (2005) Double-blind, randomized controlled pilot study of bilateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 46: 1071–1081
70. Velasco F, Velasco M, Jimenez F, Velasco AL, Marquez I (2001) Stimulation of the central median thalamic nucleus for epilepsy. Stereotact Funct Neurosurg 77: 228–232
71. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28: 421–430
72. Velasco F, Velasco M, Velasco AL, Jimenez F (1993) Effect of chronic electrical stimulation of the centromedian thalamic nuclei on various intractable seizure patterns: I. Clinical seizures and paroxysmal EEG activity. Epilepsia 34: 1052–1064
73. Velasco M, Velasco F, Velasco AL, Lujan M, Vazquez del Mercado J (1989) Epileptiform EEG activities of the centromedian thalamic nuclei in patients with intractable partial motor, complex partial, and generalized seizures. Epilepsia 30: 295–306
74. Velasco M, Velasco F, Velasco AL (2001) Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. J Clin Neurophysiol 18: 495–513
75. Velasco M, Velasco F (1982) State related brainstem regulation or cortical and motor excitability: effects on experimental focal motor seizures. In: Sterman MB (ed) Sleep and epilepsy. Academic Press, Orlando, FL
76. Walker AE (1938) An oscillographic study of the cerebello-cerebral relationships. J Neurophysical 1: 16–23
77. Wright GD, McLellan DL, Brice JG (1985) A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. J Neurol Neurosurg Psychiatry 47: 769–774

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A novel closed-loop stimulation system in the control of focal, medically refractory epilepsy

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Summary

The concept of seizure abortion after prompt detection by employing stimulation is a very appealing one. Several investigators in previous experimental and clinical studies have used stimulation of various anatomical targets with promising results. In this chapter, the authors present their experience with a novel, implantable, local closed-loop responsive neuro-stimulation system (RNS) (Neuropace, Inc., Mountain View, CA, USA). This system consists of a cranially implanted pulse generator, one or two quadripolar subdural strip or depth leads and an external programmer. The system components and technical characteristics are presented. The criteria for selecting candidates for implantation as well as the preliminary results of a clinical trial are also presented. Closed-loop stimulation system appears to be a safe treatment option with promising results for the management of patients with well-localized, focal medically-refractory epilepsy, who are not candidates for surgical resection.

Keywords: Neuromodulation; refractory epilepsy; closed-loop system; stimulation; treatment.

Introduction

It is well known that epilepsy represents the most prevalent serious neurological disorder across all age groups [28]. It has been reported that approximately 1% of the USA population sustains epilepsy [28] and this percentage increases to 5% among children and adolescents in the USA or Western Europe [13]. The incidence of medically intractable epilepsy has been reported to be approximately 6/100,000 people per year, which translates to 17,000 new cases annually only in the USA [14]. Even though surgical treatment is a valuable alternative to medical treatment in very carefully selected cases, unfortunately the majority of patients with intractable epilepsy will not have access to surgical therapy due to high technical complexity and cost of pre-operative evaluation, significant limitation in availability of human and technical resources and finally due to the involvement of eloquent cortex in the epileptogenic zones [28]. It is apparent that the development of a new treatment modality which could overcome the previously mentioned obstacles is essential for the management of patients with medically refractory epilepsy and particularly those, who are not candidates for surgical resection. The recent exponentially increasing clinical applications of neuromodulation in various neurologic disorders have rewarmed the interest of employing electrical stimulation for aborting or blocking promptly detected seizure activity.

This concept is not new; Pelops from Alexandria, approximately 20 centuries ago, was able to abort something that could be a simple partial seizure, by tying a ligature around the affected limb [11, 29]. Later on, Brown-Sequard, Jackson and Gowers independently, suggested that *counter-irritation* could be a mechanism for abating seizure activity [2, 12, 16, 29]. Employment of uncontrolled open-loop, non-contingent stimulation has been attempted in several experimental studies and human trials for the control of epilepsy; stimulation of cerebellar cortex [4, 5], cerebellar dentate nucleus [3, 32], cerebral cortex [18, 20] anterior thalamic nucleus [6, 15, 17], centromedian thalamic nucleus [3, 32, 34–36], head of caudate nucleus [3, 31, 32], hippocampus [31, 32, 37] and subthalamic nucleus [1, 27] has been employed with various clinical results. The only controlled clinical studies involved cerebellar cortex [33] and thalamic centromedian nucleus stimulation [8], and neither showed a significant effect on seizures. However, vagal nerve stimulation, which represents a cyclical type of open-loop stimulation, has been shown

to reduce seizures in a statistically significant fashion [19]. Open-looped studies on the effect of electrical stimulation on induced after discharges (AD) have shown that AD can be aborted [20] and there may be optimal parameters for accomplishing this [18, 21]. External responsive neurostimulation (RNS) studies have shown that closed-loop stimulation can significantly affect duration of spontaneously occurring electrographic seizure activity [24–26, 30].

The concept of closed-loop stimulation had been previously described, but to date, no controlled studies of its efficacy on seizure reduction had been reported [26–28]. The promising results of these initial pilot studies were confirmed by the results of a multi-center prospective clinical study, in which an external RNS was used [24, 25]. This study was conducted under a Food and Drug Administration (FDA) Investigational Device Exemption (IDE G010288) and was also approved by the Institutional Review Board (IRB) of each participating center [24, 25]. The study included 27 patients who underwent grid, strip and/or depth leads implantation for temporary invasive monitoring [24, 25]. A laptop computer was used through wired telemetry for interrogation and programming of the eRNS and responsive stimulation trials were conducted [24, 25]. In this group of patients, the use of the eRNS system had a positive electroencephalogram (EEG) effect on electrographic seizure activity in 41% (11/27) of the involved patients [24, 25]. No serious adverse effects related to the eRNS occurred in this study [24, 25] and the safety of the RNS strip and depth leads was additionally confirmed by animal experimental studies [22, 23].

In this chapter, we describe the selection criteria, the technical characteristics and the preliminary results from the implantation of a novel, local, closed-loop responsive Neurostimulation system (Neuropace Inc., Mountain View, CA, USA).

Selection criteria for implantation

Candidates for RNS implantation should have history of drug resistant, well localized, focal simple partial seizures (motor or sensory) or complex partial seizures with motor manifestations with or without secondarily generalized seizures. In our institution, ictal and interictal surface EEG, video-EEG monitoring, brain MRI, ictal SPECT and SISCOM studies, detailed neuropsychological evaluation including WADA test and when necessary invasive EEG via depth and/or subdural electrodes are employed for localizing the epileptogenic focus. The patients will either not be candidates for resective surgery, due to the eloquent nature of the involved cerebral cortex, unilateral support of their memory from the involved hippocampus, or they do not desire to undergo resective surgery but would undergo surgical implantation of an RNS due to the reversible character of the stimulator implantation. Furthermore, patients who have undergone multiple subpial transections with no satisfactory results could be considered candidates for implantation of RNS.

Candidates are subsequently required to have at least an average of four disabling seizures per month, over a three-month period before final consideration for RNS implantation. Candidates should be between the ages of 18 and 65 years and should be able to complete regular office visits and telephone appointments for the protocol requirements; in case of female patients, they should be using a reliable method of contraception. Patients who have experienced unprovoked status epilepticus in the preceding year or patients with unstable medical conditions as well as active psychosis, severe depression or ideation cannot be candidates for implantation. Additionally, patients who are pregnant or planning on becoming pregnant in the next year or patients who are on a ketogenic diet cannot be considered for implantation. Finally, patients with an active vagal nerve stimulator cannot be candidates for implantation. A detailed written informed consent is obtained from all patients prior to implantation.

RNS system description

The implanted closed-loop RNS system (Neuropace Inc., Mountain View, CA, USA) consists of the following components (Fig. 1).

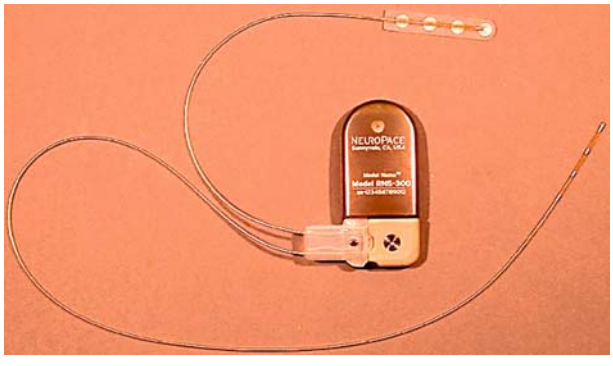

Fig. 1. The implantable Responsive Neuro-Stimulation System (Neuropace, Inc., Mountain View, CA, USA); it is shown in this picture with subdural strip and depth leads

Pulse generator

The pulse generator is a hermetically sealed neurostimulator containing the electronics, battery, telemetry coil, and connector hardware to accommodate one or two leads. The dimensions of the pulse generator are: 41 mm wide, 60 mm long, and 7 mm thick; its weight is 19.5 gm and its volume 10.5 cc^3. The pulse generator continuously analyzes the patient's electrocorticogram (ECoGs) and triggers electrical stimulation, when specific ECoG characteristics, programmed by the clinician as indicative of electrographic seizures or precursor epileptiform activities, are detected. The pulse generator then stores diagnostic information detailing detections and stimulations including multi-channel stored ECoGs. The pulse generator is curved in shape to facilitate cranial implantation and is positioned extradurally in a tailored cranial defect and held in place with a ferrule or holder (Fig. 2).

Depth lead

The depth leads are quadripolar leads designed for stereotactic implantation. Depth leads are available with 3.5 and 10 mm inter-electrode spacings, and in lengths of 30 and 44 cm. Electrodes are composed of 90% platinum and 10% iridium (Fig. 1).

Strip lead

The strip leads are quadripolar leads with 4 mm diameter circular electrodes and inter-electrode spacings of 10 mm. Leads are available in 15 and 25 cm lengths. Electrodes are composed of 90% platinum and 10% iridium (Fig. 1).

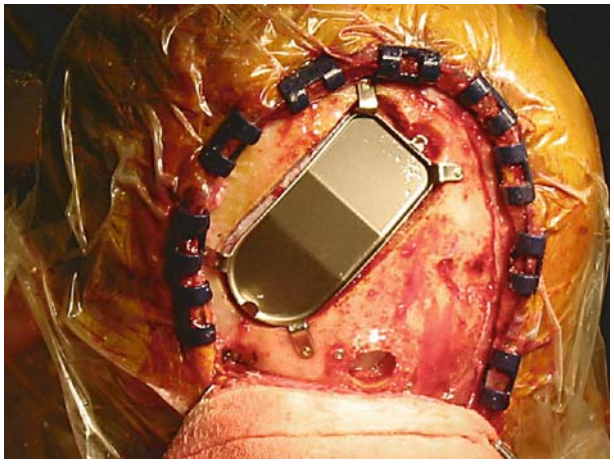

Fig. 2. Intraoperative picture demonstrating the holding ferrule secured in its final position

Programmer

The programmer is a notebook computer with specialized software and a telemetry wand, which communicates with the pulse generator. The programmer can download diagnostic and ECoG data from the pulse generator, can be used to analyze ECoGs and simulate detection setting performance, and can program the pulse generator. The programmer also has an electrophysiology study mode that allows real-time stimulation with simultaneous ECoG viewing in order to test stimulation paradigms.

RNS Technical characteristics

ECoG Storage: The RNS has a 32-minute ECoG memory buffer. The number of ECoGs stored depends on the number of recording channels and the recording length selected. Typically, two recording channels are selected with a 60-sec pre-trigger and 30-sec post-trigger duration, which allows nine ECoGs to be stored. Any additional ECoGs will overwrite the previous recordings, e.g., a 10th ECoG would overwrite the first ECoG of the previous set. ECoG storage can be triggered by any of several electrographic events including seizure onset.

Detection algorithms: The RNS utilizes any of the three seizure detection tools (line length, area, and half wave) operating on 1 or 2 detection channels. The line length tool measures the length of the ECoG signal [7] whereas the area tool measures the integrated area under the ECoG signal. The line length and area tools compare the average contained within a recent window to the average contained within a longer-term trend. When activity within the recent window exceeds the trend activity by a specified percentage, detection occurs. The line length tool is more commonly used to detect activity that does not diverge from the isoelectric baseline for significant time intervals but has significant summed line length [7], whereas the area tool is more commonly used for slower rhythmic electrographic seizure onsets that diverge from the baseline for longer periods of time and hence have large integrated areas. Finally, the half way tool measures the duration and amplitude of half waves, which are defined as ECoG segments between relative maxima and minima. When a specified number of half waves of the correct duration

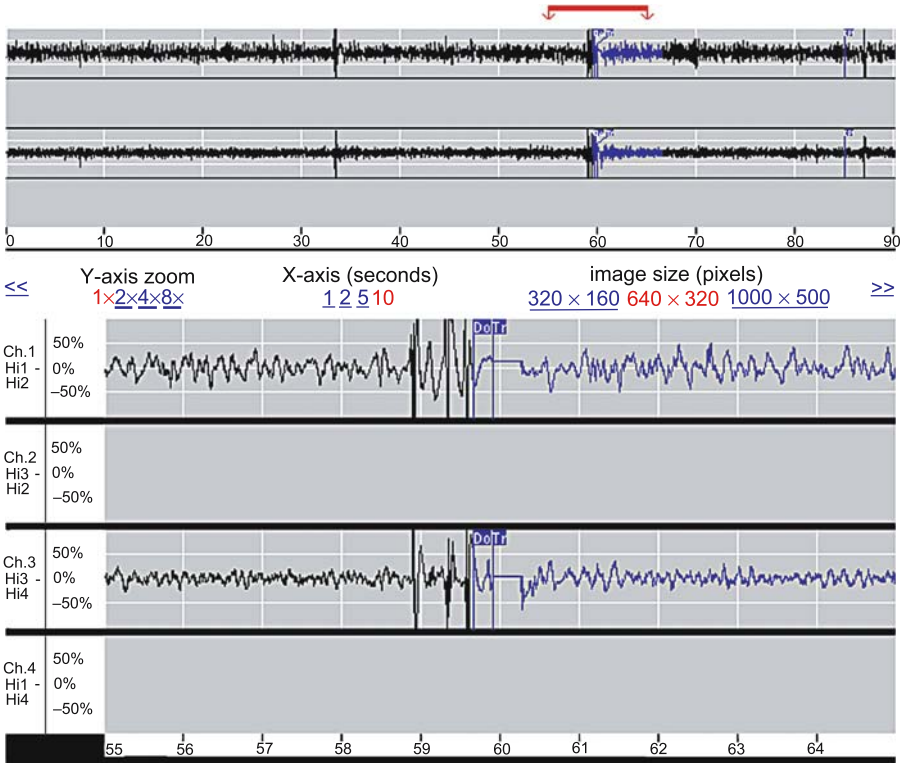

Fig. 3. Characteristic case of epileptiform activity detection and automatically delivered stimulation with subsequent abortion

and amplitude are detected within a specified window, detection occurs. It needs to be emphasized, that the sensitivity and specificity of the RNS system in the detection of actual epileptogenic activity when all three analysis tools (line length, area and half wave) are employed, is 100%.

Therapeutic stimulation: The RNS delivers charge-balanced biphasic pulses programmable from 0.5 to 12 mA amplitude, pulse widths programmable from 40 to 1000 µsec, and frequency programmable from 1 to 333 Hz (Fig. 3). Any of the electrode contacts or the pulse generator housing may be programmed as anode or cathode. After a pulse-train therapy has been delivered, a redetection algorithm determines if the epileptiform activity is still present. If so, up to 4 additional therapies may be delivered per episode. Also, each therapy may consist of one or two bursts. The parameters of each therapy and each burst may be the same or different. The RNS has a built-in charge density limit that will allow no more that 25 µCoulombs/cm^2/phase charge density to be delivered to the patient.

Surgical implantation

The implantation is usually performed under general endotracheal anesthesia unless the candidate is very cooperative in which case neuroleptanalgesia can be used. The craniotomy and implantation techniques of the RNS system have been described in detail elsewhere (Figs. 2, 4 and 5) [9, 10]. The operative blood loss is usually minimal (in all of our cases has been maintained <100 mL) while the mean duration of the surgical procedure of implantation is 3.6 hours (range 2.5–4.5 hours).

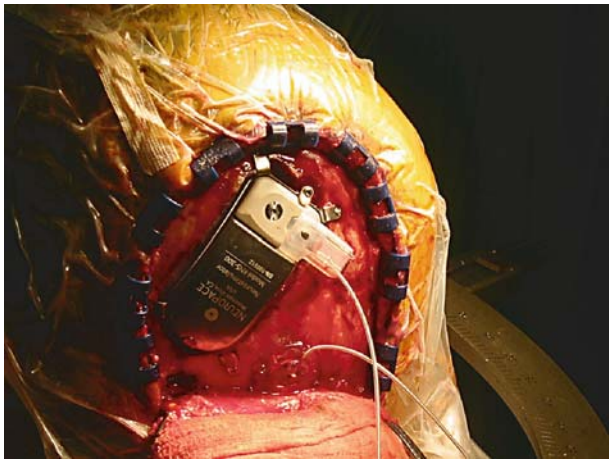

Fig. 4. Intraoperative picture demonstrating the pulse generator connected to an implanted depth lead and secured to the underlying ferrule

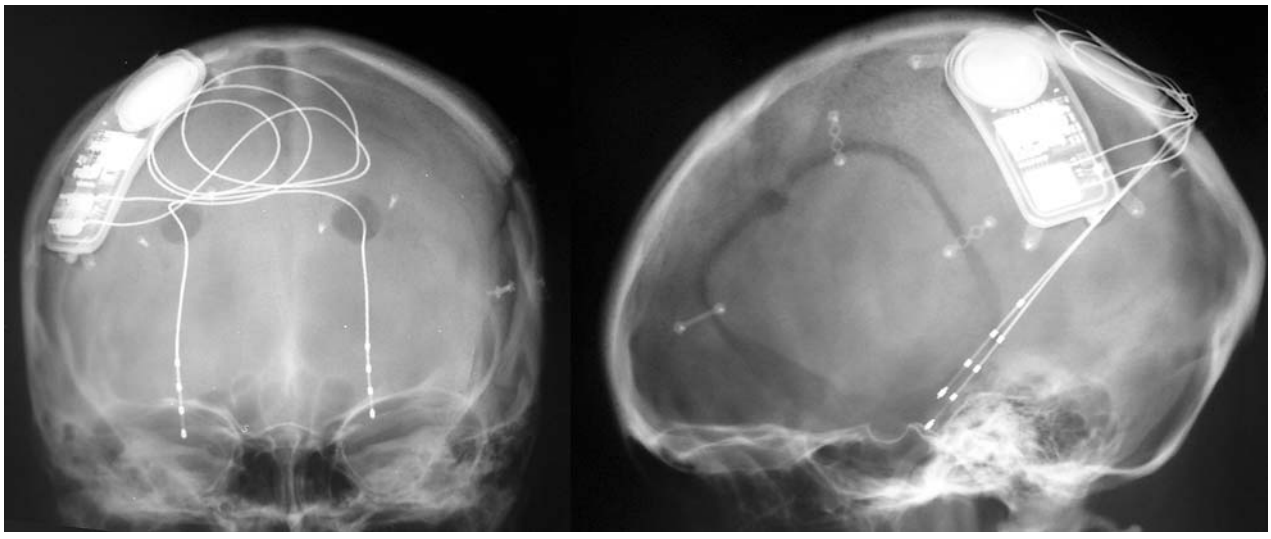

Fig. 5. Postoperative X-rays (antero-posterior and lateral views) of one of our patients demonstrating the implanted RNS system with two depth leads. The depth leads have been implanted through bilaterally placed burr holes. A craniotomy defect for previous resection is also noted

Preliminary results and complications

In our institution the above described RNS system has been implanted so far in eight patients with well localized focal epilepsy, who were considered candidates for such treatment according to the previously mentioned criteria. The follow-up period in these patients ranges between 6 and 26 months, while the mean follow-up time is 11.3 months. Interestingly, 7 (87.5%) of these patients had more than 45% reduction in their seizure frequency (with two patients having more than 75% decrease) while 1/8 patients (12.5%) had very slight increase (approximately 2%) in the frequency of her seizures, but a significant decrease in the intensity of the observed seizures.

No intra-operative or procedure related post-operative complications have occurred in our series so far. In regards to the avoidance of any complication, the theoretical risk of cerebral intra-parenchymal hemorrhage during the implantation of depth leads can be further minimized by direct visualization of the cortical entry point through the burr hole and also by the avoidance of any adjacent surface cortical veins during the pre-operative planning.

The risk of infection is not any higher than that associated with any other similar surgical procedure for implantation of neuro-stimulation devices. The utilization of a horseshoe-shaped skin incision and the implantation of the pulse generator away from the skin edges are maneuvers that could further minimize the risk of infection. In addition, the carefully designed contour shape of the implanted pulse generator significantly diminishes the potential risk of skin erosion.

Conclusion

Implantable, local, closed-loop RNS system represents an emerging alternative treatment option in patients with well-localized, focal, medically refractory epilepsy, who are not candidates for surgical resection. Additional multi-institutional prospective clinical studies are required for evaluating the clinical efficacy of this novel treatment modality. Further technical improvement of this system along with the accumulation of experience from its clinical use could lead to the development of a system, which would accurately detect and efficiently abort any detected epileptiform activity.

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References

1. Benabid A-L, Koudsie A, Chabardes S, Vercueil L, Benazzouz A, Minotti L, Le Bas J-F, Kahane P, de Sanit Martin A, Hirsch E (2004) Subthalamic nucleus and substantia nigra pars reticulata stimulation: the Grenoble experience. In: Luders HO (ed) Deep brain stimulation and epilepsy. Marting Dunitz, London, pp 335–348
2. Brown-Sequard CE (1856–1857) Researches on epilepsy: its artificial production in animals, and its etiology, nature and treatment in man. Boston Med Surg J: 55–57

3. Chkhenkeli SA, Sramka M, Lortkipandze GS, Rakviashvili TN, Bregvadze E, Magalashvili GE, Gagoshidze T, Chkhenkeli IS (2004) Electrophysiological effects and clinical results of direct brain stimulation for intractable epilepsy. Clin Neurol Neurosurg 106(4): 318–329
4. Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP (1976) Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. Arch Neurol 33(8): 559–570
5. Cooper IS, Upton AR (1978) Effects of cerebellar stimulation on epilepsy, the EEG and cerebral palsy in man. Electroencephalogr Clin Neurophysiol Suppl 34: 349–354
6. Cooper IS, Upton AR, Amin I (1980) Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. Appl Neurophysiol 43(3–5): 244–258
7. Estellar R, Echauz J, Tcheng T, Litt B, Pless B (2001) Line length: an efficient feature of seizure onset detection. IEEE: 1707–1710
8. Fisher RS, Uematsu S, Krauss GL, Cysyk BJ, McPherson R, Lesser RP, Gordon B, Schwerdt P, Rise M (1992) Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures. Epilepsia 33(5): 841–851
9. Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD (2005) Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy. A technical note. Stereotact Funct Neurosurg 83: 153–158
10. Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD, Greene D (2005) Closed-loop stimulation implantable system for the management of focal, medically refractory epilepsy: implantation technique and preliminary results. Epilepsia 46(8): 240–241
11. Siegel RE (1976) Galen on the affected parts (de locis affectis). Karger, Basel, pp 94–97
12. Gowers WR (1885) Epilepsy and other chronic convulsive diseases: their causes, symptoms and treatment. William Wood, New York, pp 235–236
13. Hauser WA (1995) Epidemiology of epilepsy in children. In: Adelson PD, Black PM (eds) Neurosurgery clinics of North America. WB Saunders Co, Philadelphia 6(3), pp 419–429
14. Hauser WA, Hesdorffer DC (2001) Epidemiology of Intractable Epilepsy. In: Luders HO, Comair YG (eds) Epilepsy surgery, 2nd edn. Lippincott Williams & Wilkins, Philadelphia, pp 55–61
15. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43(6): 603–608
16. Jackson JH (1868) Case of Convulsive attacks arrested by stopping the aura. Lancet 1: 618–619
17. Kerrigan JF, Litt B, Fisher RS, Craunston S, French JA, Blum DE, Dichter M, Shetter A, Baltuch G, Jaggi J, Krone S, Brodie M, Rise M, Graves N (2004) Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia 45(4): 346–354
18. Kinoshita M, Ikeda A, Matsumoto R, Begum T, Usui K, Yamamoto J, Matsuhashi M, Takayama M, Mikuni N, Takahashi J, Miyamoto S, Shibasaki H (2004) Electrical stimulation on human cortex suppresses fast cortical activity and epileptic spikes. Epilepsia 45(7): 787–791
19. Labar D (2004) Vagal nerve stimulation: effects on seizures. In: Luders HO (ed) Deep brain stimulation and epilepsy. Martin Dunitz, London
20. Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, Cysyk B, Krauss G, Gordon B (1999) Brief bursts of pulse stimulation terminate after-discharges caused by cortical stimulation. Neurology 53(9): 2073–2081
21. Motamedi GK, Lesser RP, Miglioretti DL, Mizuno-Matsumoto Y, Gordon B, Webber WR, Jackson DC, Sepkuty JP, Crone NE (2002) Optimizing parameters for terminating cortical after-discharges with pulse stimulation. Epilepsia 43(8): 836–846
22. Munz M, Sweasey R, Barrett C, Loftman AP, Potts D, Greene D (2003) Preclinical testing of an implantable responsive neurostimulator system in a sheep model. Society for Neuroscience. New Orleans
23. Munz M, Sweasey R, Barret C, Loftman AP, Vinters H, Popovska Z, Greene D (2003) Implantation and testing of responsive neurostimulator (RNS) system for epilepsy. American Society for Stereotactic and Functional Neurosurgery, New York
24. Murro AM, Park YD, Bergey GK, Kossof EH, Ritzl EK, Karceski SC, Flynn K, Choi H, Spencer DD, Duckrow RB, Seale C (2003) Multicenter study of acute responsive stimulation in patients with intractable epilepsy. Epilepsia 44 Suppl 9: 326
25. Murro A, Park Y, Greene D, Smith J, Ray P, King D, Loring D, Lee K (2002) Closed-loop neuro-stimulation in patient with intractable epilepsy. American Clinical Neurophysiology Society, New Orleans
26. Nair DR, Matsumoto R, Luders HO, Burgess R, Bingaman W (2004) Direct cortical electrical stimulation in the treatment of epilepsy. In: Luders HO (ed) Deep brain stimulation and epilepsy. Martin Dunitz, London
27. Neme S, Montgomery EB, Rezai A, Wilson K, Luders HO (2004) Subthalamic nucleus stimulation in patients with intractable epilepsy: the Cleveland experience. In: Luders HO (ed) Deep brain stimulation and epilepsy. Martin Dunitz, London, pp 349–358
28. Osorio I, Frei MG, Manly BF, Sunderam S, Bhavaraju NC, Wilkinson SB (2001) An introduction to contingent (closed-loop) brain electrical stimulation for seizure blockage, to ultra-short term clinical trials, and to multidimensional statistical analysis of therapeutic efficacy. J Clin Neurophysiol 18(6): 533–544
29. Osorio I, Frei MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, Wilkinson SB (2005) Automated seizure abatement in humans using electrical stimulation. Annals Neurol 57(2): 258–268
30. Peters TE, Bhavaraju NC, Frei MG, Osorio I (2001) Network system for automated seizure detection and contingent delivery of therapy. J Clin Neurophysiol 18(6): 545–549
31. Sramka M, Fritz G, Gajadosova D, Nadvornik P (1980) Central stimulation treatment of epilepsy. Acta Neurochir Suppl 30: 183–187
32. Sramka M, Fritz G, Galanda M, Nadvornik P (1976) Some observations in treatment stimulation of epilepsy. Acta Neurochir 23 Suppl: 257–262
33. Velasco F, Carrillo-Ruiz JD, Brito F, Velasco M, Velasco AL, Marquez I, Davis R (2005) Double-blind, randomized controlled pilot study of bi-lateral cerebellar stimulation for treatment of intractable motor seizures. Epilepsia 46: 1071–1081
34. Velasco F, Velasco M, Jimenez F, Velasco AL, Marquez I (2001) Stimulation of the central median thalamic nucleus for epilepsy. Stereotact Funct Neurosurg 77(1–4): 228–232
35. Velasco F, Velasco M, Ogarrio C, Fanghanel G (1987) Electrical stimulation of the centromedian thalamic nucleus in the treatment of convulsive seizures: a preliminary report. Epilepsia 28(4): 421–430
36. Velasco M, Velasco F, Velasco AL (2001) Centromedian-thalamic and hippocampal electrical stimulation for the control of intractable epileptic seizures. J Clin Neurophysiol 18(6): 495–513
37. Velasco F, Velasco M, Velasco AL, Menez D, Rocha L (2001) Electrical stimulation for epilepsy: stimulation of hippocampal foci. Stereotact Funct Neurosurg 77(1–4): 223–227

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Psychiatric disorders

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Neurosurgery for psychiatric disorders: from the excision of brain tissue to the chronic electrical stimulation of neural networks

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Summary

Neurosurgical treatment for psychiatric disorders has a long and controversial history dating back to antiquity. Both enthusiastic reports and social outcry have accompanied psychosurgical practice, particularly over the last century. Frontal lobotomy has probably been the only medical advance which was first awarded a Nobel prize in medicine and then irreparably stigmatized by scientific rejection and public criticism. In the present paper, the historical milestones of psychosurgery are briefly overviewed. The particular circumstances of the rise and fall of frontal lobotomy are also discussed. Furthermore, the clinical and surgical considerations of the four major psychosurgical procedures which are still in practice are presented.

Over the last fifteen years, the advent of deep brain stimulation (DBS) methodology coupled with accurate stereotactic techniques and guided by elaborate neuroimaging methods have revolutionized neurosurgery, particularly for the alleviation of certain disabling movement disorders. Investigationally, chronic electrical stimulation of selected brain structures, clearly implicated in the pathophysiology of neuropsychiatric disorders, has already been applied with promising results. Given the tainted past of psychiatric neurosurgery, modern neuroscientists have to move forward cautiously, in a scientifically justified and ethically approved framework. The transition from the indiscriminate destruction of brain structures to the selected electrical modulation of neural networks lies ahead; contemporary neuroscientists would substantiate this aim but should remind the controversial history of the field.

Keywords: Psychiatric disorder; psychosurgery; limbic system; history; deep brain stimulation.

Introduction

Psychosurgery, the neurosurgical treatment of psychiatric disorder, has a long, complex and controversial history dating back to antiquity. It gradually developed as a separate surgical field from the mid-19th century, but its culmination was based on the pioneering work of a few neuroscientists who, in the 1930s and 1940s, established the concept of the functional correlations between brain, emotions and behaviour. The better understanding of the neuroanatomical and physiological background of the psychiatric phenomenon disclosed a few critical brain structures, which, when excised or destroyed, could ameliorate the clinical profile of the disease. Over the next decades, four major ablative procedures dominated in psychosurgical practice: anterior cingulotomy, subacaudate tractotomy, limbic leucotomy, and capsulotomy.

In mid-1950s, the introduction of chloropromazine in the clinical setting along with subsequent psychotropic drugs reduced dramatically the number of surgical procedures performed for the alleviation of severe psychiatric symptoms. Moreover, the indiscriminate application of ablative brain procedures, basically frontal lobotomy, as well as the lack of strict patient selection guidelines and poor postoperative data blackened psychosurgery's reputation and gave way to public clamour and scientific criticism. Despite accumulating concern about neurosurgical treatment of psychiatric disorders, however, the refinement of surgical techniques and the preponderance of stereotactic methodology for the accurate placement of lesions inside the brain permitted psychosurgery to survive till the modern era.

The advent of deep brain stimulation (DBS), that is the direct electrical stimulation of deep brain structures, has revolutionized the practice of neurosurgery over the last ten years. Currently, the methodology is well established for the alleviation of the symptoms of Parkinson's disease, while it has investigationally been applied in epilepsy, pain, dystonia, and persistent vegetative state [27]. DBS outweighs conventional ablative neurosurgical procedures offering two substantial benefits: reversibility and

adjustability. Taking advantage of these unique characteristics, neurosurgeons have explored with ''stimulation'' brain targets critically implicated in the pathophysiology of severe affective diseases. It is estimated that more than 20 sufferers from obsessive-compulsive disorder worldwide underwent bilateral implantation of electrodes in the anterior limb of the internal capsule or the right nucleus accumbens prior to 2004 [19]. Moreover, the first promising results of chronic electrical stimulation of the rostral cingulate gyrus or the inferior thalamic peduncle in treatment-resistant depression have already been published [35, 44].

In the present paper, the historical cornerstones of psychiatric neurosurgery and the anatomical and clinical considerations of the four major ablative psychosurgical procedures are cited in brief. Currently, deep brain stimulation allows for the optimal scenario in which the clinical outcome is maximized while complications are minimized. Modern neuroscientists may be fortunate enough to live the era of transition from the destruction of brain tissue to the selective electrical modulation of neural networks pertaining to the pathophysiology of severe psychiatric disorders. Some of the medical, social and ethical concerns that arise from the use of DBS as a treatment option of intractable affective diseases will also be discussed.

At this point, a clarification regarding the terminology used in this paper is considered necessary. From a semantic point of view, the term ''psychosurgery'' has been stigmatized in the psychiatric community and, in most part, has been replaced by other more or less appropriate terms such as ''psychiatric neurosurgery'', ''surgery of the limbic system'' or ''neurosurgical treatment for mental disorders''. However, because this notional distinction is beyond the scope of this review, most of the above terms will be used interchangeably to denote ''any surgical procedure that aims to improve, through intervention on neural tissue, the clinical profile of psychiatric disorders, which are categorized in DSM IV and are not caused by any known structural lesion'' [3].

The origins of psychiatric neurosurgery

The origins of psychosurgery can be traced to antiquity. As early as the Neolithic period of the Stone Age [2], the prehistoric human performed primitive round or quadrate openings of the skull by using edge-cutting tools. The apparent healing signs at the borders of those bone defects witness that firstly, the sufferers had survived that intervention and secondly, this procedure was part of a ''surgical'' practice rather than result of a traumatic impact. Given that various magicoreligious notions dominated prehistoric medical practice, the above skull openings most probably were aimed at allowing spirits and demons to escape from the head. Apparently, the history of psychosurgery is as ancient as the psychiatric disease itself.

The beginning of the modern era of psychiatric neurosurgery, in the mid-19th century, coincides with the pioneering research work of few neuroscientists, such as Broca and Wernicke; both of them greatly contributed to the establishment of close brain-behaviour correlations and the clarification of the underlying neuroanatomical substrate of higher cognitive functions such as language [12, 72]. In 1888, Swiss psychiatrist Gottlieb Burckhardt performed the first psychosurgical procedure of the modern era, the so-called ''topectomy'' [14]. This involved the excision of multiple foci of the frontal, parietal, and temporal cortices in schizophrenic patients. Despite the fame of later scientists in the field of psychosurgery, Gottlieb Burckhardt should, in fact, be regarded as the founder of psychiatric neurosurgery.

The first decades of the 20th century are mainly characterized by the schism created between psychiatry and neurology; the former maximized the role of the mental, interpersonal social factors in the phenomenon of the so-called ''mental illnesses'', while the latter introduced to clinical practice various somatic therapies (electroconvulsive therapy, psychotherapy, insulin-shock therapy, and hydrotherapy). The Second World Congress of Neurology in 1935 was a landmark in the history of psychosurgery. Fulton and Jacobsen first stated that the resection of frontal association cortex may result in marked improvement of abnormal behaviour. This concept urged Egas Moniz, a charismatic Portuguese neurologist, to introduce probably the most controversial surgical intervention of the modern medical history, namely the ''frontal lobotomy'' [50, 51]. In particular, he claimed and demonstrated clinically that the excision of both afferent and efferent fibers of the frontal lobe was efficacious in the treatment of disabled mental patients. A few years later, neurologist Walter Freeman and James Watts, neurosurgeon, modified the above procedure by introducing ''frontal leucotomy'' and ''transorbital frontal lobotomy'' [22, 23]. These procedures involved the interruption of frontal white matter fibers by a leucotome; the instrument was inserted bilaterally through a 1-cm burr-hole placed above the zygomatic arch of each side of the head.

The spectrum of psychiatric disorders considered as possibly cured by these early procedures was soon

broadened to include schizophrenia, depression, childhood behaviour disorders, homosexuality and criminal behaviour. Nevertheless, serious postoperative complications such as personality change, seizures, intellectual impairment, paralysis, and death were associated with ''frontal lobotomy'' [9]. Despite these complications, the procedure was overall considered as helpful in the majority of patients and Egas Moniz was awarded the Nobel Prize in Medicine in 1949 ''for his discovery of the therapeutic value of prefrontal leucotomy in certain psychoses''.

The introduction of stereotactic apparatus by Spiegel *et al.* in 1947 [66] proved to be another turning-point in the history of psychiatric neurosurgery. The serious complications associated with frontal lobotomies, the ongoing social criticism for the abuse of this procedure and the challenging accuracy for targeting deep brain structures that the new methodology offered urged neuroscientists to work towards the refinement of their psychosurgical procedures. Over the following two decades, frontal lobotomy had, in most part, been replaced by other more selective procedures; the four prevailing amongst them have survived in contemporary neurosurgical practice as treatment options of mentally disabled patients.

Frontal lobotomy: a medical phenomenon, a social stigma

''Frontal lobotomy'' is regarded as one of the most controversial therapeutic advancements in the modern history of medicine. The appreciative and enthusiastic reports that accompanied the advent of this procedure were replaced soon by medical controversy and social backlash. Some of the various issues associated with the rise and fall of this intervention are presented in this section.

To understand why ''frontal lobotomy'' became popular in the psychiatric and neurosurgical community, one has to consider the particular social, medical and financial conditions, which related to psychiatric diseases during the period 1930–1950. In 1937, there were approximately 480 American psychiatric institutions, where over 400,000 patients lived a disabled and desperate life. In the United States, given that over 50% of the hospital admissions were for mental illnesses, it was estimated that, by 1940, more than US$ 15 billion would be necessary for the treatment of these patients [43, 71]. Additionally, 12% of the men were rejected by the armed forces because of severe mental disorders. Taken together, the dramatic increase in the asylum population and the considerable financial impact of its medical treatment convinced a great part of the scientific society that the operation could be highly cost-effective [69]. More importantly, in these early years, this notion was greatly supported by distinguished academics, complimentary reports of sufferers' relatives and laudatory articles in popular press.

Furthermore, the proposed procedures such as standard lobotomy, modified frontal leucotomy or transorbital frontal lobotomy, were not technically demanding and even neurologists or non-specialist asylum based physicians proceeded with such interventions [43]. By 1951, a total of 18,600 psychosurgical procedures had been performed in the USA [69], while in the UK 10,365 patients had received this kind of treatment by 1954 [70]. Finally, the lack of effective psychopharmacological agents greatly contributed to an environment in which frontal lobotomy was warmly welcomed.

In those early years of psychosurgery, the psychiatric diagnosis was less well defined; the psychological and cognitive scales for assessment of the patients' mental capabilities were incomplete, while certain disorders such as obsessive-compulsive disorder (OCD) were not recognized yet as distinct diagnostic entities. Most candidates for psychiatric neurosurgery were diagnosed as schizophrenic although schizophrenia is not currently considered an indication for surgery. There was a time when the major diagnostic criterion for surgical intervention was a ''fixed state of tortured self concern''; practically, all mentally disabled patients were candidates for psychiatric neurosurgery. Undeniably, this overzealous and often indiscriminate application of ablative brain procedures for the alleviation of severe mental symptoms constituted one of the main concerns about psychosurgery.

As the number of psychiatric neurosurgical procedures was rapidly increasing, the lack of strict patient selection criteria, the poor post-operative records, along with questions about efficacy and reports of permanent sequelae, enveloped psychosurgery with uncertainty and controversy. Intellectual impairment, inertia, inappropriate emotions, loss of concentration, epileptic fits and paralysis were not infrequently reported following frontal lobotomies. Over the time, postoperative sequelae appeared to be worse than the disease itself. However, the decline of frontal lobotomy coincided in fact with the introduction of chloropromazine as the first effective medication for psychosis. It was estimated that more than 2 million sufferers received the drug in 1954, the

year it was approved as a psychiatric medical treatment [19]. Moreover, the institution of stereotactic procedures in the neurosurgical treatment of mental disorders conferred accuracy, confidence, and safety for the placement of more selective and less extended lesions in brain structures.

By the mid 1950s, the number of frontal lobotomies started to decrease in favour of refined stereotactic interventions, although there are reports that, even in 1976, one third of psychiatric interventions in the UK still involved the ablation of frontal lobe white matter [7]. The great concerns about the use of psychiatric neurosurgery grew during the 1960s and 1970s [21], when its social and medical role was scrutinized. Scientific criticism and social censure were fuelled by published articles in the popular press and reputable journals, which stigmatized the role of psychiatric neurosurgery. Influential books, such as *Violence and Brain*, published by Mark and Ervin in 1970 [42], as well as popular films such as *One Flew Over the Cuckoo's Nest*, presented dramatically the psychosurgery abuse. There were even fears that lesional brain procedures used for the control of violent behaviour were being proposed for social problems. All these issues were clarified, in most part, by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [17]; its report, in 1977, concluded that psychiatric neurosurgery, when practised in a well defined ethical, medical and social framework, has a role in the treatment of mentally disabled patients.

At the dawn of the 21st century, the neurosurgical treatment of psychiatric diseases has survived because much of the concerns that plagued its historical course have effaced. The claims that ablative brain procedures were being used on minority and disadvantaged populations for social control were unsubstantiated. The prevailing refined stereotactic procedures are carrying considerably lower rates of complications and mortality. Finally, psychosurgery is, in most part, currently offered in selected, accredited neurosurgical reference centres, which fulfil the criteria of an ethical, scientifically justified, and socially approved surgical practice.

Contemporary psychosurgical procedures

Neuroanatomical background

Looking back to the history of psychiatric neurosurgery, it is noticeable that a variety of surgical techniques have been used to destroy selected brain targets, more or less extensively, but all clearly implicating the neuroanatomical substrate of psychiatric disorders. There have been at least 19 distinct target sites used in psychosurgery over the years [10], while 24 different surgical procedures had been described prior to 1954 worldwide [58]. Nevertheless, only four procedures have evolved as the safest and most clinically effective, namely anterior cingulotomy, subcaudate tractotomy, limbic leucotomy, and anterior capsulotomy.

In fact, all the above interventions selectively target distinct brain structures, which, however, constitute critical points of the same integrated neuroanatomical network. No description of the current psychosurgical procedures could be meaningful without first presenting the basic neural circuits of the frontal lobes, along with their projections and reciprocal connections with subcortical systems such as the limbic system and the basal ganglia.

In 1937, the same year that Moniz introduced frontal leucotomy, Papez [57] was the first to postulate that a specific neuronal circuit in the human brain could be responsible for emotions. Although Willis in 1664 [73] and Broca in 1878 [13] had already described the ''limbic lobe'', Papez suggested a rudimentary closed-loop network comprising the hypothalamus, hippocampi, mamillary bodies, septal nuclei, anterior thalamic nuclei, cingulate gyrus and their interconnections. According to his theory, areas of the human cortex, where higher cognitive function and thought arise, connect with the cingulate gyrus; the latter connects to the hippocampus, which in turn connects to the mammillary bodies (hypothalamus) through the fornix. The network is reciprocally integrated via retrograde connections from the mammillary bodies to the cortex through the anterior thalamic nuclei and the cingulate gyrus. The cingulate cortex evolved to become the receptive cortical region for emotional impulses; moreover, its projections to higher cortical areas provided ''emotional coloring'' to psychic processes occurring elsewhere [19, 57]. In 1952, MacLean named the above circuit ''limbic system'' [40]; notably, he expanded its anatomic borders to include other paralimbic structures, namely orbitofrontal and anterior temporal cortex, nucleus accumbens, insula, amygdala, and dorsomedial thalamic nuclei. The limbic system (Fig. 1), through its direct inputs to hypothalamus and cortex, mediates interconnections of somatic and visceral stimuli with higher cortical functions. In other words, sensory inputs, first received in primary and associate sensory areas, are then processed to the limbic system through the hypothalamus; finally, they project to

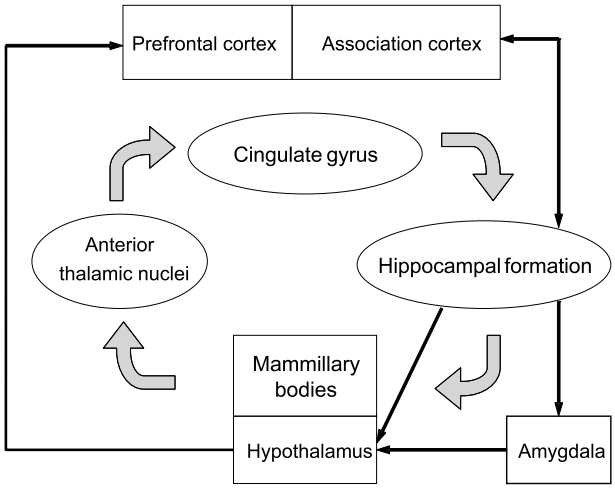

Fig. 1. Schematic diagram of the main components of the ''limbic system'' and their functional interconnections

other cortical areas, where higher order mental processes such as cognition, abstract thoughts or planning are integrated [41].

Modern neuroimaging methods (single photon emission computed tomography, positron emission tomography, and functional magnetic resonance imaging) have largely clarified that, apart from the limbic system, other inner brain structures may be directly implicated in the pathogenesis of mental illnesses [16, 31, 65]. It is well known, both from basic research and from the pathophysiology of certain neurological disorders such as Parkinson's disease, that the basal ganglia, through the well defined frontal-striatal-pallidothalamic-frontal loop, play a principal role in the control of motor function. Interestingly, recent data advocate that the above loop might also be critical in the pathophysiology of psychiatric disorders. Moreover, frontal lobe and basal ganglia dysfunction have also been demonstrated in patients suffering from obsessive-compulsive disorder (OCD) or Tourette's syndrome (TS) [60, 63]. Positron emission tomography (PET) studies have also demonstrated the functional relationships between orbitofrontal cortex, cingulate cortex, and basal ganglia in OCD [62].

To date, the exact neuroanatomical, neurochemical, and neuropathological disorders underlying psychiatric phenomena have not fully been elucidated; however, it has certainly been demonstrated that the limbic system, the cingulate cortex, and the basal ganglia are principally involved in the pathophysiology of mental symptoms. All these critical structures have proved to be reciprocally interconnected and the equilibrium of this ''circular system'' is achieved only when its component pathways are equivalently functional. This system normally has a range of ''autoregulation'' aiming to maintain the sanity of the human brain in spite of dramatic, frightening or sad events. Any disturbance in the aforementioned circuits could result in loss of the ''state of autoregulation'' and in various components of mental disease. On the contrary, interruption of any of the above neural networks can re-establish a ''state of autoregulation'' in various ways such as blocking inputs to frontal lobes and alleviate psychiatric symptoms by affecting cognition. Notably, lesions placed in separate structures of this neuronal loop can alleviate the same mental symptom, while multiple lesions severing two or more distinct circuits may sometimes have a better clinical effect than single lesions. In current psychiatric neurosurgery, each of the four major procedures in use aims to sever one or more of the above neuronal circuits.

Anterior cingulotomy

The anterior cingulum was recognized early as a key point in the Papez's 'limbic circuit', since its destruction in animals altered substantially their emotional responses [32]. Fulton first suggested anterior cingulum as a potential psychosurgical target [24, 25] and the original open procedure was first performed by Scoville [19]; this involved the excision of the anterior supracallosal fibers of the cingulate gyrus. In early 1950s, the intervention was made popular in various centers worldwide [46]; amongst others, the Massachusetts General Hospital Cingulotomy Unit has been recognized as one of the main reference centers, which has conducted several studies on bilateral anterior cingulotomy, both prospective and retrospective [6, 18, 34]. Currently, the procedure is performed under general or local anaesthesia with intravenous sedation, guided by accurate stereotactic techniques. It involves the placement of bilateral lesions 20–25 mm posterior to the anterior horn of the lateral ventricles, 2–5 mm above the roof of the lateral ventricle and 7 mm from the midline [67]. Although anterior cingulotomy was initially suggested for the treatment of intractable pain and various anxiety disorders, better results were obtained in patients suffering from intractable major depression and obsessive-compulsive disorder (OCD). Bibliographically, thirty to forty-five percent of the mentally disabled patients are categorized in the responders' group after cingulotomy; however, when less objective clinically validated rating scales are used to assess outcome, 60–70% of the sufferers experienced significant improvement [16]. Overall, the proce-

dure has proved to be effective in a significant number of treatment-refractory psychiatric patients, while it is associated with a low incidence of postoperative complications and adverse effects [67]. In contemporary psychosurgical practice, the above characteristics have rendered anterior cingulotomy to the prevailing procedure in North America.

Subcaudate tractotomy

Stereotactic subcaudate tractotomy was introduced by Knight in 1964 [37] in an effort to minimize the destructive effects of frontal lobotomy. The procedure involves the division of white matter tracts interconnecting the orbital cortex with the subcortical and limbic structures, i.e. thalamus, basal ganglia, and amygdala. The lesions are placed bilaterally in the region of the substantia inominata, just below the head of the caudate nucleus. Originally, the lesions were created by stereotactically implanted radioactive yttrium 90 seeds; in modern psychiatric neurosurgery, however, thermocoagulation with magnetic-resonance imaging (MRI) stereotactic guidance has substantially lowered the lesional volume and the correlated immediate and long-term side effects.

The surgical indications have included treatment-refractory major affective disorders (unipolar and bipolar), chronic anxiety states, chronic pain, and OCD. Although early results reported clinical improvement in more than 50% of the patients who underwent subcaudate tractotomy [26], more recent data estimated treatment response at 34% [43]. Before the early 1990s more than 1300 subcaudate tractotomies were performed in Britain, particularly at the Brook Hospital in London; the procedure has now been replaced by other psychosurgical interventions.

Limbic leucotomy

The procedure was first performed by Kelly *et al.* in 1973 [36] and essentially combined subcaudate tractotomy with anterior cingulotomy. Its rationale was that two lesions might produce better results that either method alone. The ventro-medial frontal lesion disconnected orbital-frontal-thalamic pathways, whereas the cingulum lesion was intended to interrupt an important portion of the Papez's circuit. Anxiety states, OCD, depression, and other psychiatric psychoses have constituted the main indications for limbic leucotomy. The early reports of clinical outcome were really promising as 89% of patients with OCD, 78% of patients with depression, and 66% of patients with chronic anxiety showed marked improvement of their symptoms; however, their measurements were based on a five-point global rating scale affected by subjective criteria of responsiveness [9]. Recently, when clinically validated rating scales were used, only 35–50% of the sufferers who underwent limbic leucotomy were considered as treatment responders. Apart from transient adverse effects such as lethargy, confusion, and lack of sphincter control, approximately 10% of the patients showed permanent minor memory loss or urinary difficulties [30].

Anterior capsulotomy

Although the procedure was first designed by the French neurosurgeon Talairach in the late 1940s, it became popular only when Leksell used it to alleviate a variety of psychiatric disorders [39]. The procedure involves the bilateral placement of lesions in the anterior limb of the internal capsule, where the orbito-frontal-thalamic pathways course between the caudate and putamen nuclei of the basal ganglia. According to Leksell, the targets are placed 5 mm behind the tip of the frontal horn of each lateral ventricle and 20 mm lateral to the midline at the level of the intercomissural plane; typically, the lesions are 15 mm in height and 4–5 mm in diameter. Both thermal damage and gamma-knife radiation have been used to produce the above lesions with comparable rates of clinical improvement [48].

The majority of the reported post-capsulotomy complications such as changes in mental status, memory difficulties and affective disturbances have been attributed to the circumlesional edema and mostly subside spontaneously over the first 2–3 postoperative months. However, permanent side effects such as nocturnal incontinence, seizure, memory deficits, aggressiveness, and weight gain have also been reported [15]. Today, the main indications for capsulotomy include treatment-resistant generalized anxiety disorders, OCD, and panic disorder [47] but it is also used for intractable depression. Mindus *et al.* reviewed the reported cases of anterior capsulotomy and, overall, demonstrated that 64% of the patients had experienced significant improvement in their psychiatric symptoms [49]. It is generally accepted that anterior capsulotomy is more efficacious in patients with OCD compared to cingulotomy; however, its relatively high rate of associated untoward effects remains an issue of controversy and concern.

Is any psychosurgical procedure superior to the others?

Neurosurgery for mental illness has attracted much reflection and criticism over its convoluted historical course. Unfortunately, even in current practice where stereotactic and neuroimaging technologies have substantially reduced the adverse effects of psychosurgical procedures, it has not yet been determined which procedure is optimal for which psychiatric disorder. Over the last decades, a series of objective difficulties in terms of reliability and accuracy have prevented direct comparison of the four major psychosurgical interventions. When the results from different centers or follow-up series of the same center are collated, a number of critical concerns arise: the early reports, in most part, are based on poorly defined diagnostic criteria, ambiguous surgical indications, as well as subjective outcome rating scales; the results are mostly referred to variable observation times and subjected to center bias; so far, no control groups or prospective placebo-controlled (sham operations) have been included in the psychosurgical studies; and finally, given that a considerable number of sufferers were offered psychosurgical interventions before the modern era of psychopharmacology, many of those patients would not meet today's inclusion criteria for such treatment.

Currently, several of the above obstacles have been partially overcome. For example, the use of external beam radiation appears to provide a feasible and ethical way of including control groups of patients in comparative studies [33]. Additionally, the establishment of standardized nosology for mental disorders and the introduction of validated rating scales, both subjective and objective, for psychiatric symptoms have greatly enhanced the capacity of evaluation. However, taking together the currently available data and comparative methodologies, the clinical superiority of any one of the four psychosurgical procedures is not clearly provable and convincing. Despite recent bibliographic evidence in favour of a specific psychosurgical intervention, it is generally accepted that all four procedures are roughly therapeutically equivalent. The incidence and severity of complications associated with each operation appears also to be an important criterion in the selection of the target. From that point of view, cingulotomy has been correlated with less important and more transient side effects when compared with other procedures [16]. The final decision depends upon the definitive psychiatric diagnosis, the experience of the center where the patient is referred to, and the specific surgeon's preference. Overall, limbic leucotomy and capsulotomy prevail in Europe, whereas cingulotomy is more commonly performed in North America. In the future, multicenter, double-blinded prospective studies constructed with standardized diagnostic criteria and assessment rating scales may indicate which procedure is optimal for which psychiatric disorder.

Deep brain stimulation in psychiatric neurosurgery: concerns remain

As early as the 1950s, electrical modulation of the brain was used as a therapeutic option for the alleviation of either psychiatric symptoms or chronic pain conditions. Over the next three decades, electrical brain stimulation mostly fell into oblivion following the general decline of neurosurgical psychiatry. It was only at the end of 1980s that interest in the field resurged; over the next few years, the pioneering research and clinical work of Professor Benabid established deep brain stimulation (DBS) as an alternative treatment for certain severe neurological symptoms [8]. So far, the methodology has proved particularly effective in Parkinson's disease and essential tremor. Investigational studies have given promising results in the management of neuropathic pain, Tourette's syndrome, treatment-resistant cluster headache, epilepsy and vegetative state [28].

Technically, DBS involves the (often bilateral) surgical implantation of fine electrodes in selected deep cited brain structures, guided by accurate stereotactic methodology, magnetic resonance imaging and, in many cases, physiological monitoring by microelectrode recording. A battery-operated pulse generator is then placed subcutaneously, usually below the clavicle, and extension wires are tunnelled under the skin to connect it with the intracranial leads. High frequency electrical stimulation of the involved neural networks affects substantially their functional integrity. The exact underlying mechanisms of DBS, however, have not been fully clarified yet. Although both excitatory and inhibitory effects have been demonstrated on affected brain circuits, the hypothesis that chronic high frequency (130–185 Hz) stimulation reduces neural transmission through inactivation of voltage-dependent ion channels prevails in the field [11]. Paradoxically, despite presumable brain activation following electrical stimulation, DBS, in fact, interrupts neural circuits mimicking the result of a lesion.

Deep brain stimulation methodology carries inherent advantages over the conventional lesional procedures. In theory, the intervention is fully reversible and adjustable. Postoperatively, stimulation itself may be modified, in

terms of pulse width, frequency and voltage or even discontinued in the event of untoward effects. From a clinical and research perspective, the electrical stimulation itself may be turned ''on'' or ''off'' without patient's awareness, thus providing the opportunity of conducting double blind studies. Furthermore, the multi-channel leads used for DBS enable neuroscientists to modulate the electrical circuits within the brain by altering the transmitted electric currents; this offers the possibility to change the regional zone of the surrounding brain tissue that is affected or even alter the structures targeted along the electrode without requiring further surgery. In contrast, ablative procedures may be revised only by adding further lesions; these aim either to increase the size of an existed lesion or to destroy a separate adjacent brain structure.

Despite the undoubted advantages of DBS technology, certain side effects may complicate its practice. Approximately 1–3% of the patients may develop intracerebral hemorrhage, infection, or seizures [29]. Stimulation itself may result in unwanted neurological effects such as paresthesias, limb weakness, dysarthria, memory deficits, changes in mood, and cognitive impairment. Notably, lead breaks, unpredictable battery depletion, and short battery life are all significant problems, which, not infrequently, occur with DBS.

Taking into account the murky past of psychosurgery and the aforementioned advantages of DBS, it becomes apparent that the new methodology potentially provides the optimal surgical modality for the alleviation of intractable mental illnesses. The reversibility of the ''lesion'', the adjustment of stimulation, and the low rates of intra- and postoperative complications are all significant merits, which may ameliorate the public outcry and scientific criticism that commonly surrounded the psychosurgical practice in the past. So far, the established targets of ablative procedures have indicated the brain structures that might be appropriate targets for DBS. Over the last few years, the first investigational reports of implantation of electrodes in the anterior limbs of the internal capsules or the right nucleus accumbens have provided promising results in the treatment of refractory obsessive-compulsive disorder (OCD) [1, 4, 53, 54, 68]. Moreover, the rostral cingulate gyrus has been a structure clearly implicated in the pathophysiology of affective disorders; this area has been both suggested [61] and surgically tested [44] as a target for DBS in the management of medically-resistant depression. The encouraging results from the chronic electrical stimulation of the ventral caudate nucleus [5] or the inferior thalamic peduncle [35] allow neurosurgeons and psychiatrists to further investigate alternative targets along the brain circuits underlying affective illnesses.

It is not surprising that interest in the field of psychiatric neurosurgery has been rejuvenated following the advent of deep brain stimulation. The new methodology is potentially an attractive option for some desperate psychiatric patients, a proportion of whom are suicidal. However, caution is demanded; psychosurgery's tainted past warns against overzealous practice and unsubstantiated enthusiasm in reports. Before contemplating DBS for psychiatric indications, several criteria should be met and critical queries answered [55]. First of all, it is imperative to define the group of psychiatric disorders that might benefit from DBS (OCD and depression are the main indications as yet). Second, the neuroanatomical networks underlying the disturbed behaviours should be better defined and elucidated. Furthermore, strict criteria of diagnosis, severity, disability, chronicity, and treatment refractoriness should be instituted [38]. For these purposes, multidisciplinary teams are necessary, which will include psychiatrists, neurosurgeons, neuropsychologists, neurologists, bioethicists, and legal advisers. A battery of carefully constructed protocols and standardized clinical instruments such as validated rating scales, would assure that candidates are selected with approved scientific and ethical criteria [15, 33]. The patient's capability of providing informed consent and willingness to participate in both preoperative assessment and postoperative follow-up tests are also mandatory. All proven medications, behavioural therapies and complementary treatments should have been given adequate trials before a specific psychiatric disorder is characterized as treatment-refractory [27]. The psychiatrists who are involved in the advisory committee should have appropriate experience of the most disabling and medically-resistant mental disorders. Satisfactory arrangements must be in place for the postoperative management. The neurosurgical team should have substantial experience with DBS methodology and work in close collaboration but still independently from the psychiatric committee.

Undoubtedly, DBS has opened a new avenue for research and clinical management of medically-resistant psychiatric illnesses. However, as the number of psychosurgical procedures is expected to be steadily increasing in the foreseeable future, a series of critical issues should also be considered. Candidates for DBS are the most disabled psychiatric patients, who mostly face immense suffering, severe incapacity and marital, professional and social burdens in their lives. In this vulnerable population, DBS may represent the ''last resort'' and the

future of these desperate subjects; if conventional psychiatric treatment fails to improve their symptoms, DBS has to be considered and proposed. As mentioned earlier, DBS is associated both with permanent and transient unwanted effects. Is it always clear that the possibility of postoperative complications outweigh the clinical impact of the disease itself?

From a medical economic point of view, DBS procedures usually involve the bilateral implantation of multi-channel leads and a battery-operated generator. The current cost of the complete system is up to US$ 24,000 per patient, an amount that is high even for the budget of developed countries [28]. The costs are compounded by the need to replace battery-depleted pulse generators which could occur every two years or more frequently depending on the selected stimulation parameters. New advances include rechargeable batteries with extended life, novel electrodes, which would enable neuroscientists to explore more combinations of high electrical currents, and new instrumentations, which will facilitate the technical steps of the procedure. The high cost of the implanted system, the sophisticated computer technology needed for the recognition and accurate targeting of the selected brain structure, as well as the necessary multidisciplinary teams for the pre-, intra- and postoperative therapeutic management of the psychiatric candidates indicate that DBS, at present, should be practised in a small number of critically accredited academic centers.

At the dawn of the 21st century, the new frontiers of psychiatric neurosurgery have never been more promising. The accurate stereotactic targeting of specific brain structures, the advanced neuroimaging methods, the elaborate microrecording neurophysiological monitoring, the highly effective technological products, and the deep brain stimulation methodology provide altogether the best environment for neurosurgery of mental disorders to flourish. The dark past of the field, however, should remain a vivid reminder and a cautious guide in order to move forward on a scientifically justified and bioethically approved line. It is of great importance that the patients, their care givers, and the attendant physicians understand that, at present, DBS is not a ''therapeutic'' procedure in the traditional sense; it is rather an alternative but acceptable treatment modality, which carries outstanding inherent advantages and may improve psychiatric symptoms in a limited number of strictly selected patients without causing permanent harm. Substantive, robust, critically controlled doubled blind studies will provide clear evidence of the effectiveness of DBS methodology and define the clinical spectrum of psychiatric disorders that might be improved.

References

1. Abelson JL, Curtis GC, Sagher O *et al* (2005) Deep brain stimulation for refractory obsessive-compulsive disorder. Biol Psychiatry 57: 510–516
2. Alt KW, Jeunesse C, Buitrago-Tellez CH *et al* (1997) Evidence for stone age cranial surgery. Nature 387: 360
3. American Psychiatric Association (1994) Dignostic and statistical manual of mental disorders, ed. 4. American Psychiatric Association, Washington, DC
4. Anderson D, Ahmed A (2003) Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation. J Neurosurg 98: 1104–1108
5. Aouizerate B, Cuny E, Maritn-Guehl C, Guehl D *et al* (2004) Deep brain stimulation of the ventral caudate nucleus in the treatment of obsessive-compulsive disorder and major depression. J Neurosurg 101: 682–686
6. Baer L, Rauch SL, Ballantine HT Jr *et al* (1995) Cingulotomy for intractable obsessive-compulsive disorder: prospective long-term follow-up of 18 patients. Arch Gen Psychiatry 52: 384–392
7. Barraclough GM, Mitchell-Heggs NA (1978) The use of psychosurgery for psychological disorders in the British Isles during 1974–1976. BMJ 2: 1591–1593
8. Benabid AL, Pollak P, Gervason C *et al* (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 337: 403–406
9. Binder DK, Iskandar BJ (2000) Modern neurosurgery for psychiatric disorders. Neurosurgery 47: 9–23
10. Bouckoms AJ (1988) Ethics of psychosurgery. Acta Neurochir Suppl 44: 173–178
11. Breit S, Schulz JB, Benabid AL (2004) Deep brain stimulation. Cell Tissue Res 318: 275–288
12. Broca P (1865) Sur le liege de la faculte du language articule. Bull Soc Anthropol 377–393
13. Broca P (1878) Anatomie comparée circonvolutions cérébrales: le grand lobe limbique et la scissure limbique dans la série des mammiferes. Rev Anthropol 1: 385–498
14. Burckhardt G (1891) Über Rindenexcisionen als Beitrag zur operativen Therapie der Psychosen. Allg Z Psychiatr Psych Med 47: 463–548
15. Cosgrove GR, Rauch SL (1995) Psychosurgery. Neurosurg Clin N Am 6: 167–176
16. Cosgrove GR, Rauch SL (2003) Stereotactic cingulotomy. Neurosurg Clin N Am 14: 225–235
17. Culliton BJ (1976) Psychosurgery: national commission issues surprisingly favourable report. Science 194: 299–301
18. Dougherty DD, Baer L, Cosgrove GR *et al* (2002) Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. Am J Psychiatry 159: 269–275
19. Feldman RP, Alterman RL, Goodrich JT (2001) Contemporary psychosurgery and a look to the future. J Neurosurg 95: 944–956
20. Feldman RP, Goodrich JT (2001) Psychosurgery: a historical overview. Neurosurgery 48: 647–659
21. Fins JJ (2003) From psychosurgery to neuromodulation and palliation: history's lessons for the ethical conduct and regulation of neuropsychiatric research. Neurosurg Clin N Am 14: 303–319
22. Freeman W (1948) Transorbital leucotomy. Lancet 2: 371–373
23. Freeman W, Watts J (1942) Psychosurgery. Charles C. Thomas, Springfield

24. Fulton JF (1949) Physiology of the nervous system. Oxford University Press, New York
25. Fulton JF (1951) Frontal lobotomy and affective behavior: a neurophysiological analysis. WW Norton, New York
26. Goktepe EO, Young LB, Bridges PK *et al* (1975) A further review of the results of stereotactic subcaudate tractotomy. Br J Psychiatry 126: 270–280
27. Greenberg BD (2002) Update on deep brain stimulation. J ECT 18: 193–196
28. Gross RE (2004) Deep brain stimulation in the treatment of neurological and psychiatric disease. Expert Rev Neurotherapeutics 4(3): 465–478
29. Hariz M (2002) Complications of deep brain stimulation. Mov Disord 17 Suppl 3: S162–S166
30. Hay P, Sachdev P, Cumming S *et al* (1993) Treatment of obsessive-compulsive disorder by psychosurgery. Acta Psychiatr Scand 87: 197–207
31. Insel TR (1992) Toward a neuroanatomy of obsessive-compulsive disorder. Arch Gen Psychiatry 49: 739–744
32. Jacobsen CF (1935) Functions of frontal association area in primates. Arch Neurol Psychiatry 33: 558–569
33. Jenike MA (1998) Neurosurgical treatment of obsessive-compulsive disorder. Br J Psychiatry Suppl 35: 79–90
34. Jenike MA, Baer L, Ballantine T *et al* (1991) Cingulotomy for refractory obsessive-compulsive disorder: a long-term follow-up of 33 patients. Arch J Psychiatry 48: 548–555
35. Jimenez F, Velasco F, Salin-Pascual R *et al* (2005) A patient with resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. Neurosurgery 57: 585–593
36. Kelly D, Richardson A, Mitechell-Heggs N *et al* (1973) Sterotactic limbic leucotomy: a preliminary report on forty patients. Br J Psychiatry 123: 141–148
37. Knight GC (1964) The orbital cortex as an objective in the surgical treatment of mental illness. The development of the stereotactic approach. Br J Surg 51: 114–124
38. Kopell BH, Greenberg B, Rezai AR (2004) Deep brain stimulation for psychiatric disorders. J Clin Neurophysiol 21: 51–67
39. Leksell L (1971) Stereotaxis and radiosurgery. Springfield IL, Thomas
40. MacLean PD (1952) Some psychiatric implications of physiological studies on the frontotemporal portion of the limbic system (visceral brain). Electroencephalogr Clin Neurophysiol 4: 407–418
41. MacLean PD (1955) The limbic system (''visceral brain'') and emotional behaviour. Arch Neurol Psychiatry 73: 130–134
42. Mark VH, Ervin FR (1970) Violence and the brain. Harper and Row, New York
43. Mashour GA, Walker EE, Martuza RL (2005) Psychosurgery: past, present, and future. Brain Res Rev 48: 409–419
44. Mayberg HS, Lozano AM, Voon V *et al* (2005) Deep brain stimulation for treatment-resistant depression. Neuron 45: 651–660
45. Mayberg HS, Starkstein SE, Peyser CE *et al* (1992) Paralimbic frontal lobe hypometabolism in depression associated with Huntington's disease. Neurology 42: 1791–1797
46. Meyerson BA (1998) Neurosurgical treatment of mental disorders: introduction and indications. In: Gildenberg PL, Tasker RR (eds) Textbook of stereotactic and functional neurosurgery. McGraw-Hill, USA, pp 1955–1964
47. Mindus P (1993) Present-day indications for capsulotomy. Acta Neurochir Suppl 58: 29–33
48. Mindus P, Bengstrom K, Levander SE *et al* (1987) Magnetic resonance images related to clinical outcome after psychosurgical intervention in severe anxiety disorder. J Neurol Neurosurg Psychiatry 50: 1288–1293
49. Mindus P, Rasmussen SA, Lindquist C (1994) Neurosurgical treatment for refractory obsessive-compulsive disorder: implications for understanding frontal lobe function. J Neuropsychiatry 6: 467–477
50. Moniz E (1936) Essai d' un traitement chirurgical de certaine psychoses. Bull Acad Med 115: 385–393
51. Moniz E (1937) Prefrontal leucotomy in the treatment of mental disorders. Am J Psychiatry 93: 1379–1385
52. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1977) Use of psychosurgery in practice and research: report and recommendations of National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Fed Regist 42: 26318–26332
53. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B (1999) Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet 354: 1526
54. Nuttin BJ, Gabriels LA, Cosyns PR, Meyerson BA *et al* (2003) Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 52: 1263–1274
55. Nuttin B, Gybels J, Cosyns P *et al* (2002) OCD -DBS collaborative group. Deep Brain Stimulation for Psychiatric Disorders
56. Nuttin B, Gybels J, Cosyns P *et al* (2003) Deep brain stimulation for psychiatric disorders. Clin N Am 14: xv–xvi
57. Papez JW (1937) A proposed mechanism of emotion. Arch Neurol Psychiatry 38: 725–737
58. Pippard J (1962) Leucotomy in Britain today. J Ment Sci 108: 249–255
59. Pool JL (1954) Psychosurgery in older people. J Am Geriatr Soc 2: 456–465
60. Robinson D, Wu H, Munne LA *et al* (1995) Reduced caudate volume in obsessive compulsive disorder. Arch Gen Psychiatry 52: 393–398
61. Sakas DE, Panourias IG (2006) Rostral cingulate gyrus: A putative target for deep brain stimulation in treatment-refractory depression. Med Hypotheses 66(3): 491–494
62. Saxena S, Brody AL, Maidment KM *et al* (1999) Localized orbitofrontal and subcortical metabolic changes and predictors or response to paroxetine treatment. I: obsessive-compulsive disorder. Neuropsychopharmacology 21: 683–693
63. Scarone S, Colombo C, Livian S *et al* (1992) Increased right caudate nucleus size in obsessive-compulsive disorder: detection and magnetic resonance imaging. Psychiatry Res 45: 115–121
64. Schlaepfer T, Lieb K (2005) Deep brain stimulation for the treatment of refractory depression. Lancet 366: 1420–1422
65. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z *et al* (2004) Limbic-frontal circuitry in major depression: a path modeling metanalysis. Neuroimage 22: 409–418
66. Spiegel EA, Wycis HT, Marks M, Lee ASJ (1947) Sterotaxic apparatus for operations on the human brain. Science 106: 349–350
67. Sprangler WJ, Cosgrove GR, Ballantine HT Jr *et al* (1996) Magnetic resonance image-guided stereotactic cingulotomy for intractable psychiatric disease. Neurosurgery 38: 1071–1078
68. Sturm V, Lenartz D, Koulousakis A, Treuer H *et al* (2003) The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. J Chem Neuroanat 26: 293–299
69. Swayze VW (1995) Frontal leucotomy and related psychosurgical procedures in the era before antipsychotics (1935–1954). A historical overview. Am J Psych 152: 505–515
70. Tooth GC, Newton MP (1961) Leucotomy in England and Wales (1942–1954). Report on public health and medical subjects. HMSO, London, p 104
71. Valenstein ES (1986) Great and desperate cures, Basic Books, New York
72. Wernicke C (1874) Der Aphasische Symptomen Complex. Max Cohn & Weigert, Breslau
73. Willis T (1664) Cerebri anatome. Martyn & Allestry, London

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Behavioural and physiological effects of electrical stimulation in the nucleus accumbens: a review

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Summary

Electrical stimulation (ES) in the brain is becoming a new treatment option in patients with treatment-resistant obsessive-compulsive disorder (OCD). A possible brain target might be the nucleus accumbens (NACC). This review aims to summarise the behavioural and physiological effects of ES in the NACC in humans and in animals and to discuss these findings with regard to neuroanatomical, electrophysiological and behavioural insights. The results clearly demonstrate that ES in the NACC has an effect on reward, activity, fight-or-flight, exploratory behaviour and food intake, with evidence for only moderate physiological effects. Seizures were rarely observed. Finally, the results of ES studies in patients with treatment-resistant OCD and in animal models for OCD are promising.

Keywords: Neuromodulation; electrical stimulation; behaviour; nucleus accumbens; ventral striatum; review.

Abbreviations

5-HT serotonin; *6-OH-DA* 6-hydroxydopamine; *AMY* amygdala; *DA* dopamine; *DAergic* dopaminergic; *DOPAC* 3,4-dihydroxyphenylacetic acid; *DTγE* (Des-Tyr[1])-γ-endorphin; *ES* electrical stimulation; *FCV* fast cyclic voltammetry; *GABA* gamma-aminobutyric acid; *HC* hippocampus; *HVA* homovanillic acid; *ICSS* intracranial self-stimulation; *LH* lateral hypothalamus; *MD* mediodorsal thalamic nucleus; *MDMA* methylenedioxymethamphetamine; *MFB* medial forebrain bundle; *NA* noradrenaline; *NACC* nucleus accumbens; *SN* substantia nigra; *SNc* substantia nigra pars compacta; *SNr* substantia nigra pars reticulata; *VP* ventral pallidum; *VTA* ventral tegmental area.

Introduction

Some patients with obsessive-compulsive disorder (OCD) are treatment-refractory to conventional behavioural therapy and/or pharmacological treatment. Part of these patients may benefit from a neurosurgical lesion in a specific brain target [36, 46]. In one of those brain targets, the anterior limbs of the internal capsule [60, 67], we demonstrated that high frequency ES was also therapeutically effective [77]. In contrast to neurosurgical lesions, electrical brain stimulation is a reversible technique, which is a major advantage in case severe side effects occur. Moreover, in Parkinson's disease ES has a lower rate of side effects compared to lesioning with thermocoagulation [103].

Although the clinical outcome of ES in the anterior limbs of the internal capsule is satisfactory, high voltage levels are necessary. Hence, the battery lifetime is limited to 4–12 months requiring frequent exchange of the batteries under local anaesthetic, limiting the comfort of the patient. One of the strategies to surpass the high energy consumption is to search for other brain targets that yield the same or even better therapeutic results with a lower voltage.

A possible new target for ES in patients with treatment-refractory OCD might be the nucleus acccumbens (NACC) [1, 117], which participates as the antero-ventral part of the ventral striatum in the cortico-striato-pallido-thalamo-cortical circuitry. Functional brain imaging studies indicate that this circuitry is involved in OCD [100]. Additional evidence for the involvement of the NACC in OCD comes from stereotactic lesioning studies in the anterior limbs of the internal capsule. Lesioning of the ventro-caudal part of the internal capsule was imperative for successful treatment. It is likely that such a lesion also affects the NACC [67, 110]. The

current article reviews the reported behavioural and physiological effects of ES in the NACC of humans and different mammalian species.

Methods and results

We performed a computer-aided search of Pubmed using the keywords 'nucleus accumbens', 'ventral striatum' and 'ES' and selected articles dealing with the behavioural and physiological effects of ES in the NACC. In addition, we searched the reference lists of these selected relevant articles. Because we cannot read or comprehend Chinese language one article was rejected [53]. The results of our search are described in the following sections.

Anatomy of the NACC

Core and shell NACC

The NACC has been subdivided in a core and shell subregion based on cytoarchitectonic and neurotransmitter characteristics and differences in afferent and efferent connections [142]. The shell is situated in the medial

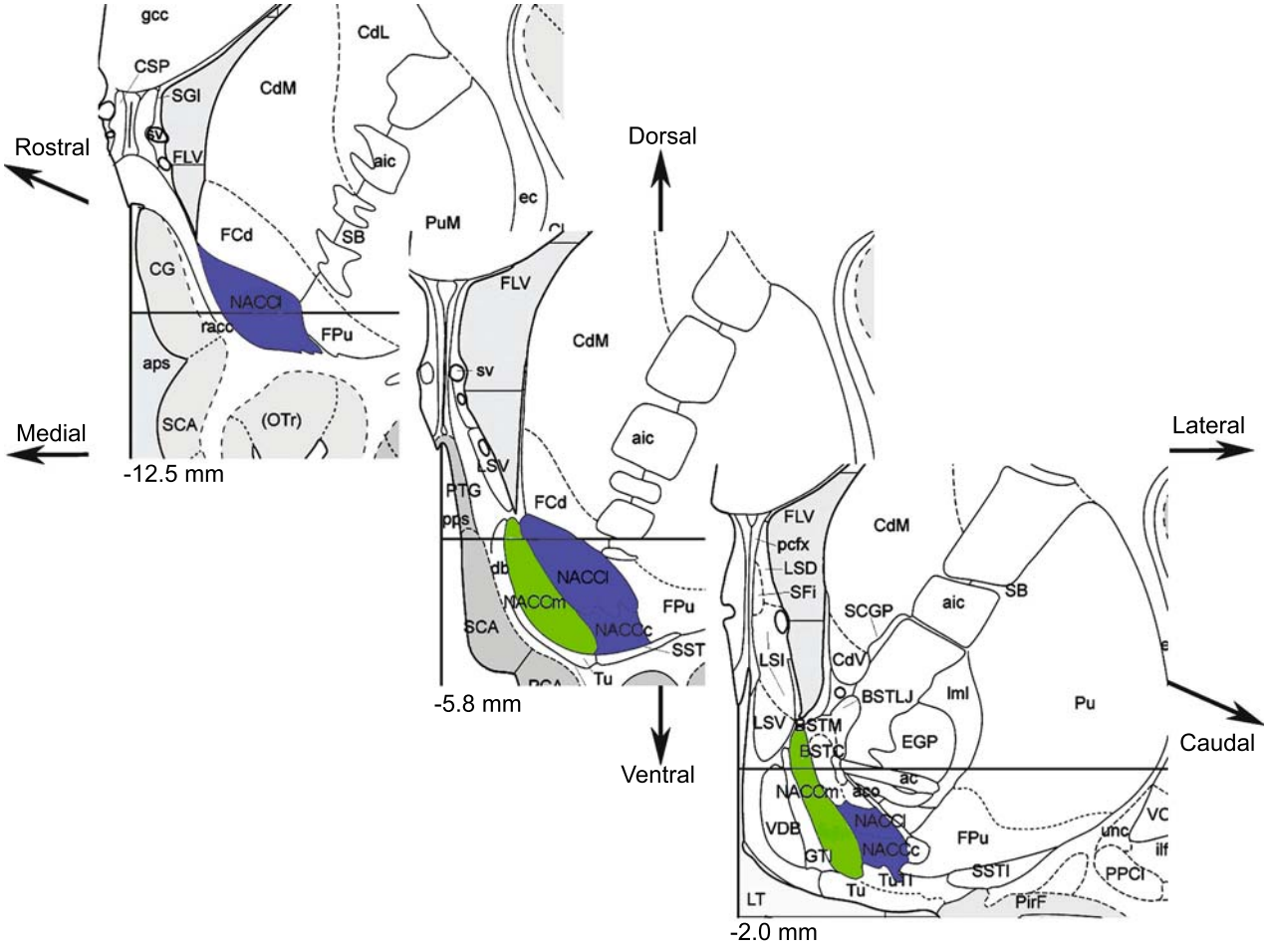

Fig. 1. NACC core and shell: Graphical representation of coronal sections through the human NACC core (blue) and shell (green) and its surrounding structures (modified from the atlas of Mai *et al.* 63). The distance from the midpoint of the anterior commissure at the midline is denoted below each coronal section. *ac* Anterior commissure; *aco* anterior commissure, olfactory limb; *aic* anterior limb of internal capsule; *aps* anterior parolfactory nucleus; *BSTC* bed nucleus of the stria terminalis, central division; *BSTLJ* bed nucleus of the stria terminalis, lateral division, juxtacapsular part; *BSTM* bed nucleus of the stria terminalis, medial division; *CdL* lateral caudate nucleus; *CdM* medial caudate nucleus; *CdV* ventral caudate nucleus; *CG* cingulate gyrus; *CSP* cavity of septum pellucidum; *db* diagonal band; *ec* external capsule; *EGP* external globus pallidus; *FCd* caudate fundus region; *FLV* frontal horn of the lateral ventricle; *FPu* putaminal fundus region; *gcc* genu of the corpus callosum; *GTI* great terminal island; *lml* external medullary lamina of the globus pallidus; *LSD* dorsolateral septal nucleus; *LSI* intermediolateral septal nucleus; *LSV* ventrolateral septal nucleus; *NACCc* acccumbens nucleus, central (subventricular) part (core); *NACCl* accumbens nucleus, lateral subventricular part (core); *NACCm* accumbens nucleus, medial (subventricular) part (shell); *OTr* olfactory trigone; *pcfx* precommissural fornix; *PirF* (pre-)piriform cortex, frontal area; *PPCI* (pre-) piriform claustrum; *pps* posterior parolfactory sulcus; *PTG* paraterminal gyrus; *PuM* medial putamen; *racc* radiation of corpus callosum; *SB* striatal cell bridges; *SCA* subcallosal area; *SCGP* supracapsular part of the globus pallidus; *SFi* septofimbrial nucleus; *SGI* substantia gliosa; *SSTI* substriatal terminal island; *sv* septal vein; *Tu* olfactory tubercle; *TuTl* tubercular terminal island(s); *unc* uncinate fasciculus; *VDB* vertical limb of the diagonal band

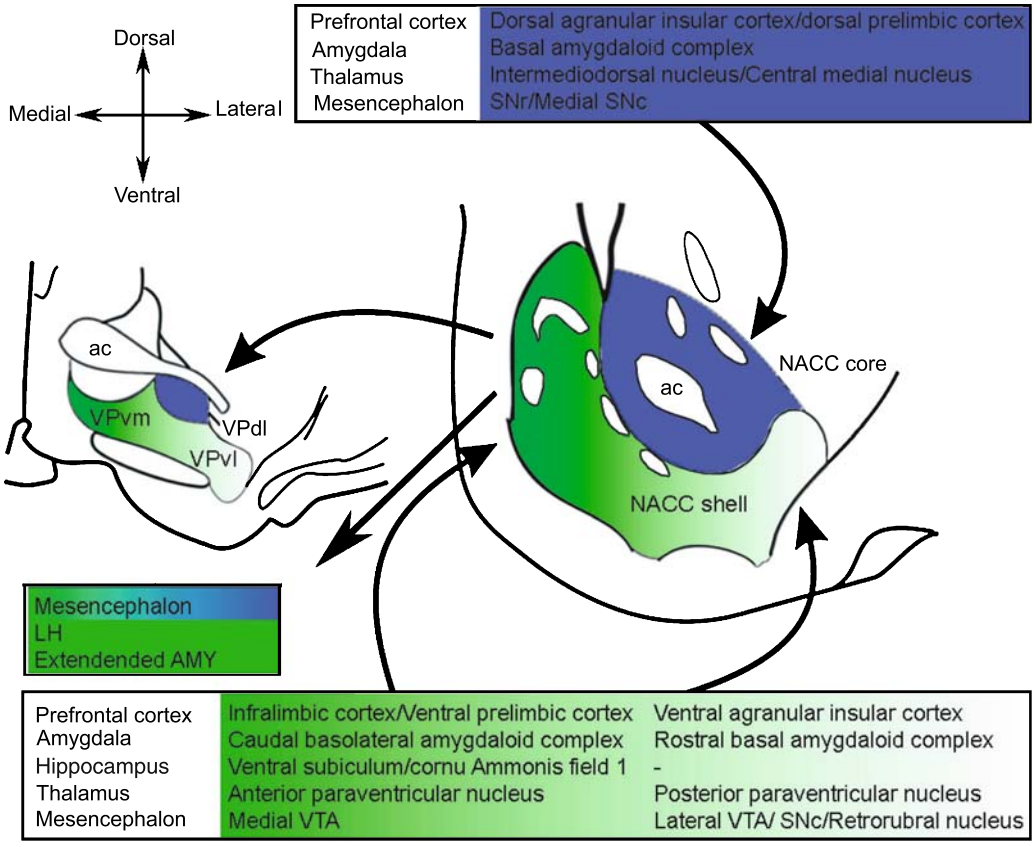

Fig. 2. Neuroanatomical connections of the NACC: The topographical organisation of the main afferents and the VP efferents of the NACC core and shell is represented in a transverse section through the NACC (right) and the VP (left) (modified from Ref 15). *ac* Anterior commissure; *NACC* nucleus accumbens; *VPdl* dorsolateral ventral pallidum; *VPvl* ventrolateral ventral pallidum; *VPvm* ventromedial ventral pallidum

and ventral part of the caudal two thirds of the NACC and encompasses the core, situated laterally in the NACC [19] (Fig. 1). The NACC core is connected to the extrapyramidal motor system and the NACC shell to limbic brain areas mediating emotional processes. In addition to the NACC shell and core, some authors have recognized a rostral pole [152].

Main afferent and efferent projections

We shortly summarize the main connections of the NACC (see Fig. 2) but refer to other reviews for in depth expositions of the NACC neuroanatomy in the rat [37] and nonhuman primates [39]. For a topographical organisation of the connections of the NACC core and the shell, we refer to the Fig. 2 (obtained with permission from 37).

The NACC receives mainly glutamatergic projections from the amygdala (AMY) [92], hippocampus (HC) [17, 61, 121, 135, 150], thalamus [6, 9] and prefrontal cortex (PFC) [11, 13, 23, 34, 71, 72, 105, 113] and a dopaminergic (DAergic) projection from the mesencephalon, i.e. ventral tegmental area (VTA) and substantia nigra (SN) [22, 85]. The major efferent projection from the NACC terminates in the ventral pallidum (VP) and is principally gamma-aminobutyric acid (GABA)ergic [14, 41, 137, 143]. The ventral pallidum, in turn, projects strongly to the substantia nigra pars compacta (mediolateral part) as well as to the limbic part of the subthalamic nucleus and its extensions into the local hypothalamus [38]. In addition, the NACC provides a recurrent projection to the VTA and SN in the mesencephalon [41]. An important difference between NACC core and shell is the efferent projection from the NACC shell to the lateral hypothalamus (LH) and the extended AMY, which does not exist in the NACC core [41].

Signal processing in the NACC

'Up' and 'down' membrane potential states

More than 90% of the projection neurons in the NACC are medium-sized neurons with spines on their dendrites [4, 12, 79]. These neurons show membrane

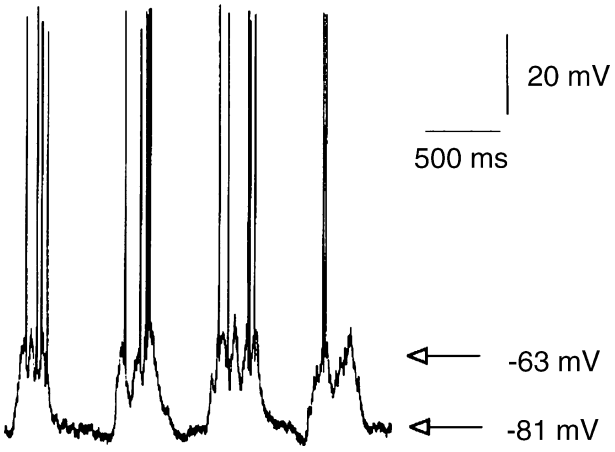

Fig. 3. Typical firing pattern of NACC neurons: Typical firing pattern of most NACC neurons exhibit 'up' and 'down' states in their membrane potential. Action potential firing is only observed during these 'up' events (reprinted from O'Donnell, 1999 [46])

potential shifts (±20 mV) from a negative 'down' state to a depolarized 'up' state [141] (Fig. 3), which are regulated by inputs from the HC [80] and the VTA [35]. The potential shifts bring the membrane potential during 100–1000 ms close to the firing threshold enabling other inputs (e.g. from the PFC) to evoke action potentials in the NACC (see Fig. 3). Hence, afferents from the HC and the VTA are able to gate other inputs. In accordance, slow frequency firing was recorded in the NACC during the 'up' state membrane transitions, taking place at a frequency less than 1 Hz [35].

Neuronal ensembles

The transitions in membrane potentials to the 'up' state occur synchronously in ensembles of NACC neurons, rather than in the global NACC or in single NACC neurons [81]. Many of the afferent projections from the abovementioned brain areas converge their input on single NACC neurons and their dendrites within these ensembles [18, 106]. Based on the topographical organisation of afferent connections to the NACC, each of these ensembles integrates different inputs. Likewise, the NACC ensembles relay the input to distinct output areas upon activation.

Presynaptic modulation of input

In addition to directly modulating the neuronal activity of NACC neurons, afferent projections also modulate the input of other afferents. For instance, VTA activation of D2 receptors on terminals of hippocampal afferents to the NACC, enhances the excitability of these neurons [136].

Behavioural effects of ES in the NACC

ES in the NACC has an effect on a wide range of behaviours, which will be discussed in the following sections. ES in the NACC has rewarding properties: animals with an electrode in the NACC will perform *self-stimulation (intracranial self-stimulation)* to apply electrical pulses in the NACC. In addition, ES in the NACC influences activity, fight-or-flight behaviour, exploratory behaviour and food intake. The effect of ES in the NACC on OCD symptoms in animal models and humans will be discussed in the following sections. Finally, the risk for seizures will be evaluated.

Reward – intracranial self stimulation (ICSS)

In 1954, Olds and Milner discovered that rats perform an operant task to apply trains of electrical pulses in the septal area and other regions of the brain [82]. This behaviour, called intracranial self-stimulation, has rewarding properties probably by activation of neural systems, which mediate natural rewards like food intake [126]. Therefore, ICSS has been used in models for depression to quantify the ability to experience pleasure. In these models, a decrease in ICSS rate or an increased threshold for ICSS is indicative for depression. The clinical effect of supposed new antidepressants was predicted in the animal models by evaluating the effect on ICSS rate or threshold. The NACC is one of the brain targets where it is possible to induce ICSS (for references, see below). In the NACC, ICSS is accompanied by a highly stereotypic backing away from the lever, sniffing, licking and digging [69].

Regional differences in ICSS rate within the NACC

The rate of ICSS in the NACC may be more than 20 per minute [95]. It depends on the NACC subregion where the electrode tip is located. In mice, differences in ICSS rates were noticed with rostro-caudal and dorso-ventral gradients. In the dorsal NACC, ICSS rates were very high rostrally but decreased more caudally. To the contrary, in the ventral NACC, ICSS rates were almost absent rostrally whereas good ICSS rates were observed caudally, with even higher values than in the dorsal NACC at this level. In regions intermediate between dorsal and ventral NACC, there was generally a good responding with higher ICSS rates caudally then rostrally [147]. In another study, a medio-lateral gradient was observed with higher ICSS rates in the medial NACC [89]. Only in one study,

in Rhesus monkeys, no ICSS was observed in the NACC [133].

ICSS in the NACC versus ICSS in other brain targets

There are also differences in ICSS rates between the NACC and other brain regions. ICSS rates in the NACC are lower than in the LH [123, 93], the medial forebrain bundle (MFB) [99, 144], the VTA [69, 123], the PFC [109] and the substantia nigra (SN) [8, 90, 144] but higher than in the caudatoputamen, the AMY and the olfactory tubercle [89]. One study found no difference in ICSS rate in the NACC versus the SN [21]. Except for the above-mentioned studies, no other comparisons in ICSS rate between NACC and other brain targets were reported. These differences in ICSS rates between brain areas, however, may depend on the duration of the test period. For instance, it was reported that rats self-stimulate at the same rate in the NACC like in the LH but that rats with an ICSS electrode in the NACC need more days to achieve these equal ICSS rates [47]. Differences in the number of days to acquire ICSS were also observed within the NACC itself. ICSS was faster acquired in dorsomedial anterior versus posterior NACC subregions [147].

Stimulation parameters

In the ICSS paradigm, animals work to obtain *trains of electrical pulses* (train duration: 0.1–1 s [99, 149] in a rewarding brain area. In the NACC, animals will respond with higher ICSS lever pressing rates if the *frequency* of these pulses in the train is increased, with a plateau at approximately 60 Hz [123]. Also changes in pulse parameters influence the ICSS rate. The ICSS rate increases as a function of *current intensity* [8, 47, 69, 109] until a plateau is reached [90]. In rats with a lesion in the VTA (and consequently with a destruction of DAergic input to the NACC), ICSS decreased at higher current intensities [21]. As far as we know, there are no studies in which the effects of different *pulse widths* were compared. In most of the studies, pulse widths between 0.2 and 0.3 ms were used [59, 148]. Typical pulse *waveforms* used to induce ICSS in the NACC were monophasic [90] and biphasic square [148] wave pulses, as well as sine wave pulses [89].

Influence of stress on ICSS in the NACC

The NACC is not only involved in processing reward but also in mediating stress responses [130] (see also below: Fight-or-flight). Exposure to acute stress results in an enhanced DA and serotonin (5-HT) release in the NACC [7]. There is evidence that stress decreases the ability to experience NACC mediated reward. Uncontrollable footshock specifically decreases the ICSS rate in the NACC immediately after and even 7 days after application of the stressor, however, without affecting ICSS rate in the SN [8]. Desmethylimipramine, a tricyclic antidepressant, reverses this footshock-induced decrease in ICSS rate in the NACC [146]. Similar findings were observed after immunological stress: injection with sheep red blood cells in mice, an antigen that induces a peak immune response at the fourth day after inoculation, reduced the response rate for ICSS in the NACC on the third, the fourth and the fifth day after inoculation. The dose of sheep red blood cells is known to influence DA activity in the NACC. Another stressor, food deprivation, had no effect on the response rate for ICSS in the NACC. This is quite remarkable since the NACC is known to be involved in food intake [54] (see also below: Food intake). In other brain areas, like the MFB [99], the LH and the substantia innominata [95] ICSS rate clearly increased after food deprivation. Finally, it was observed that the effect of stress on ICSS in the NACC depends on the mouse strain [148]. While there was a decrease in ICSS rate in DBA/2J mice after footshock stress, an increase in ICSS rate was observed in BALB/cByJ mice and no change in C57BL/6Jmice.

Effect of drugs or brain lesions on ICSS in the NACC

One way to study the mechanism of ICSS in the NACC is to administer pharmacological agents of different classes and to evaluate the effect on ICSS. For a summary of the findings of the literature we refer to Table 2.

CNS stimulants

Cocaine, amphetamine and methylenedioxymethamphetamine (MDMA) are three stimulants of the central nervous system (CNS), which all induce a significant increase in DA metabolism in the NACC (Table 1). After administration of these stimulants, rats will start ICSS in the NACC at lower stimulation frequencies and will press more and at higher rates [84, 90, 149]. Only for MDMA, a derivative of amphetamine commonly known as ecstasy, a decrease in the total number of presses was observed. MDMA affects the serotonergic system and

Table 1. *Drug effects on ICSS in the NACC*

Drug	Species	Admin. route	Dose	Effect	Ref.
CNS stimulants					
Cocaine – Mainly blocks the uptake of DA, 5-HT and NA at the neuronal plasma membrane transporters [116]; rewarding properties are mediated via simultaneous actions on DA, 5-HT and NA transporters [116]; 0.5 and 1 mg/kg systemic cocaine increases DA in the NACC shell [87]	Wistar rat	IP	5 mg/kg 15 mg/kg	↑ ICSS rate & maximal rate, ↓ stimulation frequency threshold	[59]
Amphetamine	Wistar rat	SC	100 µg	↑ ICSS rate	[118]
– release of monoamines (especially DA and NA) from nerve terminals; 0.5–3 mg/kg amphetamine increases DA in the NACC 7–25-fold [52, 88];	Wistar rat	IP	0.3 mg/kg 1 mg/kg	↑ ICSS rate; highest dose: ↑ maximal rate & ↓ stimulation threshold	[59]
1–3 mg/kg reduces 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the NACC with more than 50% [52]; no effect on 5-HT levels in the NACC, except at high dose (9 mg/kg)	Charles River rats	IP	1 mg/kg	↑ ICSS rate, also increase in function of time	[90]
	Wistar rat	IP	1 mg/kg	↑ ICSS rate	[84]
+ 6-OH-DA lesion	Wistar rat	LH	not applicable	lesions neutralized the effect of amphetamine	[84]
MDMA – binds to DA, 5-HT and NA transporters and reverses the action of these transporters, resulting in the release of DA, 5-HT and NA in the synapse; 1–3 mg/kg induces a 3 fold increase of DA and 5-HT in the NACC [52]; 1–3 mg/kg increases DOPAC in the NACC by 75–80% [52]; 3 mg/kg decreased the 5-HT metabolite 5-HIAA by 60% [52]	Wistar rat	IP	0.5 mg/kg 2 mg/kg 4 mg/kg	highest dose: ↓ ICSS total lever presses & stimulation threshold	[59]
+ Methysergide antagonist at 5-HT2 receptor and agonist at some 5-HT1 receptors [108]	Wistar rat	IP	5 mg/kg	reversal of MDMA induced decrease in ICSS rate & maximal rate	[59]
+ Ketanserin 5-HT2 receptor antagonist	Wistar rat	IP		no effect on MDMA induced decrease	[59]
Methysergide	Wistar rat	IP	5 mg/kg	no effect	[59]
D2-like DA antagonists					
Haloperidol	Wistar rat	SC	5 µg	↓ ICSS rate	[118]
– D2-like DA antagonist with α-adrenergic receptor affinity; 0.1–1 mg/kg increases DA release in the NACC by 50% [16, 58]	Rhesus monkey	IM	0.1–0.4 mg/kg (1^*/2d) during 3 wks	ICSS at 25–75% lower stimulation amplitudes. This is reversible.	[104]
	Wistar rat	IP	0.07 mg/kg 0.2 mg/kg 0.67 mg/kg	↓ ICSS rate	[76]
+ Hyoscine muscarinic acetylcholine receptor antagonist; 0.5 mg/kg increases DA in the NACC [45]	Wistar rat	IP	0.3 mg/kg 1.5 mg/kg	attenuation of haloperidol induced decrease in ICSS rate	
Spiroperidol – D2-like DA antagonist	Albino rat	NACC homo-lateral	1 µg	58%↓ ICSS rate (range 25–83%)	[69]
		NACC contra-lateral	1 µg	no effect	

(*continued*)

Table 1 (*continued*)

Drug	Species	Admin. route	Dose	Effect	Ref.
Opioids and endorphins					
Naltrexone – μ opioid receptor antagonist [122]; lower affinity for δ and κ receptors, able to reverse agonists at δ and κ sites [122]; 1 mg/kg systemic naltrexone had no effect on basal DA in the NACC but reverses ethanol or food intake induced DA release in the NACC [5, 112]	Long-Evans rat	IP	2.5 mg/kg 5 mg/kg 10 mg/kg 20 mg/kg	↓ ICSS rate & ↑ stimulation frequency necessary to obtain the same ICSS rate, not dose dependent	[123]
(Des-Tyr^1)-γ-endorphin – endogenous non-opioid peptide which probably acts on presynaptic mesolimbic dopamine receptors [120]; DTγE has no effect on basal DA release in the NACC in vitro but suppressed K+-induced DA release [102]	Wistar rat	SC	2.5 μg/kg 25 μg/kg	↓ ICSS rate, dose dependent	[118]
α-endorphin – endogenous opioid peptide; 10 and 20 μg intracerebral a-endorphin tended to decrease DA and DOPAC in the striatum and 20 μg decreased HVA [51]	Wistar rat	SC	2.5 μg/kg 25 μg/kg	no effect	[118]
Tricyclic antidepressant					
Desipramine – tricyclic antidepressant; inhibition of NA re-uptake; 5 mg/kg systemic desipramine has no effect on DA, DOPAC or HVA in the NACC [83]; in vitro has no effect on DA release in the NACC induced by electrical stimulation in the NACC [48]	CD-1 mice	IP	5 mg/kg	no effect on ICSS rate when given alone, reversal of the reduction in ICSS induced by uncontrollable footshocks	[145] [146]

Summary of drug effects on ICSS in the NACC, including drug dose and administration route. A decrease in ICSS threshold indicates that lower current intensities are needed to induce the same ICSS rate. *ICSS* Intracranial self-stimulation; *IM* intramuscular; *IP* intraperitoneal; *LH* lateral hypothalamus; *NACC* nucleus accumbens; *SC* subcutaneous

Table 2. *Lesion effects on ICSS in the NACC*

Lesion type	Species	Target	Effect	Reference
6-OH-DA lesion	Wistar rat	LH	↓ ICSS rate at 1–3 days after lesion, no effect during next 18 sessions	[84]
RF lesion		VTA	↑ ICSS rate	[109]
Blockade	?	GABAergic input to the mesolimbic DA neurons	↑ ICSS rates of the NACC	personal communication [139]

Summary of the effects of lesions in the brain on ICSS in the NACC, including the type and the target of the lesion. *6-OH-DA* 6-hydroxydopamine; *DA* dopamine; *GABA*: gamma-aminobutyric acid; *ICSS* intracranial self-stimulation; *LH* lateral hypothalamus; *NACC* nucleus accumbens; *RF* radiofrequency; *SC* subcutaneous; *VTA* ventral tegmental area

often induces motor deficits known as the '5-HT syndrome' [59]. The decrease in lever pressing is probably due to these motor deficits: concomitant administration of MDMA and methysergide, a 5-HT2 antagonist and 5-HT1 agonist which prevents these motor deficits, increased the total number of presses and ICSS rate [59]. Single methysergide administration and augmentation of MDMA with ketanserin, a drug related to methysergide but without 5-HT1 agonistic properties, had no effect. Therefore, it was concluded that the decrease in lever pressing with MDMA was due to 5-HT1 receptor mediated motor deficits.

D2-like DA antagonists

Acute administration of haloperidol and spiroperidol, two D2-like DA antagonists, decreases the ICSS rate in the NACC in rats [67, 76, 118]. Although haloperidol

may induce disturbances in motor performance [44], it is unlikely that motor deficits induced the decrease in ICSS rate. Indeed, injection of spiroperidol in the NACC only decreased the ICSS rate when it was on the same side of the ICSS electrode. The lack of effect on ICSS when injected contralateral to the ICSS electrode suggests that motor performance was intact [69]. The decrease in ICSS rate induced by haloperidol could be attenuated by administration of hyoscine (scopolamine), which is a muscarinic acetylcholine receptor antagonist [76]. Contrasting these results, one study reported that ICSS was facilitated after chronic haloperidol administration: monkeys started ICSS at lower stimulation amplitudes [104].

Opioids and endorphins

The effect of naltrexone, (Des-Tyr^1)-γ-endorphin (DTγE) and α-endorphin on ICSS in the NACC was verified. None of these agents influences basal DA release in the NACC but naltrexone and DTγE decrease evoked DA release in the NACC. It was observed that these two agents suppress ICSS in the NACC [118, 123]. In contrast, α-endorphin, has no effect on ICSS in the NACC.

Tricyclic antidepressant

Desipramine (desmethylimipramine) had no effect on ICSS in the NACC but could reverse the reduction in ICSS induced by uncontrollable footshocks [145, 146].

Brain lesions

The NACC receives a massive DAergic projection from the VTA, which is part of the mesolimbic projection. Interruption of this pathway with a 6-hydroxydopamine (6-OH-DA) lesion at the level of the LH, leads to a decrease in ICSS rate after three days [84]. After long-term recovery (21 days), however, this decrease in ICSS rate normalised and even tended to increase [84]. Indeed, Simon *et al.* demonstrated an increase in ICSS in rats with a radiofrequency lesion in the VTA after 17 days [109]. The discrepancy between the short- and long-term effects of a lesion in the afferent DAergic projection, might be attributed to increased sensitivity for DA in the NACC due to upregulation of postsynaptic DA receptors [31]. Probably therefore, no correlation was observed between the increase in ICSS rate and the decrease in DA concentration [109].

Dopamine

The studies on the effects of drugs and brain lesions on ICSS in the NACC, present evidence for the involvement of the DAergic system. Agents, which increase DA release in the NACC, are likely to increase the ICSS rate or lower its threshold and vice versa. Additional evidence comes from fast cyclic voltammetry (FCV) studies. DA is one of the neurotransmitters that oxidises after application of a voltage waveform. The resulting current flow can be measured and is proportional to the DA concentration at the microrecording electrode. With this technique, called FCV, an increase in extracellular fluid DA at a distance of 200–400 µm from the NACC stimulation electrode was measured *in vitro*. Local application of cocaine [125] facilitated DA release in the NACC induced by ES [10]. Other findings oppose the involvement of DA. Prado-Alcada and Wise mapped ICSS sites in different regions in the brain but discovered no close correspondence between the boundaries of the reward system and those of the DA terminal fields as revealed by DA fluorescence [89, 147]. However, ICSS in the medial and ventral NACC, corresponding to regions of DA and cholecystokinin (CCK) co-localization, was accompanied with significant elevations in motor activity [147].

Other behavioural effects of ES in the NACC

Activity

A significant increase in activity was reported following ES in the NACC in freely moving animals [32, 40] and in animals tested for ICSS [144], especially when stimulated in the medial NACC [147]. In addition, ES in the NACC influences changes in activity induced by the administration of different drugs. It enhanced the increase in activity after administration of amphetamine [56] and partly blocked the decrease in activity induced by a 5-HT1A agonist [117]. In contradiction to these increases in activity, stimulation in the NACC either had no effect [119] or even caused a decrease in activity in another study [93].

Fight-or-flight

Subjects facing threats dispose of a behavioural repertoire to handle the threat including opposing the threat (aggression or fighting) or flying away from it. The protagonists in the neurocircuitry involved in fight-or-flight behaviour are the AMY, the hypothalamus and the peri-

aqueductal gray [68]. The connectivity of the NACC with these brain areas suggests a role for the NACC as well in mediating these behavioural effects. Indeed, several experiments demonstrate that ES in the NACC can induce but also mitigate aggression and fighting behaviour, as well as fear.

Hano *et al.* observed violent running during NACC stimulation in rats, sometimes accompanied by backing, rearing on the hind paws, body shakes and increased muscular tone. Immediately after stimulation they noticed an increased excitement and aggression [40]. In accordance, ES in the NACC in male western fence lizards induced species-specific assertion display and challenge behaviour. In no case did stimulation elicit proper fighting in these lizards [114]. Two other reports, however, report the induction of aggression by ES in the LH and the decrease of this aggression by concomitant ES in the NACC [32, 33]. During ES in the LH, touching the region of the mouth elicits a biting reflex in cats. Stimulation at 6 or 60 Hz amplitude-dependently reduced the size of the region where these biting reflexes could be elicited. At the highest voltage level, the region for biting reflex was even completely abolished.

The effect of ES in the NACC on fear also varied considerably between studies. In one article, a decrease in fear responses was observed in cats during stimulation in the NACC [128], while in another an arrest reaction (sudden interruption of all movements) and escape behaviour were elicited at threshold and suprathreshold stimulation amplitudes, respectively [75]. In the latter study, the escape response consisted of movement of the cat to another place in the observation box, accompanied by crouching and flattening of the ears. It was suggested that the arrest-escape response was mediated via the efferent pathway to the VP, since a kainic lesion in this area increased the NACC stimulation threshold significantly (+51%). Finally, in fully conscious but restricted monkeys, no escape-like behaviour was observed [133].

Exploratory behaviour

An increase in sniffing was observed at 6Hz stimulation in the NACC in cats. Above threshold voltage, stimulation caused sniffing, searching head movements, and in-and-out tongue movements [32]. In rats, continuous ES in the NACC also increased sniffing [40] and ICSS in the NACC increased normal sniffing [47] as well as amphetamine-induced sniffing [21]. ES during 10 days preceding the amphetamine injection had, however, no effect on amphetamine-induced sniffing [56]. Remarkably, in patients with OCD bilateral as well as unilateral ES produced a transient smell sensation. These olfactory perceptions were described as ''something burning'', ''stale air'', ''an old bag'', ''some sort of glue'', ''something sweet'', or ''as in nature''. One patient also tended to sniff the air in search of the source of the smell [27].

Food intake

Several interventions locally in the NACC influence feeding behaviour [151]. Upon ES in the NACC, increases as well as decreases in food intake were reported. In a food-reinforced task, food pellets were retrieved faster during ES in the NACC [119]. Also, upon termination of ICSS in the NACC, food intake was increased in normal rats, but decreased after amphetamine injections [21]. The decrease in the latter condition was larger than during amphetamine administration alone. Finally, a sudden interruption of all movements was observed in cats, including goal directed movements as those observed when the animals advance toward a dish of food [75].

ES resulted in considerable weight gain in 5 of 11 patients suffering from treatment refractory OCD (increase of 26, 13, 12, 12 and 8 kg). The increase in body weight is probably not just a consequence of the relief of OCD symptoms in these patients, since it was not always proportionate to the improvement in symptoms. Neither is it possible to state whether the increase in body weight is due to a stimulation-induced change in the subjects metabolism or hunger drive. Although patients were not asked to keep food diaries, some of them report to eat more and to crave for sweet things. Others deny eating more, but gain weight nevertheless. During consecutive episodes without stimulation, patients sometimes lost some of the gained weight. These effects of ES in the NACC on food intake are probably mediated by the connections of the NACC, mainly the mediodorsal shell, to the LH.

Seizures

Upon termination of stimulation, seizure like behaviour characterised by extreme hyperactivity, loud meowing, urination, and profuse salivation was observed in one cat (stimulation parameters: monophasic pulses, 0.5 ms pulse duration and 60 Hz frequency) [32]. In the ICSS experiments of Jenkins *et al.*, all rats stimulated in the NACC showed involuntary motor effects gradually

increasing during 3 weeks, comprising at first wet-dog shakes, eventually developing in full clonic seizures, which increased in frequency and severity (variable train duration, biphasic pulses, 0.2 ms pulse duration, 250–400 μA, and 100 Hz frequency) [47]. In humans, no seizures were observed in the region of the anterior limbs of the internal capsule and the NACC, although stimulation was also performed with relative large pulse widths (0.06–0.45 ms) and at high frequency (100–130 Hz).

Effects of ES in the NACC on compulsive behaviour

Animal models of obsessive-compulsive disorder

To examine whether ES in the NACC shell might benefit patients with treatment-refractory OCD, we electrically stimulated in the T-maze and the schedule-induced polydipsia animal model [117]. Spontaneous alternation behaviour is the natural tendency of most species to successively explore both arms of a T-maze alternately, provided the two goal boxes are equally reinforced. Subcutaneous injection of the selective 5-HT 1A receptor agonist 8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide reduces this alternation behaviour. This behaviour models the compulsive and repetitive behaviour of patients suffering from OCD [134]. In our experiments, we found that a lesion and ES in the NACC had the same behavioural effects in this model. However, alternation behaviour further decreased, suggesting that ES in the NACC would not benefit patients with OCD [117].

In the schedule-induced polydipsia model, hungry rats that receive a food pellet every minute will drink water after each pellet delivery, what also models compulsive and repetitive behaviour of human patients [132]. The total amount of water intake during the test sessions is inappropriate and even toxic especially when considering that the animals are in a deprived state (80% of normal body weight). In contrast to earlier findings in the T-maze model, we observed a stimulation amplitude-dependent reduction of schedule-induced polydipsia at high frequency but not at low frequency stimulation (unpublished personal observations). Finally, high-frequency stimulation in the NACC core decreased quinpirole-induced compulsive checking behaviour in rats [129]. In this animal model, quinpirole-sensitised rats return more often to their home cage in an open field, that models compulsive checking behaviour in patients suffering from obsessive-compulsive disorder [111].

OCD patients

In 1999, we implanted electrodes in the anterior limbs of the internal capsule of 4 treatment-resistant OCD patients with the most ventral contact (contact 0) being located near to or in the NACC. In three of them, marked beneficial effects could be demonstrated during acute test sessions [77]. In a subsequent blinded crossover design with randomly chronic stimulation on and off, a significant decrease on the Yale-Brown Obsessive Compulsive Scale and Clinical Global Severity scores was observed in 4 of 6 patients [78]. These stimulation-induced effects could be maintained for at least 21 months. Sturm *et al.* also demonstrated a favourable outcome of ES in the NACC in OCD and other anxiety disorders [100, 115]. Unipolar stimulation (90 μs, 130 Hz, 2–6.5 V) in the right NACC resulted in a significant reduction of the symptoms in 3 of 4 patients. Bipolar stimulation was tried in one patient without additional improvement of the symptoms. In the fourth patient, a displacement of the electrode resulted in missing of the target area that might explain the negative outcome in this patient. In accordance, Lippitz *et al.* [60] showed that capsulotomies in the right hemisphere were decisive for a favourable therapeutic outcome.

Physiological effects of ES in the NACC

Physiological parameters are likely to change in concert with behaviour. Nevertheless, we describe them in a separate section, since they were in some studies analysed under a general anaesthetic. Usually, ES in the NACC has only limited or inconsistent effects on physiological parameters.

Cardiovascular effects

ES in the NACC in freely-moving rats with parameters which induced ICSS, decreased the heart rate (-8.42 ± 14.21 beats/min; mean $\pm$ SD) and increased the mean arterial pressure (9.5 ± 7.7 mmHg) [96]. Usually, the changes in mean arterial pressure preceded the changes in heart rate. During fear experiments, however, either no or inconsistent changes in heart rate were observed [128]. The cardiac responses upon ES in anaesthetized rats were also very limited. Ross and Malmo [96] found no changes in heart rate and a decrease of the mean arterial pressure in rats.

Respiratory effects

In a fear conditioning paradigm, ES in the NACC had little or no effect on respiration in awake cats except in

one of the three subjects in which an increase in respiration rate and a decrease in respiration amplitude were found [128]. In anaesthetized monkeys, there was no respiratory depression and no change in respiratory pattern or galvanic skin response [133]. In 6 of 8 patients with treatment-resistant OCD, switching the stimulator 'on' and 'off' induced a deep sigh. In addition, acute hyperventilation was observed in 4 of these patients when stimulated with particular contact combinations [27].

Hormonal changes

Koikegami *et al.* [55] found that ovulation can be induced in the unanaesthetised rabbit (a reflex-ovulating species) following a one-hour period of NACC stimulation. Also, oxytocin is released upon ES in the NACC [2]. In contrast, in female Wistar rats, ES in the NACC during 15 minutes had no significant effect on the concentration of plasma luteinising hormone although a slight elevation was present after 30 minutes [98]. Plasma cortisol and growth hormone levels were non-significantly increased in anaesthetised rhesus monkeys [25, 26, 133].

Autonomic changes

ES induced no autonomic effects like pupillary dilatation and salivation in one study [32] but increased alertness and induced pupillary dilatation and mild piloerection in another [75]. During ES in OCD patients, paresthesias or a warm feeling in certain body parts or over the whole body with transpiration and flushing were observed in all of them. Brusque abolition of stimulation frequently caused a transient hot feeling, transpiration and flushing as well [27].

Mechanisms of ES in the NACC

ES is a rather new treatment option for patients with psychiatric disorders and is subject to improvement. Insight in the underlying mechanisms of ES may contribute to adaptations in the treatment. We already mentioned that FCV experiments indicate an increase in extracellular DA 200–400 µm from the stimulation electrode in the NACC. Hence, stimulation in the NACC is likely to propagate DA release from DAergic afferents from the VTA and the SN. It is known that DA in the NACC is able to suppress spontaneous or glutamate-evoked firing of NACC neurons [124, 131, 140]. Other evidence for the mechanism of NACC ES comes from electrophysiological experiments in which the effect of ES in the NACC on cellular activity in other brain targets was evaluated with microrecording. Neurons in brain targets lying downstream from the NACC may respond with excitation, inhibition, or a combination of both (early excitation followed by a period of inhibition and vice versa). Most neurons in the VP [20, 49, 64], the VTA [62, 138, 139] and the SN [101] were inhibited when single electrical pulses were given in the NACC, although excitation was also frequently observed in some studies [20, 57, 62]. The major part of the neurons in the AMY [66, 99] and the LH were excited with single pulse ES in the NACC [99]. Neurons in the tuberoinfundibular hypothalamus were equally excited and inhibited [98] and the effect of stimulation in the NACC on neurons in the supraoptic nucleus depended on the cell type (excitation in vasopressin cells, inhibition in oxytocin cells) [107]. Finally, also neurons in the orbitofrontal cortex [94] and mediodorsal thalamic nucleus (MD) [70] responded orthodromically upon ES in the NACC. In addition to orthodromic activation, several authors reported antidromic neuronal activation in brain areas with afferents to the NACC like the prelimbic and orbitofrontal cortex [71, 94], agranular cortex [71], entorhinal cortex [24], HC [24, 136], AMY [66], MD [70], VTA [15, 29, 62, 69], SN [69, 101] and the VP [138]. It is clear from these studies that single pulse ES influences activity in several brain areas lying afferent and efferent to the NACC. Whereas low frequency stimulation may exert effects similar to single pulse stimulation, the effect of high frequency stimulation is likely to differ.

Discussion

High variability of behavioural effects

The current overview of the behavioural changes demonstrates that ES in the NACC evokes a range of diverse effects. Depending on the publication even opposite observations were reported: ES in the NACC increased but also decreased aggressive behaviour, exploratory behaviour, food intake and compulsions in a model for OCD. In the next sections, we will discuss which factors might attribute to these contrasting results.

Motivational context

The effect of ES in the NACC may depend on the behavioural paradigm in which the animal was tested. Functionally, the NACC has been regarded as an inter-

face between motivation and action. Depending on the context and the motivational status of the subject, the response might differ. The NACC is anatomically well placed to accomplish this function. This nucleus receives its major afferents from the PFC (involved in higher functions like planning), the HC (memory and previous experiences) and the AMY (emotions), areas which belong to the limbic system, and projects towards the VP, the mesencephalon, both involved in motor behaviour, and the LH (e.g. food intake, ICSS, hormone regulation). Several of the afferents are able to gate information from other afferents by depolarising (or not) the membrane potential to an 'up' state (see Signal processing in the NACC).

NACC subregional differences

Histological staining and connectivity studies demonstrate that the NACC may be divided into a core and shell subregion (see: General features of the NACC). Connectivity patterns with other brain areas differ between and even within these subregions. Hence, depending on the electrode contact location, the behavioural and physiological effects may differ considerably. For instance, rostro-caudal, dorso-ventral and medio-lateral differences were observed between ICSS rates in the NACC [89, 147]. In these reports, high ICSS rates were observed in the ventral, caudal and medial NACC. It is likely that this subregion of the NACC with high rewarding properties is the most promising target for symptom relief with ES in humans suffering from psychiatric disorders in which depression is involved (like major depression disorder and obsessive-compulsive disorder with co-morbid depression). However, it is also possible that other structures, like the projections from the internal capsule or the nearby MFB mediate the good clinical effects of ES. The latter structure has higher rewarding properties (see above).

Stimulation parameters

The *amplitude* directly affects the extent of the stimulated region and the intensity of stimulation in nearby neurons.

The behavioural effects of *high versus low frequency* stimulation are often different and may be even opposite to each other. For instance, in Parkinson's disease, bradykinesia [73], tremor and the onset of myoclonic jerks [91] worsen at 5 Hz stimulation compared to stimulation with a frequency higher than 60 Hz, which leads to symptom relief. In the NACC ICSS studies, response rates depended on the stimulation frequency (see above). There is neurophysiological evidence for the differential effects of high versus low frequency stimulation in the NACC. When recording single cell activities in the LH upon trains of electrical pulses at 50 Hz in the NACC, 16 neurons were excited and 8 neurons were inhibited (of the 31 LH neurons tested in total). Of the 8 inhibited neurons, 4 were also inhibited by single pulse stimulation whereas the other 4 and the 16 neurons, which were excited by stimulus trains, responded with excitation followed by inhibition [99]. The pulse width, on the other hand, directly influences the neuronal target element that is stimulated. Cell bodies and dendrites are optimally stimulated with a pulse width in the 1–10 ms range, small axons in the 200–700 μs range and large myelinated axons in the 30–200 μs range [43]. It is not clear whether behavioural differences in this review could be attributed to different pulse widths.

Side effects

Approximately, half of the OCD patients experienced weight gain during ES in the region of the NACC. This weight gain is probably not only due to symptom relief but also to a change in metabolism or an increase in hunger drive. From the ES experiments in animals, there is only limited evidence for physiological side effects. An increased blood pressure was observed in awake animals [96], which may increase the risk for cardiovascular diseases when it is sustained for a long period of time. However, the duration of this acute experiment was too short to take definite conclusions on increased blood pressure. Moreover, the raise in blood pressure may be related to behavioural changes induced by the ES. Seizures were observed in two animal studies in which large pulse widths and high stimulation frequency were used [32, 47]. Since stimulation in OCD patients is performed with similar stimulation parameters, the clinician has to be aware not to induce seizures when stimulating electrically in the NACC. The respiratory and hormonal changes were only of minor significance.

Finally, application of an electrical current in the brain may lead to an electrolytic lesion around the electrode tip, which depends on the electrical current and on electrode properties. First, the magnitude of the *charge density* around the electrode tip determines the susceptibility to induce a lesion. *Charge density* is the ratio of the energy per pulse over the free contact area of the electrode [65]. Second, biphasic stimulation is less det-

rimental than monophasic since every pulse is followed by a second pulse of the opposite polarity [97]. Third, platinum-iridium electrodes diminish the risk to induce an electrolytic lesion tenfold versus stainless steel electrodes [74]. For clinical applications, platinum-iridium electrodes are used. Post-mortem studies in chronically stimulated patients with intractable pain or movement disorders did not reveal electrolytic lesions around the electrode tip (e.g. Ref [3]). In most studies, there was limited gliosis around the foreign implanted material without any further implications. In one study, there was a limited lesion in a patient with Parkinson's disease probably due to migration of the electrode [42]. In this patient, the migration of the electrode was without side effects but the good clinical outcome of stimulation disappeared. In these post-mortem studies, none of the deaths was related to ES.

ES in the NACC for OCD

In the T-maze model and the schedule-induced polydipsia model, opposite findings were observed. In the former model, there was an increase in compulsive behaviour while there was a decrease in the latter. In humans, there is evidence from a limited number of patients that ES has a beneficial effect on the OCD symptoms. This puts the validity of the T-maze model into question. A good model for a psychiatric disorder has a highly predictive face, construct and discriminant validity [127]. The primary application of predictive validity is to assess the effects of potential therapeutic treatments: the model has *predictive validity* if it successfully discriminates between effective and ineffective treatments. *Face validity* concerns the degree to what extent a model resembles the condition being modelled. *Construct validity* means that the procedure in the model is based on a sound theoretical rationale. Finally, a model for OCD has *discriminant validity* when the evidence points to OCD as the disorder being modelled as distinct from a different or a non-specific psychiatric disorder [30]. In our experiments [117], the T-maze model incorrectly predicts that ES in the NACC would worsen the symptoms of OCD in humans. The face and construct validity of both models were not studied in our experiments but are discussed elsewhere [86].

ES in the NACC for other psychiatric disorders

In patients with treatment-resistant OCD, electrical stimulation in the region of the NACC significantly decreases scores on the Hamilton Depression Scale (stimulation off: 26.7, stimulation on: 13.3) [27]. Therefore, a trial with electrical stimulation in the region of NACC was recently initiated in patients suffering from treatment-resistant major depression in our laboratory. Preliminary results are promising (own observations). Finally, electrical stimulation in the NACC may also be a potential new treatment in humans suffering from severe treatment-resistant addiction. The release of dopamine in the nucleus accumbens in humans is required in reward (e.g. drug high) and for the initiation of addiction [50]. Electrical stimulation in the NACC elicits DA release and is rewarding as well [125]. It is conceivable that certain stimulation parameters suppress or override addictive behavior. As far as we know the effect of ES in the NACC on addictive behavior has not been investigated in patients. However, a stereotactic lesion in the NACC reduced the relapse rate in patients suffering from addiction [28].

Conclusion

ICSS experiments suggest that stimulation in the NACC has rewarding properties. Pharmacological studies point to the involvement of the DAergic system in mediating these rewarding effects. In addition, ES in the NACC affects general activity, fight-and-flight behaviour, exploration and food intake, although contrasting effects were often observed. In parallel with ES experiments in animal models for compulsions in OCD, a good clinical outcome was observed in patients with OCD during stimulation in the NACC.

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References

1. Abbott A (2002) Brain implants show promise against obsessive disorder. Nature 419: 658
2. Aulsebrook LH, Holland RC (1969) Central regulation of oxytocin release with and without vasopressin release. Am J Physiol 216: 818–829
3. Baskin DS, Mehler WR, Hosobuchi Y, Richardson DE, Adams JE, Flitter MA (1986) Autopsy analysis of the safety, efficacy and cartography of electrical stimulation of the central gray in humans. Brain Res 371: 231–236
4. Belleau ML, Warren RA (2000) Postnatal development of electrophysiological properties of nucleus accumbens neurons. J Neurophysiol 84: 2204–2216

5. Benjamin D, Grant ER, Pohorecky LA (1993) Naltrexone reverses ethanol-induced dopamine release in the nucleus accumbens in awake, freely moving rats. Brain Res 621: 137–140
6. Berendse HW, Groenewegen HJ (1990) Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum. J Comp Neurol 299: 187–228
7. Bland ST, Twining C, Watkins LR, Maier SF (2003) Stressor controllability modulates stress-induced serotonin but not dopamine efflux in the nucleus accumbens shell. Synapse 49: 206–208
8. Bowers WJ, Zacharko RM, Anisman H (1987) Evaluation of stressor effects on intracranial self-stimulation from the nucleus accumbens and the substantia nigra in a current intensity paradigm. Behav Brain Res 23: 85–93
9. Brog JS, Salyapongse A, Deutch AY, Zahm DS (1993) The patterns of afferent innervation of the core and shell in the ''accumbens'' part of the rat ventral striatum: immunohistochemical detection of retrogradely transported fluoro-gold. J Comp Neurol 338: 255–278
10. Brun P, Steinberg R, Le Fur G, Soubrie P (1995) Blockade of neurotensin receptor by SR 48692 potentiates the facilitatory effect of haloperidol on the evoked in vivo dopamine release in the rat nucleus accumbens. J Neurochem 64: 2073–2079
11. Buchanan SL, Thompson RH, Maxwell BL, Powell DA (1994) Efferent connections of the medial prefrontal cortex in the rabbit. Exp Brain Res 100: 469–483
12. Chang HT, Kitai ST (1985) Projection neurons of the nucleus accumbens: an intracellular labeling study. Brain Res 347: 112–116
13. Chiba T, Kayahara T, Nakano K (2001) Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, Macaca fuscata. Brain Res 888: 83–101
14. Churchill L, Kalivas PW (1994) A topographically organized gamma-aminobutyric acid projection from the ventral pallidum to the nucleus accumbens in the rat. J Comp Neurol 345: 579–595
15. Clark D, Chiodo LA (1988) Electrophysiological and pharmacological characterization of identified nigrostriatal and mesoaccumbens dopamine neurons in the rat. Synapse 2: 474–485
16. De Deurwaerdere P, Moison D, Navailles S, Porras G, Spampinato U (2005) Regionally and functionally distinct serotonin receptors control in vivo dopamine outflow in the rat nucleus accumbens. J Neurochem 94: 140–149
17. DeFrance JF, Marchand JF, Sikes RW, Chronister RB, Hubbard JI (1985) Characterization of fimbria input to nucleus accumbens. J Neurophysiol 54: 1553–1567
18. DeFrance JF, Marchand JE, Stanley JC, Sikes RW, Chronister RB (1980) Convergence of excitatory amygdaloid and hippocampal input in the nucleus accumbens septi. Brain Res 185: 183–186
19. Deutch AY, Bourdelais AJ, Zahm DS (1993) The nucleus accumbens core and shell: accumbal compartments and their functional attributes. In: Kalivas PW, Barnes CD (eds) Limbic motor circuits and neuropsychiatry. CRC Press, pp 45–88
20. Dray A, Oakley NR (1978) Projections from nucleus accumbens to globus pallidus and substantia nigra in the rat. Experientia 34: 68–70
21. Eichler AJ, Antelman SM (1979) Sensitization to amphetamine and stress may involve nucleus accumbens and medial frontal cortex. Brain Res 176: 412–416
22. Fallon JH, Moore RY (1978) Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. J Comp Neurol 180: 545–580
23. Ferry AT, Ongur D, An X, Price JL (2000) Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. J Comp Neurol 425: 447–470
24. Finch DM, Gigg J, Tan AM, Kosoyan OP (1995) Neurophysiology and neuropharmacology of projections from entorhinal cortex to striatum in the rat. Brain Res 670: 233–247
25. Frankel RJ, Jenkins JS, Wright JJ, Khan MU (1976) Effect of brain stimulation on aldosterone secretion in the rhesus monkey (Macaca Mulatta). J Endocrinol 71: 383–391
26. Frankel RJ, Jenkins JS, Wright JJ (1978) Pituitary-adrenal response to stimulation of the limbic system and lateral hypothalamus in the rhesus monkey (Macacca mulatta). Acta Endocrinol (Copenh) 88: 209–216
27. Gabriëls L (2004) Electrical brain stimulation in treatment refractory obsessive-compulsive disorder, University of Antwerpen
28. Gao G, Wang X, He S, Li W, Wang Q, Liang Q, Zhao Y, Hou F, Chen L, Li A (2003) Clinical study for alleviating opiate drug psychological dependence by a method of ablating the nucleus accumbens with stereotactic surgery. Stereotact Funct Neurosurg 81: 96–104
29. Gariano RF, Tepper JM, Sawyer SF, Young SJ, Groves PM (1989) Mesocortical dopaminergic neurons. 1. Electrophysiological properties and evidence for soma-dendritic autoreceptors. Brain Res Bull 22: 511–516
30. Geyer MA, Markou A (1995) Animal models of psychiatric disorders. In: Bloom FE, Kupfer D (eds) Psychopharmacology: fourth generation of progress. Raven, New York, pp 787–798
31. Gnanalingham KK, Smith LA, Hunter AJ, Jenner P, Marsden CD (1993) Alterations in striatal and extrastriatal D-1 and D-2 dopamine receptors in the MPTP-treated common marmoset: an autoradiographic study. Synapse 14: 184–194
32. Goldstein JM, Siegel J (1980) Suppression of attack behavior in cats by stimulation of ventral tegmental area and nucleus accumbens. Brain Res 183: 181–192
33. Goldstein JM, Siegel J (1981) Stimulation of ventral tegmental area and nucleus accumbens reduce receptive fields for hypothalamic biting reflex in cats. Exp Neurol 72: 239–246
34. Gorelova N, Yang CR (1997) The course of neural projection from the prefrontal cortex to the nucleus accumbens in the rat. Neuroscience 76: 689–706
35. Goto Y, O'Donnell P (2001) Network synchrony in the nucleus accumbens in vivo. J Neurosci 21: 4498–4504
36. Greenberg BD, Price LH, Rauch SL, Friehs G, Noren G, Malone D, Carpenter LL, Rezai AR, Rasmussen SA (2003) Neurosurgery for intractable obsessive-compulsive disorder and depression: critical issues. Neurosurg Clin N Am 14: 199–212
37. Groenewegen HJ, Wright CI, Beijer AV, Voorn P (1999) Convergence and segregation of ventral striatal inputs and outputs. Ann N Y Acad Sci 877: 49–63
38. Haber SN, Lynd-Balta E, Mitchell SJ (1993) The organization of the descending ventral pallidal projections in the monkey. J Comp Neurol 329: 111–128
39. Haber SN, McFarland NR (1999) The concept of the ventral striatum in nonhuman primates. Ann N Y Acad Sci 877: 33–48
40. Hano J, Przewlocki R, Smialowska M, Chlapowska M, Rokosz-Pelc A (1978) The effect of electric stimulation of caudate nucleus and nucleus accumbens septi on serotonergic neurons in the rat brain. Pol J Pharmacol Pharm 30: 475–481
41. Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C (1991) Specificity in the projection patterns of accumbal core and shell in the rat. Neuroscience 41: 89–125
42. Henderson JM, O'Sullivan DJ, Pell M, Fung VS, Hely MA, Morris JG, Halliday GM (2001) Lesion of thalamic centromedian – parafascicular complex after chronic deep brain stimulation. Neurology 56: 1576–1579
43. Holsheimer J, Demeulemeester H, Nuttin B, de Sutter P (2000) Identification of the target neuronal elements in electrical deep brain stimulation. Eur J Neurosci 12: 4573–4577
44. Hunt GE, McGregor IS (2002) Contrasting effects of dopamine antagonists and frequency reduction on Fos expression induced by lateral hypothalamic stimulation. Behav Brain Res 132: 187–201

45. Ichikawa J, Chung YC, Li Z, Dai J, Meltzer HY (2002) Cholinergic modulation of basal and amphetamine-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens. Brain Res 958: 176–184
46. Jenike MA (1998) Neurosurgical treatment of obsessive-compulsive disorder. Br J Psychiatry Suppl 35: 79–90
47. Jenkins OF, Atrens DM, Jackson DM (1983) Self-stimulation of the nucleus accumbens and some comparisons with hypothalamic self-stimulation. Pharmacol Biochem Behav 18: 585–591
48. Jones SR, Garris PA, Kilts CD, Wightman RM (1995) Comparison of dopamine uptake in the basolateral amygdaloid nucleus, caudate-putamen, and nucleus accumbens of the rat. J Neurochem 64: 2581–2589
49. Jones DL, Mogenson GJ (1980) Nucleus accumbens to globus pallidus GABA projection: electrophysiological and iontophoretic investigations. Brain Res 188: 93–105
50. Kalivas PW, Volkow ND (2005) The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 162: 1403–1413
51. Kameyama T, Ukai M, Noma S, Hiramatsu M (1982) Differential effects of alpha-, beta- and gamma-endorphins on dopamine metabolism in the mouse brain. Brain Res 244: 305–309
52. Kankaanpaa A, Meririnne E, Lillsunde P, Seppala T (1998) The acute effects of amphetamine derivatives on extracellular serotonin and dopamine levels in rat nucleus accumbens. Pharmacol Biochem Behav 59: 1003–1009
53. Kao CQ, Wang S (1985) Effect of stimulation of nucleus accumbens and naloxone microinjection on nociceptive unit discharges in the lateral habenular nucleus. Sheng Li Xue Bao 37: 24–30
54. Kelley AE (1999) Functional specificity of ventral striatal compartments in appetitive behaviors. Ann N Y Acad Sci 877: 71–90
55. Koikegami H, Hirata Y, Oguma J (1967) Studies on the paralimbic brain structures. Folio Psych Neurol Jpn 21: 151–180
56. Kokkinidis L, Kirkby RD, McCarter BD, Borowski TB (1989) Alterations in amphetamine-induced locomotor activity and stereotypy after electrical stimulation of the nucleus accumbens and neostriatum. Life Sci 44: 633–641
57. Lavin A, Grace AA (1996) Physiological properties of rat ventral pallidal neurons recorded intracellularly in vivo. J Neurophysiol 75: 1432–1443
58. Liegeois JF, Ichikawa J, Meltzer HY (2002) 5-HT(2A) receptor antagonism potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and inhibits that in the nucleus accumbens in a dose-dependent manner. Brain Res 947: 157–165
59. Lin HQ, Jackson DM, Atrens DM, Christie MJ, McGregor IS (1997) Serotonergic modulation of 3,4-methylenedioxymethamphetamine (MDMA)-elicited reduction of response rate but not rewarding threshold in accumbal self-stimulation. Brain Res 744: 351–357
60. Lippitz BE, Mindus P, Meyerson BA, Kihlstrom L, Lindquist C (1999) Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: relevance of the right hemisphere. Neurosurgery 44: 452–458
61. Lopes da Silva FH, Arnolds DE, Neijt HC (1984) A functional link between the limbic cortex and ventral striatum: physiology of the subiculum accumbens pathway. Exp Brain Res 55: 205–214
62. Maeda H, Mogenson GJ (1980) An electrophysiological study of inputs to neurons of the ventral tegmental area from the nucleus accumbens and medial preoptic-anterior hypothalamic areas. Brain Res 197: 365–377
63. Mai J, Assheuer J, Paxinos G (2004) Atlas of the human brain, 2nd edn. Elsevier Academic Press, London
64. Maurice N, Deniau JM, Menetrey A, Glowinski J, Thierry AM (1997) Position of the ventral pallidum in the rat prefrontal cortex-basal ganglia circuit. Neuroscience 80: 523–534
65. McCreery DB, Agnew WF, Yuen TG, Bullara L (1990) Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. IEEE Trans Biomed Eng 37: 996–1001
66. Mello LE, Tan AM, Finch DM (1992) Convergence of projections from the rat hippocampal formation, medial geniculate and basal forebrain onto single amygdaloid neurons: an in vivo extra- and intracellular electrophysiological study. Brain Res 587: 24–40
67. Meyerson BA (1998) Neurosurgical treatment of mental disorders: introduction and indications. In: Gildenberg PL, Tasker RR (eds) Textbook of stereotactic and functional neurosurgery. McGraw Hill, New York, pp 1953–1963
68. Misslin R (2003) The defense system of fear: behavior and neurocircuitry. Neurophysiol Clin 33: 55–66
69. Mogenson GJ, Takigawa M, Robertson A, Wu M (1979) Self-stimulation of the nucleus accumbens and ventral tegmented area of Tsai attenuated by microinjections of spiroperidol into the nucleus accumbens. Brain Res 171: 247–259
70. Montaron MF, Buser P (1988) Relationships between nucleus medialis dorsalis, pericruciate cortex, ventral tegmental area and nucleus accumbens in cat: an electrophysiological study. Exp Brain Res 69: 559–566
71. Montaron MF, Deniau JM, Menetrey A, Glowinski J, Thierry AM (1996) Prefrontal cortex inputs of the nucleus accumbens-nigrothalamic circuit. Neuroscience 71: 371–382
72. Morino P, Mascagni F, McDonald A, Hokfelt T (1994) Cholecystokinin corticostriatal pathway in the rat: evidence for bilateral origin from medial prefrontal cortical areas. Neuroscience 59: 939–952
73. Moro E, Esselink RJ, Xie J, Hommel M, Benabid AL, Pollak P (2002) The impact on Parkinson's disease of electrical parameter settings in STN stimulation. Neurology 59: 706–713
74. Mortimer JT, Shealy CN, Wheeler C (1970) Experimental nondestructive electrical stimulation of the brain and spinal cord. J Neurosurg 32: 553–559
75. Murer MG, Pazo JH (1993) Behavioral responses induced by electrical stimulation of the caudate nucleus in freely moving cats. Behav Brain Res 57: 9–19
76. Murzi E, Herberg LJ (1982) Anticholinergic treatment reverses haloperidol-induced blockade of self-stimulation of nucleus accumbens no less than of hypothalamus. Q J Exp Psychol B 34(Pt 1): 49–54
77. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B (1999) Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet 354: 1526
78. Nuttin BJ, Gabriels LA, Cosyns PR, Meyerson BA, Andreewitch S, Sunaert SG, Maes AF, Dupont PJ, Gybels JM, Gielen F, Demeulemeester HG (2003) Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 52: 1263–1272
79. O'Donnell P, Grace AA (1993) Physiological and morphological properties of accumbens core and shell neurons recorded in vitro. Synapse 13: 135–160
80. O'Donnell P, Grace AA (1995) Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. J Neurosci 15(5 Pt 1): 3622–3639
81. O'Donnell P, Greene J, Pabello N, Lewis BL, Grace AA (1999) Modulation of cell firing in the nucleus accumbens. Ann N Y Acad Sci 877: 157–175
82. Olds J, Milner P (1954) Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 47: 419–427
83. Pallis E, Thermos K, Spyraki C (2001) Chronic desipramine treatment selectively potentiates somatostatin-induced dopamine release in the nucleus accumbens. Eur J Neurosci 14: 763–767

84. Phillips AG, Fibiger HC (1978) The role of dopamine in maintaining intracranial self-stimulation in the ventral tegmentum, nucleus accumbens, and medial prefrontal cortex. Can J Psychol 32: 58–66
85. Phillipson OT, Griffiths AC (1985) The topographic order of inputs to nucleus accumbens in the rat. Neuroscience 16: 275–296
86. Pitman RK (1989) Animal models of compulsive behavior. Biol Psychiatry 26: 189–198
87. Pontieri FE, Tanda G, Di Chiara G (1995) Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the ''shell'' as compared with the ''core'' of the rat nucleus accumbens. Proc Natl Acad Sci USA 92: 12304–12308
81. Porras G, Di Matteo V, Fracasso C, Lucas G, De Deurwaerdere P, Caccia S, Esposito E, Spampinato U (2002) 5-HT2A and 5-HT2C/2B receptor subtypes modulate dopamine release induced in vivo by amphetamine and morphine in both the rat nucleus accumbens and striatum. Neuropsychopharmacology 26: 311–324
89. Prado-Alcala R, Wise RA (1984) Brain stimulation reward and dopamine terminal fields. I. Caudate-putamen, nucleus accumbens and amygdala. Brain Res 297: 265–273
90. Predy PA, Kokkindis L (1984) Sensitization to the effects of repeated amphetamine administration on intracranial self-stimulation: evidence for changes in reward processes. Behav Brain Res 13: 251–259
91. Rizzone M, Lanotte M, Bergamasco B, Tavella A, Torre E, Faccani G, Melcarne A, Lopiano L (2001) Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters. J Neurol Neurosurg Psychiatry 71: 215–219
92. Robinson TG, Beart PM (1988) Excitant amino acid projections from rat amygdala and thalamus to nucleus accumbens. Brain Res Bull 20: 467–471
93. Rolls ET (1971) Contrasting effects of hypothalamic and nucleus accumbens septi self-stimulation on brain stem single unit activity and cortical arousal. Brain Res 31: 275–285
94. Rolls ET (1972) Activation of amygdaloid neurones in reward, eating and drinking elicited by electrical stimulation of the brain. Brain Res 45: 365–381
95. Rolls ET, Burton MJ, Mora F (1980) Neurophysiological analysis of brain-stimulation reward in the monkey. Brain Res 194: 339–357
96. Ross AR, Malmo RB (1979) Cardiovascular responses to rewarding brain stimulation. Physiol Behav 22: 1005–1013
97. Rowland V, MacIntyre WJ, Bidder TG (1960) The production of brain lesions with electrical current. II. Bidirectional currents. J Neurosurg 17: 55–69
98. Saphier DJ (1985) Nucleus accumbens and preoptic area stimulation: tuberoinfundibular single unit responses, modulation of electrical activity and gonadotrophin secretion. Exp Brain Res 57: 400–403
99. Sasaki K, Ono T, Muramoto K, Nishino H, Fukuda M (1984) The effects of feeding and rewarding brain stimulation on lateral hypothalamic unit activity in freely moving rats. Brain Res 322: 201–211
100. Saxena S, Rauch SL (2000) Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am 23: 563–586
101. Scarnati E, Campana E, Pacitti C (1983) The functional role of the nucleus accumbens in the control of the substantia nigra: electrophysiological investigations in intact and striatum-globus pallidus lesioned rats. Brain Res 265: 249–257
102. Schoemaker H, Nickolson VJ (1980) Effects of des-Tyr-gamma-endorphin on dopamine release from various rat brain regions in vitro. Life Sci 27: 1371–1376
103. Schuurman PR, Bosch DA, Bossuyt PM, Bonsel GJ, van Someren EJ, de Bie RM, Merkus MP, Speelman JD (2000) A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 342: 461–468
104. Seeger TF, Gardner EL (1979) Enhancement of self-stimulation behavior in rats and monkeys after chronic neuroleptic treatment: evidence for mesolimbic supersensitivity. Brain Res 175: 49–57
105. Sesack SR, Deutch AY, Roth RH, Bunney BS (1989) Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. J Comp Neurol 290: 213–242
106. Sesack SR, Pickel VM (1990) In the rat medial nucleus accumbens, hippocampal and catecholaminergic terminals converge on spiny neurons and are in apposition to each other. Brain Res 527: 266–279
107. Shibuki K (1984) Supraoptic neurosecretory cells: synaptic inputs from the nucleus accumbens in the rat. Exp Brain Res 53: 341–348
108. Silberstein SD (1998) Methysergide. Cephalalgia 18: 421–435
109. Simon H, Stinus L, Tassin JP, Tassin JP, Lavielle S, Blanc G, Thierry AM, Glowinski J, Le Moal M (1979) Is the dopaminergic mesocorticolimbic system necessary for intracranial self-stimulation? Biochemical and behavioral studies from A10 cell bodies and terminals. Behav Neural Biol 27: 125–145
110. Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkotter J (2003) The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. J Chem Neuroanat 26: 293–299
111. Szechtman H, Eckert MJ, Tse WS, Boersma JT, Bonura CA, McClelland JZ, Culver KE, Eilam D (2001) Compulsive checking behavior of quinpirole-sensitized rats as an animal model of Obsessive-Compulsive Disorder (OCD): form and control. BMC Neurosci 2: 4
112. Taber MT, Zernig G, Fibiger HC (1998) Opioid receptor modulation of feeding-evoked dopamine release in the rat nucleus accumbens. Brain Res 785: 24–30
113. Takagishi M, Chiba T (1991) Efferent projections of the infralimbic (area 25) region of the medial prefrontal cortex in the rat: an anterograde tracer PHA-L study. Brain Res 566: 26–39
114. Tarr RS (1982) Species typical display behavior following stimulation of the reptilian striatum. Physiol Behav 29: 615–620
115. Tass PA, Klosterkotter J, Schneider F, Lenartz D, Koulousakis A, Sturm V (2003) Obsessive-compulsive disorder: development of demand-controlled deep brain stimulation with methods from stochastic phase resetting. Neuropsychopharmacology 28 Suppl 1: S27–S34
116. Uhl GR, Hall FS, Sora I (2002) Cocaine, reward, movement and monoamine transporters. Mol Psychiatry 7: 21–26
117. van Kuyck K, Demeulemeester H, Feys H, De Weerdt W, Dewil M, Tousseyn T, De Sutter P, Gybels J, Bogaerts K, Dom R, Nuttin B (2003) Effects of electrical stimulation or lesion in nucleus accumbens on the behaviour of rats in a T-maze after administration of 8-OH-DPAT or vehicle. Behav Brain Res 140: 165–173
118. Van Ree JM, Otte AP (1980) Effects of (Des-Tyr1)-gamma-endorphin and alpha-endorphin as compared to haloperidol and amphetamine on nucleus accumbens self-stimulation. Neuropharmacology 19: 429–434
119. Velley L, Cardo B (1979) Long-term improvement of learning after early electrical stimulation of some central nervous structures: is the effect structure and age-dependent? Brain Res Bull 4: 459–466
120. Verhoef JC, Scholtens H, Vergeer EG, Witter A (1985) Des-Tyr1-gamma-endorphin (DT gamma E) and des-enkephalin-gamma-endorphin (DE gamma E): plasma profile and brain uptake after systemic administration in the rat. Peptides 6: 467–474

121. Walaas I, Fonnum F (1979) The distribution and origin of glutamate decarboxylase and choline acetyltransferase in ventral pallidum and other basal forebrain regions. Brain Res 177: 325–336
122. Way WL, Fields HL, Schumacher MA (2001) Opioid analgesics and antagonists. In: Katzung BG (ed) Basic & Clinical Pharmacology. Lange Medical Books/McGraw-Hill, pp 512–529
123. West TE, Wise RA (1988) Effects of naltrexone on nucleus accumbens, lateral hypothalamic and ventral tegmental self-stimulation rate-frequency functions. Brain Res 462: 126–133
124. White FJ, Wang RY (1986) Electrophysiological evidence for the existence of both D-1 and D-2 dopamine receptors in the rat nucleus accumbens. J Neurosci 6: 274–280
125. Wieczorek W, Kruk ZL (1995) Influences of neuronal uptake and D2 autoreceptors on regulation of extracellular dopamine in the core, shell and rostral pole of the rat nucleus accumbens. Brain Res 699: 171–182
126. Willner P (1984) The validity of animal models of depression. Psychopharmacology (Berl) 83: 1–16
127. Willner P (1986) Validation criteria for animal models of human mental disorders: learned helplessness as a paradigm case. Prog Neuropsychopharmacol Biol Psychiatry 10: 677–690
128. Wilson WJ (1983) Nucleus accumbens inhibits specific motor but not nonspecific classically conditioned responses. Brain Res Bull 10: 505–515
129. Winter C, Jalali R, Hosmann K, Kupsch A, Morgenstern R, Juckel G (2004) High frequency stimulation of the accumbens, the subthalamic nucleus, and the amygdala differentially affects quinpirole induced compulsive checking behavior in rats. Society for Neuroscience, Washington, DC, p 118
130. Wood PB (2004) Stress and dopamine: implications for the pathophysiology of chronic widespread pain. Med Hypotheses 62: 420–424
131. Woodruff GN, McCarthy PS, Walker RJ (1976) Studies on the pharmacology of neurones in the nucleus accumbens of the rat. Brain Res 115: 233–242
132. Woods A, Smith C, Szewczak M, Dunn RW, Cornfeldt M, Corbett R (1993) Selective serotonin re-uptake inhibitors decrease schedule-induced polydipsia in rats: a potential model for obsessive compulsive disorder. Psychopharmacology (Berl) 112: 195–198
133. Wright J, Kelly D, Mitchell-Heggs N, Frankel R (1977) Respiratory changes induced by intracranial stimulation: anatomical localizing value and related functional effects in rhesus monkeys. In: Sweet WH, Obrador S, Martin-Rodriguez JG (eds) Neurosurgical treatment in psychiatry, pain, and epilepsy. University Park Press, Baltimore, pp 751–756
134. Yadin E, Friedman E, Bridger WH (1991) Spontaneous alternation behavior: an animal model for obsessive-compulsive disorder? Pharmacol Biochem Behav 40: 311–315
135. Yang CR, Mogenson GJ (1984) Electrophysiological responses of neurones in the nucleus accumbens to hippocampal stimulation and the attenuation of the excitatory responses by the mesolimbic dopaminergic system. Brain Res 324: 69–84
136. Yang CR, Mogenson GJ (1986) Dopamine enhances terminal excitability of hippocampal-accumbens neurons via D2 receptor: role of dopamine in presynaptic inhibition. J Neurosci 6: 2470–2478
137. Yang CR, Mogenson GJ (1989) Ventral pallidal neuronal responses to dopamine receptor stimulation in the nucleus accumbens. Brain Res 489: 237–246
138. Yim CY, Mogenson GJ (1980) Electrophysiological studies of neurons in the ventral tegmental area of Tsai. Brain Res 181: 301–313
139. Yim CY, Mogenson GJ (1980) Effect of picrotoxin and nipecotic acid on inhibitory response of dopaminergic neurons in the ventral tegmental area to stimulation of the nucleus accumbens. Brain Res 199: 466–473
140. Yim CY, Mogenson GJ (1982) Response of nucleus accumbens neurons to amygdala stimulation and its modification by dopamine. Brain Res 239: 401–415
141. Yim CY, Mogenson GJ (1988) Neuromodulatory action of dopamine in the nucleus accumbens: an in vivo intracellular study. Neuroscience 26: 403–415
142. Zaborszky L, Alheid GF, Beinfeld MC, Eiden LE, Heimer L, Palkovits M (1985) Cholecystokinin innervation of the ventral striatum: a morphological and radioimmunological study. Neuroscience 14: 427–453
143. Zaborszky L, Cullinan WE (1992) Projections from the nucleus accumbens to cholinergic neurons of the ventral pallidum: a correlated light and electron microscopic double-immunolabeling study in rat. Brain Res 570: 92–101
144. Zacharko RM, Bowers WJ, Kokkinidis L, Anisman H (1983) Region-specific reductions of intracranial self-stimulation after uncontrollable stress: possible effects on reward processes. Behav Brain Res 9: 129–141
145. Zacharko RM, Bowers WJ, Anisman H (1984) Responding for brain stimulation: stress and desmethylimipramine. Prog Neuropsychopharmacol Biol Psychiatry 8: 601–606
146. Zacharko RM, Bowers WJ, Kelley MS, Anisman H (1984) Prevention of stressor-induced disturbances of self-stimulation by desmethylimipramine. Brain Res 321: 175–179
147. Zacharko RM, Kasian M, Irwin J, Zalcman S, LaLonde G, MacNeil G, Anisman H (1990) Behavioral characterization of intracranial self-stimulation from mesolimbic, mesocortical, nigrostriatal, hypothalamic and extra-hypothalamic sites in the non-inbred CD-1 mouse strain. Behav Brain Res 36: 251–281
148. Zacharko RM, Lalonde GT, Kasian M, Anisman H (1987) Strain-specific effects of inescapable shock on intracranial self-stimulation from the nucleus accumbens. Brain Res 426: 164–168
149. Zacharko RM, Zalcman S, Macneil G, Andrews M, Mendella PD, Anisman H (1997) Differential effects of immunologic challenge on self-stimulation from the nucleus accumbens and the substantia nigra. Pharmacol Biochem Behav 58: 881–886
150. Zaczek R, Hedreen JC, Coyle JT (1979) Evidence for a hippocampal-septal glutamatergic pathway in the rat. Exp Neurol 65: 145–156
151. Zahm DS (2000) An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. Neurosci Biobehav Rev 24: 85–105
152. Zahm DS, Heimer L (1993) Specificity in the efferent projections of the nucleus accumbens in the rat: comparison of the rostral pole projection patterns with those of the core and shell. J Comp Neurol 327: 220–232

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Neuromodulation of the inferior thalamic peduncle for major depression and obsessive compulsive disorder

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Summary

Neuromodulation of the inferior thalamic peduncle is a new surgical treatment for major depression and obsessive-compulsive disorder. The inferior thalamic peduncle is a bundle of fibers connecting the orbito-frontal cortex with the non-specific thalamic system in a small area behind the fornix and anterior to the polar reticular thalamic nucleus. Electrical stimulation elicits characteristic frontal cortical responses (recruiting responses and direct current (DC)-shift) that confirm correct localization of this anatomical structure. A female with depression for 23 years and a male with obsessive-compulsive disorder for 9 years had stereotactic implantation of electrodes in the inferior thalamic peduncle and were evaluated over a long-term period. Initial OFF stimulation period (1 month) showed no consistent changes in the Hamilton Depression Scale (HAM-D), Yale Brown Obsessive Compulsive Scale (YBOCS), or Global Assessment of Functioning scale (GAF). The ON stimulation period (3–5 V, 130-Hz frequency, 450-msec pulse width in a continuous program) showed significant decrease in depression, obsession, and compulsion symptoms. GAF improved significantly in both cases. The neuropsychological tests battery showed no significant changes except from a reduction in the perseverative response of the obsessive-compulsive patient and better performance in manual praxias of the female depressive patient. Moderate increase in weight (5 kg on average) was observed in both cases.

Keywords: Neuromodulation; psychosurgery; major depression; obsessive compulsive disorder; electrical stimulation; thalamus.

Introduction

The majority of neurosurgical procedures to treat psychiatric disorders have been directed toward disconnecting the frontal lobe from its connections with the basal ganglia [3, 4, 6] or interrupting anatomic pathways within the limbic system [3, 4]. Neurosurgical procedures have been conducted in anatomic structures on which experience has indicated that the procedure can be more effective or cause fewer side effects.

The inferior thalamic peduncle (ITP) is a bundle of fibers connecting the non-specific thalamic system (Non-STS) and orbito-frontal cortex [8, 13–15]. This is a neural inhibitory system that has several advantages over other targets [15]. Neuromodulation has been shown to be an efficient and safe therapeutic method for psychiatric illnesses such as major depression disorder (MDD) and obsessive compulsive disorder (OCD) [1, 7, 9, 11, 12]. Neuromodulation in ITP is based on the following considerations: 1) High-frequency electrical stimulation of ITP elicits specific electrophysiological responses in prefrontal cortex [13, 14]. Recruiting responses (RR) have been defined by negative, waxing and waning form with long-term latency. These characteristics allow exact localization of the target, 2) Subcaudate tractotomy has been used successfully in the treatment of depression disorders, and this lesion involves ITP and orbitofrontal cortex [3], 3) Experimental models with lesion or cryoprobe have showed effects in the thalamo-orbitofrontal system producing a perseverative and stereotypical behavior [14, 15], and 4) Positron emission tomography (PET) scans in patients with major depression disorder and obsessive compulsive disorder have shown hypermetabolism in the orbitofrontal cortex and the anterior polar thalamic nuclei [2, 5].

A team consisting of a psychiatrist, neurosurgeons, a neurophysiologist, and a neuropsychologist at the General Hospital of México in Mexico City carried out a prospective pilot research protocol of electrical stimulation of ITP in patients with MDD and OCD. The Ethics Committee of our Institution and external

reviewers approved the final protocol and two patients were initially included. In this chapter, we will describe our selection criteria, surgical and neurophysiological procedures and the results of the treatment in these cases.

Case 1

LZO was 49 years old at the time of surgery. She was suffering from complete MDD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV-R) and additionally demonstrated border personality disorder and bulimia. The patient had suffered major depression episodes for 23 years and the last one was 2 years long with anhedonia, suicidal ideation, and two suicidal attempts. Several pharmacological combinations (selective serotoninergic inhibitor reuptakers, benzodiazepines, neuroleptics, and mood modulators) and two series of 10 sessions of electroconvulsive therapy (ECT) had been unsuccessful or associated with relapses after 1 month. Global assessment of functioning scale (GAF) score was 20. One month prior to surgery, medication was withdrawn due to several side effects. Hamilton depression scale (HAM-D) showed fluctuations ranging from 20 to 40.

Case 2

RRA was a 21-year-old male at the time of surgery. He had a diagnosis of OCD made 12 years ago and comorbidity of drug abuse with cocaine for 16 years. He suffered from obsessive ideation concerning the law of gravity loss and fear of flying out of the planet. His compulsion consisted of remaining indoors full time and writing during several hours daily on this obsession. YBOCS score fluctuated from 35 to 40. Baseline (BL) GAF was 10–20 because the patient depended on his relatives in nearly all activities. Medication with selective serotoninergic inhibitor reuptakers, benzodiazepines, neuroleptics, and mood modulators was inefficient and a continuous contention environment was necessary during 1 year. He received 6 months of cognitive behavioral therapy (CBT) without results.

Inclusion criteria

1. DSM IV R Diagnostic Criteria of MDD or OCD.
2. HAM-D score >30 in MDD and YBOCS >23 in OCD. Refractoriness to conventional treatment evaluated by two independent psychiatrists.
3. Awareness of the prospects of the disorder and the protocol conditions and ability to probe the informed consent form.
4. Illness chronicity for at least 5 years.

Exclusion criteria

1. Neurological disease confirmed by clinical examination, electroencephalography (EEG), or brain imaging.
2. Age < 18 years.
3. Anesthetic or surgical risk of grade II or greater according to the American Society of Anesthesiology.

Study design

In addition to the psychiatric scales (HAM-D and YBOCS), both patients were studied by neuropsychological test batteries (Wisconsin Cart Sorting Test, Token Test, Corsi Cube Test). The baseline evaluation was followed by an 1-month evaluation without stimulation in double-blind conditions, and subsequently, by a 12-month ON period with follow-up evaluation every 3 months.

Surgical procedure

Prior to surgery, magnetic resonance imaging (MRI) is performed in T2 fast spin echo, TE 1112, TR 4070, field of view 16.0, 256×256 matrix, and pulse sequence 1,125 2.5-mm slices without space between sections, in axial coronal and sagittal sections without the stereotactic frame. Sections must cover the area from the base of the skull to the vertex. On the day of surgery, patients have the stereotactic frame applied using local anesthesia. Two and half-mm-thick cuts with 2.5-mm displacements are obtained in a contrasted computed tomography (CT) scan study. Sections are obtained parallel to the intercommisural line. Images in this study are transformed into stereotactic coordinates and fused with MRI images using the Praezis System, 3rd version (Tamed, Freiburg, Germany). This information is used to determine the position of the commisures, fornices, internal capsule, and the length and width of the 3rd ventricle. Coordinates for ITP are as follows: (X): 3.5 mm lateral to the wall of the 3rd ventricle, (Y): 5.0 mm behind the posterior edge of anterior commisure as seen in the mid-sagittal section of the MRI and (Z): 2.5 below the level of anterior commisure–posterior commisure line (AC–PC). These coordinates correspond to the cathode of the electrode, and bipolar stimulation is utilized. It is recommended to

use tetrapolar electrodes with 1.5-mm contact-to-contact distance and 2.5-mm center-to-control distance. These coordinates intend to place two contacts of the electrode within the ITP and to avoid the fornix and hypothalamus that are located immediately anterior and medial. The electrode trajectory should be calculated on an angle of 80° with regard to the AC–PC line and no more than 25° in the coronal plane. It is possible for the trajectory to traverse the enlarged lateral ventricle in some patients. After planning the trajectory, patients are operated on under general anesthesia. Burr holes are guided stereotactically according to the selected trajectory. Electrodes are fixed with burr hole caps. One tetrapolar electrode is implanted on each side. Each electrode is directed to the center of the ITP, and its proximal end lies along the anterior border of the reticular nucleus of the thalamus. Intraoperative monitoring is performed and subsequently the electrodes are connected to a temporary extension that is externalized behind each ear and is used for stimulation and post-operative mapping.

Intraoperative monitoring

In order to verify the ITP localization, bipolar macrostimulation at 6 Hz, 1.0-msec pulse width and from 1.0 to 4.0 mAmp is carried out using contiguous pairs of contacts in ITP to obtain bilateral frontal recruiting responses elicited by unilateral stimulation. Oscilloscopic and EEG recordings are simultaneously performed in a conventional 10–20 EEG system; bipolar macrostimulation at 60 Hz, 1.0 msec and 3.0–5.0 mA is performed to obtain DC-shift. In the case of not obtaining DC-shift, the electrode location is verified and replaced. This intraoperative study must be performed with the patient in the lightest level of anesthesia; muscular relaxants may be necessary.

Postoperative monitoring

Two days after surgery, MRI is repeated to confirm electrode placement, and deep brain stimulation (DBS) is applied by Itrel 3 (Medtronic, Inc.) at high frequency (130 Hz and 0.45-msec pulse width) at different paired contacts with voltage increases from 1 to 10 V to identify side effects. DBS at low frequency (6 Hz and 1.0-msec pulse widths) at different paired contacts with increases from 0.5 to 4.0 mA is used while EEG with conventional 10–20 montage is performed to obtain recruiting responses. Finally, chronic ES at 60 Hz is performed to obtain a regional DC-shift.

Pulse generator implantation

One day after postoperative monitoring, Itrel 3 Brain Stimulation Systems are implanted in a subcutaneous (s.c.) infraclavicular pocket and are connected to leads.

Stimulation parameters

Charge density is adjusted to elicit bilateral RR. In Case 1, stimulation parameters were 3.0 V, 450 msec, 130 Hz, and continuous program that applied 3.75 microCoulombs per square cm. In Case 2, parameters were 5.0 V, 450 msec, 130 Hz, and continuous program that applied 6.25 microCoulombs per square cm.

Results

Both patients were evaluated by a psychiatric team at the baseline period of 1 month after surgery in OFF stimulation period and during ON stimulation follow-up periods every 3 months during the first year. Throughout the follow-up period, the patients and the psychiatrists were blinded to OFF or ON stimulation.

Figure 1 shows the location of electrodes in electrical stimulation of ITP on axial section (Hv, −0.5 mm).

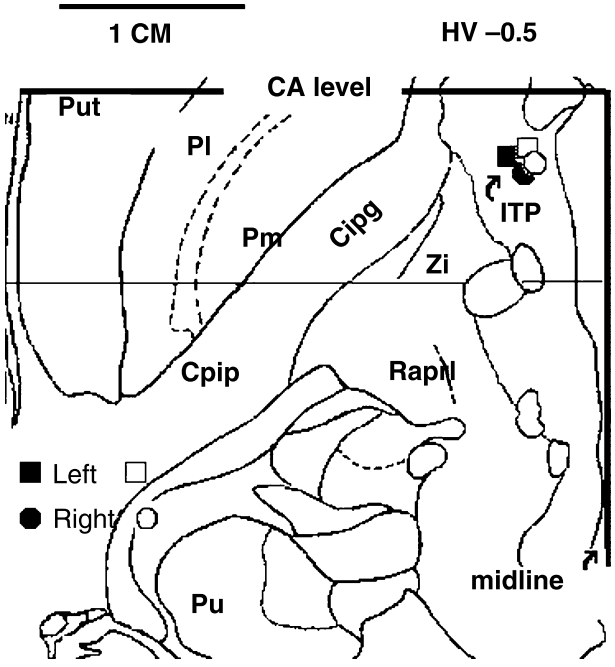

Fig. 1. Axial section from the Schaltenbrand and Warren Atlas in HV −0.5 mm. *ITP* Inferior thalamic peduncle (Pdthif in the Atlas); *Zi* zona incerta; *Raprl* prelemniscal radiations; *Put* putamen; *Pl* lateral pallidus; *Pm* medial pallidus; *Cpip* posterior branch of internal capsule; *Pu* pulvinar; *Cpig* genu of internal capsule; *circle* right electrodes, and *square* left electrodes

White geometric symbols (circles and squares) are located in the electrode implantation sites in the patient with MDD, while black symbols are located at the sites in the patient with OCD. Electrode coordinates ranged from 4 to 5 mm lateral at approximately midline, from 4 to 5 mm behind the posterior border of the anterior commisure in the axial plane that corresponds to intercommisural level, and from 1 to 2.5 mm behind the fornix.

Figure 2A shows the HAM-D score of the patient with MDD 24 months before, and Fig. 2B at 18 months after surgery. Point number 1 corresponds to the first trial of ECT that produced symptom remission for 1 month and a subsequent relapse. Points 2 and 3 depict good responses after medical treatment changes but of short duration. Poor response was observed in follow-up, with scores oscillating between 20 and 40. With regard to point 4, 1 day prior to surgery we were able to observe maximum HAM-D score, without medication, because multiple antidepressant drugs had produced serious side effects. Immediately after implantation, symptom remission was observed but electrical stimulation began 1 month afterwards. A score increase appeared within this period and the decrease of symptoms was related with turning ON the pulse generator and obtaining a good clinical response.

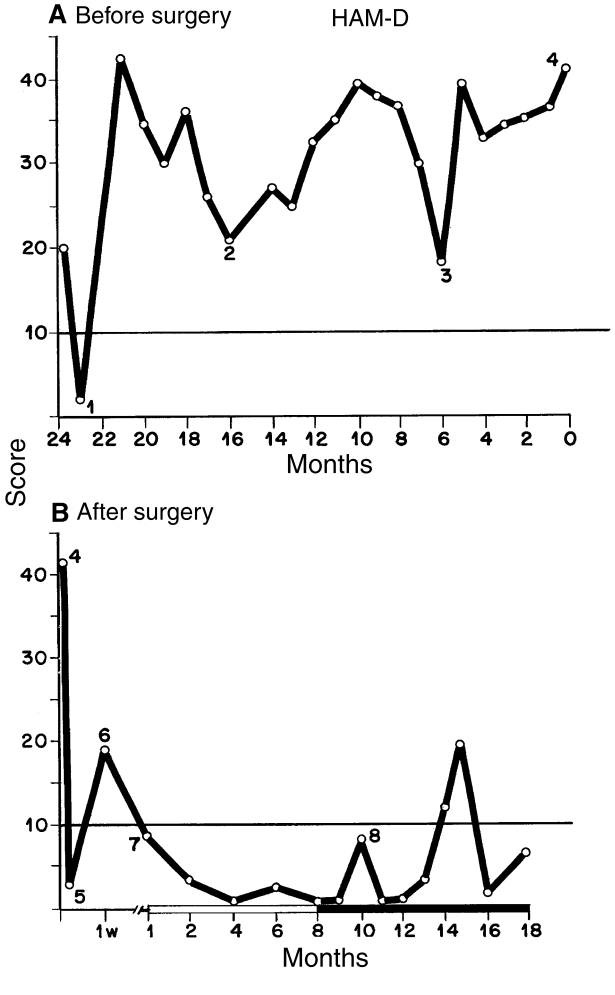

Fig. 2. In A, HAM-D scores 24 months prior to surgery. Number 1 shows responses to electroconvulsive therapy (*ECT*), numbers 2 and 3 show modification in medical treatment, and number 4 shows score on implantation day. In B, HAM-D score shows remarkable decrease after implantation without electrical stimulation. After a 1-month period in OFF, the patient underwent a double-blind period in ON (8 months) and OFF (10 months). An asymptomatic condition was observed in ON period, while a relapse and fluctuation appeared during OFF period

Figure 3 shows Yale Brown obsessive compulsive scale score in the preoperative period, 2 months and 1 week prior to implantation (BL), 1 month after implantation without stimulation (OFF), and the follow-up for 15 months. In the electrical stimulation period (black bar), an improvement of the symptoms was observed with a

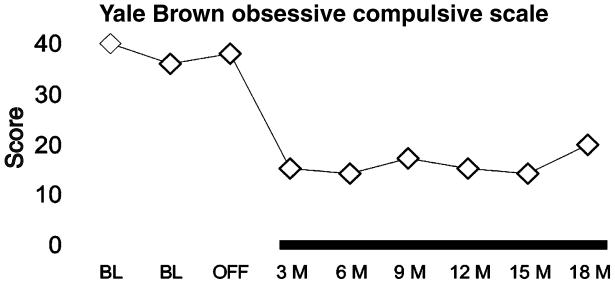

Fig. 3. It shows the Yale Brown obsessive compulsive scale score in the pre-operative period, 2 months and 1 week prior to implantation (*BL*), 1 month after implantation without stimulation (*OFF*), and follow-up during 15 months. In the electrical stimulation period (*black bar*), a decrease of the score was observed with scores ranging from 15 to 20 vs. scores compared to without stimulation ranging from 36 to 40

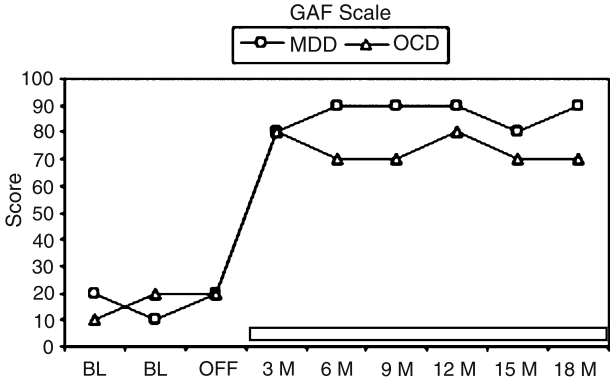

Fig. 4. Global assessment functioning scale (*GAF*) scores are shown in baseline, in OFF period (1 month), and ON period (3, 6, 9, 12, 15, and 18 months). After electrical stimulation, an improvement in functioning behavior was observed. Mild variations were documented in the case of the patient with MDD. After month 8, she was in OFF period; however, she did not show any serious relapse in GAF score. In the patient with OCD, we did not observe big score variations

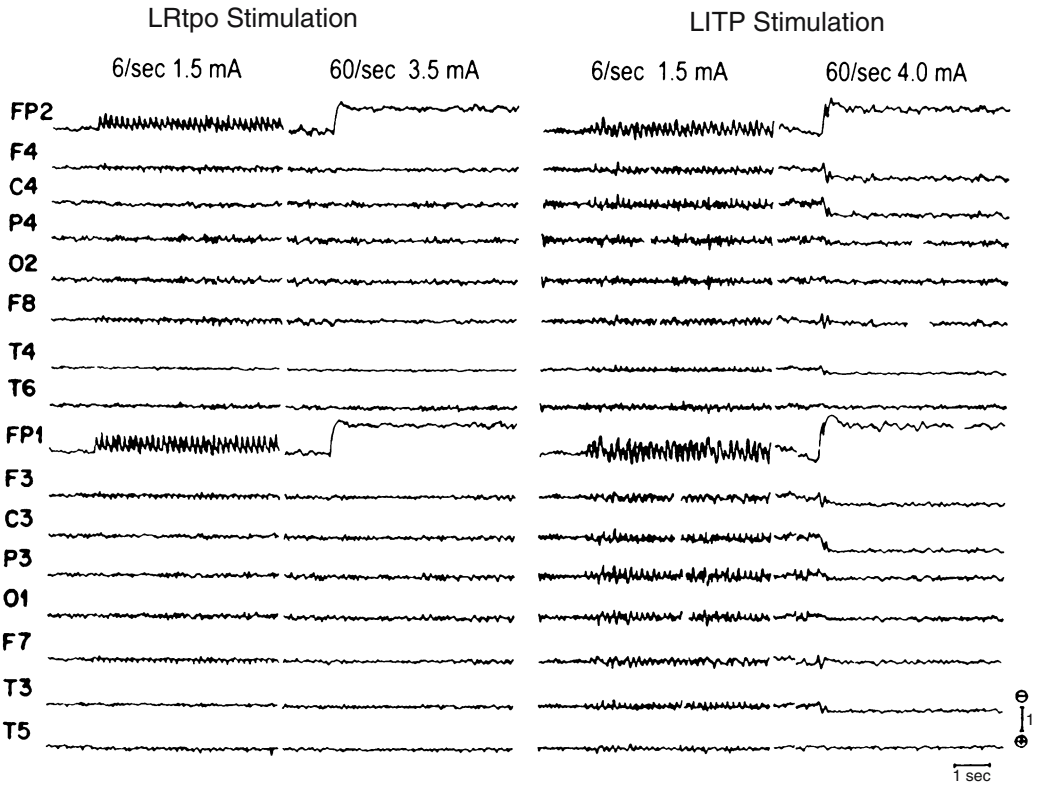

Fig. 5. Scalp distribution of electrocortical responses elicited by acute low- (6/sec) and high-frequency (60/sec) stimulation of the left reticulopolar thalamic nucleus (*L Rtpo*) and the left inferior thalamic peduncle (*LITP*). Conventional EEG recording from right and left frontopolar (*FP2, FP1*), frontal (*F4, F3*), central (*C4, C3*), parietal (*P4, P3*), occipital (*O2, O1*), frontotemporal (*F8, F7*), anterior temporal (*T4, T3*), and posterior temporal (*T6, T5*) scalp regions referred to ipsilateral ears (*A2, A1*). *Left*: Surface-negative recruiting-like responses produced by 6/sec unilateral supra-threshold stimulation of Rtpo and ITP predominantly at bilateral fronto-polar regions. *Right*: Surface-negative DC-shifts and desynchronization produced by 60/sec unilateral supra-threshold stimulation of Rtpo

decrease of the score from 15 to 20 vs; the scores without stimulation ranged from 36 to 40.

In Fig. 4, global assessment functioning (GAF) scale shows an increase of scores in both cases during electrical stimulation. Improvement in quality of life was more significant in MDD; however, the patient with OCD showed a score increase of approximately 50 points.

Figure 5 is a sample of characteristic neurophysiological responses elicited by low- or high-frequency electrical stimulation of the reticulopolar thalamic nucleus and ITP. In both anatomic areas, electrical stimulation on 6 Hertz produced recruiting responses (waxing-waning negative spikes in the frontal area). High-frequency stimulation (130 Hz) elicited a change in the level of direct current (DC-shift). These patterns of electrophysiological responses can be elicited solely by electrical stimulation of the thalamo-orbitofrontal system, but require an extra procedure to verify electrode location.

The neuropsychological tests did not show any differences. However, the Wisconsin Card Sorting Test showed decreased preservative responses in both cases and MDD manual praxias improved significantly. There were no objective chronic symptoms or serious adverse effects of ES. An increase in body weight was seen in both cases, with an average of 5 kg at the end of the study.

Conclusions

The two main advantages of ITP as a neurosurgical target in psychiatric disorders are the specific anatomic definition and the consistent neurophysiological responses. This preliminary report provides information with respect to the safe clinical use of this target. A decrease in MDD or OCD symptoms by applying neuromodulation offers a novel alternative to patients with such severe disabilities. Multicentered prospective double-blind protocols must be designed to provide valid results. The persistent neuropsychological deficit [10] observed after conventional treatment was not seen in neuromodulation of ITP, but an increase of weight by 5 kg was documented.

References

1. Abelson JL, Curtis GC, Sagher O, Albucher RC, Harrigan M, Taylor SF, Martis B, Giordani B (2005) Deep brain stimulation for refractory obsessive-compulsive disorder. Biol Psychiatry 57: 510–516
2. Baxter L, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, Alazraki A, Selin CE, Ferng HK, Munford P *et al* (1992) Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 49: 681–689
3. Binder K, Iskandar BJ (2000) Modern Neurosurgery for psychiatric disorders. Neurosurgery 47: 9–23
4. Cosgrove GR, Rauch SL (2003) Stereotactic cingulotomy. Neurosurg Clin North Am 14: 225–235
5. Drevets WC (2000) Neuroimaging studies of mood disorders. Biol Psychiatry 18: 813–829
6. Greenberg BD, Price LH, Rauch SL, Friehs G, Noren G, Malone D, Carpenter LL, Rezai AR, Rasmussen SA (2003) Neurosurgery for intractable obsessive-compulsive disorder and depression: critical issues. Neurosurg Clin North Am 14: 199–212
7. Jiménez F, Velasco F, Salín R, Hernández JA, Velasco M, Criales JL, Nicolini H (2005) Patient with difficult to treat major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. Neurosurgery 57: 585–589
8. Malakhova OE, Popovkin EM, Gudina IG (1989) Efferent connections of various parts of the orbitofrontal cortex with the thalamic structures of the cat. Neurosci Behav Physiol 19: 507–515
9. Mayberg HS, Lozano AM, Voon V, Mc Neely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. Neuron 45: 651–660
10. Nielen M, Den Boer J (2003) Neuropsychological performance of OCD patients before and after treatment with fluoxetine: evidence for persistent cognitive deficits. Psychol Med 22: 917–925
11. Nuttin B, Cosyns LG, Meyerson B, Rasmussen SA, Greenberg B, Rezai A, Fins JJ (2003) The OCD-DBS Collaborative Group. Neurosurg Clin North Am 14: xv–xvi
12. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B (1999) Electrical stimulation in anterior limb of internal capsule in patients with obsessive compulsive disorders. Lancet 354: 1526
13. Skinner JE, Lindsley DB (1967) Electrophysiological and behavioral effects of blockade of the non-specific thalamo-cortical system. Brain Res 6: 95–118
14. Velasco M, Lindsley DB (1965) Role of orbitofrontal cortex in regulation of thalamo-cortical electrical activity. Science 149: 1375–1377
15. Velasco F, Velasco M, Jiménez F, Velasco AL, Salín R (2005) Neurobiological background for performing surgical intervention in the inferior thalamic peduncle for treatment of major depression disorders. Neurosurgery 57: 439–448

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Chronic high frequency stimulation of the posteromedial hypothalamus in facial pain syndromes and behaviour disorders

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Summary

Chronic high frequency stimulation (HFS) of the posteromedial hypothalamus (PMH) has been the first direct therapeutic application of functional neuroimaging data in a restorative reversible procedure for the treatment of an otherwise refractory neurological condition; in fact, the target coordinates for the stereotactic implantation of the electrodes have been provided by positron emission tomography (PET) studies, which were performed during cluster headache attacks. HFS of PMH produced a significant and marked reduction of pain attacks in patients with chronic cluster headache (CCH) and in one patient with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). The episodes of violent behaviour and psychomotor agitation during the attacks of CCH supported the idea that the posteromedial hypothalamus could be also involved in the control of aggressiveness; this has been previously suggested, in the seventies, by the results obtained in Sano's hypothalamotomies for the treatment of abnormal aggression and disruptive behaviour. On the basis of these considerations, we have performed HFS of the PMH and controlled successfully violent and disruptive behaviour in patients refractory to the conventional sedative drugs. Finally, we also tested the same procedure in three patients with refractory atypical facial pain, but unfortunately, they did not respond to this treatment.

Keywords: Neuromodulation; posteromedian hypothalamus; cluster headache; high-frequency stimulation.

Introduction

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies recently demonstrated hypothalamic structural asymmetry and ipsilateral activation of the postero-inferior hypothalamic gray matter during the attacks of chronic cluster headache (CCH) [7, 15, 16].

Based on these neuroimaging data, electrical high frequency stimulation (HFS) of this distinct brain structure was carried out by deep brain stimulation (DBS) electrodes stereotactically implanted within the posterior hypothalamus itself. DBS induced a remission of the pain bouts and also of the autonomic dysfunction in patients with cluster headache. This was the first direct therapeutic application of functional neuroimaging data in a restorative reversible approach for the treatment of an otherwise refractory condition [4]. Moreover, CCH is the only facial pain syndrome in which violent behaviour and psychomotor agitation can develop during the pain attacks [13, 24]. These observations support the notion that focal inhibition of the posteromedial hypothalamus could explain the results obtained in the seventies in Sano's hypothalamotomies for the treatment of abnormal aggression and disruptive behaviour [19, 22]. Subsequently, the indications for chronic hypothalamic stimulation have been extended to the treatment of severe behavioural disorders unresponsive to medical treatment.

In this chapter, we report results, problems and technical suggestions collected during five years of experience in the implantation of hypothalamic electrodes for the treatment of CCH or refractory severe aggressive and disruptive behaviour. The same procedure has been carried out in other intractable facial pain syndromes including SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing), and atypical facial pain. The common factor in this heterogeneous clinical series is the selected target for high frequency electrical stimulation, namely the posteromedial hypothalamus.

Patients

Chronic cluster headache (CCH)

Sixteen patients, who fulfilled the International Headache Society criteria for the diagnosis of CCH, were included in this study [8]. Fourteen

were males and two females. All suffered from CCH for at least one year; two had CCH at onset, and in the remainder, the chronic form evolved from episodic CH. The medical treatment for these patients before referral to neurosurgery consisted of a regimen of the following drugs, provided as a single treatment or in combinations: corticosteroids, lithium, methysergide, ergotamine, calcium channel blockers, beta-blocking agents, tricyclic antidepressants, melatonin, and non steroidal anti-inflammatory drugs. All patients were hospitalized on various occasions, during which pain attacks were witnessed and assessed; cycles of high dose intravenous dexamethasone (12–20 mg/day or more) were administered, and two-to-four infiltrations of the ipsilateral sphenopalatine ganglion with a preparation containing triamcinolone acetonide (40 mg), bupivacaine (1%), carbocain (2%), and adrenalin (0.0001%) were given, without benefit. Patients eligible for DBS had normal neurological examination and brain MRI. They were also psychologically stable. Before surgery, all patients were in poor condition: one had attempted suicide on two occasions because of refractory pain, another had severe steroid myopathy and coronary artery disease contraindicating the use of triptan, and a third patient had severe steroid-myopathy and was unable to walk upstairs, but improved after steroid withdrawal. The patients were unable to work and their quality of life was severely affected. In 13 patients, the pain attacks were strictly unilateral. Patients 1, 9, and 13 (18.7%) had a history of attacks that affected each side alternately. Patient 1 received implants on both sides on separate occasions [10]. Patients 9 and 13 each received one implant on the most affected side (>95% of attacks). A month after implantation on the left side, patient 7 developed uncontrollable CH attacks on the right side, and subsequently received a right sided implant. The clinical results in terms of reduction of the frequency of attacks in CCH patients are reported in Fig. 1.

All patients were also informed of the classic surgical procedures that were available in our Institute for the treatment of the intractable CH namely open microvascular decompression, lesion of the fifth nerve in the cerebellopontine angle, and percutaneous microcompression or radiofrequency (RF) trigeminal rhizotomy [9, 14]. The first patient of the series was successfully treated in July 2000 and was reported in 2001 [10]. The patients' age at the time of surgery, in the whole series, ranged from 24 to 70 years (mean 46 years).

SUNCT

A 66-year old female patient had a 14 years history of short-lasting (2–20 seconds), severe, ''piercing and burning'' pain episodes in the right labial commissure, sometimes radiating to the jaw, ear, and occipital region. The attacks were strictly unilateral with no side shift, and were always accompanied by ipsilateral eyelid edema, eye reddening, unilateral nasal obstruction, and profuse lacrimation. Attacks were triggered by talking, chewing, face washing, teeth brushing, neck movements, or face touching, and often occurred for more than 100 times a day (mean 70; maximum 300). In the 2 years preceding the implantation, the patient experienced more than a thousand attacks per month. CT, MRI, and MR angiography of the brain were normal with no vascular ectasia observed at the cerebellopontine angle. A diagnosis of SUNCT namely short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing was made. The patient was treated with carbamazepine (1200 mg/day), gabapentin (2400 mg/day), oral and intravenous valproate (1500 mg/day), lamotrigine (300 mg/day), topiramate (200 mg/day), indomethacin (oral 200 mg/day; intramuscular up to 150 mg/day) ketorolac, coricosteroids (methylprednisolone, prednisone), and tramadol with only minimal symptom control. Cardiac status and age contraindicated the use of verapamil. In July 2003, after Ethical Committee approval and the patient's informed consent, the electrode implantation in the ipsilateral posterior hypothalamus was performed. This case has been extensively reported by the neurologists of our Institution [10].

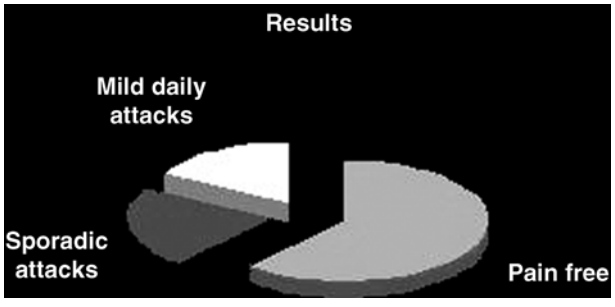

Fig. 1. Long-term results of deep brain stimulation of the posterior hypothalamus in chronic cluster headache patients

Atypical facial pain

Three patients with atypical facial pain were treated by DBS of the ipsilateral posteromedial hypothalamus.

The first patient was a 47 male with a diagnosis of an expanding right posterior mandibular carcinoma. In August 2002, a radical transmandibular tumour resection was performed. A few days after surgery hypoesthesia and burning pain developed in the II and III right trigeminal branches that progressively increased; drug therapy with carbamazepine (1000 mg), non steroidal anti-inflammatory drugs, local anesthetics, and opioids were ineffective. After a few months, the burning pain was severe, continuous, with spontaneous paroxysms several times a day. After six months, this condition was severe and the patient's quality of life (QOL) worsened dramatically. The neurological examination showed only moderate right hypoesthesia in the area innervated by the third trigeminal branch. Radiotherapy was not performed and at two years of follow up, no tumour recurrence was detected.

The second patient was a 52 year old female who had a 3 years history of facial pain. The symptoms appeared after a minor dental procedure and were described as a continuous disabling burning pain, localized to the area innervated by the II and III right trigeminal branches. Daily activities (i.e. talking, eating) were severely compromised. Attacks of exceptionally severe paroxysmal pain were also reported. Carbamazepine, lamotrigine and phenytoin at full dosages were ineffective. MRI ruled out any abnormalities and a diagnosis of atypical facial pain was made.

The third patient was a 55 year old male with a diagnosis of nasopharyngeal carcinoma. He underwent radiotherapy and few months later developed a continuous severe burning right facial pain more intense in the area innervated by the 1st and 2nd divisions of the trigeminal nerve. Paroxysmal pain was provoked by peripheral stimuli and was resistant to any kind of analgesic drug including opioids. Cerebral CT and MRI were performed after radiotherapy and showed disappearance of the tumor and ruled out any other pathology.

Disruptive behaviour

Two patients with learning disabilities affected by medically intractable impulsive and violent behaviour, as described elsewhere [2], were treated by DBS of the posteromedial hypothalamus [5].

The first patient was a 36 years old male who had suffered birth anoxia and developed progressive mental and motor retardation and myoclonic epilepsy from early childhood. At the age of 16, the cognitive impairment was found to be severe and precluded any psychometric assessment. His behaviour was impulsive, violent, and self-destructive. The medical treatment included neuroleptic (chlorpromazine 200–400 mg, thioridazine 100–300 mg, clotiapine 100–200 mg), and antiepileptic (carbamazepine 800–1200 mg,

clonazepam 6–12 mg) medication. Cerebral MRI showed mild T1 and T2 signal alteration of the basal frontal cortex. In the last two years, the patient became more aggressive and the episodes of rage increased in frequency. A severe cervical dystonia (anterocollis) also began to develop. The blood tests suggested hepatotoxicity from high-dose medication.

The second patient was a 37 year old male with congenital toxoplasmosis which resulted in labiopalatoschisis, chorioretinitis, and moderate oligophrenia. Since early childhood, the patient exhibited aggression against objects and people. The violent behaviour worsened in his teens and admission at a psychiatric institution was required when he was seventeen years old. In-patient psychiatric care was required for a long time after many attempts at community living failed. His aggressive behaviour did not allow any psychometric analysis. Occupational and sedative drug therapy including high-dosage neuroleptic, antiepileptic drugs, and benzodiazepines did not control his aggression. The neurological examination showed only mild weakness of the right leg. Cerebral CT and MRI appeared normal. After 20 years of being drug resistant with daily aggressive episodes, DBS of the posterior hypothalamus was considered.

Surgical procedure

The stereotactic implantation was performed with the Leksell frame (Eleckta, Stockholm, Sweden) under local anesthesia. When sedation was required, low doses of midazolam (0.05–0.1 mg/kg) or propofol (0.5–1 mg/kg) were used. General anesthesia was offered only in the two patients who were affected by behavioural disorders. Perioperative antibiotics were administrated to all patients. A preoperative MRI (brain axial volumetric fast spin echo inverson recovery and T2 images) was used to obtain high definition images for the precise determination of both anterior and posterior commissures and midbrain structures below the commissural plane such as the mammillary bodies and the red nucleus. MR images were fused with 2 mm thick CT slices that were obtained under sterotactic conditions by using an automated technique that is based on a mutual-information algorithm (Frame-link 4.0, Sofamor Danek Steathstation, Medtronic, Minneapolis, MN). The workstation also provided stereotactic coordinates of the target: 3 mm behind the midcommissural point, 5 mm below this point, and 2 mm lateral from the midline. The target planning that was based exclusively on the midcommisural point caused electrode misplacement in one patient as previously reported [4]. This kind of error is due to the anatomical individual variability of the angle between the brainstem and the commissural plane [35]. To correct this possible error, we introduced a third anatomical landmark, which allowed the final target registration. We called this landmark ''interpeduncular nucleus'' or ''interpeduncular point'' and it is placed in the apex of the interpeduncular cistern 8 mm below the commissural plane at the level of the maximum diameter of the mammillary bodies (Fig. 2). The Y value of the definitive target (anteroposterior coordinate to the midcommissural point in the classical midcommissural reference system) was corrected in our patients and the definitive target coordinate was chosen 2 mm posterior to the interpeduncular point instead of 3 mm posterior to the midcommissural point.

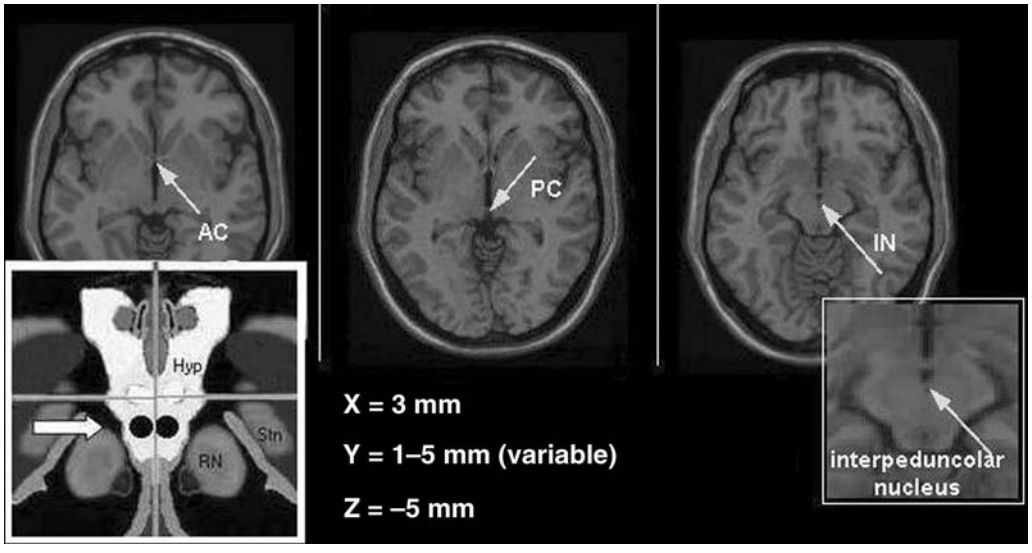

Fig. 2. The three reference points which are used to calculate and standardize the stereotactic coordinates of the target. *AC* Anterior commissure, *PC* posterior commissure, *IN* interpeduncular nucleus. *Left box* Axial slice (5 mm below the commissural plane) of the stereotactic atlas registered to the AC-PC midpoint; the black circles represent the target on both sides, *X* lateral coordinate to the commissural line, *Y* anteroposterior coordinate to the midcommissural point which varies between 1 and 5 mm according to the interpeduncular nucleus coordinates, *Z* the millimiters below the commissural plane

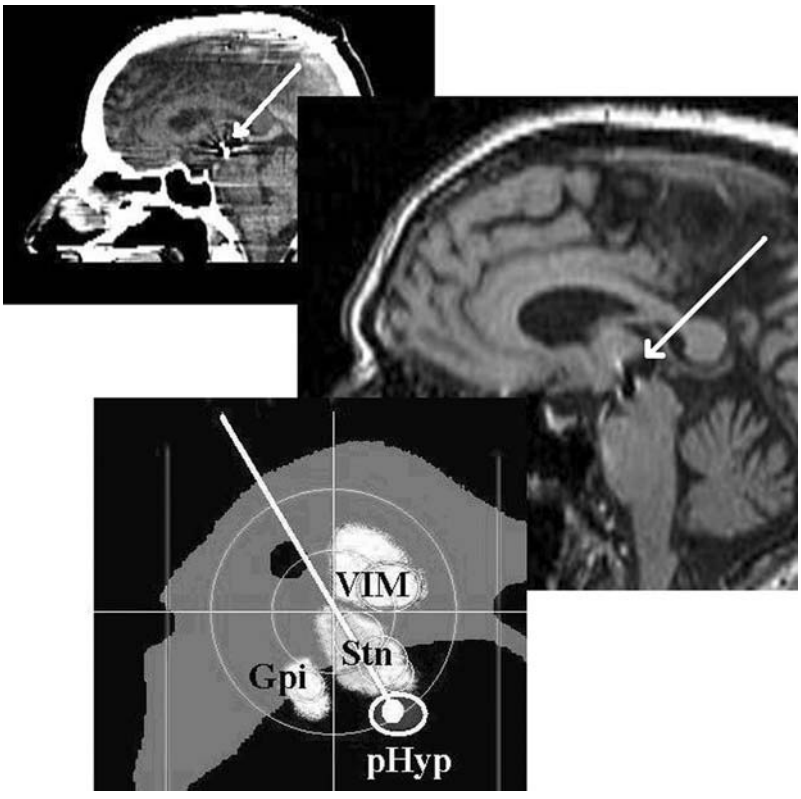

Fig. 3. Sagittal CT and MRI slices showing the active contact of the electrode stimulating the posteromedial hypothalamus (*white arrows*). The inferior box shows the target on the ventriculogram registered to the bicommissural system

A rigid cannula was inserted through a 3 mm, coronal, paramedian twist-drill hole and placed up to 10 mm from the target. This cannula was used both as a guide for microrecording (Lead Point, Medtronic) and for the placement of the definitive electrode (Quad 3389; Medtronic) [3]. Macrostimulation was carried out in patients operated under local anesthesia (1–7 V, 60 μsec, 180 Hz). All patients, subjected to stimulus intensities higher than 4 V, showed conjugated ocular deviation that was followed by verbal reports of a repeated severe negative affective experience described as: ''I feel very close to death''. No pupillary reaction or cardiovascular effects were evoked. When other side effects were ruled out at the standard parameters stimulation, the guiding cannula was removed and the electrode secured to the skull with microplates. A single unit recordings were performed at the target chosen for stereotactic implantation of the stimulating lead in two patients. Microrecordings began as soon as the microelectrode (9013-S-0842 microTargeting^{R} electrode, Medtronic Inc., Minneapolis, TN, USA) reached the presumed coordinates of the target, and were performed by means of a *Medtronic Leadpoint*^{TM} system (Medtronic Inc., Memphis, TN, USA). The response properties of the isolated neurons were obtained with the patients being fully awake.

Post-operative stereotactic CT was performed to exclude any complications and was merged with the pre-operative MRI to confirm the correct electrode placement [5] (Fig. 3). Unilateral or bilateral implantable pulse generator (IPG) (Medtronic, inc.) was then placed in the subclavicular area and connected to the brain electrode for chronic continuous electrical stimulation. During the period 1–7 days after surgery, an additional MRI study was repeated in order to ensure the electrode's position. Unilateral or bilateral continuous bipolar and then monopolar (case positive) 180 Hz, 0.5 V, 60 μsec stimulation was started using the deepest contact in the target. Voltage was gradually increased up to the therapeutic effect. No side effects developed at the therapeutic levels of electrical stimulation.

Results

Chronic cluster headache

The results of DBS on CCH patients in this study are shown in Figs. 1 and 4. Two patients (Nos. 1 and 7) had bilateral electrodes placement, one patient (No. 4) required electrode replacement after 9 months and the

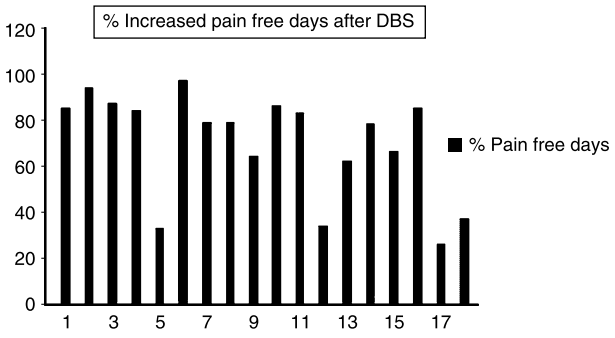

Fig. 4. Increase of number of days free from pain attacks (ordinates) in 18 patients (abscissas) after deep brain stimulation of the posteromedial hypothalamus

other patient (No. 1) one year after the second procedure due to cranial migration of the electrode. A total of 20 electrode implantations were carried out. Unilateral or bilateral continuous unipolar stimulation was administered with the following parameters: frequency 180 Hz, pulse width 60 μsec, amplitude 0.6–3.3 V (mean 2.4). All patients with CCH achieved pain relief as a result of the long term, high frequency, hypothalamic DBS which continued to the follow-up evaluation. The decrease in the frequency of attacks was never immediate but it occurred between 1 and 86 days (mean 42 days). Moreover, the maximum improvement of the pain in terms of intensity and frequency of the CH episodes was achieved progressively in the next one to five months. Abolition of pain or major improvements occurred in 13 patients: 10 patients had a complete and persistent pain-free state, and three patients (7, 11, and 13) had almost complete pain relief, although sporadic attacks still occurred. It should be noted that the drugs were completely ineffective before the surgical procedure. For the remaining three (16.7%) patients (Nos. 4, 10, and 16) the CH attacks continued. In patient 4, the attacks were reduced from seven per day to one every two days; he requires verapamil as well as methysergide for prophylaxis. In patient 10, the attacks have been reduced in intensity from excruciating to mild and the duration from 90 to 15 minutes; he injects sumatriptan (which is effective) for only about 10% of the attacks. In patient 16, the attacks have been reduced from five to one per day after 20 days of stimulation. In patient 3, it proved necessary to add long-term prophylactic medication in order to keep this patient free of attacks.

In four cases in whom the stimulation was turned off to allow cardiological or MR evaluation, the pain attacks recurred after few days and disappeared few hours after reactivation of the IPG. When hardware failure occurred, pain attacks recurred; following the repair, the IPG was switched on and the CCH attacks improved after a few days. At last follow up, on 16 CH patients, the percentage of total number of days free from pain was 71%. No major adverse effects of high-frequency hypothalamic stimulation have been reported or observed during the ongoing chronic stimulation. Oculomotor or affective responses were frequently observed in our patients particularly when the stimulation amplitude was higher than 4 V. A postoperative asymptomatic complication occurred in one case; the CT showed a mild hemorrhage in the posterior wall of the third ventricle. There were no other acute complications resulting from the implantation procedure. There was no clinical evidence of autonomic effects of hypothalamic stimulation during either acute operative electrical stimulation or chronic therapeutic stimulation. Twenty-four hours of continuous monitoring of the arterial blood pressure, in four patients evaluated before and after surgery, revealed only asymptomatic orthostatic hypotension triggered by the electrical stimulation. There were no tolerance phenomena.

SUNCT

After 15 days of bipolar stimulation offered no improvement, unipolar stimulation was started (180 Hz, 60 μsec). The pain attacks subsided after 1 month of stimulation at 0.9 V but reappeared at month 4; the amplitude was gradually increased to 1.8 V, and again the attacks subsided. After one pain-free month, in month 8, the stimulator was turned off with the patient being unaware of it; she remained pain-free for the next 3 months; in month 11, the attacks gradually reappeared and persisted, and, hence, the stimulator was turned on again at 0.9 V. In month 13, the attacks gradually reappeared and the amplitude was progressively increased to 1.8 V and the attacks disappeared. Fifteen months after surgery, the patient started experiencing sporadic attacks, and lamotrigine was given at 100 mg/day; the attacks then subsided. The patient remained unaware of the stimulation status for 8 months. Stimulation was always well tolerated; however, when amplitude was increased up to 1.4 V difficulties in conjugate eye movements appeared and subsided few minutes to few hours later. Blood pressure, heart rate, electrocardiogram, hormone levels, temperature, sleep-waking cycle, body weight, and behaviour remained normal from implantation to the latest checkup.

Atypical facial pain

After surgery, the three patients had no reduction in pain. The stimulation parameters were the same as for CCH and SUNCT patients (180 Hz, 60 μsec, mean voltage 1.3). After four months of continuous stimulation (6, 8, and 10 months, respectively) the continuous pain was the same as preoperatively. Increase of amplitude did not offer any pain relief. Amplitude higher than 3 V induced dizziness and oculomotor symptoms in all cases. Bipolar stimulation did not offer any improvement. When the IPG was switched off with the patient being unaware of it, the episodes of paroxysmal pain were described by the patient as being slightly more intense than those that occurred during stimulation.

Disruptive and aggressive behaviour

HFS of the posteromedial hypothalamus offered consistent improvement of disruptive behaviour in both patients at last follow-up.

Case 1

After two weeks from the beginning of stimulation, neuroleptic medication was withdrawn; at that time the patient appeared much more calm and more cooperative. Few weeks later, he was able to stand and walk and to interact easily with the examiners. One year later, the therapeutic effect of stimulation was still present at the same parameters (180 Hz, 60 μsec, 1 V) without any side effects. The patient regained a normal circadian rhythm, and had complete resolution of his disruptive behaviour. Therefore, he was able to provide for his self-care, underwent rehabilitation and became ambulatory; the dystonic neck posture also improved slightly. The patient's relationships with his family members and his social activities improved greatly. The frequency of epileptic seizures was reduced from 7–10 to 4–7 per day. At the follow up of 18 months, the results were stable.

Case 2

One month after the beginning of stimulation (180 Hz, 60 μsec, 1 V), the aggressive behaviour completely disappeared and the neuroleptic medication was reduced. After 3 months, no behavioural changes were observed; increase of stimulation amplitude was done (180 Hz, 60 μsec, 1.5 V) with no side effects. Three months later, the psychiatric condition was stable and the patient was then transferred to an occupational therapy center. After 15 months of DBS, the aggressive behaviour remains well controlled.

Microrecording

Two cells were recorded with a mean firing discharge rate of 14.35 and 24.77 Hz, respectively. Both neurons generated isolated action potentials during most of recordings. The inter-spike interval histograms (ISIHs) have shown the highest concentrations of intervals in the 10–15 ms range, and the percentage of ISI shorter than 5 ms. In one patient during surgery, it was possible to deliver somatic stimulation to the face, and to record the evoked firing discharge. Postoperative data analysis of the spontaneous and evoked neural discharge was performed by the Spike 2 analysis package (Cambridge Electronic Design, Cambridge, UK). Single unit events were identified, and confirmed as arising from a single neuron, using template-matching spike sorting software. This recorded neuronal activity around our target is of uncertain origin as it does not correlate with any previously anatomically described central gray matter focus; we could only confirm that neurons are present on this target.

Finally, the postoperative fused CT-MR images and controls showed the correct placement of the electrodes in all cases confirming that the ''interpeduncular nucleus'' or ''interpeduncular point'' is more strictly related to our target than the conventional midcommissural point (Fig. 3).

Discussion

The hypothalamus is a core structure of the limbic system that connects two large limbic domains: the mesial temporal structures and the orbito-frontal cortex [23]. The hypothalamus is a central component of the Papez circuit; it is connected with the hippocampus, amygdala, and limbic thalamus on one side via the mamillary bodies and the fornix and on the other side via the cingulate gyrus and the entorhinal cortex. The connection with hippocampus, amygdala, cingulate gyrus, and the entorhinal cortex could explain the role of hypothalamus in learning, memory, emotions, motivation, affiliative behaviour, and autonomic and endocrine functions [17]. The alleged activation of hypothalamus during CCH attacks is considered the origin of some other symptoms which often appear during the attack itself such as abrupt rise of the arterial pressure, psychomotor agitation, hypersexuality, hyperphagia, insomnia, aggression and focal vasomotor alterations. These observations and the results obtained in our series of patients suggest that the posterior hypothalamus is a major part of a neural network, which controls different interlaced

functions. These data suggest that hypothalamic stimulation could potentially have future applications such as in the treatment of severe sleeping disorders, malignant arterial hypertension, and eating disorders; notably, the patients submitted to hypothalamic stimulation showed increase of sleeping time, normalization of arterial blood pressure and significant weight loss. Unfortunately, current pathophysiological findings are insufficient for drawing any conclusions about the mechanisms of hypothalamic HFS; moreover, certain proposed applications, nowadays, seem too distant from becoming a sound scientific proposal. Nevertheless, the analysis of our patients allows a few solid remarks and considerations.

First, chronic neurostimulation of the posterior hypothalamus did not produce any behavioural effects in CCH patients while it produced cessation of disruptive behaviour in the two cases of severe refractory aggressiveness [4, 5, 12]. In other words, neurostimulation of the same target induced different effects in different brains in different clinical conditions [1, 6]. Similar observations were reported in Sano's series; this included patients with facial pain and psychiatric conditions who benefited by RF lesions in the same target, namely the posteromedial hypothalamus [20]. In accordance with Sano's series, one of the two reported psychiatric patients had a 50% decrease in the frequency of drug refractory multifocal epileptic seizures; it should be noted that the considerable amount of neuroleptics that were administered before the stimulation could facilitate the development of multifocal epileptic seizures. Secondly, neuropathic facial pain was completely unaffected by HFS of the posteromedial hypothalamus. This data suggests that the pathophysiological mechanisms giving rise to continuous pain of the face due to fifth nerve lesions does not involve the hypothalamus. Similarly in the Sano's series, patients affected by neuropathic facial pain had poor results after radiofrequency (RF) hypothalamotomy [19]. Thirdly, the involvement of the autonomic system has been confirmed in our patients by the dramatic and sudden disappearance of the neurovegetative dysfunction associated with CH [5, 21]. HFS of the PMH did not produce clinically relevant modifications in the blood pressure profile and in cardiac activity in any of the treated patients. More refined investigational instruments revealed only a delay in orthostatic pressure adjustments.

In conclusion, our data suggests that HFS of the PMH interacts with the mechanisms involved in episodic facial pain, behavioural disease, and neurovegetative system regulation. Future HFS of this target could be considered in the treatment of diseases which show, on imaging, hypothalamic activation. Considering the large number of involved functions, the target volume is small and the stereotactic procedure has to be very precise. This statement applies to all stereotactic procedures, but because of the potentially misleading anatomical variability of the PMH, any targeting error may result in clinical failure requiring reposition of the electrode [5]. Moreover, a recent report of a fatal outcome indicates that the procedure is not entirely free of risks [21]. The reversibility of the procedure and the absence of side effects during chronic continuous and even bilateral PMH DBS should be stressed; this made this technique ethically acceptable in these otherwise untreatable patients whose quality of life consistently improved by this neuromodulation technique. The potential therapeutic role of stimulation of this distinct brain structure is probably greater than it has been previously thought.

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References

1. Bejjani BP, Houeto JL, Hariz M, Yelnik J, Mesnage V, Bonnet AM, Pidoux B, Dormont D, Cornu P, Agid Y (2002) Aggressive behaviour induced by intraoperative stimulation in the triangle of Sano. Neurology 59: 1298–1299
2. Dosen A (1993) Diagnosis and treatment of psychiatric and behavioral disorders in mentally retarded individuals: the state of the art. J Intellect Disabil Res Suppl 37: 1–7
3. Ferroli P, Franzini A, Marras C, Maccagnano E, D'Incerti L, Broggi G (2004) A simple method to assess accuracy of deep brain stimulation electrode placement: pre-operative stereotactic CT+ postoperative MR image fusion. Stereotact Funct Neurosurg 82: 14–19
4. Franzini A, Ferroli P, Leone M, Broggi G (2003) Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery 52: 1095–1099
5. Franzini A, Marras C, Ferroli P, Bugiani O, Broggi G (2005) Stimulation of the posterior hypothalamus for medically intractable impulsive and violent behaviour. Stereotact Funct Neurosurg 83: 63–66
6. Gillberg C, Persson E, Grufman N, Themner U (1986) Psychiatric disorders in mildly and severely mentally retarded urban children and adolescents: epidemiological aspects. Br J Psychiatry 149: 68–74
7. Goadsby PJ (1982) Neuroimaging in headache. Appl Neurophysiol 45: 136–142
8. Headache Classification Committee of The International Headache Society (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24: 1–195
9. Jarrar RG, Black DF, Dodick DW, Davis DH (2003) Outcome of trigeminal nerve section in the treatment of chronic cluster headache. Neurology 60: 1360–1362

10. Leone M, Franzini A, Bussone G (2001) Stereotactic stimulation of posterior hypothalamic gray matter in a patient with intractable cluster headache. N Engl J Med 345: 1428–1429
11. Leone M, Franzini A, Broggi G, May A, Bussone G (2004) Long-term follow-up of bilateral hypothalamic stimulation for intractable cluster headache. Brain 127: 2259–2264
12. Leone M, Franzini A, D'Andrea G, Broggi G, Casucci G, Bussone G (2005) Deep brain stimulation to relieve drug-resistant SUNCT. Ann Neurol 57: 924–927
13. Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G (1983) Cluster headache: clinical findings in 180 patients. Cephalalgia 3: 21–30
14. Matharu MS, Goadsby PJ (2002) Persistence of attacks of cluster headache after trigeminal nerve root section. Brain 125: 976–984
15. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ (2000) PET and MRA findings in cluster headache and MRA in experimental pain. Neurology 55: 1328–1335
16. May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ (1998) Hypothalamic activation in cluster headache attacks. Lancet 352: 275–278
17. Mayanagi Y, Sano K, Suzuki I, Kanazawa I, Aoyagi I, Miyachi Y (1982) Stimulation and coagulation of the posteromedial hypothalamus for intractable pain, with reference to beta-endorphins. Appl Neurophysiol 45: 136–142
18. Sano K, Mayanagi Y, Sekino H, Ogashiwa M, Ishijima B (1970) Results of stimulation and destruction of the posterior hypothalamus in man. J Neurosurg 33: 689–707
19. Sano K, Sekino H, Hashimoto I, Amano K, Sugiyama H (1975) Posteromedial hypothalamotomy in the treatment of intractable pain. Confin Neurol 37: 285–290
20. Sano K, Mayanagi Y (1988) Posteromedial hypothalamotomy in treatment of violent aggressive behaviour. Acta Neurochir Suppl 44: 145–151
21. Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M, Remacle JM, de Noordhout AM (2005) Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. Brain 128: 940–947
22. Schvarcz JB, Driollet R, Rios E, Betti O (1972) Stereotactic hypothalamotomy for behaviour disorders. J Neurol Neurosurg Psychiat 35: 356–359
23. Tarnecki R, Mempel E, Fonberg E, Lagowska J (1976) Some electrophysiological characteristics of the spontaneous activity of the amygdala and effect of hypothalamic stimulation on the amygdalar units responses. Acta Neurochirurgica Suppl 23: 135–140
24. Torelli P, Manzoni GC (2003) Pain and behaviour in cluster headache. A prospective study and review of the literature. Funct Neurol 18: 205–210

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Vagus nerve stimulation for depression: rationale, anatomical and physiological basis of efficacy and future prospects

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Summary

Treatment-resistant depression (TRD) is a major public health concern due to its high costs to society. One of the novel approaches for the treatment of depression is the vagus nerve stimulation (VNS). Therapeutic brain stimulation through delivery of pulsed electrical impulses to the left cervical vagus nerve now has established safety and efficacy as an adjunct treatment for medication-resistant epilepsy and has recently been approved as an adjunct long-term treatment for chronic or recurrent depression. There is considerable evidence from both animal and human neurochemical and neuroimaging studies, that the vagus nerve and its stimulation influence limbic and higher cortical brain regions implicated in mood disorders, providing a rationale for its possible role in the treatment of psychiatric disorders. Clinical studies (open-label and comparator with treatment in naturalistic setting) in patients with TRD have produced promising results, especially when the response rates at longer-term (one- and two-year) follow-up time points are considered. Ongoing research efforts will help determine the place of VNS in the armament of therapeutic modalities available for major depression.

Keywords: Vagus nerve stimulation; major depressive disorder; treatment-resistant depression.

Introduction

Major depressive disorder affects 19 million United States residents with 9.5 million people undergoing treatment annually [22], costing the United States economy more than $40 billion per year [39]. It is the second most disabling condition in the United States, most disabling condition for females in the United States, and the fourth most disabling worldwide [61]. It increases mortality due to suicides [28] and more than 50% of suicides occur in the context of an episode of major depression [6, 24]. The large majority of depressed patients with or without a history of suicide attempts are inadequately treated for depression [65].

Despite a variety of treatments available for major depressive disorder, significant percentage of patients does not respond adequately to treatment. Depression that does not respond, lacks remission, relapses while patient is receiving an adequate dose of an antidepressant medication for sufficient duration with good adherence [76], or fails to respond to two adequate trials of different classes of antidepressants [86] is often referred to as treatment-resistant depression (TRD). TRD is a major public heath problem in that 20–40% of patients in a major depressive episode fail to show substantial clinical improvement, at least a 50% reduction in symptom score, to their first treatment with an antidepressant medication [76], thus resulting in rising medical and mental health care costs and personal suffering [47, 89]. However, many advances have been made in the management of major depression, including TRD, with the introduction of new classes of antidepressants and mood stabilizers as well as novel approaches for treatment [86].

One of the novel approaches for treatment of depression stems from non-pharmacological, somatic interventions affecting brain functions. Eight years after the U.S. Food and Drug Administration's approval of intermittent electrical stimulation of vagus nerve via a surgically implanted programmable prosthesis for medically-refractory partial-onset seizures in 1997 [34, 82], the use of vagus nerve stimulation (VNS) was also approved as an adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. Over the past eight years, VNS

has become one of the most promising new forms of therapeutic brain stimulation fulfilling the need for a long-term treatment of disabling TRD. It also represents the application of new technologies in treating mental illness for the future. Thus, the rationale, anatomical and physiological basis of efficacy as well as future prospects of VNS for depression will be discussed.

Rationale

The rationale for investigating VNS as a possible treatment for TRD is based on 1) the preclinical investigation of VNS in animal models demonstrating the direct effects of VNS on central cortical function, 2) the neuroimaging data demonstrating that VNS affects the metabolism and thus function of various important limbic structures, 3) the demonstrated efficacy of anticonvulsant medications as mood stabilizers in mood disorders [5, 16, 38, 69], 4) the similarities between VNS and electroconvulsive therapy (ECT), considered most effective antidepressant treatment, 5) the observed mood effects of VNS in patients with epilepsy, and 6) the neurochemical studies in both animals and humans revealing that VNS alters concentrations of neurotransmitters implicated in mood disorders, i.e. serotonin, norepinephrine, gamma aminobutyric acid, and glutamate within the central nervous system [8, 18, 94]. These considerations, along with the known anatomical projections of the vagus to the brain regions involved in mood regulation provided a rationale for studying VNS in a new population of subjects for treatment of TRD.

VNS, central cortical function and anticonvulsant action

In 1938, Bailey and Bremer [4] described the synchronized activity of the orbital cortex produced by VNS in cats, a first published report suggesting that VNS directly affected central function. Dell and Olson also noted slow-wave response in anterior rhinal sulcus and amygdala to VNS in awake cats with high cervical spinal section [21]. Primate studies also provided further evidence of VNS effects on basal limbic structures, thalamus, and cingulate [54]. Based on these findings, Zabara hypothesized and further investigated in dogs that VNS would have an anticonvulsant action [96, 97]. Zabara postulated that the antiepileptic mechanisms of action of VNS would involve both direct termination of an ongoing seizure as well as seizure prevention when he observed VNS-induced cortical electroencephalogram changes and seizure cessation in dogs [98].

Neuroimaging studies

The effects of VNS on the brain have been studied using a variety of neuroimaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) [18, 19]. Garnett *et al*. [33] showed, using PET, that left VNS in epilepsy caused increased regional cerebral blood flow (rCBF) in the ipsilateral anterior thalamus and the cingulate gyrus. Ko *et al*. [51] reported increased blood flow in the contralateral thalamus and posterior temporal cortex, and ipsilateral putamen and inferior cerebellum with left VNS. Henry and colleagues studied both acute and chronic effects of VNS on the brain [43–46]. High level (500 μs, 30 Hz, 30 s on, 5 min off, mean 0.5 mA) left VNS stimulation increased the blood flow to the rostral and dorsal medulla oblongata as well as bilateral orbitofrontal gyri, right entorhinal cortex and right temporal pole. Both high and low level (130 μs, 1 Hz, 30 s on, 180 min off, mean 0.85 mA) stimulation increased the blood flow to the right thalamus, right postcentral gyrus, bilateral inferior cerebellum as well as bilateral hypothalamus and anterior insula [43–45]. VNS stimulation also decreased blood flow to the bilateral amygdala, hippocampus, and posterior cingulate gyrus [43–45]. Recently, Conway *et al*. also found acute VNS-induced rCBF changes consistent with brain structures associated with depression and the afferent pathways of the vagus nerve [19].

Various SPECT studies [71, 92, 93] demonstrated decreased thalamic activity, possibly reflecting the chronic changes in the brain or the acute off effect of the VNS since SPECT was performed immediately after it was turned off or during the period when VNS was mostly off [18]. Also, Devous [23] demonstrated in six depressed patients receiving VNS in the open-label study that the patients had reduced rCBF to the left dorsolateral prefrontal, anterolateral temporal, and perisylvian temporal structures, including posterior insula. Zobel and colleagues [100] have also demonstrated rCBF changes in multiple limbic structures following 4 weeks of VNS in 12 patients with TRD.

Decreased activity in cingulate gyrus, an area known to be implicated in depression, with antidepressant response, has been reported in various studies [12, 26, 56, 95]. Therefore, modulation of activity in the cingulate gyrus by VNS, along with VNS altering the activities of the brainstem, limbic system and other central nervous system areas, implicates VNS with antidepressant activity [34].

Mood stabilizing effects of anticonvulsants

Antiepileptic drugs are now frequently utilized for their beneficial mood effects in the pharmacological treatment of mood disorders. Initially, incidental findings of psychiatric improvements during clinical trials of anticonvulsant therapies have provided the rationale for further investigating the potential utility of other drugs, such as carbamazepine, in the management of bipolar disorder [5]. In patients with bipolar disorder, both carbamazepine and valproic acid have been shown to be effective in the treatment of acute mania as well as in the prevention of recurrent manic and depressive episodes [11, 20, 68]. Other antiepileptic drugs such as gabapentin [37, 50, 57, 84] and lamotrigine [15, 16] have been shown to be effective as mood stabilizers or have demonstrated favorable positive effects in treatment of depression. In light of the growing number of modern anticonvulsant agents demonstrating beneficial effects in mood disordered patients, a possible role for VNS in the treatment of depression seemed worthy of investigation.

VNS and ECT

Electroconvulsive therapy (ECT) is considered the most effective available antidepressant treatment. In controlled comparisons with antidepressant medications, ECT has demonstrated superior clinical outcome [31, 32, 48, 58] with remission rates after ECT of approximately 70–90%, far exceeding any other form of antidepressant treatment [2, 3, 67, 78, 79]. Interestingly, ECT is known to have both antidepressant and anticonvulsant actions [75, 77]. Physical, somatic and non-pharmacological intervention modalities, and the similarities between VNS and ECT support the hypothesis that VNS may have primary antidepressant properties. It is reasonable to hypothesize that an effective antiepileptic device might also have antidepressant or mood-stabilizing effects.

The concurrent, safe use of both ECT and VNS has been described in recent literature [14].

Mood effects of VNS in epilepsy patients

During the early epilepsy trials of VNS, patients frequently stayed in the same Gainesville, Florida hotel during follow-up visits at the study site where a hotel clerk made an astute observation. He reported to VNS investigator B. J. Wilder that the VNS patients seemed to be in better spirits as time passed. Anecdotal reports of mood improvements, apparently unrelated to reduction in seizure frequency, further inspired the VNS investigators to systematically assess mood and anxiety symptoms [7, 40]. Both retrospective data analysis [85] and prospective assessments during epilepsy trials [27, 41] suggested that VNS was associated with reduction in depressive symptoms, even in the absence of improvement in seizures. Furthermore, the improvement in seizure frequency in the VNS group was not related to the improvement in mood for the individuals, further suggesting that VNS may improve mood independent of improvement in seizure frequency [41].

Neurochemical changes in central nervous system

Although basic mechanisms of action of VNS are unknown, clinical and animals studies have shown that VNS induces neurochemical changes in the central nervous system, thus providing possible mechanisms of antiseizure and neuropsychiatric effects of VNS [64]. Studies in rats, undergoing VNS, reveal increases in cellular activity, as measured through the oncogene C-fos level, in amygdala, cingulate, locus ceruleus (LC), and hypothalamus [63]. Studies have also demonstrated modulation of serotonin [8], norepinephrine [52], γ-aminobutyric acid (GABA), and glutamate [94]. Also, a study of lumbar cerebrospinal fluid (CSF) components in epilepsy patients sampled before and after 3 months of VNS showed significant increases in CSF concentrations of GABA and trend-level decreases in glutamate [8]. Other provocative findings from the CSF study were trends toward VNS-induced increases in the levels of the major metabolite of dopamine, homovanillic acid, and the major metabolite of serotonin, 5-hydroxyindoleacetic acid [8]. The modulations by VNS of neurotransmitters implicated in mood disorders, the same neurotransmitters through which many of the current treatment of mood disorders have been shown to work, further support the hypothesis that VNS has antidepressant activity.

Anatomical and physiological basis of efficacy

Anatomy of the vagus nerve

The vagus (cranial nerve X), Latin for ‘‘wandering’’, is well known for its parasympathetic efferent functions, such as autonomic control and regulation of the heart and the gut viscera. However, the vagus is actually a mixed sensory and motor nerve with approximately 80% of which is sensory fibers carrying information to the brain from the head, neck, thorax, and abdomen [30]. The cell bodies of the sensory afferent vagus are located

in the nodose ganglion and relay information to the nucleus tractus solitarius (NTS). Through the sensory afferent connections in the NTS, the vagus has extensive projections to brain regions that are thought to modulate activity in the limbic system and higher cortex [4, 21, 54]. The NTS sends the sensory information to the rest of the brain via an autonomic feedback loop, direct projections to the reticular formation in the medulla, and ascending projections to the forebrain through the parabrachial nucleus (PB) and the locus ceruleus (LC) [34, 88]. The pathways of the vagus connecting the NTS with the PB and its adjacent neighbor LC [52] carry afferent vagal input to norepinephrine-containing neurons, reaching the amygdala, hypothalamus, insula, thalamus, orbitofrontal cortex, and other limbic structures [90]. However, the connections to the amygdala and the bed nucleus of the stria terminalis are significant since these structures are implicated in emotion recognition and mood regulation [49, 90]. The NTS also has direct connections, bypassing PB and LC, to the amygdala [66, 70, 99] and hypothalamus [88, 91]. Therefore, the vagus and its sensory afferent input project to numerous brain regions implicated in neuropsychiatric disorders including mood disorders [34, 35].

Neurobiology of VNS in depression

Research in the neurobiology of direct actions VNS has on brain regions and neurotransmitter systems, implicated in mood disorders, is one of the most rapidly advancing areas of research. Emerging data appear to provide converging lines of evidence that VNS exerts measurable effects in brain regions and neurotransmitter systems implicated in mood disorders [64].

In an open-label study of VNS on six depressed patients, SPECT showed that patients had rCBF in the left dorsolateral prefrontal, anterolateral temporal, and perisylvian temporal structures, including posterior insula, at baseline, compared to normal controls [23]. After a 10-week trial of VNS, these depressed patients showed increased rCBF in the superior frontal gyrus, right mesial (posterior hippocampus) and lateral temporal cortex, apparently leading to the resolution of classic rCBF abnormalities in depressed patients, especially among those showing favorable clinical response. In seven patients with TRD after 10 weeks of VNS therapy, a PET study found that compared to baseline, metabolic activity was significantly higher in the bilateral orbitofrontal gyrus, left amygdala and parahippocampal gyrus, bilateral thalamus, left insula and right cingulate gyrus and lower in the bilateral cerebellum and right fusiform gyrus. This data represents a combination of the effects of acute VNS stimulation and chronic effects of VNS on blood flow over 10 weeks of therapy in depressed patients [18]. Also in depressed patients, the synchronized blood oxygenation level-dependent (BOLD) fMRI response to VNS, a technique developed to detect signal from an implanted device and link it to fMRI image acquisition [10], was shown activity changes in areas regulated by the vagus nerve: the orbitofrontal and parieto-occipital cortex bilaterally, the left temporal cortex, the hypothalamus, and the left amygdala [18]. The BOLD fMRI technique was also used to confirm that acute immediate regional brain activity changes vary with the frequency or total dose of stimulation [53].

In the placebo-controlled study, lumbar CSF samples collected before and after VNS therapy in 18 patients had findings consistent with the CSF findings reported for a group of seizure patients receiving 3 months of VNS, demonstrating 21% increase in the concentration of homovanillic acid, a major dopamine metabolite, in the depressed group when compared to the placebo group [17]. On the other hand, no change in CSF GABA was detected.

Dorr and Debonnel [25] recently published their findings of increased basal firing rates of dorsal raphe nucleus and LC following long-term VNS treatment in a rodent electrophysiology study confirming the notion of a novel mechanism of antidepressant action.

Future prospects

VNS and its safety

The VNS Therapy™ system, commercially manufactured by Cyberonics, Inc., includes a pocket watch-sized generator implanted subcutaneously into the left chest wall and bipolar electrode coils wrapped around the left vagus nerve near the carotid via a neck incision [1]. The coil leads are subcutaneously tunneled and connected to the programmable generator. The stimulation parameters can be assessed and controlled by a telemetric wand connected to a portable computer and held to the chest over the patient's clothing.

In 1988, patients with medication-resistant epilepsy who were not candidates for neurosurgery were implanted with the cervical VNS in a pilot study [80]. Collective data from these epilepsy trials showed that after 2 years of continuous VNS, categorical response, defined as 50% or greater reduction in seizure frequency, reached 43% and this was maintained after the 3-year

mark [60]. In addition, these epilepsy studies demonstrated that cervical VNS was well tolerated, with adverse events rarely leading to discontinuation of VNS therapy [83]. Combined data from epilepsy clinical studies ($n = 454$) show minimal surgical complications associated with implantation: infection without explantation of the device (1.8%), infection with subsequent explantation (1.1%), hoarseness or temporary vocal cord paralysis (0.7%), or hypesthesia or lower left facial paresis (0.7%) [13]. In most cases, the side effects due to intermittent stimulation, such as voice alteration or hoarseness, cough, paresthesia, dysphagia, and dyspepsia, were considered mild or moderate, and decreased over time with continued VNS at the same stimulation level. Often, the stimulation-related adverse events could be diminished by reprogramming the device to deliver a lower level stimulation or output current [87]; also the patient could completely abort a stimulation-induced adverse event by holding or taping a small magnet over the pulse generator. The treatment has been judged by the Technology and Therapeutics Committee of the American Academy of Neurology as having ''sufficient evidence ... to rank VNS for epilepsy as effective and safe, based on a preponderance of Class I evidence'' [29].

Published studies of VNS for patients with TRD also demonstrated that VNS was also well tolerated, with few patients discontinuing the study due to an adverse event. The most common adverse events, hoarseness, coughing, shortness of breath during exercise, headache, and neck pain, were considered mild, intermittent, and associated with stimulation [72, 73].

Open-label study of VNS for TRD

In an open-label study of VNS for non-psychotic, chronic or recurrent TRD in 30 patients who had failed trials for at least two classes of medications during the current depressive episode, the efficacy and safety of VNS was first studied at four United States academic sites [72]. All subjects underwent a two-week, single-blind recovery period after their implant surgery, followed by a two-week period where the VNS was activated and the output current was progressively increased to the maximum tolerated level. Subsequently, the output level of the stimulator was fixed and stimulation continued for an additional eight weeks. All patients in the trials were continued on stable psychotropic medication regimens for the entire course of the trial.

The study showed that 12 of the 30 (40%) of the patients were considered ''responders'' having a 50% or greater reduction in baseline on the Hamilton Rating Scale for Depression after 12 weeks of VNS treatment with substantial functional improvement also demonstrated by increased average score on the Global Assessment of Function from 40.6 to 61.9 during the same study period. A second cohort of 30 patients with TRD meeting the similar inclusion and exclusion criteria, were added to the study with only 6 of 29 (20.7%) patients, completing the study, meeting the criteria for a ''responder''. The overall acute response rate was 18 of 59 (30.5%) patients, with 9 of the 59 (15%) patients meeting the criteria for full remission of the depressive episode. VNS was also associated with improvements in vitality, social function, and mental health domains, based on Quality of Life assessment, even among patients who were considered VNS acute phase non-responders [81]. These results were impressive given the study population with average participant having unsuccessfully tried over 16 interventions prior to the trial.

Data analysis also revealed no dose-response relationship with final output current, and neuropsychological tests indicated neurocognitive improvements after VNS relative to baseline, especially in those who experienced decreased depressive symptoms [80, 81]. Also, the identifiable predictor of response was the degree of treatment resistance, as measured by the number of failed antidepressant trials. In general, more severely refractory patients experienced poorer responses to the 10-week VNS therapy.

Long-term data on VNS in TRD were more encouraging. After one year of VNS, 10 of 11 (91%) acute responders, from the first group of 30, had maintained their response, but more importantly 3 of 17 (18%) of the initial non-responders had achieved a reduction of depressive symptoms thus meeting the ''responder'' criteria [55]. For the entire study ($n = 59$), the response rate was 45% and the remission rate was 27% at the one-year mark and the response rate was 42% and the remission rate was 22% at the two-year mark [62]. Also at two-year mark, 39% of the initial non-responders showed substantial benefit from VNS [62]. Changes in dose or type of psychotropic medication and VNS stimulation parameters were not controlled after the exit from the initial 12-week acute phase study thus introducing the possibility that the observed improvements were not entirely attributable to the VNS. The association of adjunct VNS with sustained depressive symptom reduction and improved functional status after two years is suggestive of antidepressant efficacy.

Placebo-controlled study of VNS for depression

Encouraged by the positive results of the open-label study, a double blind placebo-controlled study investigated the efficacy of the VNS in the treatment of depression. The study design was similar to the original study and the patients were randomized in a double-blind fashion to either active VNS or a sham condition. At the end of the twelve week-long acute study period, if patients assigned to the sham arm of the study were still depressed, they crossed over to the active stimulation arm, and the long-term data were collected on all patients in the study. The investigators also revised the study exclusion criteria to exclude those with the highest levels of treatment resistance (six or more failed trials in the depressed episode), since they appeared to have the worst response rate in the previous open-label study. Two hundred and thirty five patients received VNS through this double-blind study, with placebo (sham) response rate of 10% and active VNS response rate of 15%, which failed to statistically confirm the short-term antidepressant efficacy of the VNS therapy [73].

Possible explanation for the different findings between the placebo-controlled and open-label study may be the inadequate dosing of the VNS in the placebo-controlled study. A preliminary comparison of the output current, delivered in the placebo-controlled depression study versus the initial open-label depression study and the epilepsy studies suggests that stimulation set at 1.0 mA or higher is associated with the higher rates of clinical response. Stimulation parameters were set at lower settings in the placebo-controlled study, compared to those used in the initial open-label depression studies and the epilepsy trials. Another possible explanation for the failure to see VNS separate from sham might be inadequate duration of the trial.

Naturalistic study of VNS for depression

Two hundred and five patients were in a naturalistic follow-up study with the same enrollment criteria as the randomized placebo-control trial to better delineate the long-term efficacy of VNS as an adjunct to ongoing antidepressant treatment, to determine whether statistically significant and clinically meaningful symptom reduction occurs with VNS [74]. One group who initially received 10 weeks of active VNS received 9 additional months of stimulation whereas the second group initially assigned to the sham group received 12 months of VNS. The study demonstrated a response rate of 27.2% with remission rate of 15.8%, revealing a statistically significant reduction in depressive symptoms [74]. A comparison of 1-year outcomes in VNS patients ($n = 205$) and a matched TRD group ($n = 124$) receiving ''treatment as usual'' revealed superior antidepressant benefits for those receiving adjunct VNS [36]. Categorical response rates were 27% for the VNS group and 13% for those receiving standard available treatments in a naturalistic setting [36].

Long-term outcome of VNS

As previously mentioned, there is an apparent gradual accumulation of more VNS responders over time in the open-label study. For instance, 3 of 17 (18%) of the initial non-responders had achieved a reduction of depressive symptoms thus meeting the ''responder'' criteria at the one-year mark with VNS [55]. In addition, long-term response rates from the above study showed that VNS has a sustained effect, with 70% of those classified as ''responders'' at three months continuing to be classified as ''responders'' at two years. These data suggested that VNS might require longer than standard pharmacotherapies to manifest an antidepressant effect. The longer-term data on VNS in depressed patients have helped in determining the placement of VNS in the armament of therapeutic modalities available for major depression.

Practical considerations

Surgical implantation of the VNS Therapy^{TM} system requires a procedure of low technical complexity for a surgeon with experience in the head and neck area. The surgery typically takes less than one hour in the operating room, often performed on an outpatient or day-surgery basis. General anesthesia is used in the majority of cases, but regional and local anesthesias can also be used [42]. A device ''programmer'' who is knowledgeable with the operation of the VNS Therapy^{TM} system must be present in the operating room to perform lead testing before surgical incisions are closed. The battery life of the pulse generator model is approximately six to ten years and the entire pulse generator must be surgically replaced once the battery expires.

Whole-body MRI is contraindicated in patients who have the VNS pulse generator implanted because of the potential for heating of the electrical leads. Special ''send–receive coils'' can be used to concentrate magnetic fields away from the neck area when MRI of the brain is necessary. Patients with the VNS Therapy^{TM} system should carry identification cards and should be

aware of the risks related to being in close proximity to strong magnetic fields.

The cost of the VNS Therapy™ system and its surgical implantation is approximately $24,000, making it roughly comparable to the cost of a course of ECT for depression in an inpatient setting. Early success in establishing adequate terms of coverage and reimbursement by third party payers has contributed to the wide-scale availability of VNS for patients with epilepsy in the United States. Until recently, VNS as a treatment for depression has been investigational in the United States, and as such, was offered only at academic centers conducting approved research protocols. The optimal stimulation parameters for antidepressant effects are still unknown. While it is tempting to imagine that VNS may someday replace psychotropic medications along with many undesirable side effects, it is notable that in the majority of cases to date, VNS has been investigated as an adjunct therapy rather than as a monotherapy. Therefore, the expectations of the depressed patients for dramatic symptom recovery or even cure from severe psychiatric illness may be fueled by the introduction of new technology and the highly interventional nature of the device implantation surgery. Management of such expectations should be undertaken with great care, particularly in depressed patients who are at heightened risk for acting impulsively and self-destructively on feelings of disappointment and hopelessness.

VNS for treatment of TRD

In July, 2005, the use of VNS was approved by the U.S. Food and Drug Administration for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. Such milestone opens the door for the greater availability of VNS in the treatment of TRD, which will inevitably broaden our experience with VNS. Ongoing preclinical and clinical studies of VNS should further refine the role of VNS in the treatment of TRD.

VNS for treatment of other neuropsychiatric disorders

In addition to advancing our understanding of the pathophysiology of various neuropsychiatric disorders, VNS may have other therapeutic applications, which are guided by the known anatomy of vagus connections and may shed some light into the mechanism of action of VNS. For example, as vagus nerve plays an important role in relaying information into the CNS, several theories on anxiety disorder hypothesize that faulty interpretation of the relayed peripheral information into the CNS or unreliable availability of the information may be the underlying cause. Therefore, it is possible that modulation in the flow of information into the CNS by VNS could have therapeutic potential in anxiety disorders or irritable bowel syndrome [34]. Also, since the vagus also carries hunger satiety and pain information, VNS may be considered for the treatment-resistant obesity [9], addictions, or pain syndrome. In addition, since NTS sends fibers into the dorsal raphe and areas that are known to control levels of alertness, potential treatment for sleep disorders, coma or narcolepsy may also be possible. Recent pilot data suggest a possible role for adjunct VNS in the treatment of Alzheimer's disease [59].

Conclusion

TRD is a major public health concern, thus demonstrating a tremendous need for a better, long-term treatment. In that regard, VNS has emerged as one of the most promising new forms of therapeutic brain stimulation, an application of new technology in treating mental illness. As clinical studies provide encouraging positive results towards the efficacy in treatment of TRD with VNS, VNS will continue to establish and refine its role in the treatment of TRD.

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References

1. Amar AP, Heck CN, Levy ML, Smith T, DeGiorgio CM, Oviedo S, Apuzzo ML (1998) An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique and outcome. Neurosurgery 43: 1265–1276
2. American Psychiatric Association (2000) Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry 157 Suppl 4: 1–45
3. American Psychiatric Association (2001) The practice of ECT: recommendations for treatment, training and privileging, 2nd edn. American Psychiatric Press, Washington, DC
4. Bailey P, Bremer F (1938) A sensory cortical representation of the vagus nerve: with a note on the effects of low blood pressure on the cortical electrogram. J Neurophysiol 1: 405–412
5. Ballenger JC, Post RM (1980) Carbamazepine in manic-depressive illness: a new treatment. Am J Psychiatry 137: 782–790

6. Barraclough B, Bunch J, Nelson B, Sainsbury P (1974) A hundred cases of suicide: clinical aspects. Br J Psychiatry 125: 355–373
7. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, Tarver WB, Wernicke JF (1994) Vagus nerve stimulation for treatment of partial seizures: I. a controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia 35: 616–626
8. Ben-Menachem E, Hamberger A, Hedner T, Hammond EJ, Uthman BM, Slater J, Treig T, Stefan H, Ramsay RE, Wernicke JF, Wilder BJ (1995) Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Epilepsy Res 20: 221–227
9. Bodenlos JS, Kose S, Borckardt JJ, Nahas Z, Shaw D, O'Neil PM, George MS (2006) Vagus nerve stimulation acutely alters food craving in adults with depression. Appetite Epub 2006 Oct 30
10. Bohning DE, Lomarev MP, Denslow S, Nahas Z, Shastri A, George MS (2001) Feasibility of vagus nerve stimulation-synchronized blood oxygenation level-dependent functional MRI. Invest Radiol 36: 470–479
11. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, Dilsaver SC, Davis JM, Rush AJ, Small JG *et al* (1994) Efficacy of divalproex versus lithium and placebo in the treatment of mania. JAMA 271: 918–924
12. Bremner JD, Innis RB, Salomon RM, Staib LH, Ng CK, Miller HL, Bronen RA, Krystal JH, Duncan J, Rich D, Price LH, Malison R, Dey H, Soufer R, Charney DS (1997) Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. Arch Gen Psychiatry 54: 364–374
13. Bruce DA (1998) Implantation of a vagus nerve stimulator for refractory partial seizures: surgical outcomes of 454 study patients. Epilepsia 39 Suppl 6: 92–93
14. Burke MJ, Husain MM (2006) Concomitant use of vagus nerve stimulation and electroconvulsive therapy for treatment-resistant depression. J ECT 22: 218–222
15. Calabrese JR, Bowden CL, McElroy SL, Cookson J, Andersen J, Keck PE Jr, Rhodes L, Bolden-Watson C, Zhou J, Ascher JA (1999) Spectrum of activity in lamotrigine in treatment-refractory bipolar disorder. Am J Psychiatry 156: 1019–1023
16. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD (1999) A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. J Clin Psychiatry 60: 79–88
17. Carpenter LL, Moreno FA, Kling MA, Anderson GM, Regenold WT, Labiner DM, Price LH (2004) Effects of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. Biol Psychiatry 56: 418–426
18. Chae JH, Nahas Z, Lomarev M, Denslow S, Lorberbaum JP, Bohning DE, George MS (2003) A review of functional neuroimaging studies of vagus nerve stimulation (VNS). J Psychiatr Res 37: 443–455
19. Conway CR, Sheline YI, Chibnall JT, George MS, Fletcher JW, Mintun MA (2006) Cerebral blood flow changes during vagus nerve stimulation for depression. Psychiatry Research: Neuroimaging 146: 179–184
20. Cullen M, Mitchell P, Brodaty H, Boyce P, Parker G, Hickie I, Wilhelm K (1991) Carbamazepine for treatment-resistant melancholia. J Clin Psychiatry 52: 472–476
21. Dell P, Olson R (1951) Projections 'secondaries' mesencephaliques, diencephaliques et amygdaliennes des afferences viscerales vagales. C R Seances Soc Biol Fil 145: 1088–1091
22. Depression Guideline Panel (1993) Depression in Primary Care: Volume 1. Detection and Diagnosis (Clinical Guideline No. 5, AHCPR Publication No. 93-0550). Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research, Washington, DC
23. Devous MD (2001) Effects of VNS on regional cerebral blood flow in depressed subjects. Vagus nerve stimulation (VNS) for treatment-resistant depression. Satellite Symposium in conjunction with the 7th World Congress of Biological Psychiatry. Berlin, Germany
24. Dorpat TL, Ripley HS (1960) A study of suicide in the Seattle area. Compr Psychiatry 1: 349–359
25. Dorr AE, Debonnel G (2006) Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. J Pharmacol Exp Ther 318: 890–898
26. Ebert D, Feistel H, Barocka A, Kaschka W (1994) Increased limbic flow and total sleep deprivation in major depression with melancholia. Psychiatry Res 55: 101–109
27. Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE (2000) Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 42: 203–210
28. Fawcett J (1993) The morbidity and mortality of clinical depression. Int Clin Psychopharmacol 8: 217–220
29. Fisher RS, Handforth A (1999) Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 53: 666–669
30. Foley JO, Dubois F (1937) Quantitative studies of the vagus nerve in the cat. I: the ratio of sensory and motor studies. J Comp Neurol 67: 49–67
31. Folkerts HW, Michael N, Tolle R, Schonauer K, Mucke S, Schulze-Monking H (1997) Electroconvulsive therapy vs. paroxetine in treatment-resistant depression – a randomized study. Acta Psychiatr Scand 96: 334–342
32. Gangadhar B, Kapur R, Kalyanasundaram S (1982) Comparison of electroconvulsive therapy with imipramine in endogenous depression: a double blind study. Br J Psychiatry 141: 367–371
33. Garnett ES, Nahmias C, Scheffel A, Firnau G, Upton AR (1992) Regional cerebral blood flow in man manipulated by direct vagal stimulation. Pacing Clin Electrophysiol 15: 1579–1580
34. George MS, Sackeim HA, Rush AJ, Marangell LB, Nahas Z, Husain MM, Lisanby S, Burt T, Goldman J, Ballenger JC (2000) Vagus nerve stimulation: a new tool for brain research and therapy. Biol Psychiatry 47: 287–295
35. George MS, Rush AJ, Sackeim HA, Marangell LB (2003) Vagus nerve stimulation (VNS): utility in neuropsychiatric disorders. Int J Neuropsychopharmacol 6: 73–83
36. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, Howland R, Kling MA, Moreno F, Rittberg B, Dunner D, Schwartz T, Carpenter L, Burke M, Ninan P, Goodnick P (2005) A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 58: 364–373
37. Ghaemi SN, Katzow JJ, Desai SP, Goodwin FK (1998) Gabapentin treatment of mood disorders: a preliminary study. J Clin Psychiatry 59: 426–429
38. Goodwin FK, Jamison KR (1990) Manic-depressive illness. Oxford University Press, New York
39. Greenberg PE, Stiglin LE, Finkelstein SN, Berndt ER (1993) The economic burden of depression in 1990. J Clin Psychiatry 54: 405–418
40. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW (1998) Vagus nerve stimulation for treatment of partial-onset seizures: a randomized active-control trial. Neurology 51: 48–55

41. Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper J, Labar DR (2000) A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav 1: 93–99
42. Hatton KW, McLarney JT, Pittman T, Fahy BG (2006) Vagal nerve stimulation: overview and implications for anesthesiologists. Anesth Analg 103: 1241–1249
43. Henry TR (2000) Functional imaging studies of epilepsy therapies. Adv Neurol 83: 305–317
44. Henry TR, Bakay RA, Votaw JR, Pennell PB, Epstein CM, Faber TL, Grafton ST, Hoffman JM (1998) Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and low levels of stimulation. Epilepsia 39: 983–990
45. Henry TR, Votaw JR, Bakay RA, Pennell PB, Epstein CM, Faber TL, Grafton ST, Hoffman JM (1998) Vagus nerve stimulation – induced cerebral blood flow changes differ in acute and chronic therapy of complex partial seizure. Epilepsia 39 Suppl 6: 92
46. Henry TR, Votaw JR, Pennell PB, Epstein CM, Bakay RA, Faber TL, Grafton ST, Hoffman JM (1999) Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. Neurology 52: 1166–1173
47. Hirschfeld RM, Keller MB, Panico S, Arons BS, Barlow D, Davidoff F, Endicott J, Froom J, Goldstein M, Gorman JM, Marek RG, Maurer TA, Meyer R, Philips K, Ross J, Schwenk TL, Sharfstein SS, Thase ME, Wyatt RJ (1997) The national depressive and manic-depressive association consensus statement on the undertreatment of depression. JAMA 277: 333–340
48. Janicak PG, Davis JM, Gibbons RD, Ericksen S, Chang S, Gallagher P (1985) Efficacy of ECT; a meta-analysis. Am J Psychiatry 142: 297–302
49. Ketter TA, George MS, Kimbrell TA, Benson BA, Post RM (1997) Functional brain imaging in mood and anxiety disorders. Curr Rev Mood Anxiety Disord 1: 96–112
50. Knoll J, Stegman K, Suppes T (1998) Clinical experience using gabapentin adjunctively in patients with a history of mania or hypomania. J Affect Disord 49: 229–233
51. Ko D, Heck C, Grafton S, Apuzzo ML, Couldwell WT, Chen T, Day JD, Zelman V, Smith T, DeGiorgio CM (1996) Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET $H_2{}^{15}O$ blood flow imaging. Neurosurgery 39: 426–430
52. Krahl SE, Clark KB, Smith DC, Browning RA (1998) Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. Epilepsia 39: 709–714
53. Lomarev M, Denslow S, Nahas Z, Chae JH, George MS, Bohning DE (2002) Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects. J Psychiatr Res 36: 219–227
54. MacLean PD (1990) Triune brain in evolution: role in paleocerebral functions. Plenum Press, New York
55. Marangell LB, Rush AJ, George MS, Sackeim HA, Johnson CR, Husain MM, Nahas Z, Lisanby SH (2002) Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. Biol Psychiatry 51: 280–287
56. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT (1997) Cingulate function in depression: a potential predictor of treatment response. Neuroreport 8: 1057–1061
57. McElroy SI, Soutullo CA, Keck PE Jr, Kmetz GF (1997) A pilot trial of adjunctive gabapentin in the treatment of bipolar disorder. Ann Clin Psychiatry 9: 99–103
58. Medical Research Council (1965) Clinical trial of the treatment of depressive illness. Report to the Medical Research Council by its Clinical Psychiatry Committee. Br Med J 1: 881–886
59. Merrill CA, Jonsson MA, Minthon L, Ejnell H, C-son Silander H, Blennow K, Karlsson M, Nordlund A, Rolstad S, Warkentin S, Ben-Menachem E, Sjogren MJ (2006) Vagus nerve stimulation in patients with Alzheimer's disease: additional follow-up results of a pilot study through 1 year. J Clin Psychiatry 67: 1171–1178
60. Morris GL 3rd, Mueller WM (1999) Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology 53: 1731–1735
61. Murray CJL, Lopez AD (1996) The global burden of disease in 1990: final results and their sensitivity to alternative epidemiological perspectives, discount rates, age-weights and disability weights. In: Murray CJL, Lopez AD (eds) The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Harvard University Press, Cambridge, pp 247–293
62. Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, Martinez JM, George MS (2005) Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 66: 1097–1104
63. Naritoku DK, Terry WJ, Helfert RH (1995) Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. Epilepsy Res 22: 53–62
64. Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR, George MS, Charney DS, Brannan SK (2006) VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacology 31: 1345–1355
65. Oquendo MA, Malone KM, Ellis SP, Sackeim HA, Mann JJ (1999) Inadequacy of antidepressant treatment for patients with major depression who are at risk for suicidal behavior. Am J Psychiatry 156: 190–194
66. Ottersen OP (1981) Afferent connections to the amygdaloin complex of the rat with some observations in the cat. III. Afferents from the lower brain stem. J Comp Neurol 202: 335–356
67. Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, Rummans TA, O'Connor KM, Rasmussen KG Jr, Bernstein HJ, Biggs M, Bailine SH, Kellner CH (2001) ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. J ECT 17: 244–253
68. Post RM, Ketter TA, Denicoff K, Pazzaglia PJ, Leverich GS, Marangell LB, Callahan AM, George MS, Frye MA (1996) The place of anticonvulsant therapy in bipolar illness. Psychopharmacology (Berl) 128: 115–129
69. Post RM, Denicoff KD, Frye MA, Dunn RT, Leverich GS, Osuch E, Speer A (1998) A history of the use of anticonvulsants as mood stabilizers in the last two decades of the 20th century. Neuropsychobiology 38: 152–166
70. Ricardo JA, Koh ET (1978) Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. Brain Res 153: 1–26
71. Ring HA, White S, Costa DC, Pottinger R, Dick JP, Koeze T, Sutcliffe J (2000) A SPECT study of the effect of vagal nerve stimulation on thalamic activity in patients with epilepsy. Seizure 9: 380–384
72. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, Nahas Z, Haines S, Simpson RK Jr, Goodman R (2000) Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry 47: 276–286
73. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, Rapaport MH, Zajecka J, Nierenberg AA, Husain MM, Ginsberg D, Cooke RG (2005) Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry 58: 347–354

74. Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, Lavori P, Howland R, Kling MA, Rittberg B, Carpenter L, Ninan P, Moreno F, Schwartz T, Conway C, Burke M, Barry JJ (2005) Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry 58: 355–363
75. Sackeim HA (1999) The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. J ECT 15: 5–26
76. Sackeim HA (2001) The definition and meaning of treatment-resistant depression. J Clin Psychiatry 62 Suppl 16: 10–17
77. Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR (1983) Anticonvulsant and antidepressant properties of electroconvulsive therapy: a proposed mechanism of action. Biol Psychiatry 18: 1301–1310
78. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembrino JM (1993) Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. N Engl J Med 328: 839–846
79. Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, Fitzsimons L, Moody BJ, Clark J (2000) A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 57: 425–434
80. Sackeim HA, Keilp JG, Rush AJ, George MS, Marangell LB, Dormer JS, Burt T, Lisanby SH, Husain M, Cullum CM, Oliver N, Zboyan H (2001) The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. Neuropsychiatry Neuropsychol Behav Neurol 14: 53–62
81. Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S, Simpson RK Jr, Goodman RR (2001) Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacololgy 25: 713–728
82. Schachter SC (2002) Vagus nerve stimulation therapy summary: five years after FDA approval. Neurology 59 Suppl 4: S15–S20
83. Schachter SC, Saper CB (1998) Vagus nerve stimulation (progress in epilepsy research). Epilepsia 39: 677–686
84. Schaffer CB, Schaffer LC (1997) Gabapentin in the treatment of bipolar disorder. Am J Psychiatry 154: 291–292
85. Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE (2001) Vagus nerve stimulation: clinical experience in a large patient series. J Clin Neurophysiol 18: 408–414
86. Souery D, Amsterdam J, de Montigny C, Lecrubier Y, Montgomery S, Lipp O, Racagni G, Zohar J, Mendlewicz J (1999) Treatment resistant depression: methodological overview and operational criteria. Eur Neuropsychopharmacol 9: 83–91
87. Tecoma ES, Iragui VJ (2006) Vagus nerve stimulation use and effect in epilepsy: what have we learned? Epilepsy Behav 8: 127–136
88. Ter Horst GJ, Streetland C (1994) Ascending projection of the solitary tract nucleus. In: Robin I, Barraco A (eds) Nucleus of the solitary tract. CRC Press, London
89. Thase ME, Rush AJ (1995) Treatment-resistant depression. In: Bloom F, Kupfer D (eds) Psychopharmacology: the fourth generation of progress. Raven Press, New York, pp 1081–1098
90. Van Bockstaele EJ, Peoples J, Valentino RJ (1999) Anatomic basis for differential regulation of the rostrolateral peri-locus coeruleus region by limbic afferents. Biol Psychiatry 6: 1352–1363
91. Van der Kooy D, Koda LY, McGinty JF, Gerfen CR, Bloom FE (1984) The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in the rat. J Comp Neurol 224: 1–24
92. Van Laere K, Vonck K, Boon P, Brans B, Vandekerckhove T, Dierckx R (2000) Vagus nerve stimulation in refractory epilepsy: SPECT activation study. J Nucl Med 41: 1145–1154
93. Vonck K, Boon P, Van Laere K, D'Have M, Vandekerckhove T, O'Connor S, Brans B, Dierckx R, De Reuck J (2000) Acute single photon emission computed tomographic study of vagus nerve stimulation in refractory epilepsy. Epilepsia 41: 601–609
94. Walker BR, Easton A, Gale K (1999) Regulation of limbic motor seizures by GABA and glutamate transmission in nucleus tractus solitarius. Epilepsia 40: 1051–1057
95. Wu JC, Gillin JC, Buchsbaum MS, Hershey T, Johnson JC, Bunney WE Jr (1992) Effect of sleep deprivation on brain metabolism of depressed patients. Am J Psychiatry 149: 538–543
96. Zabara J (1985) Control of hypersynchronous discharge in epilepsy. Electroencephalogr Clin Neurophysiol Suppl 61: S162
97. Zabara J (1985) Time course of seizure control to brief, repetitive stimuli. Epilepsia 26: 518
98. Zabara J (1992) Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia 33: 1005–1012
99. Zardetto-Smith AM, Gray TS (1990) Organization of the peptidergic and catecholaminergic efferents from the nucleus of the solitary tract to the rat amygdala. Brain Res Bull 25: 875–887
100. Zobel A, Joe A, Freymann N, Clusmann H, Schramm J, Reinhardt M, Biersack HJ, Maier W, Broich K (2005) Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: an exploratory approach. Psychiatry Res 139: 165–179

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Experimental and clinical aspects of the efferent auditory system

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Summary

The discovery of active mechanisms in the cochlea and the efferent auditory pathways from the brain to the cochlea demonstrated the existence of a modulation of the auditory input in the central nervous system (CNS). Otoacoustic emissions (OAEs) are weak signals that can be recorded in the ear canal and are considered a byproduct of an active process from the outer hair cells (OHCs) to the basilar membrane. The efferent auditory system plays an inhibitory role on the activity of OHCs; its stimulation reduces auditory nerve response, basilar membrane motility and OAEs amplitude. Indirect stimulation by contralateral sound is also inhibitory; a reduction of OAEs amplitude can be recorded and such an effect disappears after olivocochlear bundle section. The efferent system seems to play a role in detection of signals in noise, protection in noise-induced cochlear damage, development of hearing and processing of complex auditory signals. With respect to clinical application, OAEs suppression after contralateral auditory stimulation seems to be the only objective and non-invasive method for evaluation of the functional integrity of the medial efferent system, and, therefore, for evaluation of the structures lying along its course, at least up to the level of inferior colliculi.

Keywords: Efferent auditory system; otoacustic emission; olivocochlear bundle.

Introduction

The mammalian cochlea is an extraordinarily sensitive mechanoceptor able to separate complex acoustic stimuli into their frequency components and to encode them into meaningful patterns of nerve impulses in primary afferent neurons of the auditory nerve. Progressive and sequential information processing takes place along the auditory afferent pathways, from the auditory nerve to the cerebral cortex. However, this hierarchical organization is superimposed upon a parallel arrangement of auditory reciprocal descending projections that may be specialized in processing particular aspects of acoustic information. The discovery of active mechanisms in the cochlea and the efferent auditory pathways from the brain to the cochlea demonstrated the existence of a modulation of auditory input before it reaches the brain [19, 22].

Anatomy and physiology of the efferent auditory system

Historical background

The basic understanding that the cochlea converts sound waves into nerve impulses, which are transmitted into the brain, has existed for more than 200 years. The classical auditory theory, established by von Békésy, assumed the rise of the travelling wave in a mechanically passive and linear system, which delivered sound energy of different frequencies to different parts of the cochlea [21]. The discovery of otoacoustic emissions (OAEs) by Kemp demonstrated the cochlea capability of an active, non-linear, retrograde transmission of sound [11].

Cochlear micromechanics and generation of OAEs

Otoacoustic emissions are weak signals that can be recorded in the ear canal and are considered to reflect the cochlear activity. OAEs are emitted from the cochlea as a byproduct of an active process from the outer hair cells (OHCs) to the basilar membrane, and are responsible for enhancing the basilar membrane vibration and sharpening the frequency tuning. OAEs generation is related to active, fast and slow, motility of the OHCs, through the contraction of the actinomyosin complex in the cytoskeleton of the OHCs. The *fast contractions* follow sound-driven passive vibrations of the cochlear partition; they stimulate the actinomyosin network of the

OHCs, acting to oppose viscous damping in the cochlea and to enhance the oscillations of the basilar membrane and, thus, the mechanical stimulation of the inner hearing cells (IHCs), which are directly involved in the transformation of mechanical energy into neural activity. The *slow, tonic contractions* of the OHCs can alter the stiffness of the cochlear partition in a sharply restricted area, modifying the envelope of the travelling wave [25].

The vibrations of the stapes footplate in the oval window, driven by sound pressure waves, cause a dynamic displacement of the cochlear partition in the shape of a travelling wave. Since the walls of the endolymphatic duct are flexible, the travelling waves are transmitted to the scala tympani, and the wave-like distortion of the endolymphatic duct causes Reissner's membrane and the basilar membrane to swing from one side to the other, towards the scala tympani and scala vestibuli, alternately. The site at which maximal displacement of the endolymphatic duct occurs is the ''characteristic'' for the frequency sound. Sound-driven passive mechanical movements of the basilar membrane and OHCs are accompanied by additional induction of active, fast, mechanical movements of the OHCs and subsequent slow movements, thus creating a highly non-linear and saturating positive feedback system. The OHC fast motility, which enhances the basilar membrane motion, is linearly correlated with the intensity of sound stimuli. However, with an increase in sound pressure level, the cochlea is capable of correcting undesirable shifts of the basilar membrane by the slow OHC movements, leading to a reduction of the passive displacement, and non-linear compression of cochlear dynamics. Thus, the OHCs act as controlled mechano-amplifiers within the cochlea and feed amplified mechanical oscillations to the IHCs, responsible for transduction of mechanical energy into neural activity [13].

OAEs can be divided into two classes: spontaneous and evoked. Spontaneous OAEs (SOAEs) are continuous narrow-band signals emitted by the cochlea in the absence of any acoustical stimulation. Evoked OAEs are

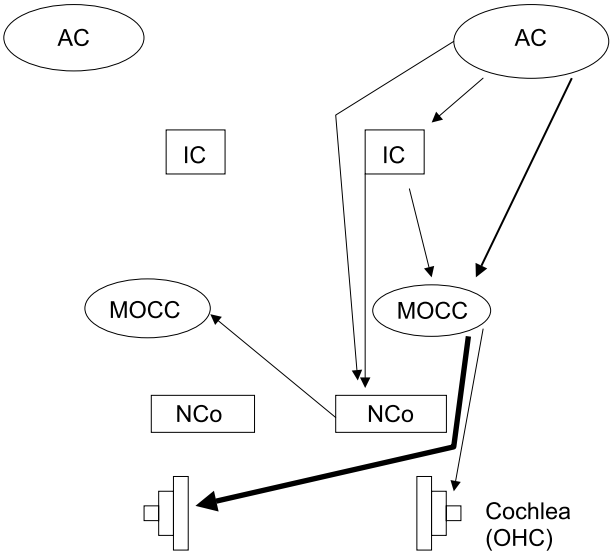

Fig. 1. Main descending auditory pathways. Schematic representation of the main descending auditory pathways susceptible for modulating MOC system activity. *AC* Auditory system; *IC* inferior colliculus; *MOCC* medial olivocochlear complex; *NCo* cochlear nucleus

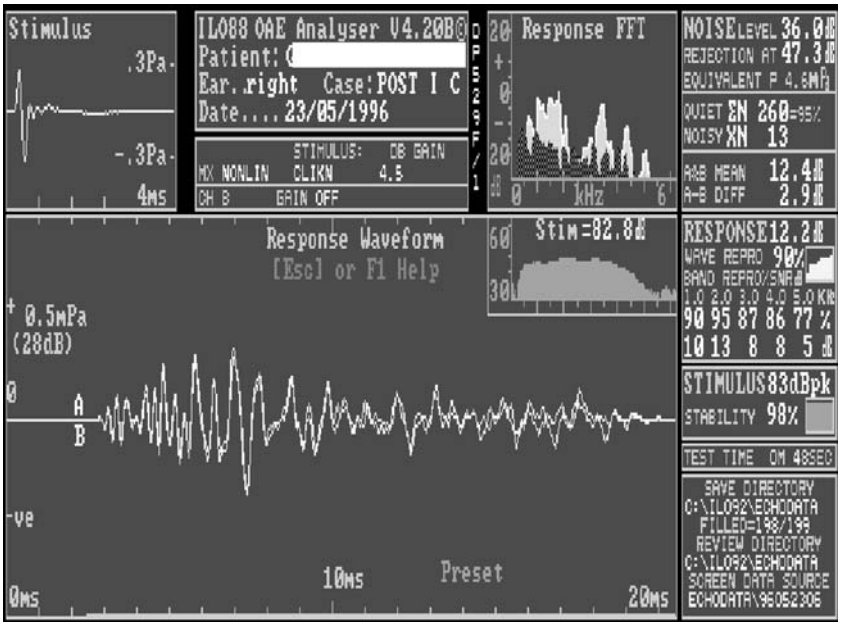

Fig. 2. TEOAEs recording in a normal subject

recorded following stimulation by different stimuli: transient evoked OAEs (TEOAEs) can be evoked by transient impulses, such as clicks or tone bursts, and distortion product OAEs (DPOAEs) can be evoked by two simultaneously applied pure tones, f_1 and f_2, at two closely spaced frequencies, which partially overlap the vibration fields in the cochlea, delivered into the ear canal. TEOAEs and DPOAEs are both generated by normally functioning OHCs, and can be recorded, essentially, in all normally hearing subjects. However, DPOAEs are more frequency-specific, and, due to the difference in recording techniques, they provide responses at higher frequencies than TEOAEs (Fig. 2).

The olivocohlear system: anatomy and physiology

The OHCs' activity is controlled by the positive feedback mechanism, involving the efferent olivocochlear (OC) system, which was first described by Rasmussen [19]. The fibres of the OC system originate from the superior olivary complex (SOC), in the medulla oblongata, which consists of medial and lateral nuclei. The two subsystems of the OC pathway are defined on the basis of their origins in the brainstem, but also differ with respect to their peripheral targets [12].

The *lateral olivocochlear bundle* arises from the lateral nucleus and its unmyelinated axons, predominantly uncrossed, synapse with the afferent fibres of the IHCs. The fibres from the medial nucleus, thick and myelinated, are arranged in the mainly crossed *medial olivocochlear (MOC) bundle*, which travels along the vestibular nerve and synapses directly at the basal surface of the OHCs [15]. The MOC system is considered to be inhibitory and responsible for the control of OHC motility (cochlear micromechanics). The olivocochlear system is only a part of the auditory efferent system and has multisinaptic connections with the upper parts of the auditory system: the main efferent projections come from the auditory cortex, both to the medial geniculate body and to the inferior colliculus; from the inferior colliculus they go to both the cochlear nucleus and the superior olivary complex (Fig. 1). It is interesting to note that, from the superior olivary complex, neurons are in direct contact with the outer hair cells of the cochlea and, in addition, receive ascending tonotopically organized bilateral input, both directly and indirectly, from the anteroventral cochlear nucleus [12].

It is known that direct electrical stimulation of the MOC bundle suppresses endocochlear potential, increases the amplitude of cochlear microphonics (CM), reduces auditory nerve response (decreasing both action potential amplitude and discharge of single auditory nerve fibres), reduces IHCs receptor potentials [2] and basilar membrane motility [8], with the same ultimate effect of reducing input to the central auditory nervous system [10]. Indirect stimulation by contralateral sound also is inhibitory but it reduces the afferent response much less than does electrical stimulation [3], thereby the MOC bundle seems to be the effector arm of a protective sound-evoked reflex [23].

The role of auditory efferent system

The medial olivocochlear complex can be considered to be as a crossroad in the auditory system: in fact, the MOC bundle is involved in peripheral loops, as an effector arm of a sound-evoked reflex, with the aim of providing both an anti-masking effect of signal-in-noise and a modulation of noise-induced permanent hearing loss, but it also takes part in central loops, as it may be influenced by feedback from higher auditory nuclei [12]. The role of the efferent auditory system in normal hearing has not yet been completely established, and different hypotheses have been proposed.

Detection of signals in noise

The MOC system is the effector arm of a sound-evoked reflex to the auditory periphery, which can be elicited by sound in either ear; it acts by decreasing OHC amplification of sound-induced motion in the inner ear. Neurophysiological measurements show that olivococochlear activation enhances the response of the auditory nerve to a transient signal presented against continuous noise [14]. The assumed mechanism for this enhancement is that olivocochlear activation suppresses the neural response to the ongoing noise, thereby reducing neural adaptation; less adapted and also less busy, the neural fibres respond more strongly to a transient signal. The MOC system can improve the detectability of high-frequency transient signals in high frequency maskers, but it cannot contribute large anti-masking effects for low frequency noise. It is important to note that the MOC system does not suppress the noise more effectively than the signal because the noise is broad-band whereas the signal is narrow-band. Rather, the important difference is that the ''noise'' is continuous while the ''signal'' is transient. The MOC reflex acts to minimize the response to long-lasting stimuli, while maximizing the response to novel stimuli [14].

Protective function in noise-induced cochlear damage

Activation of OC bundle can protect the ear from noise-induced temporary threshold shift (TTS). The experimental sectioning of the OC bundle, shows after noise exposure, substantially greater permanent threshold shift (PTS) and larger cochlear lesions of OHCs as compared to control efferented animals receiving the same noise exposure [26]. Furthermore, recent studies show that de-efferented ears sustained greater decrease in DPOAE and CM amplitude than efferented ears, whereas the OHC loss was minimal in both groups, after intense noise exposure. It has been hypothesized that, decreased CM after de-efferentation is associated with depolarization that, would increase the OHC's excitatory activity to acoustic stimulation. This, in turn, may increase the OHC's susceptibility to noise-induced damage. Indeed, it has been shown that OC stimulation, associated with hyperpolarization, could alleviate acoustic trauma by protecting the mechano-electrical transduction of OHCs [26].

Role of the OC bundle in hearing

Several studies evaluated the hearing function after vestibular neurotomy, performed in humans for the treatment of Menière's disease. The ultimate result is that hearing is not grossly affected; the only clear change is an impaired ability to focus attention in the frequency domain, however the deficit itself seems to have little impact on basic auditory processing [20]. Perhaps a strong efferent effect becomes apparent only for complex patterns of sound. In fact, there is some evidence suggesting that the MOC system enhances the *frequency resolving capacity*, the *vowel discrimination*, especially in a noisy environment and detection of *interaural intensity differences* for higher frequency signals by increasing, within the cochlea, the interaural disparity reaching the lateral superior olivary complex [20]. Since the MOC bundle is mainly inhibitory, there has been already suggestions that dysfunction of the efferent auditory system, at any level from auditory cortex to cochlea, may be a basis for *tinnitus generation*, especially in noise-induced tinnitus patients.

Development of hearing

It seems that the OC bundle is well developed at or soon after birth so that it could be involved in whatever changes in peripheral processing take place in the first months and years of life. A reasonable conjecture is that the OC bundle guides the development of the attention or listening band during the first few years of life under the pressure of the prevalent environmental sounds; during this phase, the OC bundle would play its most important role in setting the precise parameters of the peripheral frequency selectivity. Such ''auditory imprinting'' would mean that the cochlea comes to handle some classes of sounds more efficiently than other classes; one implication would be that in human infants, a damaged or malfunctioning OC bundle may lead to poorer or delayed auditory development [12].

Processing of complex auditory signals

Cortical regulation of this efferent system could be of importance to hearing functions, such as those involved in the *processing of complex signals*. The MOC system seems to be impaired in central pathologies presenting auditory abnormalities or communication difficulty, such as autism.

The behavioural effects of olivocochlear activation on auditory function are subtle, but they include enhancement of selective attention and improved processing of complex signals in noise. Issues that have been discussed include the difference between the ear's function in encoding the attributes of sounds, such as frequency, intensity and temporal patterns and the contrasting role of the central auditory system in analyzing the attribute of sound sources, such as their location, distance and movement. Several studies provide strong evidence that analysis of the spatial attributes of sound stimuli occurs centrally, and specifically at the level of the *superior olivary complex* (SOC) [12]. It has been described the case of a patient where an extensive midline pontine lesion would eliminate crossed input to both superior olivary complexes, leaving only those coming from ipsilateral ear. Testing revealed that the patient had no difficulty in detecting frequency and amplitude modulation and no general deficit in detection of auditory temporal information; however, the patient was enable to determine, by sound alone, the source of sound [9]. It might be imagined that it is the function of the entire SOC, including both the reorganization of ascending impulses occurring in the main nuclei and the complementary integration provided by the olivocochlear complex, that enables humans to function efficiently in a three-dimensional auditory world.

Clinical applications

Clinical interest in the medial efferent system has been awakened by the advances made in the field of OAEs.

Since the micromechanical properties of the OHCs are directly under the control of the medial efferent bundle, it sounds logical that stimulating this neural pathway, OHCs motility and, hence, OAEs should be affected.

OAEs find their extensive *clinical application* in the evaluation of:

- *cochlear (OHC) integrity*
- *neonatal hearing screening*
- *hearing screening of noise-exposed subjects* and
- *differential diagnosis of cochlear and retrocochlear lesions*

However, it has been recognized that they have an important role in assessing the structural and functional integrity of the MOC reflex arc. The discovery of the existence of OAEs has allowed examination of the MOC system in humans. It has been demonstrated that, in normal subjects, contralateral acoustical stimulation of the MOC system can alter the frequency and reduce the amplitude of spontaneous OAEs and reduce the amplitude and shift the phase of transient evoked OAEs (TEOAEs) and distortion product OAEs (DPOAEs) [1, 5]. OAEs suppression test seems to be the only objective and non-invasive method for the evaluation of the functional integrity of the medial efferent system, and, therefore, for the evaluation of the structures lying along its course, at least up to the level of inferior colliculi (VIII nerve, cerebello-pontine angle and pons). In preterm babies (up to 40 weeks of gestation), no suppressive effect has been evidenced, due to immaturity of the efferent auditory pathway. In fullterm babies, a slight effect has been shown. In the elderly, the suppressive effect is present but smaller than in young adults [18].

Although, literature data are rather poor and *clinical applications of the OAEs suppression test* are still being developed, the test may be useful in the evaluation of the pathological states in which an abnormality of the MOC system may exist including the following:

1. *Vestibular nerve section*: Vestibular nerve section is accompanied by the section of the MOC bundle, resulting in the absence of a MOC suppressive effect [24].
2. *Tinnitus/hyperacusis*: The alteration of the MOC effect, predominantly reduced functioning, has been observed in patients with tinnitus and hyperacusis, suggesting that the MOC system may play a role in dysfunction of the auditory system [4].
3. *Central nervous system pathology*: This may cause a lesion of the MOC arc, with a subsequently absent/reduced suppressive MOC effect. The suppressive test could contribute to neuro-otological topographic diagnosis, the identification of a lesion up to the brainstem level, either extrinsic (acoustic neuromas, meninigiomas, congenital cholesteatomas) or intrinsic (multiple sclerosis, ischemic infarcts, tumors).
4. *Neuromuscular junction disease*: Myasthenia gravis (MG) is a disorder of neuromuscular junction, characterized by early fatigue and weakness of skeletal muscles, due to defects in cholinergic transmission caused by a decrease in AChRs (acetylcholine receptors) available at the neuromuscular junction. OHCs receive direct axomatic innervation from the efferent fibres of the MOC bundle, whose endings are anatomically similar to those at the neuro-muscular junction. Acetylcholine (ACh) represents the main neurotransmitter involved in the efferent auditory system; synapses between the neural endings of the MOC bundle and the specific receptors present on the basolateral membrane of OHCs seem to be purely cholinergic [6, 16]. It has been shown that MG induces a reduction in TEOAEs and DPOAEs, which is reversed after administration of an acetylcholinesterase (AChE) inhibitor [17]; such a recovery is more evident and highly significant for middle and high frequencies due to a higher concentration of AChRs in the basal and middle cochlear turns. Furthermore, in basal condition, contralateral acoustic stimulation (CAS) does not induce significant DPOAE amplitude changes; after drug administration, CAS produces a significant decrease of DPOAE amplitudes for middle frequencies. The increased acetylcholine availability following drug consumption seems to partially restore outer hair cell function and enhance their electromotility; a further influx of acetylcholine due to controlateral auditory suppression yields to restoration of the controlateral suppression [7]. These findings also suggest that DPOAEs and suppression test may be useful in the *diagnosis of neuromuscular junction disease and for monitoring the effectiveness of treatment*.

References

1. Berlin CI, Hood LJ, Hurley A, Wen H (1994) The first Jerger lecture. Controlateral suppression of otoacoustic emissions: an index of the function of the medial olivocochlear system. Otolaryngol Head Neck Surg 110: 3–21
2. Brown MC, Nuttall AF (1984) Efferent control of cochlear inner hair cell responses in the guinea-pig. J Physiol 354: 625–646
3. Buño W (1978) Auditory nerve fibre activity influenced by contralateral ear sound stimulation. Exp Neurol 59: 62–74
4. Ceranic B, Prasher DK, Raglan E, Luxon LM (1998) Tinnitus after head injury: evidence from otoacoustic emissions. J Neurol Neurosurg Psychiatry 65: 523–529

5. Collet L, Kemp D, Veuillet E, Duclaux R, Moulin A (1990) Effect of contralateral auditory stimuli on active cochlear micromechanical properties of human subjects. Hear Res 42: 251–262
6. Dallos P, He DZZ, Lin X, Sziklai I, Mehta S, Evans BN (1997) Acetylcholine, outer hair cell electromotility, and the cochlear amplifier. J Neurosci 17: 2212–2226
7. Di Girolamo S, D'Ecclesia A, Quaranta N, Garozzo A, Evoli A, Gaetano P (2001) Effects of contralateral white noise stimulation on distortion product otoacustic emissions in myastenic patients. Hear Res 162: 80–84
8. Dolan DF, Nuttall AF (1994) Basilar membrane movement by sound is altered by electrical stimulation of the crossed olivocochlear bundle. Abstr Assoc Res Otolaryngol 17: 356
9. Griffiths TD, Bates D, Rees A, Witton C, Gholkar A, Gren GGR (1997) Sound movement detection deficit due to a brainstem lesion. J Neurol Neurosurg Psych 62: 522–526
10. Kawase T, Liberman MC (1993) Antimasking effects of the olivocochlear reflex I. Enhancement of compound action potentials to masked tones. J Neurophysiol 70: 2519–2532
11. Kemp DT (1978) Stimulated acoustic emissions from within the human auditory system. J Acoust Soc Am 64: 1386–1391
12. Khalfa S, Bougeard R, Morand N, Veuillet E, Isnard J, Guenot M, Ryvlin P, Fischer C, Collet L (2001) Evidence of peripheral auditory activity modulation by the auditory cortex in humans. Neuroscience 104: 347–351
13. Le Page EL (1989) Functional role of the olivocochlear bundle: a motor unit control system in the mammalian cochlea. Hear Res 30: 177–198
14. Liberman C, Guinan J (1998) Feedback control of the auditory periphery: antimasking effects of middle ear muscles vs. olivocochlear efferents. J Commun Disord 31: 471–483
15. Moore J (2000) Organization of the human superior olivary complex. Micr Res Technique 51: 403–412
16. Morgenstern C, Biermann E, Zangemeister WH (1995) The efferent innervation of outer hair cells in humans: physiological investigations. Acta Otolaryngol (Stockh) 115: 206–210
17. Paludetti G, Di Nardo W, D'Ecclesia A, Evoli A, Scarano E, Di Girolamo S (2001) The role of cholinergic transmission in outer hair cell functioning evaluated by distortion product otoacoustic emissions in myastenic patients. Acta Otolaryngol 121: 119–121
18. Quaranta N, Debole S, Di Girolamo S (2001) Effect of ageing on otoacoustic emissions and efferent suppression in humans. Audiology 40: 308–312
19. Rasmussen GL (1946) The olivary peduncle and other fiber projections of the superior olivary complex. J Comp Neurol 84: 152–155
20. Sharf B, Magnan J, Chays A (1997) On the role of the olivocochlear bundle in hearing: 16 cases study. Hear Res 103: 101–122
21. von Békésy G (1960) Experiments on hearing. McGraw Hill, New York
22. Warr WB, Guinan JJ Jr (1979) Efferent innervation of the organ of Corti: two separate systems. Brain Res 173: 152–155
23. Warren EH, Liberman MC (1989) Effects of contralateral sound on auditory-nerve responses. I. Contributions of cochlear efferents. Hear Res 37: 89–104
24. Williams EA, Brookes GB, Prasher DK (1993) Effects of contralateral acoustic stimulation on otoacoustic emissions following vestibular neurectomy. Scand Audiol 22: 197–203
25. Zenner HP (1986) Motile responses in outer hair cells. Hear Res 22: 83–90
26. Zheng XY, Henderson D, Hu B, Ding D, McFadden S (1997) The influence of the cochlear efferent system on chronic acoustic trauma. Hear Res 107: 147–159

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Functional outcome of auditory implants in hearing loss

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Summary

The auditory implant provides a new mechanism for hearing when a hearing aid is not enough. It is the only medical technology able to functionally restore a human sense i.e. hearing. The auditory implant is very different from a hearing aid. Hearing aids amplify sound. Auditory implants compensate for damaged or non-working parts of the inner ear because they can directly stimulate the acoustic nerve. There are two principal types of auditory implant: the cochlear implant and the auditory brainstem implant. They have common basic characteristics, but different applications. A cochlear implant attempts to replace a function lost by the cochlea, usually due to an absence of functioning hair cells; the auditory brainstem implant (ABI) is a modification of the cochlear implant, in which the electrode array is placed directly into the brain when the acoustic nerve is not anymore able to carry the auditory signal. Different types of deaf or severely hearing-impaired patients choose auditory implants. Both children and adults can be candidates for implants. The best age for implantation is still being debated, but most children who receive implants are between 2 and 6 years old. Earlier implantation seems to perform better thanks to neural plasticity. The decision to receive an implant should involve a discussion with many medical specialists and an experienced surgeon.

Keywords: Hearing aid; neuromodulation; auditory brainstem implant; ABI; cochlear implant.

Introduction and history of auditory implants

The history of auditory implants has been characterized by achieving a substantial growth in a relatively short period of time. The cochlear implants, are the result of intensive research over the last four decades. However, there is a long history of attempts to produce a hearing sensation by the electrical stimulation of the auditory system. The long-standing interest in the biological applications of electricity was the basis for the development of cochlear implants. The interest in the electrical methods of stimulating the hearing begins in the late 18th century when Alessandro Volta discovered the electrolytic cell. Volta was the first to stimulate the auditory system electrically, by connecting a battery of 30 or 40 'couples' (approximately 50 V) to two metal rods that were inserted into his ears. Crude applications of electrical stimulation were described through the 18th and 19th century in Paris, Amsterdam, London, and Berlin. The next step was taken by Duchenne of Boulogne who, in 1855, stimulated the ear with an alternating current that he produced by inserting a vibrator into a circuit containing a condenser and induction coil. In 1868, Brenner published a more extensive investigation that studied the effects of altering the polarity, rate and intensity of the stimulus, and placement of the electrodes, on the hearing sensation produced. The initial optimism surrounding the bioelectrical approaches to cure deafness was followed by a period of scepticism, as the applications appeared to be invasive and required an ongoing critical evaluation. However, in the 1930's, interest on reproducing hearing artificially was renewed, due to the introduction of the thermionic valve, which allowed for the auditory system to be stimulated electrically with significantly greater precision.

Through the 1990s, clinical and basic science studies have resulted in progress in implant technology and in clinical approaches to auditory implants. Electrodes and speech processors now produce coding strategies that are associated with successively higher performance levels. Over the years, patients with implants have become more numerous and the risks have been minimized. More people have accepted that implants are here to stay, as implants are being increasingly recommended [1, 12, 18, 22].

What is an auditory implant

There are two principal types of auditory implant: the cochlear implant and the auditory brainstem implant.

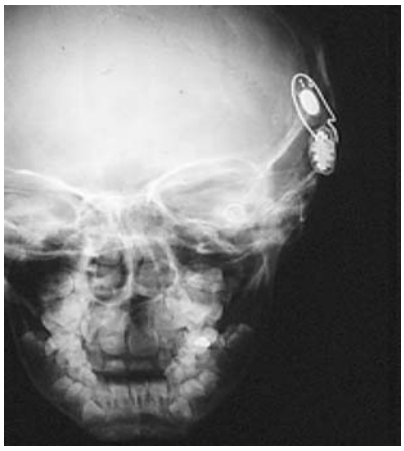

Fig. 1. Cochlear implant

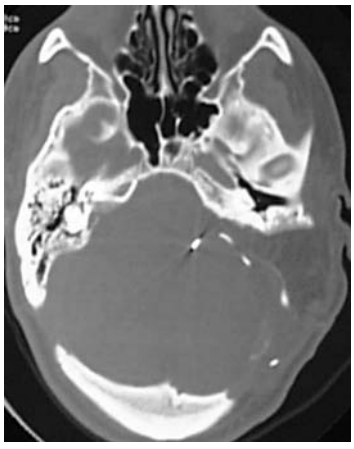

Fig. 2. Auditory brainstem implant

They have common basic characteristics, but different applications. The cochlear implants (CI) (Fig. 1) are devices which replace damaged inner ear structures that have caused profound hearing loss. In the past, profound deafness was commonly referred to as nerve deafness. This was incorrect because the problem was not the hearing nerve, but the hair cells that line the cochlea. These hair cells are able to transform mechanical sound waves coming into the ear to electrical impulses that travel through nerves to the brain and are interpreted as sound. A cochlear implant, on the other hand, attempts to replace a function lost by the cochlea, usually due to an absence of functioning hair cells. In a normal hearing ear, the hair cells within the cochlea act as transducers of mechanical and hydraulic vibration of the tympanic membrane, ossicles of the middle ear, perilymph and endolymph of the inner ear, to chemo-electric energy capable of stimulating the eighth nerve. The decrease of hair cells results in the cochlea losing ability to stimulate the eighth nerve and leads to a sensory hearing loss. The cochlear implant replaces the function of the lost hair cells by converting mechanical energy (sound waves) into electrical energy capable of exciting the auditory nerve. Cochlear implants are surgically placed within the inner ear to bypass the hair cells of the cochlea and directly stimulate the endings of the auditory nerve. Although there have been many variations, the basic design of an implant system has remained relatively stable over the years.

The auditory brainstem implant (ABI) (Fig. 2) is a modification of the cochlear implant, in which the electrode array is placed directly in to the brain. Such a modified cochlear implant is intended to be used to stimulate the cochlear nucleus in the brainstem in patients who have had their eighth nerves severed during surgery for removal of bilateral neurofibromas, as in patients with Neurofibromatosis type 2. The cochlear implant linear array of electrode contacts is replaced by a small rectangular silastic paddle containing the 21 contacts. This is surgically inserted into the lateral recess of the fourth ventricle. The need for this device is rare, but these patients are typically totally deaf and, although the benefit is not comparable to the cochlear implant results, most recipients derive significant auditory perception [1, 7, 12, 17, 18, 20, 22].

Table 1. *Most frequent complications of cochlear implants*

Cause	Frequency (%)	Type of complications		
Wound-related	57	infections	necrosis	delay in wound healing
Facial nerve-related	19	incorrect stimulation	nerve lesion	
Electrode-related	13	migration	incorrect position	incorrect compression
Other	11			

Components of the implant

The implant consists of a microphone, a speech processor that acts as the hair cells changing acoustic energy into electrical signals (analog or digital), a transmitter, and the implanted electrode component that contains a microchip that decodes and distributes the information along the cochlear nerve (CI) or on the cochlear nucleus (ABI). Depending on the sounds, the electrode delivers different stimuli to the VIII nerve or brainstem making deaf people hear a variety of sounds [18, 19, 22].

Neural plasticity and the auditory implant

The brain of a newborn can be compared to a new computer without its software or operating system installed. During both early fetal life and infancy, the auditory portion of the brain forms its neural connections, and learns how to process incoming sounds. Neurophysiologists consider the first few years of life as critical in establishing these connections because the brain is highly receptive to making new connections at this time; this is neural plasticity. Originally, implants were first allowed only in children four years of age or older. It has now become clear that the window of greatest hearing development may be the first two years of life, because of the high degree of neural plasticity. Children who are implanted earlier than two years of age seem to be able to ''wire in'' their neural connections with greater facility; the early results of cochlear implantation in very young children now appear to surpass those results obtained in older children. The age of implantation is a very important factor with great impact on each child's progress with his/her cochlear implant. Research and observation suggest that spoken language performance results are best for those who are implanted before the age of 3 years. This is the time when the brain most readily adapts and masters language. For children implanted at the youngest ages (prior to 18 months), spoken language appears to emerge most naturally. Based on the outcomes observed in many young implanted children, it appears that the stimulated sense of hearing offered through an auditory implant can offer an excellent opportunity for a child to progress in language ''developmentally'' rather than ''remedially''. The neural plasticity in children has a positive impact on the performance of a cochlear implant or even of an auditory brainstem implant; there are, however, many other factors impacting on performance: pre-implant duration of deafness, previous listening experience, status of cochlea or status of cochlear nucleus in the brainstem, cause of hearing loss, family support and motivation, quality and consistency of educational and rehabilitative environment [2, 3, 5, 15].

Candidate selection for auditory implant

A variety of requirements are considered in children and adults in order to determine candidacy for an auditory implant. These requirements continue to change, especially in relation to minimum age of implantation. Minimum age continues to be reduced due to the limited surgical risks and the improved outcomes of children implanted at younger ages. It is recommended that the preoperative process is based on a team approach that involves the family and professionals from both the medical and educational settings who are involved with the child. This will ensure that the child is an appropriate candidate for an auditory implant, that the family has realistic expectations regarding outcome, and that training and educational components are in place to assist and help the child to actualise the benefits from the implant. Obtaining accurate audiological information is the core of making appropriate recommendations related to implant candidacy. Since some audiological tests are more reliable and objective than others, obtaining a precise description of a child's hearing level requires a comprehensive audiological test battery completed by the examination of an experienced pediatric audiologist. The most widely accepted test batteries in auditory implant pre-operative patient assessment are:

1. Pure tone audiometry and/or behavioral audiometry for the search of the audiometric threshold.
2. Impedance audiometry, to exclude any middle ear pathology.
3. Speech discrimination test, to evaluate the intelligibility of the patient (the intelligibility expresses the intensity at whom the subject identifies 100% of presented words).
4. Otoacoustic emission, that verifies the sub-clinical cochlear damage.
5. Auditory brainstem response testing (ABR) to assess retrocochlear function.
6. Nuclear magnetic resonance imaging of the brain (MRI).

In the case of a pediatric patient, who is not yet fully collaborating, the Behavioral Audiometry Test may be used instead of other tests, but above all we cannot be put aside from the ABR and from the MRI. It is important that the audiologist of the implant team is experienced in fitting and facilitating hearing aid use, making recommendations related to implantation, and fitting of the implant device following implantation so that any decision regarding implantation is made by the patient or the relatives following their complete information [1, 2, 4, 5, 7, 9, 10, 13, 14]. According to the results of the audiological tests described, we can select correctly the candidates for the auditory implant.

Prerequisites of a candidate for a cochlear implant

1) Adults and children with severe to profound sensorineural hearing loss in both ears.
2) Children who are 12 months (in certain cases, younger children may be selected) to 18 years of age and adults of any age.

3) Individuals who receive insufficient benefit from hearing aids, i.e. with intelligibility inferior to 30%.
4) Children who can receive family and educational support, because participation in the educational/training programs is necessary in order to actualise benefit from the cochlear implant.
5) Individuals and families with appropriate expectations and an understanding of the necessary follow-up.
6) Individuals who are willing to wear the external apparatus.

Who is not a candidate for a cochlear implant

Certain characteristics of a child (or adult) make them unsuitable candidates for a cochlear implant. The unsuitable categories of children or adults include those who:

1) do not have the eighth nerve (auditory), which carries sound from the cochlea to the brain as determined by magnetic resonance imaging (MRI) during the candidacy pre-operative process;
2) have significant residual hearing levels and receive good benefit from traditional hearing aid devices;
3) have post-meningitis cochlear ossification or bilateral schwannoma.

Who is a candidate for auditory brainstem implant (ABI)

We consider an auditory brainstem implant (ABI) medically necessary in patients older than 12 years who have lost both auditory nerves due to disease (neurofibromatosis or von Recklinghausen's disease) [5, 6, 10, 13, 15, 16, 18, 22].

Benefits and limitations of auditory implants

A sensorineural auditory lesion constitutes a deficit only partially correctable with the acoustic prosthesis. A cochlear or auditory brainstem implant can provide access to sound by bypassing respectively the damaged hair cells in the cochlea or the cochlear nerve, thereby enabling the user to perceive sound; the implants convert sound into electrical signals and send these signals to the auditory nerve and to the brain; they provide more access to speech information than traditional hearing aids (digital or analogic) and provide improved speech perception for many children. Cochlear implants and auditory brainstem implants do not interpret sound [1, 5, 7, 12, 18, 22]. However, with intensive training they can offer useful hearing and speech to a significant portion of profoundly deaf children.

Results

The outcomes of prelingually deaf children and postlingually deaf adults are fundamentally different. It is right to distinguish between these two categories of subjects: adults and children, because the procedure and the purpose for which the cochlear implant is applied are completely different. In adults with postlingual deafness, i.e. deaf after the acquisition of language, (usually language acquisition is complete after 4 or 5 years of age), the implant has the assignment to re-acquire a function previously possessed. In children deaf at the moment of birth or in children who became deaf in the first 3 years of life and were prevented from developing language (prelingual deafness), the implant has the assignment to support this development through a demanding and prolonged logopaedical assistance. In any case, the relatively older age in prelingually deaf children is not a contraindication but the potential for rehabilitation is smaller. Initially, implantations were usually performed in those who had become deaf after they had acquired speech (postlingual deafness). These individuals derived significant benefit from their auditory implants. Congenitally deaf children or adults, (deaf from birth), did not have as much success with the first implants. Currently, we are quite certain that prelingual deaf children or adults are good candidates for an implant and the younger a congenitally deaf child receives an auditory implant, the better the long-term results will be. Parents of children who receive CI or ABI, must appreciate the considerable time commitment involved in the process of implantation and the required ongoing educational process. They must agree to return with the child to the implant center for follow-up testing and monitoring of the implant. The parents must also be willing to cooperate and work with the child's educators to provide appropriate re- habilitation [4, 8, 9, 11, 12, 20].

Complications

As with any surgical procedure, there are certain risks associated with CI or ABI surgery. In a literature review, the rate of surgical complications is about 2% in CI, and higher in ABI surgery. Inner ear surgery carries the risk of damage to the balance organs or the facial nerve; this could lead to dizziness or a temporary or permanent facial paralysis. After surgery, it is possible that pro-

blems could occur with the implanted device. Although the devices are extremely reliable, the electronic components could malfunction, or the implanted component could become infected or begin to extrude (come out through the skin). There may also be complications due to the electrical pulses delivered by the cochlear implant, for example facial nerve stimulation or other non-auditory sensation. This can usually be resolved by adjusting the programming of the speech processor [10, 13, 19].

References

1. Bosman AJ, Snik AF, van der Pouw CT, Mylanus EA, Cremers CW (2001) Audiometric evaluation of bilateral fitted bone anchored hearing-aids. Audiology 40: 158–167
2. Brimacombe JA, Arndt PL, Staller SJ (1995) Multichannel cochlear implants in adults with residual hearing. Cochlear implants in adults and children, 100th NIH Consensus Development Conference, May 1995, Bethesda, MD, pp 31–35
3. Eisenberg LS (1982) Use of the cochlear implant by the prelingually deaf. Ann Otol Rhinol Laryngol 91 Suppl: 62–66
4. House WF, Berliner KI (1982) Cochlear implants: progress and perspectives. Ann Otol Rhinol Laryngol 91: 1–124
5. House WF, Urban J (1973) Long term results of electrode implantation and electronic stimulation of the cochlear in man. Ann Otol Rhinol Laryngol 82: 504–514
6. Leder SB, Spitzer JB, Flevaris-Phillips C, Kirchner JC, Milner P, Richardson F (1987) Innovative approaches to selection of cochlear implant candidates. J Rehabil Deaf 21: 27
7. Nikolopoulos T, Archbold S, O'Donoghue G (1999) The development of auditory perception in children following cochlear implantation. Int J Pediatr Otorhinolaryngol 49 Suppl 1: 189–191
8. Osberger MJ (1995) Speech perception in children. Cochlear implants in adults and children, 100th NIH Consensus Development Conference, May 1995, Bethesda, MD, pp 63–66
9. Owens E, Kessler DK (1989) Cochlear implants in young deaf children. College Hill, Boston
10. Kileny PR (1994) Use of electrophysiologic measures in the management of children with cochlear implants: brainstem, middle latency, and cognitive (P300) responses. Am J Otol 12: 37–47
11. Kileny PR, Zwolan TA, Zimmerman-Phillips S, Telian SA (1994) Electrically evoked auditory brainstem response in pediatric patients with cochlear implants. Arch Otolaryngol Head Neck Surg 120: 1083–1090
12. Rothera M, Conway M, Brightwell A, Graham J (1986) Evaluation of patient for cochlear implant by promontory stimulation. Br J Aud 20: 25–28
13. Shallop J, Arndt P, Turnacliff K (1992) Expanded indications for cochlear implantation: perceptual results in seven adults with residual hearing. J Speech Lang Pathol Audiol 16: 141–148
14. Shannon RV, Fayad J, Moore J, Lo WW, Otto S, Nelson RA, O'Leary M (1994) Auditory brainstem implant: II. Postsurgical issues and performance. Otoloaryngol Head Neck Surg 108: 634–642
15. Smith L, Simmons FB (1983) Estimating eighth nerve survival by electrical stimulation. Ann Otol Rhinol Laryngol 92: 19–23
16. Tyler RS, Preece JP, Lowder MW (1983) The Iowa cochlear implant tests. University of Iowa, Iowa City
17. Van der Pouw C (1998) Bone anchored hearing. Short and long term results. Thesis, The Netherlands, Nijmegen
18. Vermeulen AM, Beijk CM, Brokx JP, van den Borne S, van den Broek P (1995) Development of speech perception abilities of profound deaf children: a comparison between children with cochlear implants and those with conventional hearing aids. Ann Otol Rhinol Laryngol 104: 215–217
19. Waltzman SB, Cohen NL (2000) Cochlear implants. Thieme, New York
20. Waltzman SB, Fisher SG, Niparko JK, Cohen NL (1995) Predictors of postoperative performance with cochlear implants. Ann Otol Rhinol Laryngol 104 Suppl 65: 15–18
21. Wazen JJ, Spitzer J, Ghossaini SN, Kacker A, Zschommler A (2001) Results of the bone anchored hearing aid in unilateral hearing loss. Laryngoscope 111: 955–958
22. Weber BP, Dillo W, Dietrich B, Maneke I, Bertram B, Lenarz T(1998) Pediatric cochlear implantation in cochlear malformations. Am J Otol 19: 747–753

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Auditory brainstem implants: current state and future directions with special reference to the subtonsillar approach for implantation

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Summary

In this article, the authors describe the current state of the auditory brainstem implant (ABI), comparing it to that of the cochlear implant (CI). The CI restores hearing by stimulating the cochlear nerve in the cochlea in patients whose deafness has been caused by inner ear disease; the ABI restores hearing by stimulating the cochlear nucleus of the brainstem in patients who are deaf because of bilateral cochlear nerve dysfunction. Up to now, about 500 patients worldwide have undergone ABI and had their hearing restored, most of whom suffer from neurofibromatosis type 2. Hearing performance, however, is not as good as that offered by the cochlear implant. To improve the quality of hearing, new techniques such as advanced coding strategies and penetrating electrodes, are now being introduced.

Keywords: Neuromodulation; restoration of hearing; auditory brainstem implant; neurofibromatosis type 2; bilateral cochlear nerve dysfunction; subtonsillar approach.

Introduction

Restorative neurosurgery proceeds in two ways, either by exploiting new biological findings or by utilizing nerve-computer interface technology. Stem cells are now expected to repair the injured spinal cord and cochlear implants (CI) have already restored hearing in many patients. These examples represent each one of these methodologies, respectively. The auditory brainstem implant (ABI) is an extension of the CI technology. CI restores hearing by stimulating the cochlear nerve, the first neuron, instead of the cochlea, whereas the ABI does it by stimulating the second neuron at the cochlear nucleus in the brainstem. The first ABI procedure was performed on a patient with neurofibromatosis type 2 (NF2) in 1979 at the House Ear Institute in Los Angeles, USA [4, 6]. The ABI has subsequently developed along with the CI and, up to now, it has been implanted in about 500 patients worldwide. The authors describe its current state and discuss possible future directions in this field.

Basic structure

The ABI has the same structure as the CI except for the shape of the electrode array. In both implants, a small microphone, which is worn behind the ear, picks up sounds in the environment. A thin cable conveys sounds from the microphone to the speech processor, a cigarette-case-sized mini computer, which converts sounds into coded signals. The coded signals are then sent back up the cable to the transmitting coil, which transmits signals through the skin to the receiver/stimulator embedded in the skull. The receiver/stimulator delivers the correct amount of electrical stimuli, through its electrodes, either to the cochlea with the use of CI or to the cochlear nucleus with the use of ABI (Fig. 1). The electrode array of the CI consists of 22 small rings on a thin string carrier suitable for insertion into the cochlea, and that of the ABI has up to 21 tiny discs arranged on a several millimeter sized plate. Figure 2 shows a craniogram of a patient with ABI [15].

Indications

The ABI is applied to patients deafened by bilateral cochlear nerve dysfunction without involvement of the auditory tract in the brainstem. Most of them suffer from NF2, a genetic disorder characterized by bilateral acoustic schwannomas [3]. A few patients with unilateral cerebellopontine angle tumor and contralateral cochlear

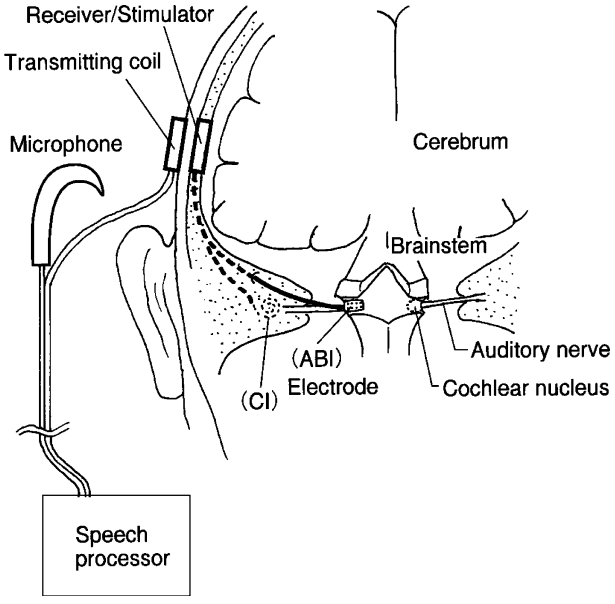

Fig. 1. Diagram showing the relative position of cochlear implant (*CI*) and auditory brainstem implant (*ABI*). The basic structure of ABI is similar to that of CI except for the shape of the electrode array

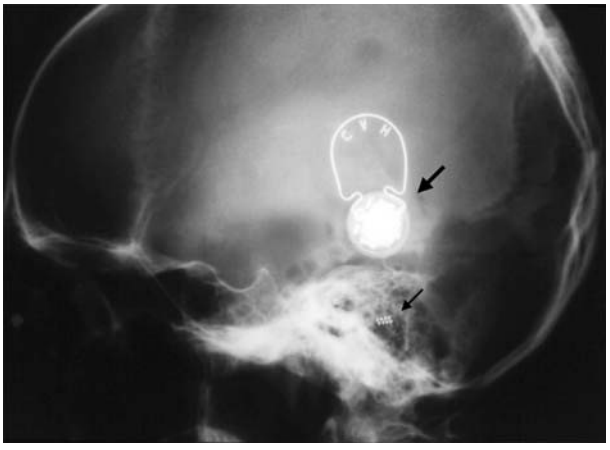

Fig. 2. Plain X-ray craniogram of a patient with auditory brainstem implant. Receiver/stimulator (*large arrow*) and 8-channel electrodes (*small arrow*) are clearly visible

Table 1. *Patient selection criteria for auditory brainstem implants in Europe*

1) Indications
– Life threatening bilateral tumors (cerebellopontine angle tumor, e.g. NF2), head trauma
2) Age: 18 years or older
3) Surgical procedure on the first or second side either at the same time with tumor removal or as a separate procedure
4) No previous history of stereotactic radiosurgery (e.g. gamma knife)
5) Unilateral ABI implantation
6) Suitable medical and psychological condition

nerve injury are also candidates for ABI [18]. Table 1 shows the patient selection criteria in Europe [12]. In a patient with deafness caused by inner ear disease and contralateral cochlear nerve impairment, the CI precedes the ABI because at present auditory performance of the CI is superior to that of the ABI [10].

Surgical approaches for ABI

Neurosurgeons and neurotologists perform the implantation of ABI via either translabyrinthine or retrosigmoid approaches; in USA, most surgeons prefer the translabyrinthine approach, while in Europe, one third of the procedures are done through a retrosigmoid approach [18]. Selection of the operative approach depends on the surgeon's preference, which usually matches that for the removal of an acoustic tumor. The lateral recess of the 4th ventricle is opened antero-laterally, so the translabyrinthine approach seems more suitable for the implantation than the retrosigmoid one. However, surgeons cannot visualize the entire surface of the cochlear nucleus, especially the medial portion, by either approach. To improve the operative view, the authors proposed the subtonsillar approach, a new midline route, which enables surgeons to expose the entire area of the lateral recess and to apply even the penetrating electrode safely (see below in "Future directions") [16]. There is controversy over whether the ABI should be placed after tumor removal in one-stage surgery, or as a second procedure (two-stage surgery). Most of the re-expansion of the brainstem after removal of large tumors occurs as early as within 2 weeks [17]. Therefore, in small tumors, not accompanied by brainstem

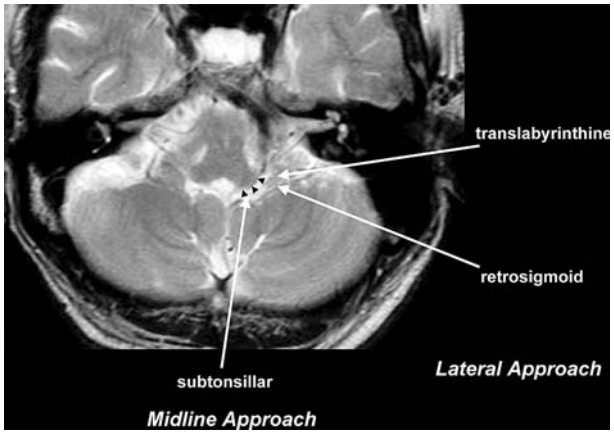

Fig. 3. Surgical approaches for placement of auditory brainstem implants. Lateral approaches such as tranlabyrinthine and retrosigmoid do not expose the medial portion of the cochlear nucleus, whereas the midline route, i.e. the subtonsillar approach, enables surgeons to view the entire surface of the cochlear nucleus. Triangles indicate the location of the cochlear nucleus

deformity, one-stage surgery is preferable because it poses fewer burdens on the patient. In large tumors, a two-stage surgery seems better because it has a reduced risk of sliding of the electrode array away from the position of implantation during the early postoperative period. In addition to the anatomical landmarks [8, 14], intra-operative monitoring of electrically evoked auditory brainstem responses (EABRs) plays a cardinal role in proper placement of the electrode array [20]. The EABRs typically appear one to three peaks later than the wave II of the ordinary ABR because, instead of click sounds, electrical pulses directly stimulate the cochlear nucleus through the electrode. Figure 3 shows examples of ABR from normal-hearing, and EABRs though the CI or the ABI [19].

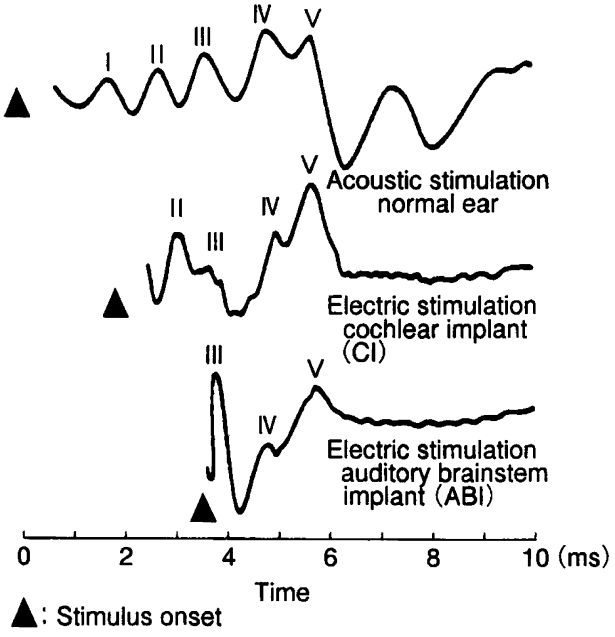

Fig. 4. Comparison of auditory brainstem responses from normal-hearing, cochlear implant and auditory brainstem implant (Waring *et al.* [19], with permission). Electrical stimulation through ABI induces 1–3 peaks within 4 msec after stimulus onset

Operative results

Clinical trials of ABIs using either an 8- or a 21-channel device (Cochlear Corp., Australia) were carried out in a total of 144 patients among 10 institutes in USA and 12 in Europe headed by Germany [2, 12]. Eighty-six percent of the patients became able to perceive auditory sensation; 14% demonstrated clinically significant open-set sentence recognition scores at 3–6 months, and 93% showed improved performance on sentence understanding when the ABI was used in conjunction with lip-reading. These performances almost correspond to those of the prototype CI with a single pair of electrodes. When some electrodes were initially stimulated, most patients felt, as a side effect, a tingling sensation on the face, extremities, or trunk, mostly ipsilateral to ABI, thus inevitably limiting the number of available electrodes. In European series using the 21-channel device, the average of 9.4 electrodes became finally useful [18]. Sixty-five percent of the patients use the ABI for longer than 8 hours a day [2].

Future directions

The cochlea is embedded in the temporal bone and has a clear tonotopic organization, allowing the CI to deliver a good auditory performance through its stable electrode. In contrast, the ABI has the following disadvantages compared to the CI: 1) the number of available electrodes is often limited due to the side effects mentioned above, 2) the tonotopic gradient on the surface of the cochlear nucleus is not very clear, leading to insufficient frequency discrimination, and 3) the electrode array can easily shift in the early postoperative period. To overcome these difficulties, the use of a penetrating electrode array is thought to be promising, not only because of good anchoring of the electrode but also because of better tonotopy from the surface towards the inside in the cochlear nucleus (Fig. 4) [5, 11]. Developments in the coding strategies that transform sounds to electrical signals in the CI, such as continuous interleaved sampling (CIS) and advanced combination encoders (ACE) [7], will also enhance the results obtained from the ABI. Neural response telemetry (NRT) is a method that enables direct measurement of auditory tract compound action potentials from the ABI, just like from the CI [1, 7]. Although negative report appeared [13], NRT is still expected to assist with the placement of the ABI electrode array intra-operatively and with programming the sound processor postoperatively [9].

Closing remarks

Hearing, as well as vision, is sensed through a specialized sensory system consisting of highly differentiated cells. Hence, it is expected that restoration of hearing with a computer-aided artificial organ, like the cochlear implant, will precede restoration by biological technology for the time being. The authors have summarized the current state of the ABI, which is improving as an evolution of the cochlear implant.

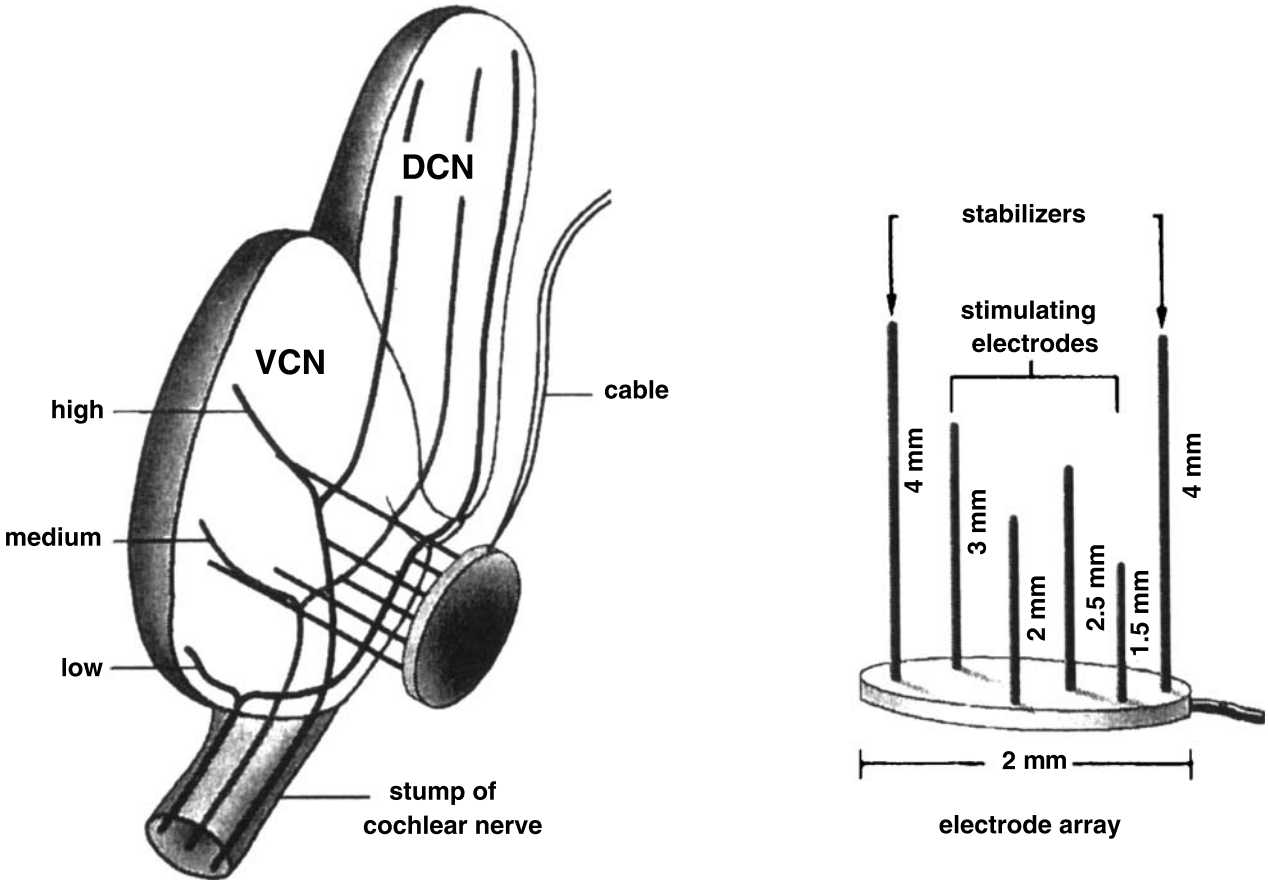

Fig. 5. Illustration of penetrating electrodes [5]. Stable fixation of the array and better auditory performance are expected. *DCN* Dorsal cochlear nucleus, *VCN* ventral cochlear nucleus

References

1. Brickley GJ, Conway MJ, Craddock LC (2000) Initial results of neural response telemetry recording of electrical compound action potentials from the United Kingdom. Ann Otol Rhinol Laryngol Suppl 185: 9–12
2. Ebinger K, Otto S, Arcaroli J, Staller S, Arndt P (2000) Multichannel auditory brainstem implant: US clinical trial results. J Laryngol Otol 114 Suppl 27: 50–53
3. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, Viskochil D (1997) The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 278: 51–57
4. Hitselberger WE, House WF, Edgerton BJ, Whitaker S (1984) Cochlear nucleus implant. Otolaryngol Head Neck Surg 92: 52–54
5. Hitselberger WE (2002) Personal communication
6. House WF, Hitselberger WE (2001) Twenty-year of the first auditory brainstem nucleus implant. Ann Otol Rhinol Laryngol 110: 103–104
7. Kiefer J, Hohl S, Stuerzebecher E, Pfennigdorff T, Gstoeettner W (2001) Comparison of speech recognition with different speech coding strategies (SPEAK, CIS, and ACE) and their relationship to telemetric measures of compound action potentials in the nucleus CI 24 M cochlear implant system. Audiology 40: 32–42
8. Klose AK, Sollmann WP (2000) Anatomical variations of landmarks for implantation at the cochlear nucleus. J Laryngol Otol 114 Suppl 27: 8–10
9. Kuhta J, Otto SR, Waring M, Shannon R (2003) Intraoperative neuromonitoring with compound action potentials in auditory brainstem implants In: Baguley D, Ramsden R, Moffat D (eds) Conference proceedings: Fourth International Conference on Vestibular Schwannoma and Other CPA Lesions. Immediate Proceedings Ltd., Bungay Suffolk, pp 204–205
10. Marangos N, Stecker M, Laszig R (2000) Topodiagnosis of deafness: strategy for treatment of neurofibromatosis type 2. J Laryngol Otol 114 Suppl 27: 3–7
11. McCreery DG, Shannon RV, Moore JK, Chatterjee M (1998) Accessing the tonotopic organization of the ventral cochlear nucleus by intranuclear microstimulation. IEEE Trans Rehab Eng 6: 391–399
12. Nevison B (1999) Clinical results from the European trial of the Nucleus 21 channel auditory brainstem implant. Presented at the Second International Auditory Brainstem Implant Symposium. April 23, 1999, Freiburg, Germany
13. Otto SR, Waring MD, Kuchta J (2005) Neural response telemetry and auditory/nonauditory sensations in 15 recipients of auditory brainstem implants. J Am Acad Audilo 16: 219–227
14. Quester R, Schoeder R (1999) Topographic anatomy of the cochlear nuclear region at the floor of the fourth ventricle in humans. J Neurosurg 91: 446–476
15. Seki Y, Umezu H, Usui M, Kumakawa K, Kumagai F, Komatsuzaki A, Hitselberger WE (2000) Restoration of hearing with an auditory brainstem implant in a patient with neurofibromatosis type 2: case report. Neurol Med Chir 40: 524–527

16. Seki Y, Samejima N, Kumakawa K, Komatsuzaki A (2003) Subtonsillar placement of auditory brainstem implant. Acta Neurochir Suppl 87: 85–87
17. Seki Y, Samejima N (2005) Re-expansion of the brainstem after removal of large acoustic neurinomas. Presented at the 64th Annual Meeting of the Japan Neurosurgical Society. October 5, 2005, Yokohama, Japan
18. Sollmann WP, Laszig R, Marangos N (2000) Surgical experiences in 58 cases using the Nucleus 22 multichannel auditory brainstem implant. J Laryngol Otol 114 Suppl 27: 23–26
19. Waring MD, Ponton CW, Don M, Masuda A (1994) Brainstem and cortical responses evoked by electrical stimulation of human cochlear nucleus. In: Hochmair-Desoyer IJ, Hochmair ES (eds) Advances in cochlear implants. Mainz, Wien, pp 16–20
20. Waring MD (1995) Auditory brainstem responses evoked by electrical stimulation of the cochlear nucleus in human subjects. Electroenceph Clin Neurophysiol 96: 338–347

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Auditory brainstem implants: past, present and future prospects

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Summary

The purpose of the auditory brainstem implant (ABI) is to directly stimulate the cochlear nucleus complex and offer restoration of hearing in patients suffering from profound retrocochlear sensorineural hearing loss. Electrical stimulation of the auditory pathway via an ABI has been proven to be a safe and effective procedure. The function of current ABIs is similar to that of cochlear implants in terms of device hardware with the exception of the electrode array and the sound-signal processing mechanism. The main limitation of ABI is that electrical stimulation is performed on the surface of the cochlear nuclei, thereby making impractical the selective activation of deeper layers by corresponding optimal frequencies. In this article, we review the anatomical, and experimental basis of ABIs and the indications, and surgical technique for their implantation. To the best of our knowledge, we describe the first pathology images of the cochlear nucleus in a patient who had received an ABI.

Keywords: Neuromodulation; hearing loss; auditory pathway; treatment; ABI; rehabilitation.

Introduction

Since the initial applications in the early eighties, electrical stimulation of the auditory pathway at the cochlear nuclei, has proved to be an adequately safe procedure for rehabilitation of the hearing-impaired patients; the auditory brainstem implant (ABI) bypasses the affected structures and provides an adequate ascending stimulus. The majority of patients benefiting from ABIs suffer from neurofibromatosis type 2 (NF2), a severe and disabling disease which is associated with bilateral tumours in the cochleo-vestibular nerve, and consequently, bilateral retrocochlear sensorineural hearing loss (SNHL). The several disabilities induced by NF2 and associated to SNHL in these patients may affect the results of ABIs; the patient's audiological condition becomes an important selection criterion for this procedure. Patient education and rehabilitation, and a multidisciplinary approach to treatment, are of paramount importance in order to obtain the maximum benefit of this prosthetic auditory stimulation procedure [15].

Although currently about 500 patients around the world have received an ABI device, retrocochlear hearing impairment remains a challenging clinical problem. Given the clinical variety of retrocochlear SNHL, patients' performance with ABI cannot be predicted, and, hence, the results are generally poorer and more variable compared to those obtained with a cochlear implant (CI) [27]. In general, the auditory results with respect to word and sentence recognition in an open-set context are limited [16]. Nevertheless, recent reports show that ABIs are safe, have an acceptable ratio of surgical morbidity, and allow most patients to improve their communication abilities, especially lip-reading and awareness of environmental sounds [15]. This is particularly important in an emerging group of candidates who suffer from other causes of cochlear or retrocochlear SNHL namely cochlear ossification, and cochlear agenesis [4].

ABI design

The ABI device was designed initially to be fitted onto the cochlear nuclei, within the cerebellopontine area, simultaneously or after translabyrinthine or suboccipital tumour removal, in NF2 patients. Since the initial, single-channel, ball-type ABI electrode was developed in 1979, by Drs. House and Hitselberger at the House Ear Institute (Los Angeles, CA), ABIs have undergone substantial engineering modifications. Similarly to CIs, currents ABIs are made of an implantable part (electrodes and receiver-stimulator), and an external part, i.e. a speech processor worn by the patient and a

transmission coil, placed over the skin, that transmits sound to the implant. These devices use surface electrodes for neural stimulation, built in platinum or platinum–iridium. The number of electrodes varies in the commercially available ABIs: 21 electrodes in the Nucleus 24 (Cochlear Ltd., Australia), 15 electrodes in the Digisonic (Laboratories MXM, France), and 12 in the Combi 40+ (MED-EL, Austria). Surface contact electrodes are disc-shaped, and are mounted on a silicone or Silastic plate that faces the cochlear nucleus complex (CNC). The other side of the plate is provided with a stripe of Dacron or polyester mesh that favours encapsulation, and helps prevent migration of the device.

Clinical experience demonstrated the safety and biotolerance of ABIs. It is important that when stimulation is performed, according to existing recommendations, the response of neural tissue to chronic electrical stimuli shows that no substantial damage occurs and that ascending auditory activation is clinically safe [27]. Sound-coding strategies used by the speech processor are similar to those currently used in CIs. The selection of speech processing strategies is dependent on the following variables: a) correct surgical placement, b) degree of functionality of the auditory pathway, c) number of active electrodes with different pitch perception, d) type of speech processor, and e) type of internally implanted device [15]. During programming sessions, electrodes producing non-auditory sensations are disconnected.

Neuroanatomical basis for ABIs

The target area for electrical stimulation of the ascending auditory pathway with ABIs is the cochlear nucleus complex (CNC). The CNC has an intricate structure and is divided into 3 regions based on the cell-morphology, and the structures with which they connect. These subdivisions are the Anterior Ventral Cochlear Nucleus (AVCN), the Posterior Ventral Cochlear Nucleus (PVCN), and the Dorsal Cochlear Nucleus (DCN). The CNC receives its ascending afferent input from the auditory nerve, and is the first station in the auditory pathway where neural processing occurs. The CNC contains a variety of cell types encoding different auditory functions, and consequently, for any given sound, there are multiple neural representations of that sound in the outputs of the CNC [2].

The CNC has a tonotopic organisation, which is strictly projected by cochlear ascending frequency-related fibers. Thus, apical cochlear fibers (transmitting low-frequency sounds) project mainly to the ventral portion of the AVCN, PVCN, and DCN, in contrast to basal cochlear fibers (transmitting high-frequency sounds) that project mainly to the dorsal portions of each subdivision of the CNC [18]. This organisation is best defined in the DCN, the most superficial and exposed part of the CNC at the brainstem, where the axis of the tonotopic gradient is oriented parallel to the brainstem surface [14]. Although this issue might be a theoretical advantage for electrical stimulation, most important ascending information is processed in the deepest part of the AVCN, which is almost unexposed within the lateral recess area. This relative inaccessibility of the tonotopic axis of the CNC prompted some investigators to evaluate the feasibility of intranuclear stimulation [19, 25]. Moreover, surface ABI electrical stimulation may be distorted because of tumour-induced anatomo-physiological changes of the area [4]. The above limitations can contribute to the patient's impaired perception of sound frequency, intensity, and temporal cues, and may explain in part why ABI-patients have limited auditory results with the use of their devices [27]. Recent reports show that in NF2 patients, either the tumor or the process of its removal could cause irreversible CN damage, and reduce speech understanding significantly [4]. Conversely, this is not the case in non-tumour patients, whose auditory performance is comparable to the most successful CI users. Currently available ABIs are not inserted inside the CNC. Instead, ABIs are placed onto the surface of the CNC within the lateral recess of the fourth

Fig. 1. Macroscopic preparation of autopsy. Coronal section of the brain from a successful patient of our ABI program, who died from pneumonia 2 years after implantation. The ABI has been removed from the implantation site, making visible the Dacron mesh integrated in to the scar tissue. The brain and brainstem appear shrunken because of the formalin fixation

Fig. 2. Scan of a microscopic slide of the brainstem (hematoxilin and eosin stain). The section corresponds to the patient in Fig. 1. At both sides of the brain stem, the fat tissue used in subsequent surgical procedures is visible. On the left side of the section, the CNC is visible; the ABI was placed on top of it. Between the cerebellum and the CNC, a refringent material is present. This corresponds to Dacron fibers of the mesh used for device stabilisation. The architecture of the CNC is fairly well preserved, as both ventral and dorsal nuclei are recognisable, with typical cytology of the cochlear nuclei preserved. There was no evidence of intranuclear damage due to either intolerance of ABI materials, or to the electrical stimulation

ventricle (Figs. 1, 2). Such placement increases the likelihood of electrical stimulation of other surrounding cranial nerves or other neural structures. These unwanted non-auditory side-effects can be programmed-out at mapping sessions [31].

Experimental basis for ABIs

Similarly to what happened in other medical advances, the clinical rationale for ABI had been already set up [10, 17] before any integrated experimental evidence was available. This prompted us to start, in 1995, an experimental research study using non-human primates that completed the existing knowledge on electrical stimulation of CNC in the lower species [20, 28, 29, 35]. The research aimed at knowing the macaques normal neuroanatomy, the effects of surgical auditory translabyrinthine deafferentation [3, 11, 12], and the changes after ABI implantation [21, 22]. In a group of primates, we used a dummy ABI to mimic the surgical-related changes, and an active ABI. The ABI was similar, in terms of materials and types of stimulation, to that we used clinically on the CNC surface. A total of fourteen non-human primates underwent a translabyrinthine bilateral auditory deafferentation, and simultaneous unilateral active ABI ($n=8$) or dummy ABI ($n=6$) implantation. The ABI was connected via a cable to an external stimulator in the 8 animals undergoing chronic electrical stimulation.

In addition to the pathological examination, the volume and number of neurons of the CNC were estimated in both groups of animals. No mortality or major complications occurred. Brainstem neuropathological lesions or changes were observed in relation to the surgical trauma, and were mainly located at the cerebellar flocculus. The CNCs of the operated animals maintained their gross structure and preserved their neuron types but were reduced in size and showed changes associated with degeneration of the cochlear nerve fibers. In all implanted animals, we found a local superficial reaction around the ABI. In one stimulated animal, an asymptomatic brainstem abscess occurred. The electrical stimulation protocol could not be completed in two animals because of cable breaks or ABI extrusion. Nevertheless, neuropathological and stereological studies did not reveal significant changes in the CNC morphology, its volume or in the number of neurons. The most important factor contributing to tissue damage seems to be the intensity of the current. The duration of stimulation does not seem to have an influence on the damage, and hence, a prolonged period of stimulation does not seem to cause further damage.

Surgical anatomy and procedures

In NF2 patients, most surgical teams encourage ABI implantation at the time of first tumour removal. This may allow them to gain experience with the device while hearing is still present in the contralateral ear [15]. The choice on the surgical approach to the CNC-translabyrinthine or retrolabyrinthine-depends on the surgical team's preference and on the individual case, as the approach itself is not a major factor influencing surgical success [27]. A *translabyrinthine* approach is more common among otologists as it permits a complete control of the facial nerve, does not require cerebellar retraction, and provides a better access to the lateral recess, facilitating the ABI insertion. A disadvantage of this approach is a limited exposure and control of lower cranial nerves and vessels of the posterior fossa. In our opinion, this procedure is the first choice for patients with a tumour near the fundus and normal anatomy of the temporal bone. The *suboccipital approach* is traditionally preferred by most neurosurgeons, as it is performed more quickly and enables an optimal exposure of the posterior fossa, including cranial nerves and vessels. Disadvantages of this approach are the limited control of the lateral recess and fundus of the internal auditory canal, the retraction trauma of the cerebellum, and the

higher risk of injury to the facial nerve. Nevertheless, it might be the choice for ABI candidates who have normal anatomical landmarks and no tumours.

The CNC is located superficially bulging in the dorsolateral aspect of the brain stem, and forming the ''acoustic tubercle''. The ventral portion of the CNC lies over the cerebellar peduncle, while the DCN is in contact with the lateral recess of the IV ventricle. Anatomic landmarks for intraoperative localisation of the CNC include the stump of cranial nerve VIII, cranial nerves VII and IX entering the brainstem, choroid plexus, and tenia, which is a layer over the foramen of Luschka [1, 26]. Probably, the single best landmark – when present – is the stump of the cranial nerve VIII as it can be followed right into the medial surface of the foramen [15], and the IX cranial nerve.

Continuous electrophysiological monitoring during ABI surgery has become an established procedure [7]. Intraoperative monitoring should include at least facial and glossopharyngeal nerves, and acoustic function if present. Once the anatomical landmarks and far-field electrical auditory brainstem responses (EABR) target the site for implantation, the ABI is inserted with the electrodes facing the CNC. The implant is to be stimulated *in situ* to confirm correct placement over the CNC, the integrity of the system, and also to determine the necessary levels of stimulation for the auditory activation. These fine adjustments are achieved through recording the EABR.

Indications for ABI

Currently, the main limitation of ABI-implantation is that electrical stimulation is performed on the surface of the cochlear nuclei, lacking the possibility of selectively providing an optimum frequency activation of the cochlear nuclei. ABIs have limited access to the tonotopic axis of the cochlear nuclei because ascending projections follow a strict frequency-related pattern affecting both VCN and DCN. To improve the access to pitch information, new developments the penetrating ABIs (PABIs) are currently under investigation and in some cases have been clinically tested. Similarly to cochlear implants, selection criteria for brainstem implants continue to evolve, as experience is gained. Initial criteria for clinical trials were quite strict [27], but they have been broadened. Currently, the most commonly accepted inclusion criteria are: NF2 or a traumatic lesion of both auditory nerves, and age over 12 years [30]. A profound bilateral SNHL is only required for patients with traumatic cochlear nerve avulsion, but is not a pre-requisite for patients with NF2 [5]. These may have serviceable hearing in one or both sides when implanted, depending upon the natural history of the disease, and the surgical approach for tumour removal.

Surgical implantation of the ABI in NF2 patients may be done in the first or the second tumour-removal procedure, or in a separate one. Patients should be willing to enrol in the ABI program, and should be in adequately good medical condition so that they can follow a regular program of rehabilitation sessions. Previous conventional otoneurosurgical or stereotactic radiosurgery (*gamma-knife*) treatments of cerebello-pontine angle tumours were initially exclusion criteria for ABI, due to the concerns of some investigators about the degenerative effect these could have on the structure of the cochlear nucleus and the reduced likelihood of electrically induced auditory sensation [27]. Nevertheless, increasing experience shows that such patients can also be offered an ABI, and have similar auditory performance to patients who have not been treated previously by either surgical or radiotherapeutic methods [13, 34]. In addition, there is a patient population who suffer from bilateral SNHL due to severe lesions of the cochlear nerve (aplasia, nerve avulsion, neuropathy), or severe cochlear abnormalities (malformations, acquired ossification), in whom CI may be either impossible or very demanding, or even useless [4]. In non-tumour patients, the absence of distortion in the anatomy of the auditory pathway allows an effective and fairly well organised activation of the auditory pathway [5].

Another emerging indication for ABI is the fortunately uncommon condition of bilateral cochlear agenesis. Besides the promising auditory results in these children, one of the most important things that Colletti's group demonstrated was the presence of consistent intraoperative electrophysiologic central auditory activity during ABI surgery for cochlear nerve aplasia [6], making the classical axiom ''function follows anatomy'' invalid for the auditory pathway. Patients with extensive bilateral ossifying labyrinthitis have poor and inconsistent results after CI due to partial insertions and the associated severe degeneration of peripheral sensorineural elements [9]. In cases of cochlear hypoplasia, in severely ossified cochleae only a restricted number of electrodes can be positioned within the cochlea or aside the modiolus, thus providing a limited effective stimulation. ABI can be an efficient mean of auditory rehabilitation in cases of bilateral SNHL with totally ossified cochleae [8].

Future prospects

Currently, the main limitation of ABI implantation is that electrical stimulation is performed on the surface of the cochlear nuclei, without the possibility of selectively providing an optimum frequency activation of the cochlear nuclei. ABIs have a limited access to the tonotopic axis of the CNC. To improve the access to pitch information, new developments like PABIs are currently under experimental investigation. The group of McCreery *et al*. [25] at the Huntington Medical Research Institute (Pasadena, CA, USA) have successfully implanted a PABI device in cats. They demonstrated the ability of the electrode arrays to evoke tonotopically localised neural activation in the next auditory relay station of the brainstem, the inferior colliculus; in some cases, these devices have been already clinically tested. The House Ear Institute (Los Angeles, CA, USA) and the Huntington Medical Research Institute have started a clinical trial approved by the FDA and have started to report their results [33]. PABI may offer the following additional advantages: a decrease of non-auditory side effects given to more direct stimulation; an increase in the number of electrode contacts providing more numerous channels for stimulation, a reduction in power consumption and the possibility to use faster speech strategies. Since 2000, our group in the University of Navarra has been working on experimental PABI using the same macaque model we have used for ABIs; this is done in collaboration with the Huntington Medical Research Institute which provided the insertion tools needed in surgery. In the first group of primates, we have used a dummy PABIs, and our preliminary results are very promising [23, 24]; the surgical procedure is quite similar to ABI implantation and is well tolerated by the animals (Figs. 3, 4). Currently we are working on a second group of primates to study PABI electrical stimulation.

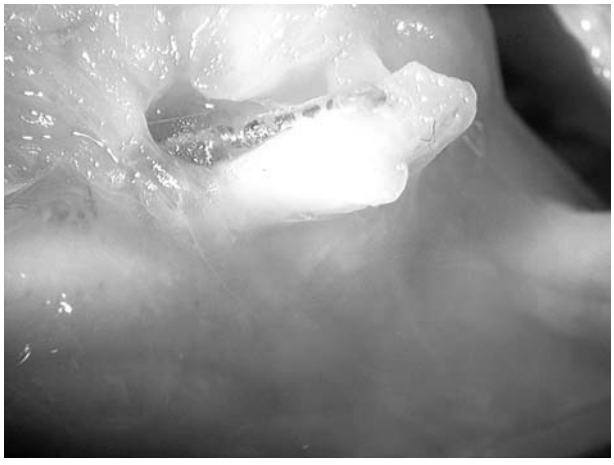

Fig. 3. Macroscopic autopsy preparation. Lateral view of the brain after a successful PABI implantation in a macaque. The cable of the PABI has been cut before the device was removed. The stump of the VIII cranial nerve is recognized and the PABI is seen with the plate *in situ*, over the CNC area, and the pins inserted within the CNC (not visible)

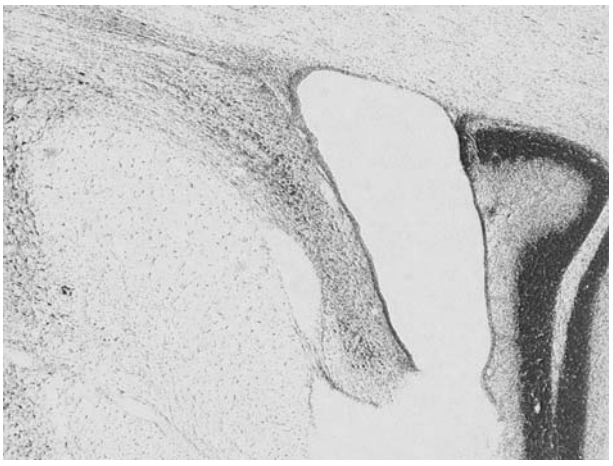

Fig. 4. Microscopic view of the brain stem (Nissl stain). The section corresponds to the animal in Fig. 3. On the left side, the pontobulbar part of the brain stem, and on the right, the flocculus of the cerebellum are seen. The photograph is centred on the CNC and shows the dorsal nucleus on the upper part, and the ventral nucleus on the distal part. The pseudocapsule which surrounded the ABI is visible

Conclusions

The indications for ABI continue to evolve in parallel with the growing experience of implant centres and the improvements in technology. Amazing clinical advances by reputed clinicians lead to emerging indications and open new frontiers for physiological or anatomical research and provide insights into auditory signal processing in the nervous system [32].

References

1. Brackmann D, Hitselberger WE, Nelson RA, Moore J, Waring MD, Portillo F, Shannon RV, Telischi FF (1993) Auditory brainstem implant: I. issues in surgical implantation. Otolaryngol Head Neck Surg 108: 624–633
2. Cant NB, Benson CG (2003) Parallel auditory pathways: projection patterns of the different neuronal populations in the dorsal and ventral cochlear nuclei. Brain Res Bull 60: 457–474
3. Cervera-Paz FJ (2001) Los núcleos cocleares del primate *Macaca fascicularis*. Citoarquitectura normal y efectos de la sección bilateral del nervio coclear. University of Navarra, Thesis
4. Colletti V, Fiorino FG, Carner M, Miorelli V, Guida M, Colletti L (2004) Auditory brainstem implant as a salvage treatment after unsuccessful cochlear implantation. Otol Neurotol 25: 485–496

5. Colletti V, Shannon RV (2005) Open set speech perception with auditory brainstem implant? Laryngoscope 115: 1974–1978
6. Colletti V, Carner M, Fiorino F, Sacchetto L, Miorelli V, Orsi A, Cilurzo F, Pacini L (2002) Hearing restoration with auditory brainstem implant in three children with cochlear nerve aplasia. Otol Neurotol 23: 682–693
7. Frohne C, Matthies C, Lesinki-Schiedat A, Battmer RD, Lenarz T (2000) Extensive monitoring during auditory brainstem implant surgery. J Laryngol Otol 114 Suppl 27: 11–14
8. Grayeli AB, Bouccara D, Kalamarides M, Ambert-Dahan E, Coudert C, Cyna-Gorse F, Sollmann WP, Rey A, Sterkers O (2003) Auditory brainstem implant in bilateral and completely ossified cochleae. Otol Neurotol 24: 79–82
9. Green JD, Marion MS, Hinojosa R (1991) Labirinthitis ossificans: histopathologic consideration for cochlear implantation. Otolaryngol Head Neck Surg 104: 320–326
10. Hitselberger W, House WF, Edgerton BJ, Whitaker S (1984) Cochlear nucleus implant. Otolaryngol Head Neck Surg 92: 52–54
11. Insausti AM, Cruz-Orive LM, Jaúregui I, Manrique M, Insausti R (1999) Stereological assessment of the glial reaction to chronic deafferentation of the cochlear nuclei in the macaque monkey (*M. fascicularis*). J Comp Neurol 414: 485–494
12. Insausti AM, Insausti R, Cruz-Orive LM, Manrique M (2000) Stereological analysis of the cochlear nuclei of monkey (*Macaca fascicularis*) after deafferentation. Image Anal Stereol 19: 133–137
13. Kalamarides M, Grayeli AB, Bouccara D, Dahan EA, Sollmann WP, Sterkers O, Rey A (2001) Hearing restoration with auditory brainstem implants after radiosurgery for neurofibromatosis type 2. J Neurosurg 95: 1028–1033
14. Kaltenbach JA, Melica RJ, Falzarano PR (1996) Alterations in the tonotopic map of the cochlear nucleus following cochlear damage. In: Salvi J *et al* (eds) Auditory system plasticity and regeneration. Thieme Medical Publishers, New York, pp 317–332
15. Kanowitz SJ, Shapiro WH, Golfinos JG, Cohen NL, Roland JT Jr (2004) Auditory brainstem implantation in patients with neurofibromatosis type 2. Laryngoscope 114: 2135–2146
16. Kuchta J (2004) Neuroprosthetic hearing with auditory brainstem implants. Biomed Tech (Berl) 49: 83–87
17. Laszig R, Kuzma J, Seifert V, Lehnhardt E (1991) The Hannover auditory brainstem implant: a multiple-electrode prosthesis. Eur Arch Otorhinolaryngol 248: 420–421
18. Leake PA, Snyder RL, Hradek GT (2002) Postnatal refinement of auditory nerve projections to the cochlear nucleus in cats. J Comp Neurol 448: 6–27
19. Liu X, McPhee G, Seldon HL, Clark GM (1997) Acute study on the neuronal excitability of the cochlear nuclei of the guinea pig following electrical stimulation. Acta Otolaryngol 117: 363–375
20. Liu X, McPhee G, Seldon HL, Clark GM (1997) Histological and physiological effects of the central auditory prosthesis: surface versus penetrating electrodes. Hear Res 114: 264–274
21. Manrique M, Cervera-Paz FJ, Jaúregui I, Vanaclocha V, Pérez N (2000) Auditory brainstem implantation in primates: lessons learned for human surgery and application. J Laryngol Otol Suppl 27: 18–22
22. Manrique M, Jauregui I, Insausti A, Insausti R, Cervera-Paz FJ, Perez N, Vanaclocha V (2000) Experimental study following inactive implantation of an auditory brainstem implant in nonhuman primates. Ann Otol Rhinol Laryngol 109: 163–169
23. Manrique M (2001) New perspectives in auditory brainstem stimulation with penetrating electrodes. 3rd International symposium on auditory brainstem implant. Freiburg, Germany
24. Manrique M (2003) Penetrating electrodes for auditory brainstem implant. 4th International symposium on electronic implants in otology and conventional hearing aids. Tolouse, France
25. McCreery DB, Shannon RV, Moore JK, Chatterjee M (1998) Accessing the tonotopic organization of the ventral cochlear nucleus by intranuclear microstimulation. IEEE Trans Rehabil Eng 6: 391–399
26. McElveen JT, Hitselberger WE, House WF (1987) Surgical accessibility of the cochlear complex in man: surgical landmarks. Otolaryng Head Neck 96: 135–140
27. Nevison B, Laszig R, Sollmann WP, Lenarz T, Sterkers O, Ramsden R, Fraysse B, Manrique M, Rask-Andersen H, Garcia-Ibanez E, Colletti V, von Wallenberg E (2002) Results from a European clinical investigation of the nucleus multichannel auditory brainstem implant. Ear Hear 23: 170–183
28. Ni D, Seldon HL, Shepherd RK, Clark GM (1993) Effect of chronic electrical stimulation on cochlear nucleus neuron size in normal hearing kittens. Acta Otolaryngol 113: 489–497
29. Niparko JK, Altschuler RA, Xue XL, Wiler JA, Anderson DJ (1989) Surgical implantation and biocompatibility of central nervous system auditory prostheses. Ann Otol Rhinol Laryngol 98: 965–970
30. Otto SR, Brackmann DE, Hitselberger W (2004) Auditory brainstem implantation in 12- to 18-year-olds. Arch Otolaryngol Head Neck Surg 130: 656–659
31. Ramsden RT (2002) Cochlear implants and brain stem implants. Br Med Bull 63: 183–193
32. Rauschecker JP, Shannon RV (2002) Sending sound to the brain. Science 8: 295: 1025–1029
33. Shannon RV (2004) Psychophysical and speech results from the first patients with the penetrating auditory brainstem implant (PABI). VIII International cochlear implant conference. Indianapolis, USA
34. Wu H, Kalamarides M, Bouccara D, Dahan EA, Viala P, Sollmann WP, Rey A, Sterkers O (2000) Auditory brainstem implant (Nucleus 21-channel) in neurofibromatosis type 2 patients previously operated on: preliminary results. Adv Otorhinolaryngol 57: 236–239
35. Yuen TGH, Agnew WF, Bullara LA, Jacques S, McCreery DB (1981) Histological evaluation of neural damage from electrical stimulation: considerations for the selection of parameters for clinical application. Neurosurgery 9: 292–299

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Twenty-five years of auditory brainstem implants: perspectives

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Summary

The auditory brainstem implant (ABI) provides auditory sensations, recognition of environmental sounds and aid in spoken communication in more than 300 patients worldwide. It is no more a device under investigation but it is widely accepted for the treatment of patients who have lost hearing due to bilateral tumors of the vestibulocochlear nerve. Most of these patients are completely deaf when the implant is switched off. In contrast to the cochlear implants (CI), only few of the implanted patients achieve open-set speech recognition without the help of visual cues. In the last few years, patients with lesions other than tumors have also been implanted. Auditory perceptual performance in patients who are deaf due to trauma, cochlea aplasia or other non-tumor lesions of the cochlea or the vestibulocochlear nerve turned out to be much better than in NF2 tumor patients. Until recently, the target region for ABI implantation has been the ventral cochlear nucleus (CN). The electrodes are implanted via the translabyrinthine or retrosigmoid approach. Currently, new targets along the central auditory pathways and new, minimally invasive techniques for implantation are under investigation. These techniques may further improve auditory perceptual performance in ABI patients and provide hearing to a variety of types of central deafness.

Keywords: Neuromodulation; auditory; ABI; AMI; brainstem; deafness; hearing; midbrain; neuroprothetics; implant; SAI; stereotaxy.

Functional neurorehabilitation

For centuries, physicians and engineers have had the vision of implanting devices into humans to compensate for a variety of disabilities of the nervous system. Galvani and Benjamin Franklin conducted experiments and applied electrical stimuli to paralyzed muscles. In the last 30 years, the field of functional rehabilitation with neural prostheses has evolved rapidly due to progress in microelectronics. Currently, a considerable number of bionic devices restore the connection between sound, vision, and the central nervous system. The most common prosthesis is the cardiac pacemaker, although it does not actually stimulate nerve cells but muscle cells. Another electrical device, the phrenic nerve stimulator has been developed to help the function of breathing in patients with upper spinal cord injury. Research on motor prostheses that enable paralyzed patients to use their hands or to walk is in progress; however, the long-term benefits in these conditions are still unclear. The most sensitive and problematic part of these devices up to now is not the stimulating device itself, but the creation of an efficient and stable electro-neural interface. By far the most successful neuroprosthetic device is the ''bionic ear'', i.e. the cochlear implant (CI) and the auditory brainstem implant (ABI) [4, 5, 7, 9]. This is partly due to the fact that auditory information is very much based on temporal perception, which can easily be transmitted by only few electrodes. Conversely, other senses such as vision are dependent on high-resolution spatial information, and require many more individual channels to transmit information. Hence, the restoration of hearing by CI or ABI is a motivating field for both oto- and neurosurgeons. Sucessfull implantation programs are dependent on very close collaboration of specialists from these two disciplines.

Indications for auditory brainstem implants

Thousands of patients become deaf every year due to various reasons. The loss of hearing is a significant disability because it imposes limitations in communication and every day life. In most types of acquired deafness, conventional hearing aids or CIs can offer some degree of hearing and speech perception. CIs provide a useful substitute for natural hearing to

thousands of deaf adults and children worldwide. These devices stimulate electrically the nerve fibers in the cochlea and enable most users to carry on a conversation without any visual cues, such as over the telephone. There are, however, many situations where conventional hearing aids or CIs are not likely to be effective. This is the case of patients with Neurofibromatosis Type 2 (NF2), a genetic disease that is typically associated with bilateral tumors of the hearing nerve (Fig. 2). ABIs have been developed for patients suffering from bilateral lesions that can cause complete malfunction of the VIIIth nerves. In NF2-patients, a CI is not effective. Approximately, one in every 40,000 people suffers from this chromosomal disorder, which may be familiar or occur spontaneously. The disorder itself causes the growth of tumors in the spine and the head. Implantation of ABIs is also indicated to patients who have two spontaneous acoustic neuromas or a unilateral acoustic neuroma combined with contralateral VIIIth nerve dysfunction due to a cogenital condition or head trauma. Several sites along the central auditory pathway are potentially suitable locations for electrical stimulation (Fig. 4). Until recently, the target of rehabilitative functional neurostimulation of the auditory system has been the ventral cochlear nucleus (VCN), mainly, because its surface is easily accessible during the surgical procedure for removing acoustic neuromas.

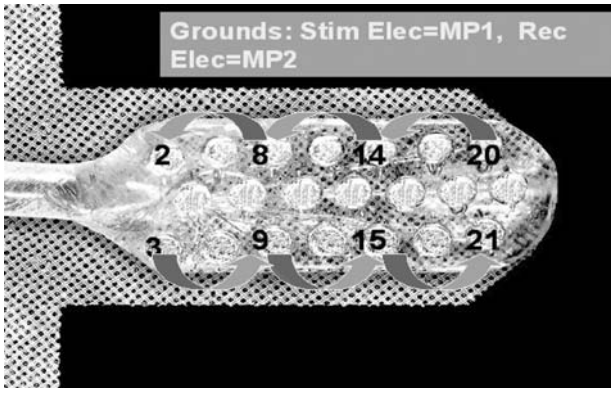

Fig. 1. Nucleus-24 multi-channel electrode with monopolar pattern of stimulation and recording used for the intraoperative mapping of the electrode array with neural response telemetry. Electrode numbers 2–21 are shown with No. 20/21 being the most distal and No. 2/3 being the most proximal contacts. The T-shaped Teflon mesh is intended to keep the electrode in place, once implanted. On the silicone carrier 21 platinium electrodes are located, each measuring 0.7 mm

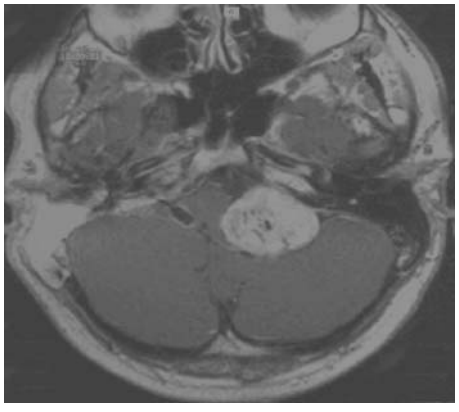

Fig. 2. Magnetic resonance imaging (*MRI*) of the cerebellopontine angle in the axial plane in a patient with NF2. A nucleus-24 multichannel brainstem implant is brought into the lateral recess of the 4th ventricle at the left side of the picture. The electrode carrier is slightly rotated so that the individual electrodes which are in contact with the surface of the cochlear nucleus become visible. On the right side of the picture, there is still a large tumor compressing the brainstem which will be removed in another operation

ABI technology

The ABI works in the following manner. Sounds are picked up by a small microphone located close to the external ear. A thin cord carries the sounds from the microphone to a miniaturized speech processor. The speech processor filters and analyzes the sound, and digitizes it into coded signals. The coded signals are sent through a thin cable from the speech processor to the transmitting coil. The transmitting coil sends the coded signals as radio signals to the implant under the skin. The implant delivers the appropriate electrical signals to the set of electrodes (electrode array) on the cochlear nucleus in the brainstem (Fig. 1). The electrodes stimulate the cochlear nucleus, producing responses that can be interpreted by the brain as sound. The degree of environmental sound discrimination and speech recognition is highly variable among ABI recipients. While several ABI patients obtain a relatively high level of sound-only speech perception, the majority perform at lower levels. Even more than in cochlear implantation, the perceptual performance of these patients is dependent on a variety of individual factors such as the survival of neurons in the cochlear nuclei, differences in surgical placement, anatomic variations, experience, and the ability to capitalize on modest auditory cues. As in CI, the performance of ABI recipients also varies depending on the way the system is programmed [10–13]. Not all ABI electrodes provide auditory sensations without side effects, and most patients can use only a portion of the implanted electrodes on the array.

Audiological aspects

Speech perception is dependent on both temporal and spectral (frequency) cues. In normal hearing, the different frequencies of incoming sounds create a displacement at different points along the basilar membrane of the cochlea. This way the cochlea acts like a spectrum analyzer. It decomposes complex sounds into their frequency components. In auditory implants, the speech processor and the individual electrodes have to take over this task. Recently, there has been an intensive discussion regarding how many individual channels of spectral information are necessary to achieve good consonant and vowel recognition. Although a limited degree of word and sentence recognition is possible even in the absence of spectral cues, a significant intra-individual improvement of perceptual performance has been demonstrated from single-channel to multi-channel electrodes in CI recipients. Studies have shown that, in cochlear implant listeners, spectral information has greater importance in vowel than in consonant recognition. There are relatively fewer differences in duration and amplitude among vowels than among consonants. Consonant recognition by implant users may be more dependent on temporal cues than vowel recognition and therefore consonants may be identifiable with less spectral information, i.e. fewer electrodes. In CIs, group data have shown significant improvements in speech recognition as the number of electrodes was increased from 1 to 4 electrodes. The present ABI patients showed a similar pattern when tested for vowel, word, and sentence recognition [9]. However, when tested for sound effect recognition, consonants, and stress pattern recognition, no significant correlation between perceptual performance and the number of available electrodes (>4) was observed. In these tests, performance above chance level was obtained with only one functional auditory electrode. This is probably due to the use of primarily temporal cues in these tests.

The ABI is highly beneficial in most patients with bilateral vestibular schwannomas who otherwise would remain completely deaf. The limited effectiveness of current ABIs in comparison to CIs is a consequence of the architecture of the ventral cochlear nucleus. Within the nucleus, different bands are represented by layers of neural tissue stacked in parallel to the brain surface: the deeper the layer, the higher the frequency. Therefore the generated sound perceptions have a reduced pitch range. Open-set comprehension of speech requires a minimum of about four frequency channels [3, 6, 14, 17]. It is not clear why some ABI listeners fail to utilize the total amount of spectral information provided by multiple electrodes. Several factors have been proposed to explain the high variability of speech performance and the inability of implant listeners to utilize all spectral cues: anatomic variations, survival patterns of neurons in the cochlear nuclei, and differences in surgical placement. Another factor that might limit the listener's ability to understand speech is the current spread that occurs between electrodes.

Channel interaction may reduce the effective tonotopic selectivity of a multi-electrode array. In CI patients, it has been shown that patients with more intense electrode interaction have lower speech recognition scores. Theoretically, electrical current spread should be greater at higher stimulation levels and for monopolar stimulation modes. However, other studies have shown that equivalent or even better speech perception can be obtained with monopolar stimulation modes. Increasing the number of electrodes above a critical number on the small ABI electrode array may increase the amount of electrode interaction that limits ABI performance, thereby resulting in an asynchronous or even deteriorating performance above a certain electrode number [3]. Although multiple channels of spectral information are provided by the independently stimulated ABI electrodes on the brainstem surface, the current fields produced at the electrodes may spread broadly and result in considerable interaction between neurons in the cochlear nucleus.

ABI implantation: surgical technique

At the House Ear Institute, the translabyrinthine approach (TLA) is used for tumor removal and ABI implantation in all cases. Between 1979 and 2003, 131 patients with neurofibromatosis Type 2 (NF2) received the Nucleus 8 electrode multi-channel ABI (Cochlear Corporation, Englewood, CO). Implantation is performed during the excision of the first-side or second-side tumor [13–15]. The TLA provides a wide angle of view posterior to the vestibulocochlear nerve and the lateral recess. This is of special importance in ABI operations since following tumor resection, the anatomical landmarks are sometimes not easy to identify. The TLA requires minimal cerebellar retraction and allows early identification of the facial nerve during the operation. Since this approach leaves the operated side completely deaf, it is not indicated when the patient has usable hearing that possibly can be preserved. The operation is performed with the patient in the supine

position with the head turned away from the surgeon. Via a postauricular incision, a mastoidectomy is carried out with exposure of the middle fossa plate, the sinodural angle, the sigmoid sinus, the posterior fossa dura, and the semicircular canals. The sigmoid sinus is uncovered to allow extradural retraction with a surgical irrigator. A labyrinthectomy is carried out and the facial nerve is identified by locating the vertical crest (Bill's bar) in the internal auditory canal. After this, the posterior fossa dura is opened and the tumor and the cerebellopontine angle (CPA) are exposed.

The standard TLA incision has been modified by placing a postauricular incision far enough posteriorly to allow sufficient flap coverage of the implant. The receiver/stimulator (R/S) portion of the implant is secured before placement of the electrode. A bony depression is created for the R/S in the area just superior and posterior to the bony defect. Suture holes are made in the bone and the implant is then securely sutured in position. A plane is developed between the proximal portion of the cochlear nerve and the choroid plexus. The cochlear nerve is followed medially as it enters the lateral recess of the fourth ventricle. Confirmation of the foramen of Luschka is made by observing the outflow of cerebrospinal fluid (CSF) when a Valsalva maneuver is induced by the anesthesiologist. The tenia of the fourth ventricle is elevated and the device is placed into the lateral recess over the surface of the dorsal and ventral cochlear nuclei. The two cochlear nuclei lie dorsal lateral (dorsal cochlear nucleus) and ventral lateral (ventral cochlear nucleus) to the inferior cerebellar peduncle at the rostral pole of the medulla. The cell groups corresponding to the vestibular division of the VIIIth nerve are located more medially to the inferior cerebellar peduncle in the brainstem. The choroid plexus and the taenia serve as landmarks for the opening of the lateral recess. Verification of appropriate electrode placement and system integrity is accomplished, prior to closure, through recording of the electrical auditory brainstem response (EABR) [1, 22–24] and recording of compound action potentials (CAP) with neural response telemetry (NRT) (Fig. 3) [2, 16, 17, 21]. Neural integrity of the seventh and ninth cranial nerves is also monitored constantly with electromyography throughout the procedure.

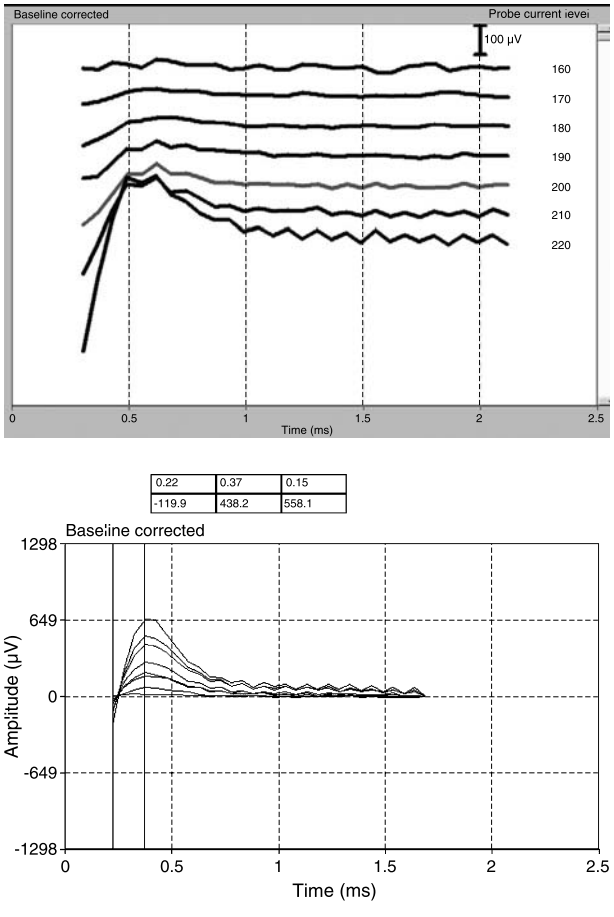

Fig. 3. Intraoperative neural response telemetry waveforms: The electrically evoked whole nerve action potential relates to functions that are obtained using the neural response telemetry system of the Nucleus CI24M device (Cochlear corporation). The panel shows a series of waveforms and the responses that have been offset from each other. The parameter on this figure is the stimulation current level in device programming units (*top*). In the amplitude growth function displayed below, the increasing amplitude of the NRT response is shown with increasing stimulus amplitude (*bottom*)

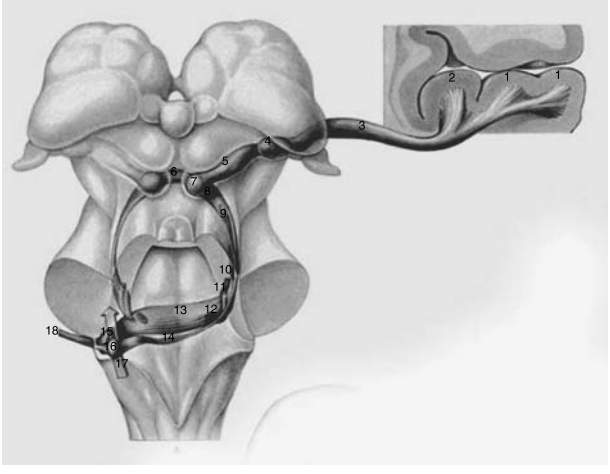

Fig. 4. Central auditory pathways with 2 = cerebral cortex, 7 = inferior colliculus, 16 = cochlear nucleus (adapted from interBRAIN, Springer, Heidelberg, Germany, 1998)

Postoperative management

Patients are tested and programmed initially about six weeks postoperatively and every 3 months in the first year thereafter. The volume is slowly raised to the point at which the patient first detects sound, then to a comfortable level, always paying attention for any possible nonauditory sensations that might be associated with the sounds. The device is programmed so that loud sounds do not cause discomfort or nonauditory sensations. Threshold and comfort levels are measured in monopolar mode (receiver case ground) for each electrode, and non-auditory side-effects (NASE) are ranked on a visual analogue scale ranging from 0 to 4 with grade 1 = slightly noticeable and 4 = intolerable. NASE can be managed in most patients by altering (usually increasing) stimulus pulse duration or by selecting a different ground electrode [8]. If significant NASE (Grade 3–4) persist in spite of processor reprogramming, the electrode is deactivated even if it provides auditory sensations. Electrodes are also excluded from the map when stimulation does not evoke any auditory sensations. Although facial nerve-associated motor side-effects (FASE) may occur in auditory brainstem implants, they are a surprisingly rare finding. We have noticed FASE in only 6 out of 119 implanted devices (4.89%) at the initial stimulation. Most FASE are probably not due to direct stimulation of the facial nerve in the brainstem but to antidromic stimulation of the inferior cerebellar peduncle (ICP). This anatomic structure is in close relation to the electrode array in the lateral recessus of the fourth ventricle. Direct stimulation of this ascending tract causes tingling sensations while antidromic stimulation of the ICP may induce motoric side effects like FASE.

Many anatomical and physiological factors may influence the perceptual performance and the prevalence of NASE after ABI electrode implantation. Earlier studies [14, 19, 21, 22] have shown that the electrodes become fixed in the wall of the lateral recess by fibrous tissue, during the first postoperative days. This encapsulating tissue may significantly add resistance to the transmission of current from the array to the stimulated neurons and may be a contributing factor for elevated thresholds or even system failure in some patients. On the other hand, this fibrous capsule seems to provide long-term stability for the implanted electrodes. Another factor influencing the postoperative perceptual performance is the number of viable, neurons in the cochlear nucleus that can be stimulated after many years of deafness. We have not observed a clear relation between the duration of preoperative deafness and post-implant perceptual performance; hence, even long-lasting preoperative deafness is not considered to be a contraindication to ABI implantation. Recently, good results could be also achieved in patients who underwent radiosurgery for their vestibular schwannomas; this was previously considered a contraindication to ABI implantation. Although the audiological results are below average and the operation may be more difficult than in non-irradiated patients, preoperative radiosurgery should not generally be considered a contraindication to ABI implantation. A positive intraoperative EABR is associated with good post-implant hearing even in patients who have undergone convergent beam irradiation for their vestibular schwannomas.

The number of functional electrodes providing auditory sensation remained stable in most ABI recipients when it was re-evaluated after 3–36 months. In 44 of 61 patients, there was no change in the number of functional electrodes on the array over time. In 7 patients, the number of usable electrodes increased by one and in 6 patients it decreased by one electrode. In 4 of 61 patients, the number of functional electrodes increased by more than 1. No patient ''lost'' more than 1 electrode over time. Intra-individual changes in the number of functional electrodes were not statistically significant. Since the first clinical testing of the device was performed around the sixth postoperative week, these findings indicate that neither postoperative electrode movement nor encapsulating fibrous tissue represent a significant problem in the long-term. Nevertheless, movement that is not detected by functional testing may occur before the first audiological testing in the sixth postoperative week.

New targets, new approaches

In general, ABIs perform less well than CIs, probably because the surface electrodes of the present ABI are only partially capable of accessing the tonotopic axis of the cochlear nucleus (CN) [1, 2, 15, 16]. The CN contains many anatomically and functionally distinct subunits with individual tonotopic organization. In contrast to CI electrodes, which are spaced along the normal tonotopic axis of the scala tympani, the ABI surface electrode has only limited access to the tonotopic axis of the CN. This issue is the primary motivating factor for the development and clinical application of penetrating ABI (PABI) microelectrodes for the CN. PABI can stimulate the human CN in a more three-dimensional, spatially selective manner than surface electrodes, thereby

obtaining a better access to its individual tonotopic subunits. In functional neurostimulation with CN surface electrodes, the appropriate ranking of spectral bands, according to the individual pitch provided by each electrode, appears to be of greater importance to a good auditory performance than the absolute number of implanted electrodes. PABIs have been developed and implanted to overcome some of the limitations associated with surface electrodes and improve ABI performance by providing a wider tonotopic range and improved specificity. Until August 2005, 5 NF2 patients have been implanted at the House Ear institute with a 14 channel surface electrode in combination with a 8-channel PABI electrode. Patients who hear with this penetrating device prefer a combination of surface and penetrating electrodes. Due to the wider frequency spectrum, the subjective quality of the sounds perceived is better in PABI compared to surface ABI. Up to now, no significant improvement of perceptual performance was found in the first PABI patients when compared to the surface ABI patients. The long-term follow up will show if the implantation of penetrating electrodes into the CN represents a significant clinical progress when compared to the surface electrodes only.

In Germany, two groups are working on new approaches to the central auditory pathways. In Hannover, the ''auditory midbrain implant (AMI)'' was developed for open implantation into the inferior colliculus. In animal studies, the 5 mm AMI electrode was inserted via a suboccipital craniotomy (personal communication). At the University of Cologne, we have developed the stereotactic auditory implant (SAI), a penetrating deep-brain electrode for minimally invasive implantation into the inferior colliculus (IC) and CN. Implantation into the brainstem (CN) or midbrain (IC) may be performed through a small burr hole under local anaesthesia. Using stereotactic technique, minimally invasive electrode placement can be achieved with a target accuracy below 1 mm (Fig. 5). The fully awake patient allows the best possible functional neuromonitoring and direct communication with the patient regarding the effect of stimulation, i.e. hearing and side effects. In 2001, in collaboration with Chris Schreiner from the University of San Francisco and Dough McCreery from the Huntington Memorial Research Institute in Pasadena, USA, we recorded cortical responses after electrical stimulation of the inferior colliculus. In the future, minimally invasive implantation into the IC seems to be a very promising method for providing a considerable amount of hearing in patients deafened by either tumor or non-tumoral lesions of the central auditory pathways.

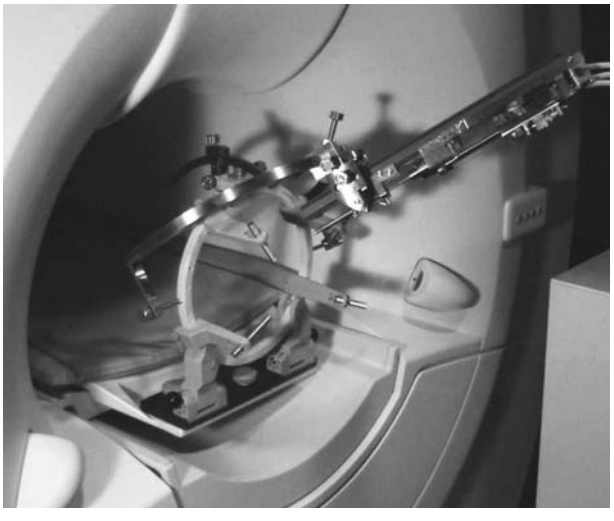

Fig. 5. Computer assisted stereotactic guiding system and intraoperative MRI (Department of Stereotaxy and Functional Neurosurgery, Cologne University, Cologne, Germany)

References

1. Brown CJ, Abbas PJ, Fryauf-Bertschy H, Kelsay D, Gantz BJ (1994) Intraoperative and postoperative electrically evoked auditory brain stem responses in nucleus cochlear implant users: implications for the fitting process. Ear Hear 15: 168–176
2. Dillier NW, Lai WK, Almqvist B, Frohne C, Muller-Deile J, Stecker M, Von Wallenberg E (2002) Measurement of the electrically evoked compound action potential via a neural response telemetry system. Ann Otol Rhinol Laryngol 111: 407–414
3. Dorman MF, Loizou PC, Rainey D (1997) Speech understanding as a function of the number of channels of stimulation for processors using sine-wave and noise-band outputs. J Acoust Soc Am 102: 2403–2411
4. Edgerton BJ, House WF, Hitselberger W (1984) Hearing by cochlear nucleus stimulation in humans. Ann Otol Rhinol Laryngol Suppl 91: 117–124
5. Eisenberg LS, Aaltan A, Portillio F, Mobley JP, House WF (1987) Electrical stimulation of the auditory brain stem structure in deafened adults. J Rehabil Res Dev 24: 9–22
6. Friesen LM, Shannon VB, Baskent D, Wang X (2001) Speech recognition in noise as a function of the number of spectral channels: comparison of acoustic hearing and cochlear implants. J Acoust Soc Am 110: 1150–1163
7. Kuchta J, Behr R, Walger W, Michel O, Klug N (2002) Rehabilitation of hearing and communication functions in patients with NF2. Acta Neurochir Suppl 79: 109–111
8. Kuchta J (2004) Neuroprosthetic hearing with auditory brainstem implants. Biomed Tech 49: 83–87
9. Kuchta J, Otto SR, Shannon RV, Hitselberger WE, Brackmann DE (2004) The multichannel auditory brainstem implant: how many electrodes make sense? J Neurosurg 100: 16–23
10. Matthies C, Thomas S, Moshrefi M, Lesinski-Schiedat A, Frohne C, Battmer RD, Lenarz T, Samii M (2000) Auditory brainstem implants: current neurosurgical experiences and perspective. J Laryngol Otol Suppl 27: 32–36

11. McDermott Hj, McKay CM, Vandali AE (1992) A new portable sound processor for the University of Melbourne/Nucleus multi-electrode cochlear implant. J Acoust Soc Am 91: 3367–3371
12. McElveen JT Jr, Hitselberger WE, House WF, Mobley JP, Terr LI (1985) Electrical stimulation of the cochlear nuclei. Am J Otol Suppl 6: 88–91
13. Otto SR, Shannon RV, Brackmann DE, Hitselberger WE, Staller S, Menapace C (1998) The multichannel auditory brainstem implant (ABI): results in 20 patients. Otolaryngol Head Neck Surg 118: 291–303
14. Otto SR, Ebinger K, Staller S (2000) Clinical trials with the auditory brainstem implant. In: Waltzmann S, Cohne N (eds) Cochlear Implants. Thieme Medical Publishers Inc., New York, pp 357–366
15. Otto S, Brackman DE, Hitselberger WE, Kuchta J (2002) The multichannel auditory brainstem implant update: performance in 61 patients. J Neurosurg 96: 1063–1071
16. Otto SR, Waring MD, Kuchta J (2005) Neural response telemetry and auditory/nonauditory sensations in 15 recipients of auditory brainstem implants. J Am Acad Audiol 16: 219–227
17. Seligman PM, McDermott HJ (1995) Architecture of the Spectra-22 speech processor. Annals of Otology, Rhinol Laryngol 104 Suppl 166: 139–141
18. Shannon RV, Zeng FG, Wygonski J, Kamath V, Ekelid M (1995) Speech recognition with primarily temporal cues. Science 270: 303–304
19. Shannon RV, Fayad J, Moore J, Lo WM, Otto S, Nelson RA, O'Leary M (1993) Auditory brainstem implant: 2. postsurgical issues and performance. Otolaryngol Head Neck Surg 108: 634–642
20. Shannon RV (1983) Multichannel electrical stimulation of the auditory nerve in man. I. Basic Psychophysics. Hear Res 11: 157–189
21. Stypulkowski PH, Van den Honert C (1984) Physiological properties of the electrically stimulated auditory nerve. I. Compound action potential recordings. Hear Res 14: 205–223
22. Terr LI, Mobley JP, House WF (1989) Biocompatibility of the central electroauditory prosthesis and the human cochlear nuclei. Am J Otolaryngol 10: 339–342
23. Terr LI, Fayad J, Hitselberger W, Zakhari R (1990) Cochlear nucleus anatomy related to central electroauditory prosthesis implantation. Otolaryngol Head Neck Surg 102: 717–721
24. Waring MD (1995) Auditory brain-stem responses evoked by electrical stimulation of the cochlear nucleus in human subjects. Electroencephalogr Clin Neurophysiol 96: 338–347
25. Waring MD (1995) Intraoperative electrophysiologic monitoring to assist placement of auditory brainstem implant. Ann Otol Rhinol Laryngol Suppl 166: 33–36

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Auditory cortex stimulation for tinnitus

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Summary

Functional imaging techniques have demonstrated a relationship between the intensity of tinnitus and the degree of reorganization of the primary auditory cortex. Studies in experimental animals and humans have revealed that tinnitus is associated with a synchronized hyperactivity in the auditory cortex and proposed that the underlying pathophysiological mechanism is thalamocortical dysrhythmia; hence, decreased auditory stimulation results in decreased firing rate, and decreased lateral inhibition. Consequently, the surrounding brain area becomes hyperactive, firing at gamma band rates; this is considered a necessary precondition of auditory consciousness, and also tinnitus. Synchronization of the gamma band activity could possibly induce a topographical reorganization based on Hebbian mechanisms. Therefore, it seems logical to try to suppress tinnitus by modifying the tinnitus-related auditory cortex reorganization and hyperactivity. This can be achieved using neuronavigation-guided transcranial magnetic stimulation (TMS), which is capable of modulating cortical activity. If TMS is capable of suppressing tinnitus, the effect should be maintained by implanting electrodes over the area of electrophysiological signal abnormality on the auditory cortex. The results in the first patients treated by auditory cortex stimulation demonstrate a statistically significant tinnitus suppression in cases of unilateral pure tone tinnitus without suppression of white or narrow band noise. Hence, auditory cortex stimulation could become a physiologically guided treatment for a selected category of patients with severe tinnitus.

Keywords: Neuromodulation; auditory cortex; deafferentation; neurostimulation; phantom; tinnitus; auditory cortex; transcranial magnetic stimulation; TMS.

Introduction

Tinnitus is a symptom of a similar high prevalence in USA and Europe; in the population, 10–15% have chronic tinnitus that requires medical attention [1, 41, 71, 87]. Severe tinnitus is age-related and afflicts 2% of the population in their twenties, 6% in the fifties, and 10% above the age of 70. Mild tinnitus that requires intermittent or continuous treatment is more common; it afflicts 25% of the population in their twenties and up to 35% in their seventies [94]. Severe tinnitus leads to depression an approximate 50% of the sufferers, to insomnia a 40% and to profound deterioration in the quality of life a 20% [71, 83]. Among noise-exposed workers, the prevalence increases up to 24% [2, 83].

Developmental and adult plasticity and the pathophysiology of tinnitus

Any lesion along the auditory tract which interferes with its ascending or descending pathways can generate tinnitus [18]. The auditory system develops in two stages [54, 112]. The first stage of synapse and auditory tract formation seems to be genetically determined [97] and requires the release of a chemotropic factor [54, 100]. This is followed by fine-tuning of the synapses leading to the formation of a tonotopic structure [89, 97]. In animals that are born deaf, the auditory system has a rudimentary tonotopic organization [40, 63]. The development of finely tuned tonotopy requires electrical activity initiated by the auditory input during a critical period [39, 58, 95]. It is the result of self-organization [21] via apoptotic resorption of surplus synapses and neurons [92, 100]. In addition to auditory input, electrical stimulation of the cochlea can also modify the rudimentary tonotopic organization in animals that never have had any auditory input and hence, influence the development of tonotopy [59, 60].

The mature auditory system demonstrates an important capacity for reorganization and adaptations to the changes in the auditory environment [32, 104]. Tinnitus probably arises as a result of this reorganization [18, 74]. Magnetoencephalographic (MEG) data co-registered with magnetic resonance imaging (MRI) aka magnetic source imaging (MSI) has demonstrated this reorganization of the auditory cortex in patients suffering from tinnitus. A shift of the cortical representation of the tinnitus frequency into an area which is adjacent to the normally expected tonotopic location is noted in the contralateral auditory cortex of patients with unilateral tinnitus. Furthermore, a strong positive correlation has been found between the intensity of the tinnitus and the degree of cortical reorganization; these findings are similar to earlier data in the somatosensory system, which demonstrated that the intensity of phantom limb pain is highly correlated with the degree of cortical reorganization [30].

Deafferentation tinnitus and synchronized auditory hyperactivity

When lesions are created in the cochlea, high-frequency sound which enters the cochlea is split into its different constituent frequencies. However, if the high-frequency processing hair cells (for example 4000 Hz), have become non-functional, their associated auditory nerve fibers will not fire anymore in response to the high-frequency sounds. Due to their tonotopic structure, immediately after lesioning, neurons in the entire high-frequency section of the ascending auditory pathway will not be firing anymore [49, 91]. However, neurons that normally respond to frequencies, at the margins of the response areas of affected neurons, will increase their firing rate; this has been shown in the cochlear nuclei [51, 53], inferior colliculus [91] [8], medial geniculate body, and cortex [24, 91]. This hyperactivity reaches its maximal level approximately 2 weeks after deafferentation [91]. In tinnitus, firing rate and synchrony are increased, in both the extralemniscal and lemniscal systems; burst firing is increased in the extralemniscal system [8, 24, 25], inner hair cells [85, 86], auditory nerve [73], dorsal and external inferior colliculus [8], thalamus [47], and secondary auditory cortex [24, 25]. Furthermore, quinine, known to generate tinnitus, induces an increased regularity in burst firing at the auditory cortex, inferior colliculus and frontal cortex [34]. This fits with the finding that in tinnitus, increased synchrony is found in the cochlear nerve [7, 23, 69, 73] and auditory cortex [78, 79]. In tinnitus, increased tonic firing rate is present in the lemniscal system and, specifically, in the lemniscal dorsal cochlear nucleus [5, 50, 52, 53, 117, 119], inferior colliculus [33, 44–46], and primary auditory cortex [57]. Interestingly, in primary auditory cortex (A1) both burst firing and tonic firing are increased and generate tinnitus [79].

Neural correlate of tinnitus: 40 Hz thalamocortical firing

How does this increased firing in the lemniscal and extralemniscal system lead to tinnitus? The electroencephalogram (EEG) power spectrum (i.e. firing rate) and the level of consciousness are related [118]: the higher the frequency and the lower the amplitude are in the EEG, the higher the level of consciousness is. Low-frequency delta waves between 0.5 and 4 Hz with large amplitudes are observed in deep sleep, anaesthesia, and coma. Higher frequency theta waves and 4–7 Hz are seen in light sleep. Lower amplitude but higher frequency alpha waves 8–13 Hz are seen in the parietal and occipital sensory areas in the resting state with the eyes closed. It has been proposed that alpha waves are associated with a scanning activity of the brain [93] and not with a mere idling rhythm [77]. Beta waves at 13–30 Hz are seen primarily in frontal areas when people attend to something. Data from the visual system suggests that beta activity provides an excitatory background for the appearance of oscillations in the gamma band [3], and increases the information flow to the cortex. Synchronization of separate gamma-band activities, present in different corticothalamic columns [102], is proposed to bind [36, 37] dispersed neural gamma activity into one coherent auditory perception [15, 48, 64, 65, 88, 105]. Coherent gamma band activity in the cortex in general [37, 101], and auditory cortex specifically, is normally present in locally restricted areas for short periods of time [15, 66, 68, 70, 101]. It has been proposed that this temporal coherence establishes feature specification and cognitive binding through synchronization [13, 37, 101]. Gamma oscillations after standard and target auditory stimuli reveal an early (26–59 ms) phase-locked gamma oscillation. Around 200 ms, a non-phase locked gamma response is found for both standard and target stimuli in temporal posterior electrodes. At about 360 ms, a phase-locked oscillation is observed only after target stimuli. The first gamma oscillation may be a recognition [43], the second a comparison with what is stored and the third a context update (based on the new signal) [38].

Thus, gamma activity per se is not synonymous with tinnitus, but it is most likely an essential requirement for tinnitus to be heard. This fits with what is known on auditory consciousness: gamma band activity in the auditory cortex correlates with the conscious perception of auditory signals [48].

Thalamocortical dysrhythmia

Llinas who elaborated on the evidence that tinnitus correlates with gamma band activity developed this hypothesis further and proposed the 'thalamocortical dysrhythmia' model [67]. This model can be summarized as follows: the thalamus and cortex are interconnected and act in a coherent way. In the sleeping state, the thalamus fires at 4–7 Hz and during slow wave sleep at 1–3 Hz. In the resting awake state, the thalamus fires at around 10 Hz, driving the cortex to fire at the same rate. When auditory stimuli are presented, the thalamocortical rhythm becomes activated and increases its firing rate to approximately 40 Hz. However, in a deafferented state, the firing rate in the thalamocortical columns slows down

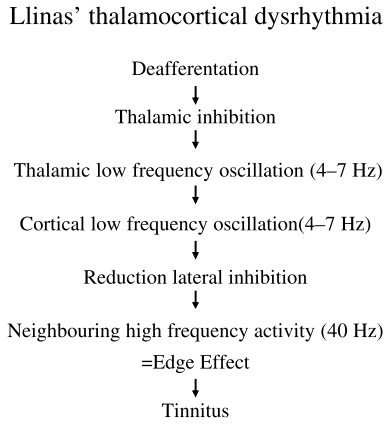

Fig. 1. Schematic representation of Llinas' thalamocortical dysrhythmia model [67] applied to tinnitus

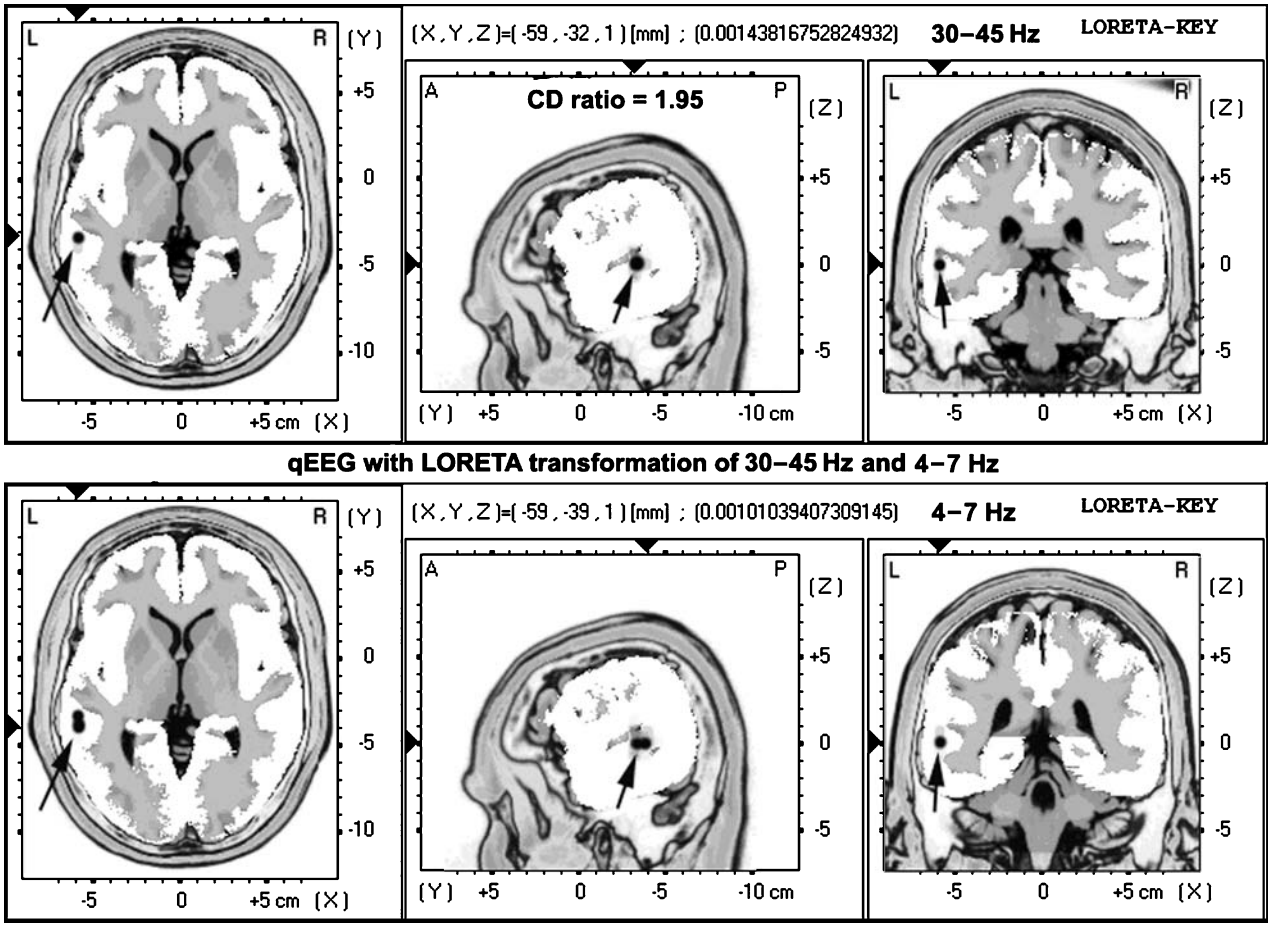

Fig. 2. Representative example of LORETA transformations [81] of filtered spontaneous theta and gamma activity represented on a standardized MRI scan using a cortical solution space, demonstrating increased theta and gamma activity in the auditory cortex contralateral to the side to which the unilateral tinnitus is perceived. The gamma band current density left/right ratio of the auditory cortex is a measure of asymmetric gamma activity in the auditory cortex (*CD ratio* 1 means that gamma band activity in left and right auditory cortex is equal)

in the awake state to 4–7 Hz, decreasing lateral inhibition, with a resultant halo of 40 Hz activity, known as the ''edge effect''. It has been proposed that this spontaneous and constant 40 Hz hyperactivity causes tinnitus [66].

Tinnitus is usually constantly present, which suggests that the tinnitus-related gamma activity is constantly present as well, in contrast to the normal physiological gamma activity which waxes and wanes [15, 66, 68, 70, 101]. Therefore, it should be possible to visualize the tinnitus associated constant, dysrhythmic theta-gamma activity by doing quantitative EEG recordings, filtered at theta (4–7 Hz) and gamma (30–45 Hz), and applying LORETA (low resolution tomography) transformations [11]. LORETA transformations can demonstrate filtered EEG activity of any desired spectrum and localize this activity on a standard MRI; this process results in a functional image of spontaneous cortical electrical brain activity. Our first LORETA results do demonstrate that it is indeed possible to visualize thalamocortical dysrhythmia (Fig. 2).

Repetitive stimulus presentation results in decreased neuronal response to that stimulus; this is known as auditory habituation at the single cell level [106] and auditory mismatch negativity at multiple cell level [75, 106]. Tinnitus is usually present constantly, i.e. there is no auditory habituation to this specific sound, at the tinnitus specific frequency. As mentioned above, following cochlear injury, deafferented neurons become sensitive to neighbouring intact edge-frequencies, and enhance the central representation of these frequencies. Using EEG-mismatch negativity, in tinnitus sufferers, abnormalities have been demonstrated that are specific to the frequencies located at the audiometrically normal region which is adjacent to the lesion edge [111]; this is compatible with Llinas' thalamocortical dysrhythmia model [67].

Thalamocortical dysrhythmia and reorganization

Increased 'synchronized' firing (in the gamma band) and decreased lateral inhibition after deafferentation may induce cortical reorganization by stabilizing synchronized network activity and segregating non-synchronized thalamocortical input [26]; synchronized activity promotes establishment of new connections (Hebbian plasticity) and desynchronized activity may promote loss of connections. Thus, increased synchronization of high-frequency gamma band firing could induce cortical reorganization and through such activity expression of neural plasticity. Understanding these mechanisms may promote development of treatments for tinnitus.

Magnetic and electrical auditory cortex stimulation for tinnitus

Based on the hypothesis that synchronized 40 Hz activity is the neural substrate for tinnitus, three approaches are proposed for modifying this hyperactivity: transcranial magnetic stimulation (TMS), intracranial electrical stimulation and neurobiofeedback. These treatments are based on the following hypotheses:

1. Tinnitus is the result of reorganization of neural networks which is induced by deafferentation (peripheral or central lesion in the auditory system) and causes synchronized hyperactivity in the auditory cortex.
2. This reorganization and the resulting synchronized hyperactivity can be visualized using functional imaging techniques such as PET, SPECT, fMRI, MSI or LORETA.
3. TMS can be used as a non-invasive test to verify whether it is possible to modify the cortical reorganization and the synchronized hyperactivity.
4. If it is possible to modify a patient's tinnitus by TMS, an intracranial electrode can be implanted on the primary or secondary auditory cortex in order to modulate neuronal hyperactivity and suppress tinnitus.

Visualizing tinnitus by visualizing cortical reorganization and synchronized hyperactivity

In tinnitus sufferers, cortical reorganization and tinnitus intensity can be visualized using MSI [74]. However, MEG is an expensive labour intensive technique, restricted to a very small number of research centers. Therefore, using fMRI as a method for visualizing tinnitus would be advantageous in routine clinical practise. Recently, much progress has been made in the development of scanning protocols which do not require the special pre- and postprocessing techniques that are not convenient in clinical settings. Activation of both cortical and subcortical auditory structures can now be demonstrated by an fMRI block design of 12 runs; in this, frequency specific tones or narrow band sounds are matched to the patient's tinnitus and presented binaurally through headphones. The sound is alternated and switched on for 50 seconds and off for 50 seconds. This block design is combined with the clustered volume acquisition (CVA) technique in which the acquisition time (AT) is shorter than the TR, namely 3000 ms; this allows

a 2000 ms silent gap in between each echo planar imaging (EPI) volume acquisition [96], and hence, the implementation of this protocol in clinical practice.

Pathophysiology of tinnitus and fMRI

fMRI measures a relative difference in oxygen consumption between a resting state and active state. This is based on the fact that deoxyhemoglobin in venous blood is a naturally occurring paramagnetic contrast agent. Hence, in vivo contrast images of brain microvasculature reflect the oxygen level in blood. This blood oxygenation level-dependent (BOLD) contrast follows changes in blood oxygen which are induced by altered metabolic demand or blood flow. Thus, BOLD contrast can provide in vivo real-time brain maps of blood oxygenation under normal physiological conditions [80]. A focal area of increased oxygen consumption can be depicted by subtraction of two MRI images, one at rest and one with increased oxygen consumption that is induced by a specific task. Increased oxygen consumption is related to increased metabolic demands and the BOLD effect is related to increased firing rates. Both EEG [31] and MEG [4] event-related synchronizations (time-locked,

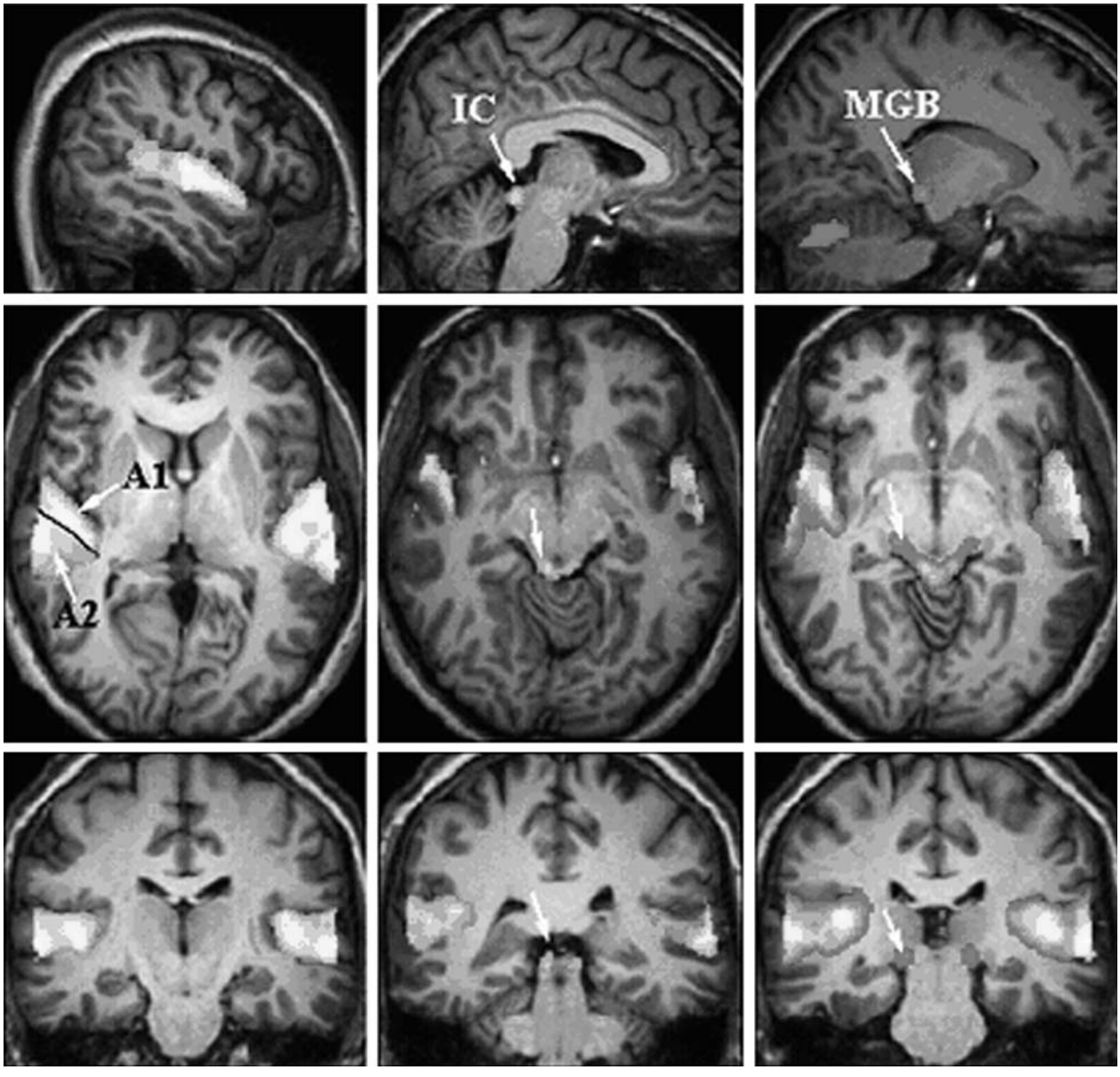

Fig. 3. fMRI activation of the auditory tract demonstrates activation of the inferior colliculus, medial geniculate body (*thalamus*) and auditory cortices, both primary and secondary auditory cortex

but not phase-locked) in the gamma band (32–38 Hz) correlate with the BOLD effect on fMRI; this suggests that the gamma band synchronized activity associated with tinnitus can be visualized on fMRI.

fMRI of tinnitus

The above scanning paradigm uses music as a stimulus and visualizes adequately the auditory pathways in tinnitus patients [96]. fMRI activation is symmetrical in patients with bilateral tinnitus in all investigated areas of the auditory pathways [auditory cortex (AC), thalamus and inferior colliculus (IC)]. fMRI activation is significantly decreased in the left primary AC and left IC (in patients with right-sided tinnitus), and in the right medial geniculate body (MGB) (in patients with left-sided tinnitus). fMRI activation always represents a difference in neural activity, instead of the absolute neural activity. In tinnitus patients, an increase of spontaneous neural activity means that, in rest condition, the affected brain area is more active than the unaffected side; in the active condition, sound presentation will induce only a limited increase in activity in comparison to the non-affected side. This is known as the saturation model and explains the finding that constant pathological neuronal hyperactivity is related to hypoactivation in fMRI [96]. A similar study using tinnitus pitch and character specific stimuli is currently being conducted.

Effects of TMS on tinnitus

Transcranial magnetic stimulation (TMS) is a generally accepted method to study cortical plasticity [14, 107, 108]. It delivers electrical current of up to 8 Amp at the coil and induces a magnetic field pulse of up to 2.5 Tesla. The changing magnetic field creates an electrical field of 500 V/m and this results in neural activity [109]. The area that can be influenced directly by TMS depends on coil configuration, and has an average diameter of 3 cm [12]. Only recently TMS has been used in tinnitus [17, 27, 61, 84]. This followed developments in fMRI [17, 20], PET [27, 61, 62], and neuronavigation-guided TMS that made it possible to target accurately the areas of abnormal brain functioning which are associated with tinnitus. TMS at frequencies of 10 Hz or higher is capable of suppressing tinnitus transiently [17, 84], whereas repetitive TMS (rTMS) at 1 Hz for 33 minutes daily (2000 pulses) for 5 days results in tinnitus suppression for long periods [27, 61, 62]. Therefore, rTMS can be used to study cortical plasticity [108], to treat tinnitus [27, 61, 62, 84] and possibly as a prognostic tool of the efficacy of an implanted electrode [17]. TMS is non-invasive and could be an ideal tool for selecting patients that could benefit from the implantation of an electrical stimulating device over the auditory cortex.

The mechanism of tinnitus suppression by TMS is unknown; TMS could interfere with the neural correlate of tinnitus, i.e. the constant, synchronized 40 Hz thalamocortical hyperactivity. Low frequency TMS ($<$10 Hz) and high frequency ($>$10 Hz) TMS probably suppress tinnitus by a different mechanism. Indeed, it has been demonstrated that low frequency stimulation has an opposite effect than that of high-frequency stimulation [56, 99]. High-frequency TMS ($\geq$10 Hz) increases metabolic activity in the underlying cortex [55, 82, 98], whereas low-frequency TMS decreases the metabolism or does not induce a hypermetabolism [56, 99]. High frequency (10 Hz) TMS might induce a transient dysfunction (virtual lesion) in the underlying auditory cortex [84]; this desynchronizes the 40 Hz thalamocortical activity temporarily, and results in a transient suppression of tinnitus [17, 20, 84]. Low-frequency TMS at 1 Hz, on the other hand, reduces cortical excitability [10, 35] for periods of up to 30 minutes [9]; this correlates with the longer suppression of tinnitus seen at 1 Hz stimulation [27, 61, 62].

Effects of electrical stimulation of auditory cortex on tinnitus

The abundant descending connections from the auditory cortex to the medial geniculate body (thalamus) [113, 115], inferior colliculus [114, 116], superior olivary complex [22], and cochlear nuclei [110] are the anatomical substrate for mediating electrical stimulation of the cortex to subcortical structures. This means that focal electrical stimulation of the auditory cortex may activate the corticofugal system and result in a reorganization of thalamus [103], inferior colliculus [120], and auditory cortex itself [11, 90]. This electrical stimulation evokes frequency shifts [11, 103, 104, 120] and results in a sharpened tuning of the auditory neurons. This corticofugal system may operate as a positive feedback mechanism which, in combination with lateral inhibition, adjusts and sharpens the tuning of neurons in the thalamus and inferior colliculus (egocentric selection) [11, 103, 104, 120]. In other words, the corticofugal system could act as a mechanism for reorganization of the thalamus and inferior colliculus, adjusting the frequency

maps to the auditory experience [11, 32, 104]. Auditory cortex stimulation at the cortical deafferented area could therefore reverse thalamocortical dysrhythmia by the following mechanisms: a) induction of egocentric selection of the deafferented frequencies which fire at 4–7 Hz, or b) suppression by lateral inhibition of the surrounding hyperactive frequencies which fire at 40 Hz. Electrical stimulation of the auditory cerebral cortex can be done in three different ways: 1) epidurally in an area overlying the secondary auditory cortex, 2) intradurally, on the intrasulcal grey matter of the primary auditory cortex, and 3) inside the parenchyma in the white matter tracts.

Epidural secondary auditory cortex stimulation

In patients undergoing diagnostic implantations of recording and stimulation electrodes for treatment of intractable epilepsy, reciprocal functional pathways have been demonstrated between Heschl's gyrus (primary auditory cortex, A1) and the acoustically responsive posterior lateral superior temporal gyrus (PLST) [6]. Electrical stimulation of the PLST may reach the primary auditory cortex and suppress its hyperactivity that is associated with tinnitus [16]. Before an implantation, the patient first undergoes tinnitus matching tests to determine the pitch of tinnitus. Then, fMRI scans are used to localize the auditory cortex area that corresponds to tinnitus. If TMS is capable of suppressing tinnitus transiently, we implant the electrode epidurally, using fMRI-guided neuronavigation [17, 19]. This technique has been used in 12 patients suffering from unilateral tinnitus ($n = 10$) or bilateral tinnitus ($n = 2$). Tinnitus suppression was highly dependent on the characteristics of the tinnitus; in pure tone unilateral tinnitus, the average suppression was 97%, in unilateral white or narrow band noise was 24%, and in bilateral tinnitus the average suppression was negligible [19] (Fig. 4). Interestingly, in patients with unilateral tinnitus, characterized by the presence of both white noise and pure tone tinnitus, only the pure tone component of the tinnitus got suppressed.

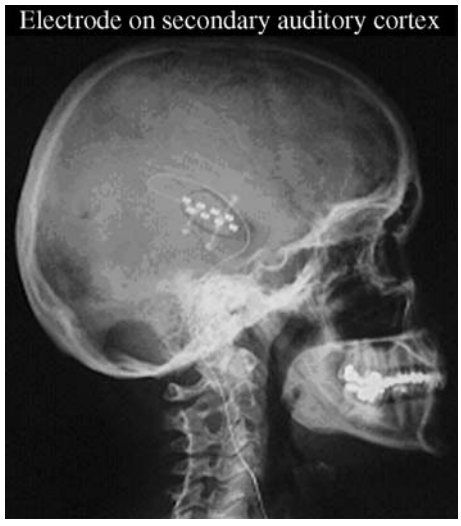

Fig. 5. Postoperative X-ray of epidural secondary cortex electrode

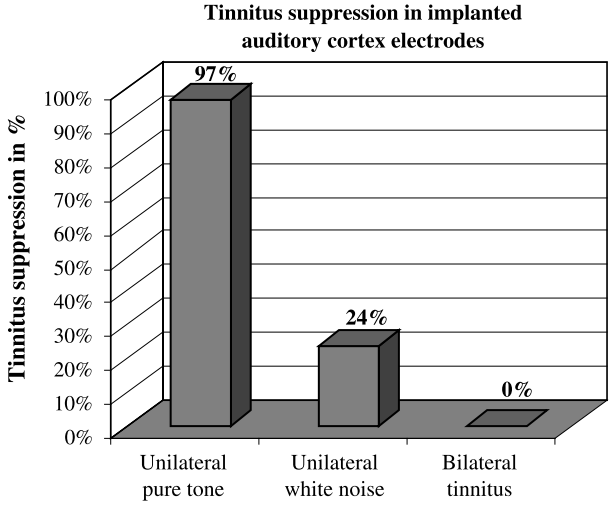

Fig. 4. Degree of tinnitus suppression achieved with implanted electrodes. Suppression is very good in unilateral pure tone tinnitus (97% average tinnitus suppression), poor in white or narrow band noise (24% average tinnitus suppression) and absent in bilateral tinnitus in this pilot study (Mann–Whitney test: $U = 25$, $p < 0.01$)

Intradural intrasulcal grey matter stimulation of the primary auditory cortex

The epidural application of electrodes for cortical stimulation is preferred because it is simpler and safer. In many patients, however, suppression of tinnitus can be achieved for only shorts period of time (1–3 days); after this, the effect wears off, despite several reprogrammings of the stimulation. This might be due to the plasticity of the secondary auditory cortex. It has been suggested that the secondary sensory cortex may have greater plasticity potential than the primary sensory cortex. GAP-43 is a marker for neural plasticity. In mammals, GAP-43 mRNA studies have demonstrated that synaptic remodelling occurs more easily in secondary [28, 42] and association [76] cortices than in the primary cortex. In the thalamus, in the ventral part of the medial geniculate body (MGB) there is less GAP-43 mRNA expression than in the dorsal and medial MGB [29]. This suggests that the lemniscal thalamocortical system,

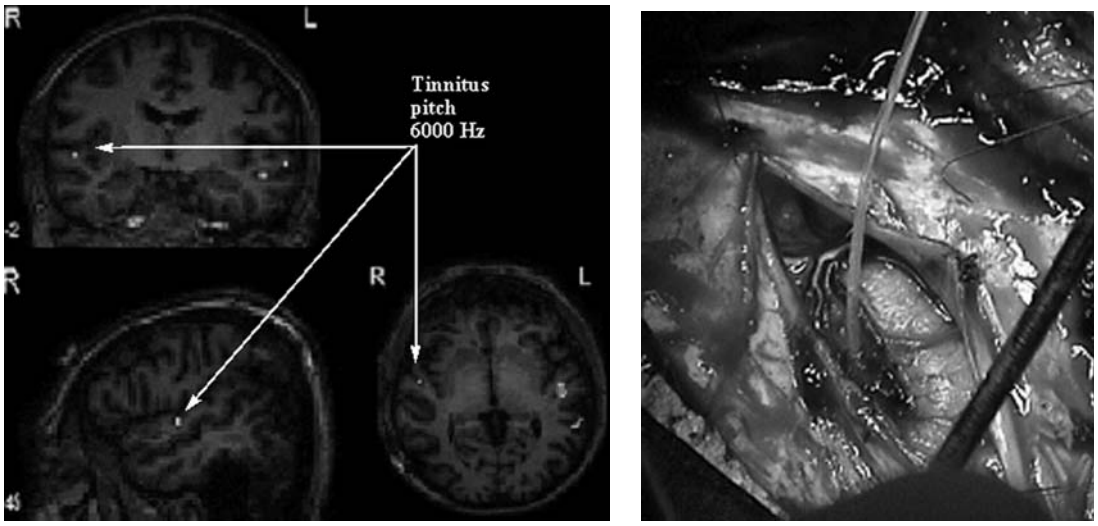

Fig. 6. *Left*: fMRI of tinnitus generator at 6000 Hz. *Right*: intraoperative picture of electrode insertion

which has connections predominantly with the primary auditory cortex, has smaller plasticity potential than the extralemniscal system [72], which has connections predominantly with the secondary auditory cortex [72]. In four patients, an electrode was inserted intradurally in the Sylvian fissure in the primary auditory cortex. In two patients, the objective was to obtain a stable tinnitus suppression, because in previously performed epidural stimulation the parameters had to be reprogrammed every 2–3 days. In both these patients, the intradural stimulation resulted in a stable suppression of tinnitus. In two other patients with narrow band tinnitus, the epidural electrode offered no suppression of tinnitus (0 and 10%, respectively); despite the intradural placement of the electrode, both these patients failed to improve.

Intradural intraparenchymatous deep white matter stimulation of the primary auditory cortex

In cooperation with Drs. Michael Seidman and Kost Elisevich a third approach has been developed, the MEG-based neuronavigation-guided deep white matter stimulation below layer 6 of the primary auditory cortex. Only one patient has undergone this type of implantation; notably, the electrode was capable of suppressing the bilateral tinnitus completely. Further investigations

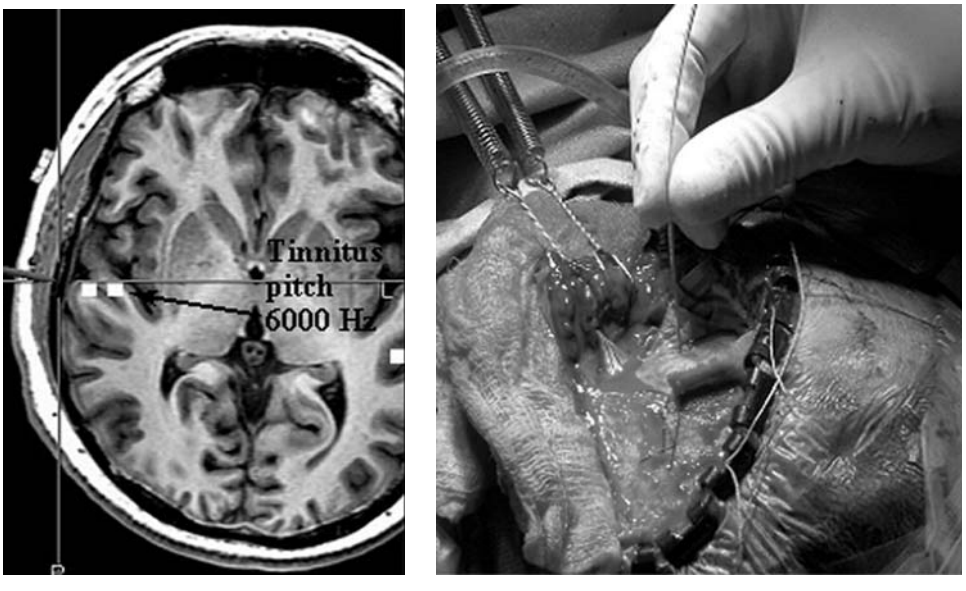

Fig. 7. *Left*: Magnetic source image showing the location of the structure that is presumed to generate the patient's tinnitus, centered at 6000 Hz. *Right*: Intraoperative pictures of electrode insertion. Images courtesy of Dr. Seidman

will demonstrate whether this technique could have wider applications other than primary or secondary cortex stimulation.

Side effects and complications

The stimulation parameters were chosen in order to: a) suppress tinnitus without inducing side effects, and b) keep the patient unaware of the stimulation. Side effects may occur when high frequency and high intensity stimulation is used; these include a feeling of intoxication, altered spatial localization of external sounds, word finding problems, dizziness, vertigo and hearing perception changes (hearing is perceived as being clearer, even for their own voice) [19]. Certain patients who had their tinnitus suppressed successfully used to suffer also from a feeling of ''aural pressure''; this was decreased in all those patients. However, the feeling of ''aural pressure'' and the tinnitus do not decrease with identical stimulation programming [19]. In 2 of 12 patients, epileptic seizures occurred. This was probably due to prolonged stimulation without free intervals in patients having an external stimulator; the latter cannot be programmed by the investigator, but relies on patient cooperation. In patients implanted with an internal pulse generator (IPG), no epileptic seizures were observed under the following usual stimulation protocols: a) high frequency stimulation (>10 Hz) in cyclic mode, 5 seconds on, 5 seconds off or b) low frequency stimulation (<10 Hz) in a similar cyclic mode of parameters or a cyclic mode of 1–15 minutes on, 30 seconds to 5 minutes off.

Conclusions

The treatment of tinnitus that is described in this chapter is based on the hypothesis that pure tone tinnitus perception correlates to focal neuronal hyperactivity in the primary and/or secondary auditory cortices. This hyperactivity can be visualized using magnetic source imaging or functional MRI. The high resolution images obtained can be used to guide epidural or intradural neuromodulation by implantable electrodes. The results of this study suggest that patients with unilateral pure tone tinnitus, which can be suppressed by TMS, are good candidates for stimulation by implanted electrodes. Studies using TMS suggest that: a) the longer the tinnitus exists, the less tinnitus suppression can be achieved, and b) high frequency stimulation is more efficient in suppressing tinnitus of recent origin, while low frequency TMS is more efficient in suppressing chronic tinnitus.

References

1. Axelsson A, Ringdahl A (1989) Tinnitus – a study of its prevalence and characteristics. Br J Audiol 23: 53–62
2. Axelsson A, Prasher D (2000) Tinnitus induced by occupational and leisure noise. Noise Health 2: 47–54
3. Bekisz M, Wrobel A (1999) Coupling of beta and gamma activity in corticothalamic system of cats attending to visual stimuli. Neuroreport 10: 3589–3594
4. Brookes MJ, Gibson AM, Hall SD, Furlong PL, Barnes GR, Hillebrand A, Singh KD, Holliday IE, Francis ST, Morris PG (2005) GLM-beamformer method demonstrates stationary field, alpha ERD and gamma ERS co-localisation with fMRI BOLD response in visual cortex. Neuroimage 26: 302–308
5. Brozoski TJ, Bauer CA, Caspary DM (2002) Elevated fusiform cell activity in the dorsal cochlear nucleus of chinchillas with psychophysical evidence of tinnitus. J Neurosci 22: 2383–2390
6. Brugge JF, Volkov IO, Garell PC, Reale RA, Howard MA 3rd (2003) Functional connections between auditory cortex on Heschl's gyrus and on the lateral superior temporal gyrus in humans. J Neurophysiol 90: 3750–3763
7. Cazals Y, Horner KC, Huang ZW (1998) Alterations in average spectrum of cochleoneural activity by long-term salicylate treatment in the guinea pig: a plausible index of tinnitus. J Neurophysiol 80: 2113–2120
8. Chen GD, Jastreboff PJ (1995) Salicylate-induced abnormal activity in the inferior colliculus of rats. Hear Res 82: 158–178
9. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48: 1398–1403
10. Chen R (2000) Studies of human motor physiology with transcranial magnetic stimulation. Muscle Nerve Suppl 9: S26–S32
11. Chowdhury SA, Suga N (2000) Reorganization of the frequency map of the auditory cortex evoked by cortical electrical stimulation in the big brown bat. J Neurophysiol 83: 1856–1863
12. Cohen LG, Roth BJ, Nilsson J, Dang N, Panizza M, Bandinelli S, Friauf W, Hallett M (1990) Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. Electroencephalogr Clin Neurophysiol 75: 350–357
13. Contreras D, Llinas R (2001) Voltage-sensitive dye imaging of neocortical spatiotemporal dynamics to afferent activation frequency. J Neurosci 21: 9403–9413
14. Corthout E, Uttl B, Walsh V, Hallett M, Cowey A (2000) Plasticity revealed by transcranial magnetic stimulation of early visual cortex. Neuroreport 11: 1565–1569
15. Crone NE, Boatman D, Gordon B, Hao L (2001) Induced electrocorticographic gamma activity during auditory perception. Brazier Award-winning article, 2001. Clin Neurophysiol 112: 565–582
16. De Ridder D (2004) Tinnitus and auditory cortex: answer to a letter to the editor. J Neurosurg 101: 172–172
17. De Ridder D, De Mulder G, Walsh V, Muggleton N, Sunaert S, Moller A (2004) Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus. Case report. J Neurosurg 100: 560–564
18. De Ridder D, Ryu H, Moller AR, Nowe V, Van de Heyning P, Verlooy J (2004) Functional anatomy of the human cochlear nerve and its role in microvascular decompressions for tinnitus. Neurosurgery 54: 381–388
19. De Ridder D, De Mulder G, Verstraeten E, Kovacs S, Smits M, Sunaert S, Van Der Kelen K, Van de Heyning P, Moller A (2005) Primary and secondary auditory cortex stimulation for intractable tinnitus. ORL (in press)

20. De Ridder D, Verstraeten E, Van der Kelen K, De Mulder G, Sunaert S, Verlooy J, Van de Heyning P, Moller A (2005) Transcranial magnetic stimulation for tinnitus: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otol Neurotol 26: 616–619
21. Deacon T (1997) Evolution and intelligence: beyond the argument from design. In: Scheibel A, Schopf J (eds) The origin and evolution of intelligence. Jones and Bartlett, Boston, pp 103–136
22. Doucet JR, Molavi DL, Ryugo DK (2003) The source of corticocollicular and corticobulbar projections in area Te1 of the rat. Exp Brain Res 153: 461–466
23. Eggermont JJ (1990) On the pathophysiology of tinnitus; a review and a peripheral model. Hear Res 48: 111–123
24. Eggermont JJ, Kenmochi M (1998) Salicylate and quinine selectively increase spontaneous firing rates in secondary auditory cortex. Hear Res 117: 149–160
25. Eggermont JJ (2003) Central tinnitus. Auris Nasus Larynx 30 Suppl: S7–S12
26. Eggermont JJ, Roberts LE (2004) The neuroscience of tinnitus. Trends Neurosci 27: 676–682
27. Eichhammer P, Langguth B, Marienhagen J, Kleinjung T, Hajak G (2003) Neuronavigated repetitive transcranial magnetic stimulation in patients with tinnitus: a short case series. Biol Psychiatry 54: 862–865
28. Feig SL (2004) Corticothalamic cells in layers 5 and 6 of primary and secondary sensory cortex express GAP-43 mRNA in the adult rat. J Comp Neurol 468: 96–111
29. Feig SL (2005) The differential distribution of the growth-associated protein-43 in first and higher order thalamic nuclei of the adult rat. Neuroscience 136: 1147–1157
30. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E (1995) Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 375: 482–484
31. Foucher JR, Otzenberger H, Gounot D (2003) The BOLD response and the gamma oscillations respond differently than evoked potentials: an interleaved EEG-fMRI study. BMC Neurosci 4: 22
32. Gao E, Suga N (1998) Experience-dependent corticofugal adjustment of midbrain frequency map in bat auditory system. Proc Natl Acad Sci USA 95: 12663–12670
33. Gerken GM (1996) Central tinnitus and lateral inhibition: an auditory brainstem model. Hear Res 97: 75–83
34. Gopal KV, Gross GW (2004) Unique responses of auditory cortex networks in vitro to low concentrations of quinine. Hear Res 192: 10–22
35. Gorsler A, Baumer T, Weiller C, Munchau A, Liepert J (2003) Interhemispheric effects of high and low frequency rTMS in healthy humans. Clin Neurophysiol 114: 1800–1807
36. Gray CM, Konig P, Engel AK, Singer W (1989) Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature 338: 334–337
37. Gray CM, Singer W (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. Proc Natl Acad Sci USA 86: 1698–1702
38. Gurtubay IG, Alegre M, Labarga A, Malanda A, Artieda J (2004) Gamma band responses to target and non-target auditory stimuli in humans. Neurosci Lett 367: 6–9
39. Harrison RV, Ibrahim D, Mount RJ (1998) Plasticity of tonotopic maps in auditory midbrain following partial cochlear damage in the developing chinchilla. Exp Brain Res 123: 449–460
40. Hartmann R, Shepherd RK, Heid S, Klinke R (1997) Response of the primary auditory cortex to electrical stimulation of the auditory nerve in the congenitally deaf white cat. Hear Res 112: 115–133
41. Heller AJ (2003) Classification and epidemiology of tinnitus. Otolaryngol Clin North Am 36: 239–248
42. Higo N, Oishi T, Yamashita A, Matsuda K, Hayashi M (1999) Quantitative non-radioactive in situ hybridization study of GAP-43 and SCG10 mRNAs in the cerebral cortex of adult and infant macaque monkeys. Cereb Cortex 9: 317–331
43. Hopfield JJ, Brody CD (2001) What is a moment? Transient synchrony as a collective mechanism for spatiotemporal integration. Proc Natl Acad Sci USA 98: 1282–1287
44. Jastreboff PJ, Sasaki CT (1986) Salicylate-induced changes in spontaneous activity of single units in the inferior colliculus of the guinea pig. J Acoust Soc Am 80: 1384–1391
45. Jastreboff PJ, Brennan JF, Sasaki CT (1988) An animal model for tinnitus. Laryngoscope 98: 280–286
46. Jastreboff PJ (1990) Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res 8: 221–254
47. Jeanmonod D, Magnin M, Morel A (1996) Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. Brain 119(Pt 2): 363–375
48. Joliot M, Ribary U, Llinas R (1994) Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. Proc Natl Acad Sci USA 91: 11748–11751
49. Kaltenbach JA, Czaja JM, Kaplan CR (1992) Changes in the tonotopic map of the dorsal cochlear nucleus following induction of cochlear lesions by exposure to intense sound. Hear Res 59: 213–223
50. Kaltenbach JA, Godfrey DA, Neumann JB, McCaslin DL, Afman CE, Zhang J (1998) Changes in spontaneous neural activity in the dorsal cochlear nucleus following exposure to intense sound: relation to threshold shift. Hear Res 124: 78–84
51. Kaltenbach JA (2000) Neurophysiologic mechanisms of tinnitus. J Am Acad Audiol 11: 125–137
52. Kaltenbach JA, Afman CE (2000) Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus. Hear Res 140: 165–172
53. Kaltenbach JA, Zacharek MA, Zhang J, Frederick S (2004) Activity in the dorsal cochlear nucleus of hamsters previously tested for tinnitus following intense tone exposure. Neurosci Lett 355: 121–125
54. Kandel ER (1991) Cellular mechanisms of hearing and the biological basis of individuality. In: Kandel E, Schwartz J, Jessell T (eds) Principles of neural science. Appleton & Lange, Norwalk, Connecticut, pp 1009–1031
55. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, Repella JD, Danielson AL, Willis MW, Benson BE, Speer AM, Osuch E, George MS, Post RM (1999) Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry 46: 1603–1613
56. Kimbrell TA, Dunn RT, George MS, Danielson AL, Willis MW, Repella JD, Benson BE, Herscovitch P, Post RM, Wassermann EM (2002) Left prefrontal-repetitive transcranial magnetic stimulation (rTMS) and regional cerebral glucose metabolism in normal volunteers. Psychiatry Res 115: 101–113
57. Komiya H, Eggermont JJ (2000) Spontaneous firing activity of cortical neurons in adult cats with reorganized tonotopic map following pure-tone trauma. Acta Otolaryngol 120: 750–756
58. Kral A, Hartmann R, Tillein J, Heid S, Klinke R (2001) Delayed maturation and sensitive periods in the auditory cortex. Audiol Neurootol 6: 346–362
59. Kral A, Hartmann R, Tillein J, Heid S, Klinke R (2002) Hearing after congenital deafness: central auditory plasticity and sensory deprivation. Cereb Cortex 12: 797–807

60. Kral A, Tillein J, Heid S, Hartmann R, Klinke R (2005) Postnatal cortical development in congenital auditory deprivation. Cereb Cortex 15: 552–562
61. Langguth B, Eichhammer P, Wiegand R, Marienhegen J, Maenner P, Jacob P, Hajak G (2003) Neuronavigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment. Neuroreport 14: 977–980
62. Langguth B, Eichhammer P, Zowe M, Marienhagen J, Kleinjung T, Jacob P, Sand P, Hajak G (2004) Low frequency repetitive transcranial magnetic stimulation (rTMS) for the treatment of chronic tinnitus – are there long-term effects?. Psychiatr Prax 31 Suppl 1: S52–S54
63. Leake PA, Snyder RL, Rebscher SJ, Moore CM, Vollmer M (2000) Plasticity in central representations in the inferior colliculus induced by chronic single- vs. two-channel electrical stimulation by a cochlear implant after neonatal deafness. Hear Res 147: 221–241
64. Llinas R, Ribary U, Joliot M, Wang X (1994) Content and context in temporal thalamocortical binding. In: Buzsaki G, Llinas R, Singer W (eds) Temporal coding in the brain. Springer-Verlag, Berlin, pp 251–272
65. Llinas R, Ribary U, Contreras D, Pedroarena C (1998) The neuronal basis for consciousness. Philos Trans R Soc Lond B Biol Sci 353: 1841–1849
66. Llinas R, Urbano FJ, Leznik E, Ramirez RR, van Marle HJ (2005) Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci 28: 325–333
67. Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP (1999) Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci USA 96: 15222–15227
68. MacDonald KD, Barth DS (1995) High frequency (gamma-band) oscillating potentials in rat somatosensory and auditory cortex. Brain Res 694: 1–12
69. Martin WH, Schwegler JW, Scheibelhoffer J, Ronis ML (1993) Salicylate-induced changes in cat auditory nerve activity. Laryngoscope 103: 600–604
70. Menon V, Freeman WJ, Cutillo BA, Desmond JE, Ward MF, Bressler SL, Laxer KD, Barbaro N, Gevins AS (1996) Spatio-temporal correlations in human gamma band electrocorticograms. Electroencephalogr Clin Neurophysiol 98: 89–102
71. Meyershoff W (1992) Tinnitus. In: Meyershoff W, Ria D (eds) Otolaryngology head and neck surgery. WB Saunders Company, Philadelphia, pp 435–446
72. Moller A (2003) Sensory systems: Anatomy, Physiology, and Pathophysiology. Academic Press, Amsterdam
73. Moller AR (1984) Pathophysiology of tinnitus. Ann Otol Rhinol Laryngol 93: 39–44
74. Muhlnickel W, Elbert T, Taub E, Flor H (1998) Reorganization of auditory cortex in tinnitus. Proc Natl Acad Sci USA 95: 10340–10343
75. Naatanen R, Paavilainen P, Tiitinen H, Jiang D, Alho K (1993) Attention and mismatch negativity. Psychophysiology 30: 436–450
76. Neve RL, Finch EA, Bird ED, Benowitz LI (1988) Growth-associated protein GAP-43 is expressed selectively in associative regions of the adult human brain. Proc Natl Acad Sci USA 85: 3638–3642
77. Nunez P (2002) Electroencephalography. In: Ramachandran V (ed) Encyclopedia of the human brain, vol 2. AcademicPress, Amsterdam, pp 169–179
78. Ochi K, Eggermont JJ (1996) Effects of salicylate on neural activity in cat primary auditory cortex. Hear Res 95: 63–76
79. Ochi K, Eggermont JJ (1997) Effects of quinine on neural activity in cat primary auditory cortex. Hear Res 105: 105–118
80. Ogawa S, Lee TM, Kay AR, Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 87: 9868–9872
81. Pascual-Marqui RD, Michel CM, Lehmann D (1994) Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 18: 49–65
82. Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC (1997) Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J Neurosci 17: 3178–3184
83. Phoon WH, Lee HS, Chia SE (1993) Tinnitus in noise-exposed workers. Occup Med (Lond) 43: 35–38
84. Plewnia C, Bartels M, Gerloff C (2003) Transient suppression of tinnitus by transcranial magnetic stimulation. Ann Neurol 53: 263–266
85. Puel JL (1995) Chemical synaptic transmission in the cochlea. Prog Neurobiol 47: 449–476
86. Puel JL, Ruel J, Guitton M, Wang J, Pujol R (2002) The inner hair cell synaptic complex: physiology, pharmacology and new therapeutic strategies. Audiol Neurootol 7: 49–54
87. Quaranta A, Assennato G, Sallustio V (1996) Epidemiology of hearing problems among adults in Italy. Scand Audiol Suppl 42: 9–13
88. Ribary U, Ioannides AA, Singh KD, Hasson R, Bolton JP, Lado F, Mogilner A, Llinas R (1991) Magnetic field tomography of coherent thalamocortical 40-Hz oscillations in humans. Proc Natl Acad Sci USA 88: 11037–11041
89. Rubsamen R (1992) Postnatal development of central auditory frequency maps. J Comp Physiol [A] 170: 129–143
90. Sakai M, Suga N (2002) Centripetal and centrifugal reorganizations of frequency map of auditory cortex in gerbils. Proc Natl Acad Sci USA 99: 7108–7112
91. Salvi RJ, Wang J, Ding D (2000) Auditory plasticity and hyperactivity following cochlear damage. Hear Res 147: 261–274
92. Sanes DH, Song J, Tyson J (1992) Refinement of dendritic arbors along the tonotopic axis of the gerbil lateral superior olive. Brain Res Dev Brain Res 67: 47–55
93. Shevelev IA, Kostelianetz NB, Kamenkovich VM, Sharaev GA (1991) EEG alpha-wave in the visual cortex: check of the hypothesis of the scanning process. Int J Psychophysiol 11: 195–201
94. Sindhusake D, Mitchell P, Newall P, Golding M, Rochtchina E, Rubin G (2003) Prevalence and characteristics of tinnitus in older adults: the Blue Mountains Hearing Study. Int J Audiol 42: 289–294
95. Sininger YS, Doyle KJ, Moore JK (1999) The case for early identification of hearing loss in children. Auditory system development, experimental auditory deprivation, and development of speech perception and hearing. Pediatr Clin North Am 46: 1–14
96. Smits M, Kovacs S, De Ridder D, Peeters R, Van Hecke P, Sunaert S (2004) Lateralization of signal change in the auditory pathway in patients with lateralized tinnitus studied with functional Magnetic Resonance Imaging (fMRI). Radiology 233 Suppl: abstract 12–06
97. Snyder RL, Leake PA (1997) Topography of spiral ganglion projections to cochlear nucleus during postnatal development in cats. J Comp Neurol 384: 293–311
98. Speer AM, Kimbrell TA, Wassermann EM, J DR, Willis MW, Herscovitch P, Post RM (2000) Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 48: 1133–1141
99. Speer AM, Willis MW, Herscovitch P, Daube-Witherspoon M, Shelton JR, Benson BE, Post RM, Wassermann EM (2003) Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with H215O positron emission tomography: II. effects of prefrontal cortex rTMS. Biol Psychiatry 54: 826–832

100. Staecker H, Galinovic-Schwartz V, Liu W, Lefebvre P, Kopke R, Malgrange B, Moonen G, Van De Water TR (1996) The role of the neurotrophins in maturation and maintenance of postnatal auditory innervation. Am J Otol 17: 486–492
101. Steriade M, Amzica F, Contreras D (1996) Synchronization of fast (30–40 Hz) spontaneous cortical rhythms during brain activation. J Neurosci 16: 392–417
102. Steriade M (2000) Corticothalamic resonance, states of vigilance and mentation. Neuroscience 101: 243–276
103. Suga N, Zhang Y, Yan J (1997) Sharpening of frequency tuning by inhibition in the thalamic auditory nucleus of the mustached bat. J Neurophysiol 77: 2098–2114
104. Suga N, Gao E, Zhang Y, Ma X, Olsen JF (2000) The corticofugal system for hearing: recent progress. Proc Natl Acad Sci USA 97: 11807–11814
105. Tiitinen H, Sinkkonen J, Reinikainen K, Alho K, Lavikainen J, Naatanen R (1993) Selective attention enhances the auditory 40-Hz transient response in humans. Nature 364: 59–60
106. Ulanovsky N, Las L, Nelken I (2003) Processing of low-probability sounds by cortical neurons. Nat Neurosci 6: 391–398
107. Walsh V, Ashbridge E, Cowey A (1998) Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. Neuropsychologia 36: 45–49
108. Walsh V, Ashbridge E, Cowey A (1998) Cortical plasticity in perceptual learning demonstrated by transcranial magnetic stimulation. Neuropsychologia 36: 363–367
109. Walsh V, Rushworth M (1999) A primer of magnetic stimulation as a tool for neuropsychology. Neuropsychologia 37: 125–135
110. Weedman DL, Ryugo DK (1996) Pyramidal cells in primary auditory cortex project to cochlear nucleus in rat. Brain Res 706: 97–102
111. Weisz N, Voss S, Berg P, Elbert T (2004) Abnormal auditory mismatch response in tinnitus sufferers with high-frequency hearing loss is associated with subjective distress level. BMC Neurosci 5: 8
112. Whitehead MC, Morest DK (1985) The development of innervation patterns in the avian cochlea. Neuroscience 14: 255–276
113. Winer JA, Larue DT (1987) Patterns of reciprocity in auditory thalamocortical and corticothalamic connections: study with horseradish peroxidase and autoradiographic methods in the rat medial geniculate body. J Comp Neurol 257: 282–315
114. Winer JA, Larue DT, Diehl JJ, Hefti BJ (1998) Auditory cortical projections to the cat inferior colliculus. J Comp Neurol 400: 147–174
115. Winer JA, Diehl JJ, Larue DT (2001) Projections of auditory cortex to the medial geniculate body of the cat. J Comp Neurol 430: 27–55
116. Winer JA, Chernock ML, Larue DT, Cheung SW (2002) Descending projections to the inferior colliculus from the posterior thalamus and the auditory cortex in rat, cat, and monkey. Hear Res 168: 181–195
117. Zacharek MA, Kaltenbach JA, Mathog TA, Zhang J (2002) Effects of cochlear ablation on noise induced hyperactivity in the hamster dorsal cochlear nucleus: implications for the origin of noise induced tinnitus. Hear Res 172: 137–143
118. Zeman A (2002) Consciousness, a user's guide. Yale University Press, New Haven
119. Zhang JS, Kaltenbach JA (1998) Increases in spontaneous activity in the dorsal cochlear nucleus of the rat following exposure to high-intensity sound. Neurosci Lett 250: 197–200
120. Zhang Y, Suga N (2000) Modulation of responses and frequency tuning of thalamic and collicular neurons by cortical activation in mustached bats. J Neurophysiol 84: 325–333

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Visual disorders

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Implantable visual prostheses

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Summary

Visual impairment and blindness is primarily caused by optic neuropathies like injuries and glaucomas, as well as retinopathies like age-related macular degeneration (MD), systemic diseases like diabetes, hypertonia and hereditary *retinitis pigmentosa* (RP). These pathological conditions may affect retinal photoreceptors, or retinal pigment epithelium, or particular subsets of retinal neurons, and in particular retinal ganglion cells (RGCs). The RGCs which connect the retina with the brain are unique cells with extremely long axons bridging the distance from the retina to visual relays within the thalamus and midbrain, being therefore vulnerable to heterogeneous pathological conditions along this pathway. When becoming mature, RGCs loose the ability to divide and to regenerate their accidentally or experimentally injured axons. Consequently, any loss of RGCs is irreversible and results to loss of visual function. The advent of micro- and nanotechnology, and the construction of artificial implants prompted to create visual prostheses which aimed at compensating for the loss of visual function in particular cases. The purpose of the present contribution is to review the considerable engineering expertise that is essential to fabricate current visual prostheses in connection with their functional features and applicability to the animal and human eye. In this chapter, 1) Retinal and cortical implants are introduced, with particular emphasis given to the requirements they have to fulfil in order to replace very complex functions like vision. 2) Advanced work on material research is presented both from the technological and from the biocompatibility aspect as prerequisites of any perspectives for implantation. 3) Ultimately, experimental studies are presented showing the shaping of implants, the procedures of testing their biocompatibility and essential modifications to improve the interfaces between technical devices and the biological environment. The review ends by pointing to future perspectives in the rapidly accelerating process of visual prosthetics and in the increasing hope that restoration of the visual system becomes reality.

Keywords: Neuromodulation; visual prosthesis; neural implants; microelectrodes; biocompatibility; surface modification; nerve regeneration.

Introduction

Violations to central nervous system (CNS) pathways are unlikely to be followed by substantial replacement of cells or axonal regeneration; small frustrated acts of cell renewal from adult stem cells or sprouting occur but do not result in complete recovery of function. In addition, topological relationships within the limited intracerebral space hinder interventions [1] which are feasible in peripheral nerves. Difficulties in subsidiary surgery apply therefore especially to the CNS where most surgical interventions are not possible without destroying neighbouring parts of the nerve tissue. Even smaller surgical interventions may enhance the numbers of damaged neurons by activating additional local cascades operated by glial cells. Parts of these cascades are initialized by microglial cells which are functioning as an intracerebral network obviously developed to efficiently remove the sick neurons and therefore to preserve the remaining structural and functional integrity of the tissue. In addition, astrocytes are responsible to fill the structural gaps with proliferation and to communicate with all other elements, thus balancing the deficits [3].

Like within the entire CNS, damage to the optic nerve of higher vertebrates often has dramatic functional consequences for vision. The first one is that the microenvironment of the optic nerve is inhospitable; the axonal regrowth and inhibitory factors prevent the formation of new growth cones at the stumps of injured axons [10]. Consequently, spontaneous regeneration of axons fails within the optic nerve, and then retinofugal axons degenerate both in anterograde and in retrograde direction [10]. Concomitantly, ganglion cell bodies within the retina undergo atrophy; due to atrophy, a pale optic nerve head becomes visible in the weeks and months that follow after injuries, with irreversible loss of vision. The failure of functional visual recovery, together with the inability of retinal ganglion cells (RGCs) to become replaced by neurons after disposal is associated with

additional cascades of interactive events between neurons and glial cells which result in glial proliferation [3] and in inadequate tissue proliferative repair, called gliosis. Advances in various areas of microtechnology and electronics together with large scale application of informatics challenge us to develop visual prostheses which may replace loss of visual function. The efforts to design and microfabricate multichannel retinal prosthesis has been considerably boosted by initial reports of successful application [4–6, 9, 12, 13, 22]. Although these appeared encouraging, most attempts fall short of offering a chance for vision. The goal of this work is to critically review some aspects of these visual prostheses, particularly the required functional abilities of implants, and the design of microelectrode arrays (MEAs) for optimal function and bio-(neuro-)compatibility. In addition, the review summarizes the anticipated difficulties we are faced with in view of the limited tools to create bio-technological hybrids; these implantable devices may share in common both the technologically, imposed informatics and the biologically acceptable function.

Requirements for visual prostheses

In contrast to peripheral organs which offer opportunities of both intrinsic tissue repair and prosthetic replacement, the nervous system is the most complex and most vulnerable biological system. To this end, most approaches to either replace or substitute neuronal elements within the CNS failed [1]. On the other hand, recording of signals within the CNS, and in particular within the optic pathway like electroretinogram (ERG) and visually evoked potentials (VEP) are routinely performed. However, stimulation in order to treat defects in a proper way are under development and may encounter difficulties arising from the complexity and high vulnerability of the tissue [2]. A number of proposed ideas for electronic implants was based on a reductionist view rather than considering the complexity of the neuronal circuitries. Keeping in line with the fact that nerve cells and fibres are vulnerable and different from the ''microwires'' or ''microcables'' used in electronics would encourage to create multidisciplinary teams covering these aspects, too. Nerve cells consist of complex biological membranes with integrated receptors and delicate interactive elements for on-line sensing the environment and transmitting information *via* molecules, action potentials and changes in their chemo-electrical activity. The principal requirements to any implantable structures are therefore features mimicking essential biological functions of nerves and replacing these functions depending on the scope of implantation.

Besides of the clinical scope of neuroprosthetics in the human visual system, one goal of using implants in basic research is to understand fundamental principles of intraretinal circuitry, to analyse processing of visual information, to unravel principles of connectivity within the central visual relay nuclei and to study cell–cell interactions in subsets of neuronal populations [7, 8, 16, 17]. Another goal is to replace functions which are lost due to damage of photoreceptors, or ganglion cells or of whole retinal areas. Fabrication of microarrays has provided impressing capabilities, of course seen carefully under the constraints of neuroanatomy and neurophysiology. In fact, construction and implantation of electrodes for nerve signal recording and nerve stimulation has accompanied neurobiology over its entire evolution [1].

The success of visual prostheses depends basically on their capability to record visual signals and/or to stimulate the retina or the optic nerve, or central visual nuclei. It is therefore reasonable to assume that such implants have to fulfil highly specialized requirements both in relation to the electrodes and the insulating material which carries the electrodes. Last not least, a further prerequisite is the biocompatibility for retina- or nerve-specific implants, or more strictly spoken, their neurocompatibility. The choice of the material will also depend on the possibilities and restrictions arising from the fabrication process. In microelectronics, *silicone* is most frequently used [10, 11]. However, in the majority of implantation cases, it will be favourable to use more flexible materials for the implants in order to limit mechanical damage of biological tissue. As one of these flexible materials, *polyimide* attracted attention in recent years [10, 11].

Retinal prostheses

Efforts to device a retinal prosthesis were undertaken in the 1980s with interdisciplinary approaches. Retinal prostheses are intended to mimic the function of lost photoreceptor cells which are the first in the excitation chain which follows an optical stimulus (Fig. 1). Conceptually, an implanted prosthetic device applies light-dependent electrical pulses to the RGCs which are then transmitted as a series of action potentials to the brain to result there in a meaningful image. Retinal implants can reasonably be placed either ''on top'' of the retina (epiretinal implant), i.e. between the ganglion cell layer and the vitreous [6, 12, 13, 22] or ''underneath'' the retina

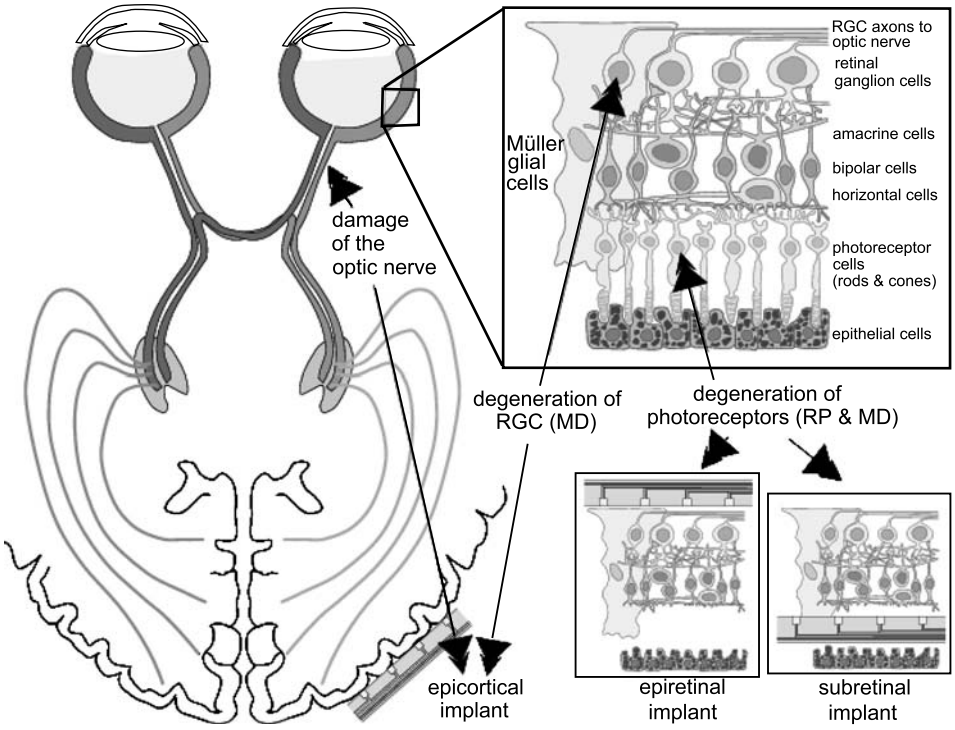

Fig. 1. The mostly favoured visual implants. If the retinal ganglion cells (*RGC*) are still intact, then the stimulating implant can be implanted into the eye, either onto the RGC layer (epiretinal implant) or by replacing photoreceptor cells (subretinal implant); nerve signals of stimulated RGC are then forwarded into the brain. *RP* Retinitis pigmentosa; *MD* macular degeneration

(subretinal implant), i.e. directly at the place of the lost photoreceptor cells [4, 5, 23, 24] (Fig. 1). Both concepts are being pursued over years and each of them appears to show mechanical and biological advantages and fundamental disadvantages. With an epiretinal implant, the distance between electrodes and RGCs are smaller (Fig. 1), and hence, they can be stimulated more directly. In addition, the axons traversing from more distant sites than the location of the implant may come under the influence of the stimulating electric fields. Thus, excitation of these axons markedly lowers local specificity of stimulation at the site of implantation. With a subretinal implant, the electrodes could perform directly the function of photoreceptor cells by giving a stimulus upon irradiation. Subsequent information processing would be performed by the interneurons of the retina and ultimately be inferred to RGCs.

With epiretinal implants, numerous experiments have been performed to achieve excitation of RGC cell bodies rather than axons [4–6, 22]. This task is complicated because the detailed position of stimulating electrodes relative to the cell bodies cannot be accurately controlled. Perceptual testing has been performed in humans with retinal stimulation from intraocular implants lasting hours within the eye. Patterned electrical stimulation induced patterned perceptions, thus encouraging to pursue further engineering of geometrically adaptable implants [4–6, 22]. The ultrathin microelectrode array that has been used in human eyes is being modified with development of low-power sophisticated electronics, while encapsulation with stable polymers aims to protect them from erosion. This may facilitate long-term implantation in the future.

With subretinal implants, stimulation is supposed to be more similar to the natural way because incoming light would be applied as an electrical signal directly at the place where it hits the retina, as it is done on the photoreceptor cells [8, 21, 23, 24] (Fig. 1). Consequently, the concept of most subretinal implants consists of an array of photodiodes which directly supply an electrical pulse upon light exposure. Further processing of these signals would then be carried out by the neuronal layers of the retina [18], and RGCs would finally transmit the visual information to the brain. Naturally, neuronal layers beneath the ganglion cell layer are necessary for this concept [18]. However, it must be expected that they degenerate step by step because photoreceptors which supply stimulating signals are lost. In fact, such a degeneration has been observed in all retinal layers, but it is claimed that remaining neurons should be sufficient for the application

of a visual prosthesis [18]. Subretinal implants should be energetically driven by incident light which may also convey the natural form of visual images to the implant. The suitable population of persons to be considered for subretinal implants suffer of retinitis pigmentosa (RP). However, the implants have not been successfully tested yet, and initial approaches were performed in blind individuals without improvement of sight. Yet, the microfabrication, encapsulation and miniaturization of these implants have gone over a long way and acceptable multielectrode arrays have been created. These have been tested *in vitro* and in various animal models [8, 9, 16, 21, 23, 24].

Retinal implants are inserted through the anterior part of the eye, and animal experiments are performed mainly with rabbits and cats [8, 21]. The whole surgery is very delicate because the retina is very thin and vulnerable. The vitreous is removed using a vitrectomy-instrument as used in retinal surgery. For epiretinal implants, it is crucial to remove the vitreous completely at the place of implant attachment because otherwise firm adhesion cannot be achieved. For this purpose, it is advantageous that the vitreous of the rabbit quickly contracts and forms strands upon trauma, and therefore, it can be grasped and removed. The epiretinal implant can be now placed onto the retina. In subretinal implants, the retina is incised, e.g. with a sharply edged canule, and the inner retina may be separated from the pigment epithelium. The subretinal implant can then be inserted between the inner retina and the epithelium. Finally, the detached parts of the inner retina must be attached.

Biocompatibility and stability of retinal implants

Retinal implants have to meet very high requirements with respect to their biocompatibility and long-term stability. Moreover, an implant within the eye must be especially compatible and stable because in such a delicate organ an inflammation or extensive scar formation would have catastrophic consequences, and surgical interventions cannot be repeated for several times. It is clear that a retinal implant should be flexible, tiny and without sharp edges, particularly when implanted beneath the retina. The shape of the implant must fit the convexity of the eyeball that can be achieved by the use of flexible materials, thus ultimately merging the electronic devices with the eye. Chronic implantation will require chronically biocompatible interfaces in a reciprocal way that ensures both preservation of the tissue from implant-derived toxicity and of the implant material from tissue-derived erosion. To date, long-term implantation experiments with retinal implants have been performed only on animals. The purpose of these experiments was to evaluate biocompatibility and long-term stability of the implants. Currently, cats [21] and rabbits with subretinal implants measuring 3 mm in diameter and 50–100 μm thick are being kept for observation, and it seems that the implants are well tolerated by the ocular tissue [8, 23]. The means to evaluate function of implanted electrodes is recording of cortical visually evoked potentials (VEPs). They should appear in a similar manner as if the stimulus would be given by an equivalent optical signal. Electrical cortical responses could be elicited by stimulating electrodes which were placed on the lens of the eye in rabbits after chemically induced photoreceptor degeneration [12, 17]. Bipolar strip electrodes into the subretinal space of adult rabbits were driven by external photodiodes and, when flashed in a remote position, cortical responses were obtained similar to the normal light-induced VEPs produced by the pre-implanted eye [5]. Small electrodes within the sclera of blind patients resulted in *phosphenes* which could be elicited upon application of short biphasic pulses [13]. Patients who previously had been able to see were able to localise the position of the phosphenes accurately according to the retinal area stimulated, which indicates a certain conservation of the visual map. Two subjects were able to recognise movement of electrodes by detecting movement of the phosphenes, and they also could see two phosphenes when two electrodes were active. This is not surprising since phosphenes can also be produced by irritation of horizontal cells, whose localisation is determined within the inner retina. Phosphenes are rather ''tactile'' signals, but may be well used as orientation guides upon blindness.

One challenge towards creating chronically implantable electrodes is delivery of adequate quanta of energy needed for stimulation. Photodiodes used for retina implants are still to weak, that means voltage produced by them upon irradiation with incident light is still insufficient. Therefore, it is tried to overcome this problem by installation of a small infrared laser device which is worn by the patient on eye glasses. The laser beam directed onto the photodiodes is controlled by a computer-assisted video camera. In one possible design, the photodiodes are situated directly on the MEA, and the most straightforward concept is to combine one photodiode with one electrode. In order to avoid damage of retinal neurons by the laser beam, this design is applicable only

for epiretinal implants. In an other design, the receiving photodiodes are placed at the edge of the retina, and thin wires lead to the stimulating microarray underneath or above the retina. For the epiretinal implant, different concepts for the encoding of the optic information are developed [4–6, 17]. Finally, a subretinal implant should not disrupt supply of oxygen and nutrients to the retina. Therefore, MEAs have been designed with holes in order to allow exchange of substances [23].

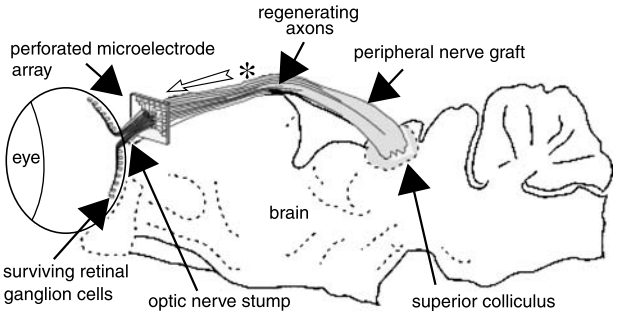

Fig. 2. Principal concept for the regenerating optic nerve electrodes. Axons regenerating from the proximal stump of an incised optic nerve grow through a permissible array of electrodes carried by a substrate. The array may be designed as a kind of mesh or sieve. Latticed arrangements are also possible. The apertures (*holes*) of the substrate determine and fix the position of the regenerating axons relative to the electrodes. The distal portion of the optic nerve is replaced by an autologous peripheral nerve graft that is populated by regenerating optic nerve axons traversing to the midbrain

Implants along the ascending visual pathway

The term ''*cuff electrodes*'' applies to those devices which engulf the entire circumference of the optic nerve. The shape of these tube-like electrodes or of the array of electrodes has to be adapted to the natural arrangement and thickness of the nerve by also considering the vascularisation at the site of implantation, which will be preferably the intraorbital portion of the nerve. While the length is varying from few to more than 10 mm, the width may be adapted to just contact the optic nerve outline. Modern cuff electrodes try to avoid disturbance of the vascularisation and to replace metallic devices by the introduction of flexible materials and adaptable geometries, like a helix-shaped electrode [1] which allows adjustment of the implant to the actual diameter of the nerve fibre bundle. The disadvantage of cuff electrodes was that they do not accurately fulfil the requirements for accurate measurements or stimulation, because they only allow recording of superficial sum potentials with the axons in the centre of the nerve cylinder to contribute less significantly to the measured signal. In accordance, the inner axons were less affected by stimulation than the superficial axons of the bundle. A second disadvantage was proper fixation because the cuff may rotate around the nerve or shift along the nerve, both leading to loss of selectivity.

A different approach is performed by the so-called ''electrodes for regenerative nerves'' (Fig. 2). They are designed as a microarray placed on a sieve-shaped (i.e. perforated) plate which contains holes which can be round or rectangular or even shaped as long narrow slots. The microelectrodes are situated nearby the holes or are part of the hole's wall in order to optimally record or to stimulate. The principal idea can be described very briefly: The nerve is cut firstly, then the electrode array is adapted into the expected path of the regenerating fibres in a fashion that the nerve fibres are allowed to regenerate through the perforations of the device (Figs. 2, 3). The distal stump of the cut nerve is aligned at the opposite side of the electrode array in order to be used by the axons exiting from the perforations as a guidance path

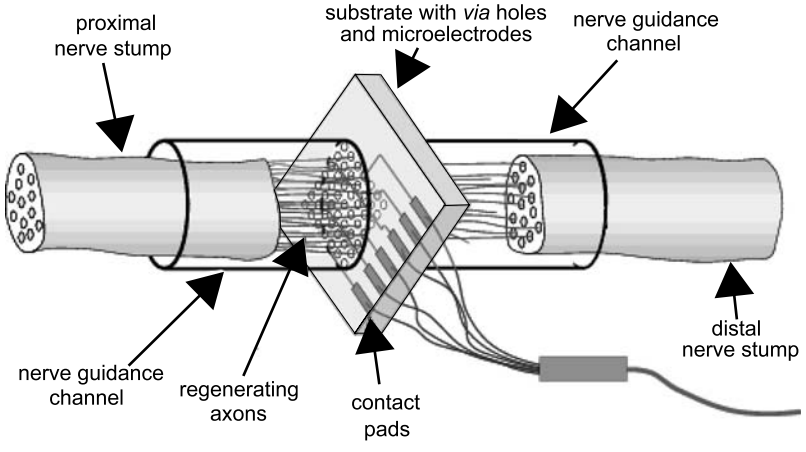

Fig. 3. Scheme of proposed application of an array for regenerative nerves in the optic nerve. The implant is placed into the path of the regenerating optic nerve. Axons grow through the holes into the peripheral graft

for further growth. In most cases, the perineural sheath of the nerve can be replaced in the area of insertion with polymeric tubes which act as mechanical stabilisers. In the case of optic nerve, best choice is to replace the distal portion of the nerve with a peripheral nerve piece bridging the distance to the brain [20] (Fig. 3).

The advantage of this approach is that with this device the electrodes are in intimate contact with the nerve fibres, thus allowing both accurate recording and efficient stimulation. Both procedures are expected to be performed in a relatively reliable manner because with a proper choice of the hole diameter a predictable number of axons would regenerate through individual perforations. Moreover, the microelectrodes remain always in the same position relatively to the nerve fibres because the fibres are mechanically fixed by the holes they grow through (Figs. 2, 3).

The obvious drawback of this method is that the nerve has to be cut in order to regenerate through the implanted device. The success of the whole operation can be evaluated only several weeks later, when the axons have regenerated through the device. The second disadvantage is its applicability only in the optic nerve, because other central nerve pathways do not regenerate spontaneously and are less accessible to replacement strategies. The third disadvantage is that the device limits the regeneration of some neurites, namely of those, whose growth cones hit on the device and fail to elongate within one of the pre-drilled holes. In spite of these limitations, such electrodes display an elegant way of application in the peripheral nerves [11, 14]. The biological and technical aspects concerning the electrodes with perforating paths are complex and do not permit a simplification in use, neither a generalisation in terms of their applicability, mainly because of the traumatic procedure of implantation. Although techniques of microfabrication have been developing rapidly during the last years, some problems arise if a large number of microelectrodes with the accompanying connections has to be placed and fixed on a silicon chip. These problems are enhanced in electrodes for regeneration, because the holes occupy a large part of the total surface area and limit *per se* the number of connections with individual holes. The shortage of surface of a microchip limits both the number and the size of holes for a given electrode.

According to current knowledge, the optic nerve may receive a key role in the attempt to transfer the microtechnology from peripheral nerves into the CNS. One possible approach is sketched in Fig. 2. It is based on the optic nerve regeneration model which was established in the eighties [10, 20] and was studied extensively during the last years [20]. After incision of the optic nerve, the stump of the optic nerve is connected with an autologous peripheral nerve graft which permits the axons of the retinal ganglion cells (RGCs) to regenerate and leads the regenerating axons into their natural area of destination, e.g. the *superior colliculus* or the thalamus. Vision of the animal could be restored partially, as could be shown by the restoration of the pupilloconstriction reflex and by behavioural and electrophysiological experiments [20].

Cortical prostheses

When the ascending visual pathway is interrupted, no information can be conducted from the eye to the visual cortex. The desire to reconstruct visual abilities by direct stimulation of the visual cortex has been therefore proposed [2, 9, 19]. Cortical implants consist of a microarrays placed under the skull directly on the appropriate site of the visual cortex, and the electrodes stimulate cortical neurons to elicit visual sensations. In fact, patients with such implanted electrodes reported to ''see'' phosphenes. There have been numerous investigations about necessary properties of such an electrode array. On the other hand, useful information about the organisation of the visual cortex, i.e. the retinocortical map, could be gained by electrical stimulation experiments. Several experiments were performed to correlate the position of the electrodes with the spatial positioning of the phosphenes in the visual field. In order to enable the patients to recognise more complex structures, e.g. letters, a matrix of phosphenes must be created by simultaneous stimulation by many electrodes. Such a matrix was simulated by a monitor covered with an opaque perforated mask, and from the experiments was concluded that a MEA consisting of 25×25 electrodes on an area of $1 \times 1\,\mathrm{cm}^2$ should produce a phosphene image with a visual acuity of approximately $20/30$, provided that the MEA is implanted near the foveal representation of the visual cortex [4]. Increase of the numbers of implanted microelectrodes to 38 in the right visual cortex of a 42-year-old woman who had been blind over 22 years also resulted in production of phosphenes [19].

Both within the retina and along the visual pathway including the visual cortex, *two-dimensional microelectrode arrays (MEAs)* are required. Improvement of engineering by the use of silicon and polyimide insulation technology and encapsulation methods made it possible to create not only planar two-dimensional MEAs but also penetrating electrode structures. The substrate carrying

the electrodes is either needle- or wedge-shaped to allow penetration of the nervous tissue which makes possible recording from and stimulation of axons not only on the surface but also in a well-defined depth within the tissue, e.g. within the optic nerve. Implanting such a device is naturally associated with a partial damage of some structures within the tissue, i.e. some neurons will be destroyed, and a certain portion of the axons will be disrupted. Current efforts are directed to miniaturise the penetrating parts of the implant and to use more flexible materials, so-called ''flexible nerve plates''. The electrode array was successfully applied for the recording of local visually evoked responses in the visual cortex of cats at sub-sets of 15 electrodes (see ref. 10 for review). One of the disadvantages of MEAs is that, on the insulating substrate (e.g. polyimide), conducting electrode sites and leads must be positioned. A second problem is that cross-talk between the leads has to be avoided. A third drawback is that with increasing number of electrodes the number of leads increases too, which demands an intricate on-chip design and reliable connections and cables to electronic processing units. Ultimately, the whole set-up must operate reliably over a long time period and processing of a high number of channels requires a sophisticated microelectronics with high energy-consumption that limits practical use.

Suitable electrode materials and interactions with biological tissue

It is obvious that requirements towards implants within the extremely sensitive nervous system are very high. Nevertheless, there are certain materials (metals and polymers) which meet these requirements at least to a big extent. *Platinum* is the electrode material of choice, because it is stable and inert. The amount of platinum ions released into the surrounding tissue may be neglected even after long-term of stimulation. During the last years, *iridium* has become of increasing importance because a stable oxide film can be formed on the surface of iridium electrodes. This oxide film has a big charge delivery capacity and is, for this reason, well-suited for stimulating electrodes. *Carbon fibres* or *glassy carbon* are also used as electrode materials, and they are biocompatible and stable, though they have a higher roughness than metals. Platinum and iridium are established materials in microelectronics, and also carbon can be deposited onto microelectronic structures. Polymers are used as carrier material and for encapsulation purposes. Most common materials are *epoxy resins, polytetrafluoroethylene (PTFE, Teflon®), silicone rubbers and polyimide*. These polymers are biocompatible, electrically insulating and stable. The bulk properties of the polymers can be modified to a certain degree, and also surface modification procedures are performed in order to improve biocompatibility.

When a device is implanted, proteins may be deposited onto the surface of the implant and interact with it. A dozen proteins can be found in biological liquids at concentrations higher than 1 mg/ml, and certainly they will form major parts of layers formed on the implant at least in the initial state of adsorption. The details of this process depend on the surface of the implant, the composition of the biological environment and the nature of the adsorbed proteins. Adsorption of proteins such as collagen or fibronectin can favour adhesion of tissue cells. An encapsulation of the implant by autologous material (astrocytes, protein layers, endothelial cells, fibroblasts) is desirable in order to integrate the implant into the organism and ''mask'' it in order to avoid undesired reactions of the immune system, thus promoting incorporation and acceptance of the implant. On the other hand, it was reported that fibronectin and fibrinogen might enhance the adhesion of different bacteria. Besides of protein deposition, inflammatory reactions can be another consequence of an implantation. Inflammations involve vascular, neurological, humoral and cellular responses, and the following acute-phase response is characterised by stress-induced changes in the neuroendocrine and immune systems.

In addition to subcellular and inflammatory responses, when an implant is placed into the retina or brain, astrocytes can be observed to respond quickly to this injury as they react to every damage [3]. They proliferate in the vicinity of the implant and extend their processes towards it forming a gliosis. In order to enhance biocompatibility of implanted materials, reduce macrophage adhesion onto the implants and prevent inflammatory reactions, surface modifications of materials intended for implantation are widely studied. These investigations are performed particularly with polymers because they are the main material used for housing, encapsulation and insulation purposes. Whereas attraction and adhesion of macrophages and other white blood cells to an implant can favour inflammations, inhibition of such an adhesion would be an important factor of biocompatibility.

Conclusions and future perspectives

Replacement of damaged or diseased retina and visual pathway by artificial implants with recording and/or

stimulating electrodes has been a goal of many efforts for several decades. The construction and application of a neuroprosthesis is a common matter of different fields of research, such as neurobiology, medicine, computer science, microelectronics, microtechnology, surface science, electrophysiology and electrochemistry. The high complexity of both structure and function of the nervous system is, however, a real obstacle on the way to apply simple neuroprostheses, whereas really functioning, easy-to-handle and long-term stable neuroprostheses are still not available yet.

In the field of replacement of sensory functions, besides hearing by cochlear implants, visual prostheses are the target of ongoing efforts. Since the visual system is the most complicated sensory one, the natural impediments are particularly large. A satisfactory prosthetic replacement of visual function can be the result of biological research to unravel the mechanisms of visual function and microelectronic improvements which will allow parallel processing of detectable photic stimuli. In particular, the problems of energy supply to the implants and the transmission of signals from technological transplants to biological targets remain a challenge. However, retinal prosthetics may become a reality due to the groundbreaking developments in the construction of miniaturized and multiarrayed implants which are just in the stage of passing to the application in animal and human eyes.

References

1. Agnew WF, McCreery DB (eds) (1990) Neural prostheses. Fundamental studies. Prentice Hall, Englewood Cliffs, New Jersey
2. Boss JH, Shajrawi I, Aunullah J, Mendes D (1995) The relativity of biocompatibility. A critique of the concept of biocompatibility. Isr J Med Sci 31: 203–209
3. Cavanagh JB (1970) The proliferation of astrocytes around a needle wound in the rat brain. J Anat 106: 471–487
4. Cha K, Horch K, Normann RA (1992) Simulation of a phosphene-based visual field: visual acuity in a pixelized vision system. Ann Biomed Eng 20: 439–449
5. Chow AY, Chow VY (1997) Subretinal electrical stimulation of the rabbit retina. Neurosci Lett 225: 13–16
6. Eckmiller R (1997) Learning retina implants with epiretinal contacts. Ophthalmic Res 29: 281–289
7. Ensell G, Banks DJ, Ewins DJ, Balachandran W, Richards PR (1996) Silicon-based microelectrodes for neurophysiology fabricated using a gold metallization/nitride passivation system. J Microelectromech Syst 5: 117–121
8. Gekeler F, Kobuch K, Schwahn HN, Stett A, Shinoda K, Zrenner E (2004) Subretinal electrical stimulation of the rabbit retina with acutely implanted electrode arrays. Graefes Arch Clin Exp Ophthalmol 242: 587–596
9. Hambrecht FT (1995) Visual prostheses based on direct interfaces with the visual system. Baillière's Clin Neurol 4: 147–165
10. Heiduschka P, Thanos S (1998) Implantable bioelectric interfaces surfaces for lost nerve functions. Progr Neurobiol 55: 433–461
11. Heiduschka P, Romann I, Stieglitz T, Thanos S (2000) Perforated microelectrode arrays omplanted in the regenerating adult central nervous system. Exp Neurol 171: 1–10
12. Humayun MS, Propst RH, de Juan E Jr, McCormick K, Hickingbotham D (1994) Bipolar surface electrical stimulation of the vertebrate retina. Arch Ophthalmol 112: 110–116
13. Humayun MS, de Juan E Jr, Dagnelie G, Greenberg RJ, Propst RH, Phillips DH (1996) Visual perception elicited by electrical stimulation of retina in blind humans. Arch Ophthalmol 114: 40–46
14. Kovacs GTA, Storment CW, Rosen JM (1992) Regeneration microelectrode array for peripheral nerve recording and stimulation. IEEE Trans Biomed Eng 39: 893–902
15. Martin GR, Timpl R (1987) Laminin and other basement membrane components. Ann Rev Cell Biol 3: 57–85
16. Nisch W, Böck J, Egert U, Hämmerle H, Mohr A (1994) A thin film microelectrode array for monitoring extracellular neuronal activity in vitro. Biosens Bioelectron 9: 737–741
17. Rizzo JF, Miller S, Denison T, Herndon T, Wyatt JL (1996) Electrically evoked cortical potentials from stimulation of rabbit retina with a microfabricated electrode array. Invest Ophthalmol Vis Sci 37: S707
18. Santos A, Humayun MS, de Juan E Jr, Greenburg RJ, Marsh MJ, Klock IB, Milam AH (1997) Preservation of the inner retina in retinitis pigmentosa. A morphometric analysis. Arch Ophthalmol 115: 511–515
19. Schmidt EM, Bak MJ, Hambrecht FT, Kufta CV, O'Rourke DK, Vallabhanath P (1996) Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. Brain 119: 507–522
20. Thanos S, Naskar R, Heiduschka P (1997) Regenerating ganglion cell axons in the adult rat establish retinofugal topography and restore visual function. Exp Brain Res 114: 483–491
21. Volcker M, Shinoda K, Sachs H, Gmenier H, Schwarz T, Kohler K, Inhoffen W, Bartz-Schmidt KU, Zrenner E, Gekeler F (2004) In vivo assessment of subretinally implanted microphotodiode arrays in cats by optical coherence tomography and fluorescence angiography. Graefe's Arch Clin Exp Ophthalmol 242: 792–799
22. Wyatt Jl, Rizzo JF (1996) Ocular implants for the blind. IEEE Spectrum 33: 47–53
23. Zrenner E, Miliczek K-D, Gabel VP, Graft HG, Guenther E, Haemmerle H, Hoefflinger B, Kohler K, Nisch W, Schubert M, Stett A, Weiss S (1997) The development of subretinal microphotodiodes for replacement of degenerated photoreceptors. Ophthalmic Res 29: 269–280
24. Zrenner E (2002) Will retinal implants restore vision? Science 295: 1022–1025

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Restoring visual perception using microsystem technologies: engineering and manufacturing perspectives

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Summary

Microsystem technologies offer significant advantages in the development of neural prostheses. In the last two decades, it has become feasible to develop intelligent prostheses that are fully implantable into the human body with respect to functionality, complexity, size, weight, and compactness. Design and development enforce collaboration of various disciplines including physicians, engineers, and scientists. The retina implant system can be taken as one sophisticated example of a prosthesis which bypasses neural defects and enables direct electrical stimulation of nerve cells. This micro implantable visual prosthesis assists blind patients to return to the normal course of life. The retina implant is intended for patients suffering from retinitis pigmentosa or macular degeneration.

In this contribution, we focus on the epiretinal prosthesis and discuss topics like system design, data and power transfer, fabrication, packaging and testing. In detail, the system is based upon an implantable micro electro stimulator which is powered and controlled via a wireless inductive link. Microelectronic circuits for data encoding and stimulation are assembled on flexible substrates with an integrated electrode array. The implant system is encapsulated using parylene C and silicone rubber. Results extracted from experiments in vivo demonstrate the retinotopic activation of the visual cortex.

Keywords: Retina implant; visual prosthesis; retinitis pigmentosa; neuromodulation; microsystem.

Introduction

Owing to the favourable trends in the field of semiconductor technology, smart multi-functional microsystems can be designed and developed for various applications. Nowadays, it is viable to manufacture effective biomedical microchip implants due to technological progress in the field of microelectronics, information engineering, computer science, medical engineering, microsystem design, and fabrication during the last decade. High functionality, miniaturisation, compactness, small size, and low weight make a strong case for medical applications like neural prostheses. The emerging complementary metal oxide semiconductor (CMOS) technology plays a major role in these cutting-edge applications. One important advantage of CMOS technology is related with the power dissipation which is negligible compared to other technologies.

All implants aiming at restoring neural functions require a sensor such as a microphone or an imager which records a signal of the environment. A signal processing device makes those signals interpretable for the neurons before carrying them to the place of interest, and an interface stimulates the corresponding nerve cells. The cochlear implant is indicative of realizing a commercial neural implant for the first time. Cochlear implants are hearing prostheses that can help people with certain kinds of hearing impairment or people who are entirely deaf. The implant imitates the tonotopic organization of the basilar membrane of the inner ear. The cochlear implant bypasses the damaged hair cells and stimulates the cochlear nerves directly by means of electrical impulses. This allows the brain to interpret the frequency of sound as it would if the hair cells of the basilar membrane were functioning properly. As a result of the more complex structure of the retina and due to the larger amount of information transfer, scientists have to meet a serious challenge to realize a retinal implant, even though experiments using electrical stimulation of the retina to study its function were performed more than 50 years ago [5].

Electrical stimulation of the retina has been considered as a possible new treatment in cases of blindness associated with retinitis pigmentosa (RP) or other progressive degenerations of the retina. These diseases cause

degeneration of retinal photoreceptor cells, but the process typically spares parts of the ganglion cell layer. This remaining retinal network can be stimulated multifocally and electrically with electrodes, as it is already proven in animal models.

By law, blindness is defined by via acuity and field of vision: People whose visual acuity is less than 2% or whose visual field is less than 5° are considered to be blind. According to the World Health Organization [19] more than 8 million people were legally blind due to retinal degeneration in 1997, mostly caused by macular degeneration (MD) and retinitis pigmentosa (RP). Despite progressive retina degeneration, about 30% of the RP patient's ganglion cells stay intact. During the 60's of the last century, researchers suggested bypassing degenerated photoreceptors by means of technical aid [4]. Initial experiments at that time did not result in any applicable operating model due to restrictions imposed by available technologies. In 1999, Humayun *et al.* implanted epiretinal micro-contact devices which were connected with a cable to a receiver located outside the eye [6]. They have proven in multiple tests that an electrical stimulation of the retina led to recognizable shapes as visual sensory perception in patients suffering from RP or MD. In contrast to Humayun, Chow *et al.* used microphotodiodes driven by light which they implanted in the subretinal space. Here, patients also reported some visual sensation [1]. The Dobelle Institute pursued a different approach. Their system, which remained experimental, uses a tiny camera mounted on glasses worn by the blind person. The camera images are relayed to a portable computer and transmitted via cable to surgically implanted electrodes attached to the brain's visual cortex. Patients reported that they could recognize large objects and walk without help [21].

In 1995, the German government launched a program to develop a completely wireless device for the electrical stimulation of the inner retinal surface. Currently, two different basic approaches are pursued in Germany: the epiretinal system and the subretinal system. The first system is made up of extraocular components for image capturing, signal processing, power and signal transmission and it also consists of an intraocular electrode array and an interface to receive power and signals to generate current pulses for retinal stimulation [2, 15]. The subretinal system uses microphotodiodes which are directly implanted between the defective photoreceptors and the ganglion cells [20]. In spite of all progress, a remotely controlled implantable medical device for human application is still not available for medical use. After considerable progress in the fabrication of microsystems based upon flexible substrates and further development in the integration of functions in very small microchips, the construction of such a device seems now to be possible. In the following paragraphs, the epiretinal approach is described.

System design and components

The epiretinal retina implant system provides visual sensation by applying electro-stimulation to the intact retinal ganglion cell layer. Like the cochlea implant, it consists of an implant and an external part with image sensor and a signal processing module. The architecture of the retina implant system is shown in Fig. 1, the components of the system are visualized in Fig. 2. A CMOS image sensor which provides high dynamic

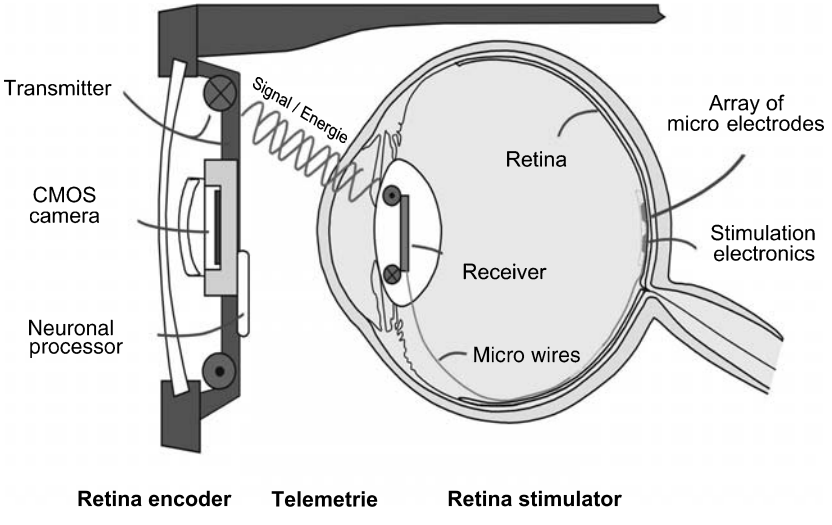

Fig. 1. Architecture of the retina implant system

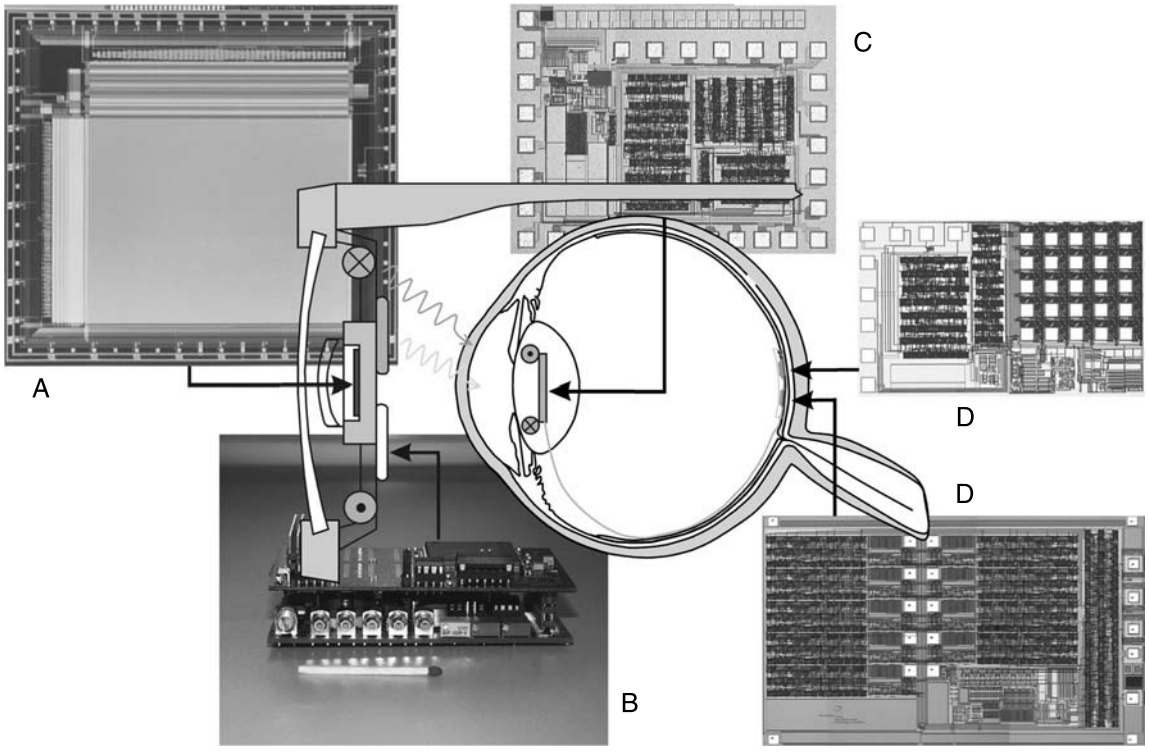

Fig. 2. Microsystem components of the retina implant system: (A) the CMOS imager, (B) the transmitter, (C) the receiver chip, and (D) two stimulation chips to drive either 9 or 25 electrodes

brightness range similar to the human eye generates images of the scenery, before passing them to the retina encoder. The adaptive retina encoder undertakes all tasks of the cell layers between photoreceptors and ganglion cells with respect to signal processing, and computes the receptive field function. Its output signal, which is a spatially and temporarily resolved stimulation pattern, is transmitted wireless to the implant via an inductive link also responsible for power transmission.

The implantable stimulator has been realised in CMOS technology and includes a highly flexible multi-electrode array, a programmable stimulation pulse generator, and the telemetry receiver which is responsible for data recovery and power reception. After data processing the stimulation pattern is converted into electrical pulse trains inside the stimulator unit. These pulses arrive via the microelectrode array at the layer of ganglion cells, which are then spatially resolved stimulated. Then, these pulses are transferred to the visual cortex via the optic nerve.

Data acquisition

In order to guarantee acuity and contrast at different degrees of illumination the human visual system locally adapts its sensitivity to the average brightness over more than 160 dB. In detail, the human eye uses three different mechanisms for adaptation: 1. varying the diameter of the pupil, 2. control of neurons, and 3. change of photochemical sensitization. According to the theory of image formation the observable irradiance at a certain point of the image plane is proportional to the product of the spatial reflectance from the object surface and the irradiance illuminating this point. While the reflectance component contains most of the visually relevant information about the object characteristics, the spatial distribution and the intensity of the illumination component are irrelevant in most cases. The illumination component, however, makes it generally difficult to extract the relevant image information since the variation of reflectance within a scene are low compared to temporal and spatial variations of illumination. Assuming natural conditions the dynamic range of surface reflectance is about less than 40 dB, whereas scene illumination varies up to 9 decades. Hence, dedicated artificial vision systems emulating human eye should be able to compress the dynamic range of an image signal by emphasizing the reflectance component and suppressing the illumination component.

In the retina implant presented here, for image acquisition a low-power image sensor is used (380×300 pixel

array with orthogonal grid structure, see Fig. 2). This imager has a linear pixel characteristic, since it uses photocurrent integration. A rolling shutter supersedes any additional shutter transistor and storage capacitance in each pixel. Well designed column readout amplifiers significantly reduce the total power dissipation in order to make the device suitable for battery-powered applications. The linear CMOS imager has a chip size of 88 mm^2, a pixel pitch of $17 \times 17\ \mu m^2$, and a power dissipation of only 35 mW at 14 MHz pixel clock which yields a 100 fps full frame readout. The imager exhibits high sensitivity and a very low fixed pattern noise (FPN). The imager can be addressed via Firewire interface [12]. Based on this chip, a miniaturized camera has been realized to be used in the implant.

Data encoding

The ganglion cells expect suitable signals comparable to the output of the photoreceptor cells. Therefore, an encoder has to emulate the transduction, the dynamic behaviour of pigment bleaching, the spatial and dynamic behaviour of horizontal cell feedback, and the temporal latency of cone cell responses. The information processing of parts of the 5-layered neuronal retina is simulated via individually adjustable, spatio-temporal filters with receptive field characteristics [3, 7]. The retina encoder has been implemented on a digital signal processor (DSP). The fast functional modulation of a retina encoder (RE) with 256 receptive field filters which means a high dimensional functional dimension was demonstrated using neuronal nets and evolution strategies. They are based on learning processes in dialogue with normally sighted subjects.

Wireless RF energy and data transmission

Telemetry inductive powering is a simple alternative to batteries in implantable devices that require small size, low weight, and extended operation lifetime. The telemetry link used here consists of a transformer-like coupled pair of coils. In addition, this link can also transfer data in order to cut complexity. Due to the rather small size of the receiver coil, the power transmission efficiency in these devices is expected to be rather low. In order to supply enough power to the receiver, an efficient class-E power amplifier is used. Unfortunately, the transmission is susceptible to efficiency degradation because of mismatch between switching frequency of the transmitter and the resonant frequency of the implant. This mismatch can cause excessive power loss in the active device and may disturb data transmission. To circumvent the mismatch problem the link is operated in weak coupling mode.

The transmitter module also seen in Fig. 2, contains a parallel interface, a Field Programmable Gate Array (FPGA) to realize the digital part, a bitstream generator, a class E output amplifier, and an externally connected antenna. After being imported from the DSP via standard interface, the image information is Hamming and Manchester coded in the FPGA. For the clock recovery, the data set is duplicated by the Manchester coding, and for error detection, the set is again duplicated by Hamming coding. Then, the bit stream generator converts these parallel data into a serial signal. The FPGA possesses multiple serial interfaces for inductive data transmission. The class E output amplifier which provides extraordinarily high DC-to-AC efficiency of up to 96% generates the RF signal to feed the externally connected coil. The retina implant employs the wireless RF link both for power transmission and for transmission of data by ASK modulating the carrier frequency. The inductive link operates at a carrier frequency of 13.56 MHz in the open IMS band. The modulation factor is kept low to ensure sufficient power transmission over the required distance. At the moment, the data rate of 200 kbps is sufficient [8].

Power and data recovery

The retina implant is a wireless device, only controlled by the RF signal. Inside the eye, the ASK data must be separated from the RF carrier frequency by demodulating and decoding the signal before being sampled. Simultaneously, the operation power for both the receiver and the stimulator must be recovered from the RF signal. An intra-ocular, monolithic receiving coil inside the eye acquires the electromagnetic signals and passes them onto the microchip which operates as a receiver. This receiver has been realized again in CMOS technology. The wireless connection is implemented as RF coupling using LC resonators. The CMOS receiver carries out all tasks necessary for power and data recovery. After subsequently limiting and rectifying the electrical power is extracted from the carrier. After deriving the internal clock from the Manchester code, the ASK signals are demodulated, decoded and error-corrected using Hamming code. These extracted signals, i.e. data, reset and clock, are forwarded to the stimulator chip via flexible integrated microcable [8].

Electrical stimulation

As a principle task, the stimulation electronics have to allocate enough current beyond a specific threshold in order to trigger phosphenes in the visual cortex. Since the implant is inductively powered, the maximum deliverable current is limited. Thus, the developers make high demands on micro-cables and on the electrodes. In addition to biocompatibility due to close contact to the ganglion cells, they should feature a low impedance and a high charge-delivery capacity. According to the received parameters, the electrical stimulator unit generates bipolar stimulation pulses. Two types of CMOS stimulator chips have been developed so far: a simple chip which can drive an array of 25 electrodes and another, a more advanced one, which can separately drive a set of 9 electrodes plus an indifferent electrode [8]. Both chips are shown in Fig. 2. The bipolar pulses are adjustable with respect to pulse widths from 20 to 1130 µs, pulse polarity, and pulse current from 0 to 100 µA. Programmable pulse rates of up to 500 Hz can be selected.

Two types of microelectrode arrays have been developed. The first electrode type was manufactured by applying backside etching to a separation by implantation of oxygen (SIMOX) silicon wafer with electrodes made of titanium nitride. The second type, a flexible electrode array, has been manufactured by structuring a polyamide film [13]. This polyamide film can also be used as a flexible base structure on which all electronic components of the implantable device can be assembled. The impedance is further improved by using a three-dimensional electrode structure. By varying the shape of the electrodes, the potential distribution can be influenced significantly to optimize charge transfer. Since gold-plated 3D electrodes cannot deliver a sufficient amount of charge, the electrode surface has been coated by a layer of IrO_x [10].

Assembly of the implant

A medical device like the retina implant which is used for epiretinal stimulation of the ganglion cells has to meet severe requirements with respect to weight and size. On the one hand, ophthalmologic prostheses are constricted by the dimension of the eyeball, on the other hand the surgeons cannot place and fix heavy parts inside the eyeball. Besides, the system itself must guarantee durability and biocompatibility, and it has to feature sufficient planar flexibility because the surgeon has to adapt it to the eyeball and bend it into the retina shape by applying a minimum force. As a result, all required components have to be extremely miniaturised. In addition, electronic circuitry must be integrated into a minimum volume.

In order to gain patients' acceptance the extraocular system has to be miniaturized to a magnitude that image acquisition, image processing, retina encoder, transmitter, and power supply can be integrated into a portable unit. In order to fulfill all above mentioned requirements the implant has been designed as a microsystem. All components of the system were mounted onto a flexible tape whose dimensions specify the extension of the implant. The tape contains the wire lines between the components and the electrodes for stimulation. Bending and handling is assured during the implantation due to its planar flexibility. Thus, the implant can be placed and fixed with ease.

The devices have been completely coated with parylene C, which has become the generic name of poly-para-xylenes, using a vapour deposition polymerisation process. Parylene C which has one chlorine atom on the benzene ring offers favourable qualities due to its low permeability to moisture and corrosive gases. This material prevents short circuits and is non-cytotoxic according to the international standard ISO 10993-12 [16]. Finally, the devices were encapsulated into shaping biocompatible silicon (poly-dimethyl-siloxane, PDMS) by means of a vulcanization process. The second layer protects the electronics and serves as a further passivation. The implant acts as an artificial intraocular lens after the implantation.

The first generation of intraocular devices was designed as a hybrid microsystem mounted on a tiny and flexible foil which connects the microchips and the electrode array. This insulating polyimide foil has a thickness of 15 µm and is produced with a technique compliant to the requirements for neural microimplants [14]. The electrode array, the microcable and the electronic circuits were monolithically integrated CMOS technology to reduce the size and to increase the yield. The electrodes were made of platinum; their diameter is about 70 µm and the inter-electrode distance about 750 µm. The assembly with s-shaped connections ensures three-dimensional flexibility and adapts to the shape of the eye after implantation. As well, its size matches the restrictions of the eye. A hybrid coil, a capacitor and a diode were mounted by means of the surface mount technology (SMT). The receiver and the stimulator electronics were assembled on the substrate with the Micro-Flex Interconnection (MFI) technique [9] that reaches

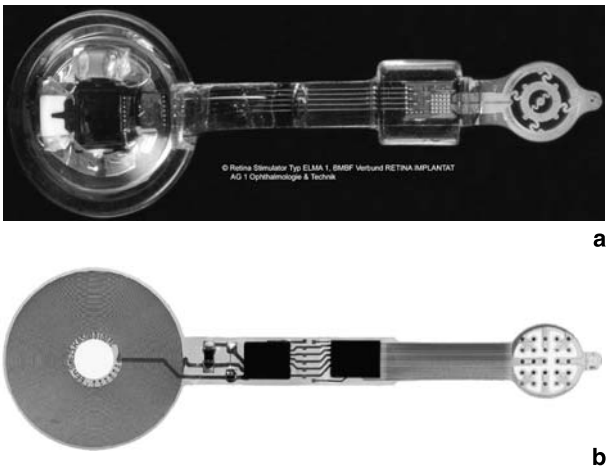

Fig. 3. Two generations of implants: (a) top photo: the encapsulated hybrid assembly and (b) bottom photo: the nearly monolithic implant before encapsulation

the integration density of flip-chip assembling without the use of solder or any other additional material but gold. For secure electrical insulation, the entire implant except the electrodes was coated with parylene C. Finally, the receiver and stimulator parts of the implant were moulded into silicone, see Fig. 3. The receiver was designed in the shape of an artificial intraocular lens with a central 2×2 mm aperture. In this way, already existing implantation techniques can be adopted and the vitreoretinal surgical procedures can be visually monitored.

From the manufacturer's point of view, the complex and fragile hybrid assembly limits the yield of the prototypes. In order to overcome this problem the second generation of implants is integrated almost entirely using a monolithic integration [10], see Fig. 3. Thus, the reliability can be improved tremendously, and the integration density is further increased. The CMOS chips have been fabricated using standard silicon wafers. Using microsystem technology, the flexible structure including biocompatibly insulated wiring, is then deposited straight onto these wafers. The manually wound coil is replaced by a planar coil embedded on the flexible polyimid-carrier which was already described above. Like the coil, the electrodes were fabricated using microelectro-plating of gold. The gold surfaces were than covered with noble metals like platinum or iridium. In short, the monolithic fabrication also reduces the number of time and cost consuming assembly steps. The increased density of integration is important for the next generation of implants, which will have 200 electrodes. While the implants are still on a wafer, the functional test can easily be performed.

Results

After fabrication, preliminary electrical tests were performed which demonstrated the functionality of all microsystem components. Then, these components were assembled into a hybrid implant. Before performing animal experiments several in vitro tests were carried out to check the functionality of the entire system. The structural biocompatibility of the approach was investigated in chronic implantations of non-functional stimulation arrays. The thin and flexible polyimide sheets did not harm the retina. Neither they did not initiate any morphological changes in the retinal layers, nor they did not influence visually evoked potentials in the operated eye in comparison to control measurements [11].

Then, the function of epiretinal implants was tested in two appropriate animal models: minipig and cat. Since the anatomy of the minipig's eye is similar to the one of a human those surgical experiences can be adopted to clinical tests. Although the morphology of the cat's eye differs considerably from that of the human, the cat was chosen for a functional test of the prosthesis because the functional anatomy of the cat's visual system is well understood.

After anaesthetisation, the main part of the surgery begins with a complete excision of the lens and the vitreous body. Before inserting the implant into the eye, the vitreous body is stabilized by a liquid with high surface tension, and the back capsule is opened. After the closure of the wound, the heavy liquid of the posterior eye segment is replaced with a normal electrolyte solution in order to slowly lower the electrode array onto the retina. For further stabilization, the electrode array is tacked with a titanium retinal nail [17]. Histological and

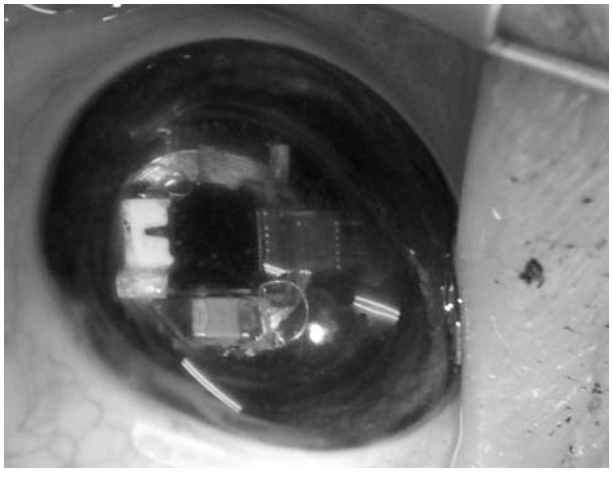

Fig. 4. Photo of an implanted device several weeks after eye surgery

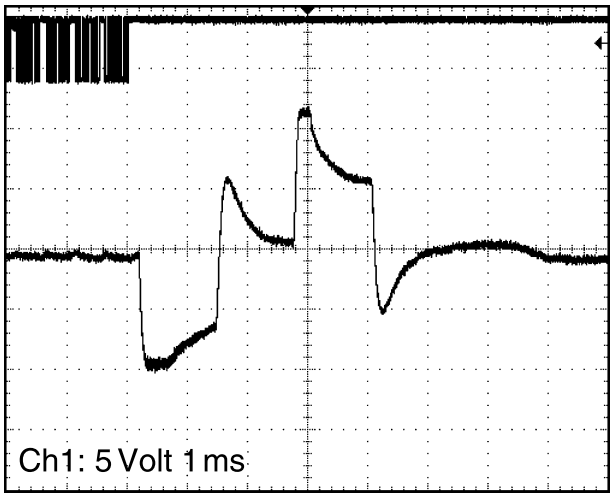

Fig. 5. Stimulus response from a minig's sclera

functional examination showed a good tolerance and an intact retina structure underneath the implant. Figure 4 shows photos of an implant inside a minipig's eye.

The hybrid version of the implant was successfully implanted into three cat eyes [18] and several minipig eyes. For the functional verification of the cortical activation via retina prosthesis, the configuration was slightly changed. The camera and the retina encoder were replaced by a software-based pattern generator. In this way, comparisons between different tests are simplified. Wireless power and data transfer to the implanted microsystem were demonstrated by recording stimulus artefacts from the animal sclera (see Fig. 5). As a standard stimulation paradigm, charge-balanced pulse trains were applied with a pulse width of 250 µs for each phase (negative polarity first) and a stimulation amplitude of about 100 µA for each polarity. In order to test the electrical function of the prosthesis after the implantation, recordings were performed with one silver electrode placed episclerally at the implanted eye and an indifferent electrode at the forehead. By registrating cortical evoked potentials via silver-chloride electrodes which were epidurally fixed above the primary visual cortex of one hemisphere the function of the implant system has been successfully proven at a minipig. In a cat, the spatial distribution of cortical neuronal activity in response to retinal stimulation was monitored using the method of optical imaging. Optical imaging of intrinsic signals can reveal neuronal activity changes at high spatial resolution across large cortical regions [3]. Cortical potentials were recorded after both visual and electrical stimulation with short biphasic charge-balanced currents over a period of several hours.

Discussion

As the most important result, the presented epiretinal prosthesis elicited cortical activation that had been expected on the basis of previous investigations with ''cable bound'' electrodes and hand-held devices [6, 11]. As far as we know, these data result from the first successful experiments in which local cortical activation was generated by a wireless retinal prosthesis. This prosthesis was completely implanted into the eye and remotely controlled via an inductive link. Intrinsic stimulation signals revealed a shift of cortical response that was well correlated with a change in the position of the activated retinal electrodes.

At last, only patients can tell whether electrically elicited sensation can be really called vision.

For a successful clinical test, complex spatio-temporal stimulus patterns are needed in order to adapt the system to the patient's specific perception. Since the devices are implanted for chronic use they have to meet tough demands on biocompatibility, and particularly signal and power transfer should be reliable for a long-term use.

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References

1. Chow AY, Pardue MT, Perlman JI, Ball SL, Chow VY, Hetling JR, Peyman GA, Liang C, Stubbs EB Jr, Peachey NS (2002) Subretinal implantation of semiconductor-based photodiodes: durability of novel implant designs. J Rehabil Res Dev 39: 313–321
2. Eckmiller R (1997) Learning retina implants with epiretinal contacts. Ophthalmic Res 29: 281–289
3. Grinvald A, Shoham D, Shmuel A, Glaser DE, Vanzetta I, Shtoyerman E, Slovin H, Wijnbergen C, Hildesheim R, Sterkin A, Arieli A (1999) In-vivo optical imaging of cortical architecture and dynamics. In: Windhorst U, Johansson H (eds) Modern techniques in neuroscience research. Springer, Berlin Heidelberg, pp 893–969
4. Dawson WW, Radtke ND (1977) The electrical stimulation of the retina by indwelling electrodes. Invest Ophthalmol Vis Sci 16: 249–252
5. Hartline HK, Wagner HG, MacNichol Efjr (1952) The peripheral origin of nervous activity in the visual system. Cold Spr Harb Symp quant Biol 17: 125–141

6. Humayun MS, de Juan E Jr, Weiland JD, Dagnelie G, Katona S, Greenberg R, Suzuki S (1999) Pattern electrical stimulation of the human retina. Vision Res 39: 2569–2576
7. Hünermann R, Eckmiller R (1998) Implementation of tunable receptive field (RF) filters for learning retina implants. In: Niklasson LF, Bodén MB, Ziemke TB (eds) Proc of ICANN'98, Skövde. Springer, Berlin Heidelberg New York, pp 887–892
8. Krisch I, Görtz M, Trieu H-K, Mokwa W, Hosticka B-J (2003) Development and functional test of an epiretinal prosthesis. Applications – trends – visions. Proc of 2nd VDE World Microtechnologies Congress, October 13–15, 2003, International Congress Centre, Munich, Germany. VDE Verlag, Berlin, pp 233–238
9. Meyer JU, Stieglitz T, Scholz O, Haberer W, Beutel H (2001) High density interconnects and flexible hybrid assemblies for active biomedical implants. IEEE Trans Adv Pack 24: 366–374
10. Mokwa W (2004) MEMs Technologies for epiretinal stimulation of the retina. J Micromech Microeng 14: S12–S16
11. Schanze T, Wilms M, Eger M, Hesse L, Eckhorn R (2002) Activation zones in cat visual cortex evoked by electrical retina stimulation. Graefes Arch Clin Exp Ophthalmol 240: 947–954
12. Schwarz M, Hauschild R, Hosticka BJ, Huppertz J, Kneip T, Kolnsberg S, Ewe L, Trieu HK (2000) Single chip CMOS imagers and flexible microelectronic stimulators for a retina implant system. Sens Actuators 83: 40–46
13. Slavcheva E, Ewe L, Schnakenberg U, Mokwa W (2002) Electrochemical characterisation of different biocompatible metallic materials as planar and 3D-electrodes in neural stimulation microarrays. Proc 2nd European Medical & Biological Engineering Conference, Vienna, pp 784–785
14. Stieglitz T, Beutel H, Schuettler M, Meyer JU (2000) Micromachined, polyimide-based devices for flexible neural interfaces. Biomed Microdev 2: 283–294
15. Stieglitz T, Beutel H, Keller R, Blau C, Meyer JU (1997) Development of flexible stimulation devices for a retina implant system. Proceedings of the 19th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, pp 2307–2310
16. Stieglitz T (2004) Considerations on surface and structural biocompatibility as prerequisite for long-term stability of neural prostheses. J Nanosci Nanotech 4: 496–503
17. Walter P, Szurman P, Vobig M, Berk H, Luedtke-Handjery HC, Richter H, Mittermayer C, Heimann K, Sellhaus B (1999) Successful long-term implantation of electrically inactive epiretinal microelectrode arrays in rabbits. Retina 19: 546–552
18. Walter P, Kisvárday ZF, Görtz M, Alteheld N, Rössler G, Stieglitz T, Eysel UT (2005) Cortical activation with a completely implanted wireless retinal prosthesis. Invest Ophthalmol Vis Sci 46: 1780–1785
19. World Health Organisation (2005) Blindness and visual disability: other leading causes worldwide. Retrieved from http://www.who.int/mediacentre/factsheets/fs282/en/index.html
20. Zrenner E, Gekeler F, Gabel VP, Graf HG, Graf M, Guenther E, Haemmerle H, Hoefflinger B, Kobuch K, Kohler K, Nisch W, Sachs H, Schlosshauer B, Schubert M, Schwahn H, Stelle M, Stett A, Troeger B, Weiss S (2001) Subretinal microphotodiode array as replacement for degenerated photoreceptors? Ophthalmologe 98: 357–363
21. Retrieved from http://www.artificialvision.com

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A neuroprosthesis for restoring sight

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Summary

Macular degeneration (MD) and retinitis pigmentosa (RP), two diseases that cause degeneration of retinal photoreceptor cells, are the leading causes of blindness in the United States. Anatomical studies have shown that other retinal neuronal cells (bipolar cells, ganglion cells) are preserved in these diseases and they are capable of eliciting visual percepts when electrically stimulated. We describe the design of a prototype 16-electrode retinal prosthesis, and the physiological and clinical results on six blind patients with RP who had the device implanted. The US Department of Energy *artificial retina program* is described. The goal of the program is construction of a 1000-electrode retinal neuroprosthesis with the potential of enabling blind patients to read large print and ambulate with ease.

Keywords: Macular degeneration; retinitis pigmentosa; blindness; artificial vision; retina; neuroprosthesis; electrical stimulation; neuromodulation.

Introduction

There are one million blind individuals in the United States, the majority suffering vision loss as a result of two diseases of the retina: macular degeneration (MD), and retinitis pigmentosa (RP). MD is a common disease, with increased incidence in the elderly that affects the central (macula) region of the retina [14]. RP is a disorder that affects 1:4000 individuals and includes several related but distinct genetic disorders [18]. RP primarily affects peripheral vision [18]. In both conditions, the cause of visual impairment is degeneration of the light-capturing photoreceptive cells (rods and cones) located in the outer cell layer of the retina. There have been numerous clinical trials of pharmacological, biological and physical therapies to reverse the progressive loss of sight resulting from MD and RP, but to date, none have been successful [15]. Recently a neuroprosthetic device that replaces the lost function of retinal photoreceptive cells and electrically stimulates remaining nerve cells in RP has shown encouraging clinical results. In this chapter, we review the anatomical and physiological rationale for the retinal prosthesis, the design of the 16-microelectrode prototype device, and initial clinical results. In conclusions, we describe the challenges involved in constructing the US Department of Energy (DOE) sponsored high-density multi-electrode array which has the promise of enabling patients with retinal blindness to ambulate with ease in every day life, and to read large print – two important quality of life indicators for the visually impaired.

The visual pathway in sighted individuals and patients with retinal blindness

Light entering the eye is focused by the lens onto the retina, a thin (0.5 mm) tissue that lines the inside of the eye. The retina consists of three discrete neuronal layers separated by regions of synaptic connections (Fig. 1). The outermost layer, photoreceptive cells, consists of approximately, 100 million rods and cones. Photons are absorbed by visual pigment (rhodopsin) in the rods and cones and visual messages are passed by chemical neurotransmitters through the vertical pathway in the retina to the bipolar cells (inner nuclear layer) and then to the ganglion cells. The axons of the ganglion cells make up the optic nerve that transmits signals to visual centers in the brain. Other cell types (amacrine and horizontal cells in the inner nuclear layer), and numerous subtypes of all the cells described above add to the complexity of retinal organization [17]. Images from the outside world are captured on the retina in a correct spatial orientation (Fig. 1), and this ''retinotopic'' transmission of images is maintained through the entire visual pathway.

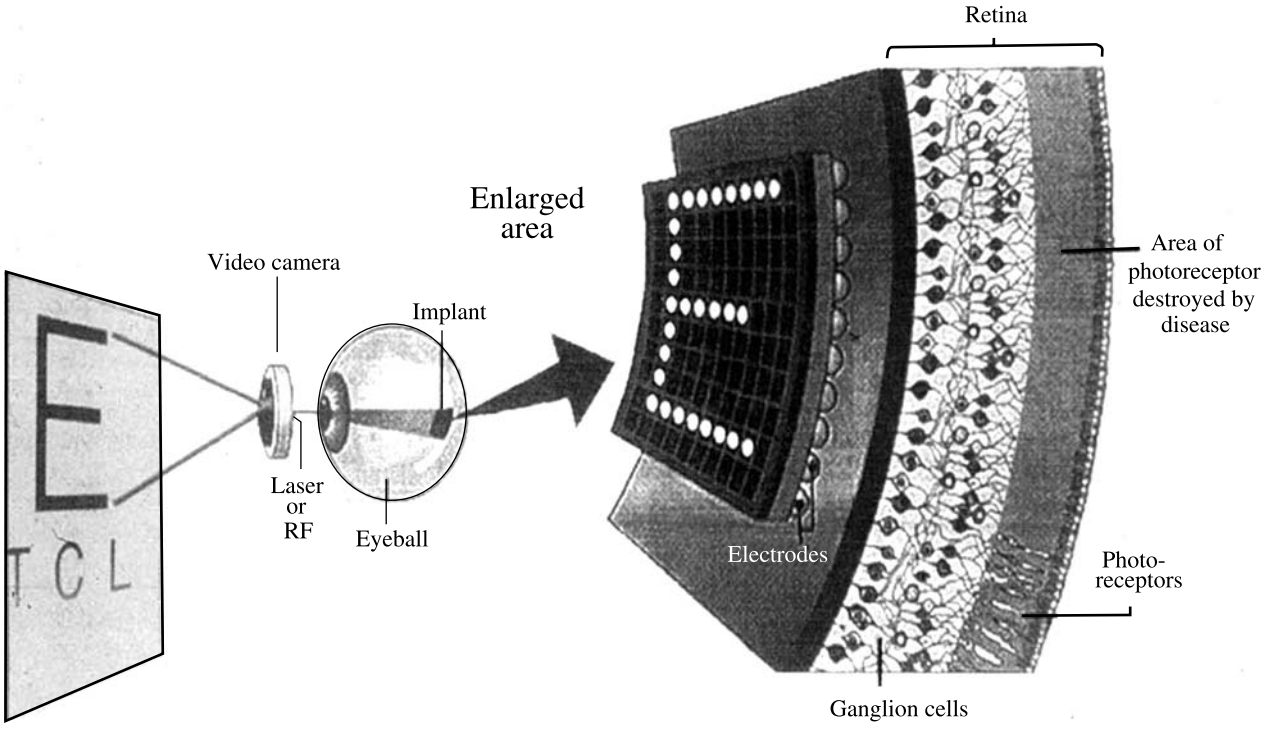

Fig. 1. An epiretinal prosthesis in contact with the retina. The three cell layers of the retina are depicted. The inner nuclear layer (bipolar, horizontal and amacrine cells) is located between the photoreceptor and ganglion cell layers. The figure illustrates the retinotopic display of the letter "E" on the electrode array. Reprinted with permission of the Doheny Institute

There are two aspects of retinal structure which are of particular importance in developing a functional retinal neuroprosthesis:

1) Both anatomical and physiological experiments have revealed that there is considerable image processing that occurs in the neuronal networks of the retina before visual signals are sent to the brain cortex where the final perception of sight occurs. Retinal processing occurs with respect to color, image sharpening, movement and other aspects of definition of a visual image [23]. Retinal processing is illustrated by the anatomical finding that there are more than 100 million photoreceptive cells that capture photons but only 1 million ganglion cell axons that transmit those visual signals to the brain.
2) While complex processing of visual images occurs in the inner nuclear layer and ganglion cells of the retina, the final visual signals are transmitted to the brain along ganglion cell axons in the form of a constantly changing train of action potential spikes. The neural code for this digital signal system is not completely understood [13].

The optic nerve travels posteriorly to the brain where there is a separation of the left and right visual worlds at the optic chiasma. The tracts then synapse at the lateral geniculate ganglion (LGG) in the thalamus. Neurons leaving the LGG send their axons to the visual cortex in the occipital lobe of brain. The visual cortex is separated into modules which generate perceptions of the different components of an image – contours, colors, motion, form, texture, dimensionality, etc. The enormous contribution of higher orders of brain function in vision is illustrated by PET and fMRI scans that demonstrate at least ten discrete anatomical and functional modules in the visual cortex that interpret and integrate visual perceptions [22]. It is relevant that deaf patients with implanted artificial cochlears are able to learn to interpret the artificial sounds generated by stimulating the cochlear nerve [5], and it is anticipated that humans will learn, with time, to "see" the outside world through the artificial visual percepts generated by a retinal neuroprosthesis.

It had been presumed that degeneration of photoreceptive cells in RP patients would result in disuse atrophy of downstream neurons. However, quantitative anatomical studies have shown that patients with extensive photoreceptive degeneration had minimal to 50% loss of inner nuclear layer cells and ganglion cells [19, 21]. Cell loss was greatest in the ganglion cell layer but not nearly as extensive as that seen in the photore-

ceptive layer. In RP, neuronal cells were preserved to the greatest degree in the macula, the central 4×4 mm region of the retina involved in high-acuity vision. Further, in human volunteer experiments, electrodes were inserted in the eye of patients with photoreceptive cell degeneration [10]. Electrical stimulation of the electrode elicited a visual percept, a sensation of streaks or dots of light (phosphenes), as described in more detail below. These findings raise the possibility of restoring some degree of vision in patients with retinal blindness through permanently implanted devices that electrically stimulate remaining intact ganglion and inner cell layer neurons. It should be noted that the most successful neuroprosthesis to date, the artificial cochlea, bypasses distal signal-transducing receptors to stimulate more proximal ganglion cells. Stimulation of as few as 10% of the normal number of ganglion cell can elicit auditory perceptions [8].

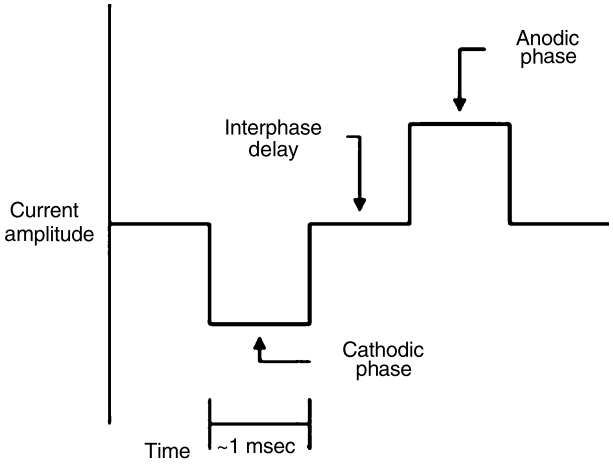

Fig. 2. The biphasic current pulse delivered by electrodes to stimulate the human retina

Electrical stimulation of the visual pathway in patients with retinal degeneration

Studies on the electrical stimulation of the visual system as a means of eliciting visual images have been ongoing for more than 70 years [1, 9]. Scientists have placed stimulating electrodes in the visual cortex [6], optic tracts in the brain [3], optic nerve [20], and retina in an attempt to elicit visual percepts in normal and blind individuals. Operative difficulties and risks to patients have militated against electrode placement inside the cranial cavity as a realistic therapeutic approach to cure blindness. Further, the complex process of image reconstruction in the post-retinal pathway indicates that the retina is the structure of choice for implanting a visual neuroprosthesis. Prototype electrodes arrays have been placed in the orbit behind the eye (trans-scleral approach), directly beneath the retina and in the eye cavity directly attached to the retinal surface (epi-retinal) [4, 7, 11, 25, 26]. The advantages of the epi-retinal approach are the ease and safety of the surgical procedure and the electrodes can be placed in close proximity to the cells being stimulated, decreasing threshold currents and avoiding diffusion of the stimulating current. The fluid in the eye (vitreous) can also act as a heat sink.

A series of clinical experiments were conducted in patients with MD and RP in which electrodes were surgically introduced into the eye under local anesthesia and placed in proximity to the retinal surface [10, 24]. Electrical stimulation resulted in the perception of phosphenes. Patients could discern multiple spots of light in the correct spatial orientation when multiple electrodes were stimulated. When the electrode was passed across the retinal surface, the patient perceived movement of the phosphene. One of the overriding questions in an electrically-based visual neuroprosthesis is whether a patient can interpret multiple spots of light into specific patterns and shapes. Humayun et al. [11] have presented data showing that patients can perceive simple forms in response to patterned electrical stimulation using multiple stimulating electrodes.

Studies of electrical stimulation of the retina in animals and humans have established safe and efficient parameters of the current pulse that can elicit a visual response (Fig. 2) (summarized in Ref. 11). A cathode-first biphasic rectangular current pulse with an interphase delay is preferred since monophasic pulses can cause tissue injury after chronic stimulation. The interphase delay ensures that the depolarization of the neuron is not reversed; the 2nd phase pulse decreases the net charge remaining on the electrode tip. The half-phase amplitude found to elicit visual responses in patients was in the range of 10–1000 mA. Threshold currents vary considerably among patients most likely because of differences in electrode placement (proximity to viable cells) and the physical state of the diseased retina beneath the electrode. It will be advantageous to determine the current threshold for each electrode, even in high-density electrode arrays, when placed in a diseased, non-homogenous retina. This procedure will customize the electrode array for each patient. The reported duration of the current pulse has been in the range of 1 to a few msecs, at a frequency of 1 Hz.

The platinum electrodes used in reported patient studies had a tip diameter in the range of 100–200 μm.

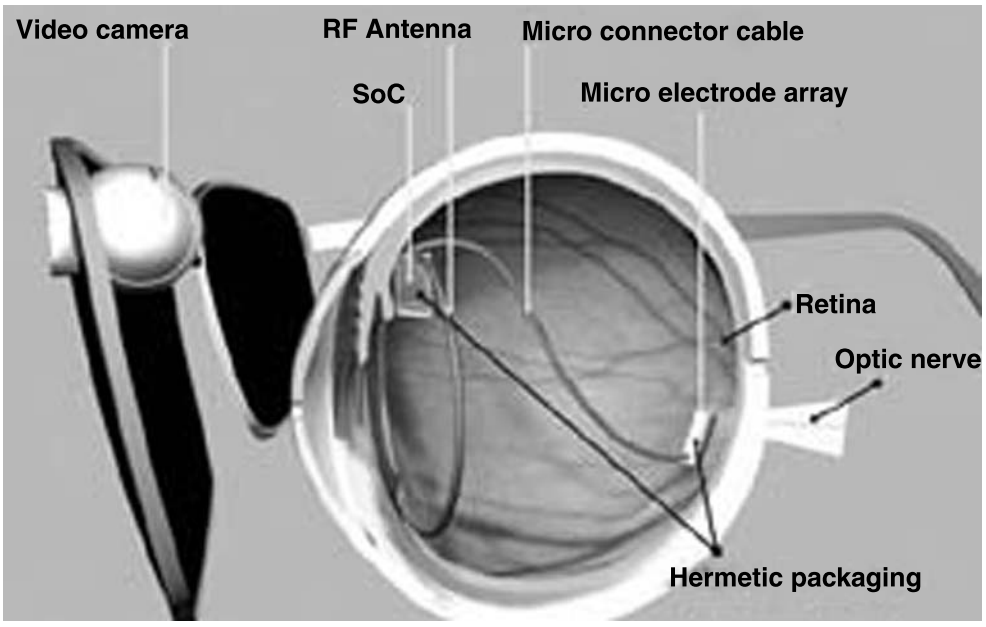

Fig. 3. The general concept of an epiretinal neuroprosthesis. The video camera sends an image to an image processing unit and then to an encoder (not shown) before relaying signals to intraocular electronics stimulate the microelectrodes in defined patterns. Reprinted with permission from the Annual Review of Biomedical Engineering, Volume 7, 2005 by Annual Reviews, www.annualreviews.org

Ganglion cells have a cell body diameter of 10–20 μm, indicating that clusters of cells are undoubtedly being stimulated to elicit a phosphene. The threshold charge density at the tip of the electrode (amplitude × duration × frequency/tip surface area) has been shown to be well below the safety limits for platinum electrodes (100 microcoulombs/cm^2) [2]. The charge density for smaller diameter electrodes envisioned in 500–1000 electrode arrays will have to be determined experimentally so that the higher charge densities do not generate toxic electrochemical products at the electrode/neural tissue interface.

The proto-type 16 electrode visual neuroprosthesis: design and initial clinical results

An FDA-approved 16 electrode epi-retinal neuroprosthesis has been developed by the Doheny Eye Institute of the University of Southern California and Second Sight, LLC of Valencia, CA and has been implanted into six blind RP patients. The goals of the clinical trials were to determine the safety of a long term, active epi-retinal device and as a proof of principle that rudimental vision is possible with a device that contains a small number of stimulating electrodes. The general concept, depicted in Fig. 3, is that visual images captured by a camera are converted to pixels and the image data transmitted to an intra-ocular component that translates the

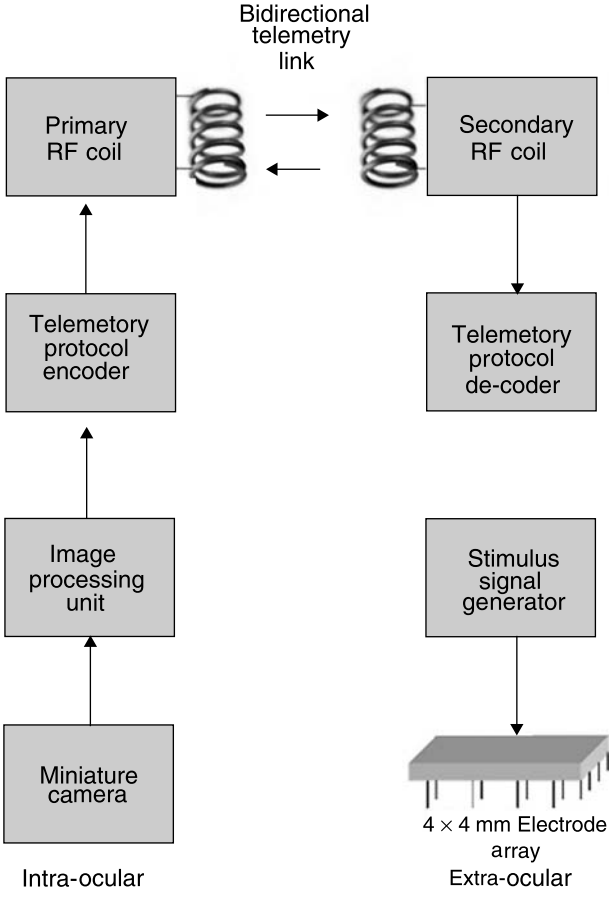

Fig. 4. A simplified block diagram of the extraocular and intraocular components of a prototype retinal prosthesis (derived from Liu et al. [16])

signal into electrical pulses that stimulate the retina through a two-dimensional electrode array [11]. The advantages of separate extra- and intra-ocular components are that the surgeon is not constrained by the small size of the orbit and upgraded electronics can replace the extra-ocular system without the need for surgery. The system is powered by a small replaceable battery worn on the patient's belt.

The extra-ocular system (Fig. 4) consists of a miniaturized camera, embedded into a pair of eyeglasses that captures black and white images and sends them to the video processing unit (VPU). The VPU divides the image into 16 pixels that are processed with respect to light/dark, brightness and grey scale. The telemetry protocol chip processes (encodes and modulates) the image data and the modulated radio frequency carrier is then inductively transmitted to the intraocular unit. A bidirectional telemetry link is essential to send both data and power to the implanted components and to relay data in the opposite direction from the electrode array (e.g. changes in electrode impedance).

The electronics in the implanted system [16] decodes the data signal by reversing the processing used to encode it and the stimulating chip sends electrical current pulses of the correct waveform to specific electrodes for patterned stimulation of the retina. The electrode array is composed of 16 platinum electrodes (200 mu diameter) embedded in silicone rubber. The electrode array is fixed to the retina with a metal alloy opthalmologic tack. With the exception of the inductive link, electrical signals are transmitted through a multi-wired cable.

Clinical and physiological studies of the six patients who have undergone implantation of the retina prosthesis are yielding a wealth of information of safety, tolerability, and efficacy of the device [12]. It should be noted that the patients studied had bare or no light perceptions often for many decades. The most important findings are described below:

1) The implantation procedure is well tolerated with no major adverse surgical outcomes. The implanted devices have caused no problems during the course of the study to date; the first patient studied has a functional device in place for three years.
2) A battery of stringent, standardized tests is repeatedly performed on all patients. Following device implantation, patients were able to distinguish light from dark and can detect visual percepts from each electrode in the correct spatial orientation. Further, patients were capable of finding and counting large objects on a screen. Objects in the physical world (e.g. cup, plate, and knife) were distinguished from one another. Subjects could sense movement of objects across a screen.
3) Current threshold that elicited visual percepts varied within and between patients ranging from $\sim$10 to 1000 mA. However, the threshold and impedance values remained stable over time.

Future challenges for development of dense multi-electrode arrays

The clinical experiments described above demonstrate that a retinal neuroprosthesis is safe over the short term and can provide a rudimentary form of artificial vision. Nevertheless, psychophysical data has shown that it would be necessary to have an artificial visual system with more than 500 pixels (electrodes) to navigate a room, read large print and recognize faces; these are considered standard quality of life indicators for the visually impaired. With this in mind, the US Department of Energy (DOE) embarked on an *Artificial Retina Program* in 2002 with the goal of developing a 1000 electrode epiretinal neuroprosthesis. The program is a collaboration of the Doheny Eye Institute of the University of Southern California, Second Sight, LLC, five DOE National Laboratories (Lawrence Livermore National Laboratory, Los Alamos National Laboratory, Sandia National Laboratory, Argonne National Laboratory, and Oak Ridge National Laboratory) and three additional universities (The University of California at Santa Cruz, North Carolina State University, and California Institute of Technology).

The problems inherent in scaling up a 16 electrode device into one that contains 1000 electrodes are formidable. These include packaging additional microelectronics that fit into the same physical space, developing more advanced wireless telemetry to obviate the large numbers of wires entering the eye, and applying new classes of hermetic seals around the implantable microelectronics, wires and interconnects to avoid current leakage. The implantable device must withstand a constant saline environment at body temperature for decades. Finding suitable materials to support the large number of metal electrodes envisioned for the array is a daunting problem. The material that holds the dense array of metal electrodes as well as the high-density cable containing wires must be flexible and conformable, biologically inert, able to withstand manipulation by the surgeon, and demonstrate long-term integrity. It is unlikely that materials used for low-density arrays (e.g. rubber silicone, polyamide) will be useful. The mechan-

ical and electrical lifetime of these materials must be in excess of ten years. The goal of developing a 1000 electrode retinal prosthesis will be reached in intermediate steps (60, 200 electrode arrays) and technical innovations will be integrated into the final device design. It is anticipated that a high-density 1000 electrode retinal prosthesis will be implanted into a patient by 2009.

References

1. Brindley GS, Lewin WS (1968) The sensations produced by electrical stimulation of the visual cortex. J Physiol (London) 196: 479–493
2. Brummer SB, Turner MJ (1977) Electrochemical considerations for safe electrical stimulation of the nervous system with platinum electrodes. IEEE Trans Biomed Eng 24: 59–63
3. Chapanis NP, Uematsu S, Konigsmark B, Walker AE (1973) Central phosphenes in man: a report of three cases. Neuropsychologia 11: 1–19
4. Chow A, Chow V (1997) Subretinal electrical stimulation of the rabbit retina. Neuroscience Lett 225: 13–16
5. Dawson PW, Blamey PJ, Dettman SJ (1995) A clinical report on speech prediction of cochlear implant users. Ear Hear 16: 551–561
6. Dobelle WH, Mladejovsky MG, Grivin JP (1974) Artificial vision for the blind: electrical stimulation of the cortex offers hope for a functional prosthesis. Science 189: 440–443
7. Eckmiller R (1997) Learning retina implants with epiretinal contacts. Ophthalmic Res 29: 281–289
8. Fayad J, Linthicum FH (1990) Cochlear implants: histologic data. Rev Laryngol Otol Rhinol 111: 439–442
9. Foerster O (1924) Beitrage zur pathophysiologie der sehrbahn und der sehphaere. J Psychol Neurol (Leipzig) 39: 463–485
10. Humayun MS, de Juan E, Dagnelie G, Greenberg RJ, Propst RH, Phillips DH (1996) Visual perception elicited by electrical stimulation of the retina in blind patients. Arch Ophthalmol 114: 40–46
11. Humayun MS, deJuan E, Weiland J, Dagnelie G, Katona S, Greenberg R, Suzuki S (1999) Pattern electrical stimulation of the human retina. Vision Res 39: 2569–2576
12. Humayun MS, Freda R, Fine I, Roy A, Fujii G, Greenberg RJ, Little J, Mech B, Weiland JD, de Juan E Jr (2005) Implanted intraocular retinal prosthesis in six blind patients. Invest Ophthalmol Vis Sci 46: E-abstract 1144
13. Keat J, Reinagel P, ReId RC, Meister M (2001) Predicting every spike: a model of response of visual neurons. Neuron 30: 807–817
14. Klein R, Peto T, Bird A, Vannewkirk MR (2004) The epidemiology of age-related macular degeneration. Am J Ophthalmol 137: 486–495
15. Liu M, Regillo CD (2004) A review of treatments for macular degeneration: a synopsis of currently approved treatments and ongoing clinical trials. Curr Opin Ophthalmol 15: 221–226
16. Liu W, Vichienchom K, Clements M, DeMarco SC, Hughes C, McGucken E, Humayun MS, De Juan E, Weiland JD, Greenberg R (2000) A neuro-stimulus chip with telemetry unit for a retinal prosthetic device. IEEE J Solid State Circuits 35: 1487–1497
17. Masland RH (2004) The fundamental plan of the retina. Nat Rev Neurosci 4: 877–886
18. Rivolta C, Sharon D, DeAngelis MM, Dryja TP (2002) Retinitis pigmentosa and allied diseases: numerous diseases, genes and inheritance patterns. Human Mol Genet 1: 1219–1227
19. Santos A, Humayun MS, de Juan E Jr, Greenburg RJ, Marsh MJ, Klock IB, Milam AH (1997) Preservation of the inner retina in retinitis pigmentosa: a morphometric analysis. Arch Ophthalmol 115: 511–515
20. Shandurina AN, Lyskov EB (1986) Evoked potentials to contact electrical stimuli of the optic nerves. Hum Physiol 12: 9–16
21. Stone JL, Barlow WE, Humayun MS, de Juan E Jr, Milam AH (1992) Morphometric analysis of macular photoreceptors and ganglion cells in retinas with retinitis pigmentosa. Arch Ophthalmol 110: 1634–1639
22. Tootell BH, Dale AM, Sereno MI, Malach R (1996) New images from the human visual cortex. Trends Neurosci 19: 481–488
23. Wassle H (2004) Parallel processing in the mammalian retina. Nat Rev Neurosci 5: 747–757
24. Weiland J, Humayun M, Dagnelie G, de Juan E Jr, Greenberg RJ, Iliff NT (1999) Understanding the origin of visual percepts elicited by electrical stimulation of the human retina. Graefes Arch Clin Exp Ophthalmol 237: 1007–1013
25. Wyatt J, Rizzo JF (1996) Ocular implants for the blind. IEEE Spectrum 112: 47–53
26. Zrenner E, Miliczek KD, Gabel VP, Graf HG, Guenther E, Haemmerle H, Hoefflinger B, Kohler K, Nisch W, Schubert M, Stett A, Weiss S (1997) The development of subretinal microphotodiodes for replacement of degenerated photoreceptors. Ophthmalmic Res 29: 269–280

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Towards the bionic eye – the retina implant: surgical, opthalmological and histopathological perspectives

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Summary

Degenerations of the outer retina such as retinitis pigmentosa (RP) lead to blindness due to photoreceptor loss. There is a secondary loss of inner retinal cells but significant numbers of bipolar and ganglion cells remain intact for many years. Currently, no therapeutic option to restore vision in these blind subjects is available. Short-term pattern electrical stimulation of the retina using implanted electrode arrays in subjects blind from RP showed that ambulatory vision and limited character recognition are possible. To produce artificial vision by electrical retinal stimulation, a wireless intraocular visual prosthesis was developed. Images of the environment, taken by a camera are pre-processed by an external visual encoder. The stimulus patterns are transmitted to the implanted device wirelessly and electrical impulses are released by microcontact electrodes onto the retinal surface. Towards a human application, the biocompatibility of the utilised materials and the feasibility of the surgical implantation procedure were stated. In acute stimulation tests, thresholds were determined and proved to be within a safe range. The local and retinotopic activation of the visual cortex measured by optical imaging of intrinsic signals was demonstrated upon electrical retinal stimulation with a completely wireless and remotely controlled retinal implant. Potential obstacles are reviewed and further steps towards a successful prosthesis development are discussed.

Keywords: Retina implant; artificial vision; neuromodulation; visual prosthesis; active implants; electrical stimulation; bionic eye; implantation technique; epiretinal implant; retinitis pigmentosa.

Introduction

Although there are many examples of electrical devices that can support or mimic the function of defective organs – such as pacemakers for individuals suffering from heart disease or cochlear implants for the hearing impaired – restoring vision, with electrical devices implanted into the eye, is much more difficult [29, 33]. Sight is an extremely complex form of information processing. The precondition of vision is an elaborated interaction between the retina and the visual cortex. The retina may be considered as the first ''neuroprocessor'' in the visual pathway. Roughly 130 million photoreceptor cells (rods and cones) in the outermost layer of the retina transform local luminance, colour patterns, motions and other qualities of the visual perception into electrical signals. The first remarkable data pre-processing of these signals is then performed by a network of retinal neurons: horizontal cells, bipolar cells, amacrine cells, and ganglion cells; due to its complexity, this process is still not completely understood. Visual information from the retina's sensory neuroepithelium are transformed into electrical signals carried by the ganglion neurons, whose axons form the optic nerve. The optic nerve transmits visual information via the lateral geniculate nucleus to the primary visual cortex of the brain.

Despite all progress in surgical and medical therapy there are still incurable diseases in ophthalmology. Progressive retinal degenerations of the outer retina like retinitis pigmentosa (RP) often end in total and unpreventable blindness. RP is the leading cause for inherited blindness [3]. Gene therapy and growth factors must be considered as experimental attempts for a causal therapy. The utilisation of viral vectors implies unpredictable risks [4, 28]. Recent studies on blind human subjects revealed that a large number of ganglion cells remain intact and are capable of transmitting signals to the brain to evoke partial visual perception [13, 15, 25, 35]. This provided hope to compensate for the visual defects by bypassing the damaged photoreceptors with retinal prostheses. In a first stage the aim is to regain a moderate amount of vision such as perception of location and shape of large objects and, subsequently, to achieve reading quality [6].

In the early 1990s, researchers started developing prostheses that could be implanted directly adjacent to the retina. The breakthrough in the development of a retinal prosthesis was only possible due to rapid progress in microsystem technologies with its possibility of high integration of electronic components on limited space. In addition, current advancements in ophthalmic surgical techniques and instruments have enabled us to handle even complex situations [1, 22]. In such applications, it is necessary that the utilised materials remain stable and relatively inert to minimise their impact on remaining retinal tissue. Furthermore, electrical parameters for the stimulation of retinal nerve cells must be determined and electronic circuits to accommodate the large brightness and contrast variances of the environment have to be developed. Before retinal implants can be tested in patients, surgical techniques for implanting, fixing, and removing these electronic prostheses in the eye must be developed. In addition, suitable animal models for testing retinal prostheses must be found, ethical questions addressed, and regulatory matters considered [2, 5, 10, 17, 18, 20, 21, 26, 36, 40]. There is also the question of which patients are best suited to receive retina implants [41, 42]. Up to now, a remotely controlled implantable medical device for human application is still not available. Prototype devices for short term electrical stimulation of the retina have already been implanted in humans suffering from RP-related blindness. Humayun *et al.* [12, 13, 14, 16] and Rizzo *et al.* [23, 24] implanted epiretinal microcontact devices connected with a cable to a pulse generator outside the eye. In both groups, patients reported some visual sensations. In the following sections the principle of the German retina implant, operation techniques and first functional results on acute stimulation trials in animals will be discussed.

General principle of the retina implant

In 1995, a German research team for the development of an epiretinal implant (EPI-RET) launched a program to develop a completely wireless device for the electrical stimulation of the inner retinal surface. The system consists of extraocular components for image capturing, signal processing and energy and signal transmission. The completely implantable intraocular device comprises a receiver for energy and data, a current generator and the electrode array coupled to the ganglion cells for retinal stimulation [6, 8, 11, 30, 38]. The general design of the system is shown in Fig. 1 of the Chapter by Krisch and Hosticka.

The intraocular device, shown in Figs. 2a, b, is designed as a hybrid microsystem mounted on a flexible foil carrying and connecting the microchips and the electrode array. The foil is made of polyimide with a thickness of 15. It's production fulfils the requirements for neural microimplants [27, 31]. The electrode array, the microcable and the electronic circuits are monolithically integrated to reduce size and to increase functional reliability. The electrodes are made of platinum with a diameter of 70 μm and an inter-electrode distance

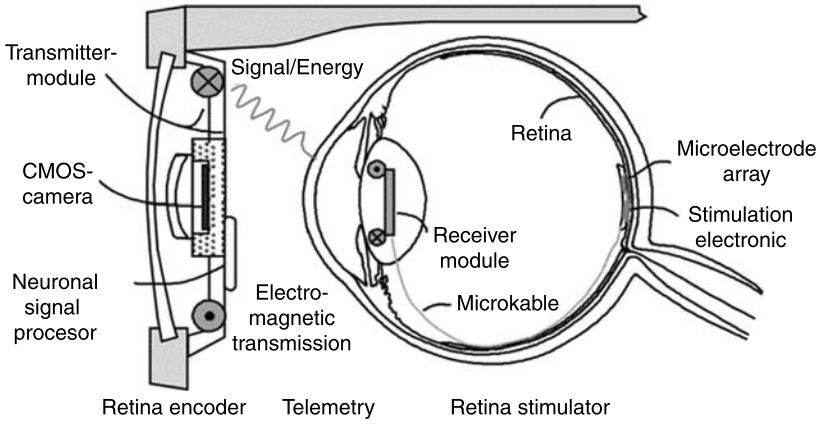

Fig. 1. General concept of the epiretinal retina implant approach. The CMOS-camera unit, integrated into a spectacles frame, captures scenes of the environment which are then analysed by a so called retina encoder (*RE*), representing a tiny "pocket processor" to calculate the stimulation sequences [6]. The data are transferred to a transmitter module. Energy to drive the implant is transmitted wirelessly by magnetic coupling together with a radio frequency signal, encoding the stimulation pulse parameters for each of 25 retinal microelectrodes into the receiver module of intraocular implant. After separating energy and data signals from the RF-field, the decoded information is transferred via a microcable to the stimulating unit. The retina stimulator itself represents a microelectrode array on a flexible polyimide foil adherent to the retinal surface applying the electrical pulses

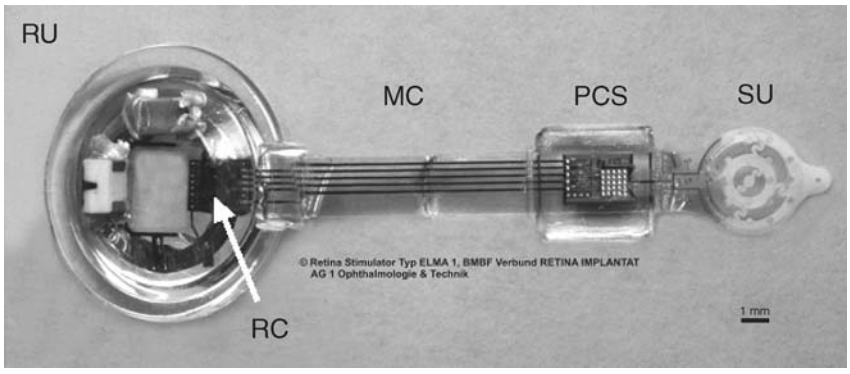

Fig. 2a. Photograph of the EPI-RET intraocular device. At *left* is the artificial lens (made of Polydimethylsiloxane; PDMS) with the receiver unit (*RU*) and the receiver microchip (*RC*) for data and energy transfer. The *right* part shows the stimulator unit (*SU*) with an array of 25 microelectrodes. SU and RU are connected via a flexible microcable (*MC*). The programmable current sources (*PCS*) can drive up to 25 electrodes simultaneously and the bipolar current pulses are adjustable to pulses from 0 to 1130 µs with currents from 0 to 100 µA at a pulse rate up to 500 Hz

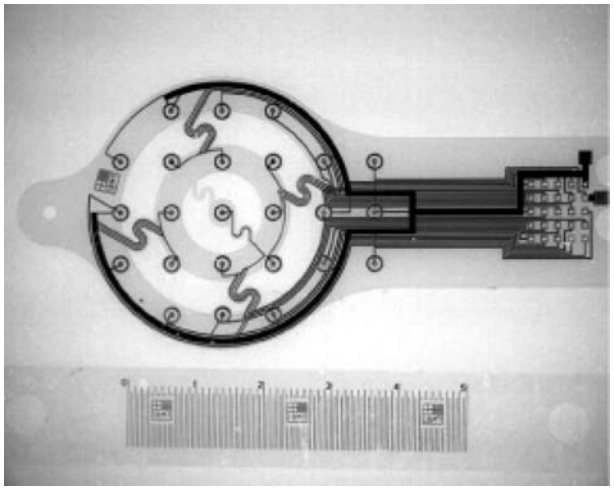

Fig. 2b. Magnified photograph of the stimulator unit (*SU*) with the electrode array before assembly of the stimulator chip (pad array on the *right*). The SU is composed of a thin and flexible polyimide foil as substrate, microwires and a parylene C coating, except on the stimulation electrodes. For electrical stimulation, different inner electrode dots can be used as cathode and anode, or inner dot and outer ring can be used as electrode pair, respectively. Electrode diameter (inner dot): 70 µm, electrode distance: 750 µm

of 750 µm. The substrate containing the individual electrodes comprises three rings with s-shaped connections in order to ensure a good three-dimensional flexibility and to adapt to the curvature of the eye after implantation (Fig. 2b). A combination of hybrid and monolithic integration technology was chosen to implement a complex system that matches the restricted size of the eye [32]. A wire coil, a capacitor and a diode were connected by means of the surface mount technology (SMT). The receiver and the stimulator electronics were fabricated as ''application specific integrated circuits'' (ASICs) using silicon technology. They were assembled on the substrate with the MicroFlex Interconnection (MFI) technique [19] that reaches the integration density of flip-chip assembling without the use of solder or any other additional material but gold. For final electrical insulation, the entire implant except the electrodes was coated with poly-para-xylylene parylene C using a vapour deposition polymerisation process. This material prevents short circuits and is non-cytotoxic according to the international standard ISO 10993-12 [34]. Finally, the receiver and stimulator part of the implant were moulded into polydimethylsiloxane (PDMS). The receiver was designed in the shape of an artificial intraocular lens with a central 2×2 mm aperture (Fig. 2a). Hereby the vitreoretinal surgical procedure can be visually monitored.

Surgical implantation procedure

The surgical procedure consisted of modified standard techniques of human ophthalmic surgery. It was demonstrated that the implantation of such complex structures is technically demanding but feasible [17, 39]. Experimental implantations were successfully conducted in cats, rabbits and pigs by our group. The surgical method comprised a lensectomy and a vitrectomy. Therefore the conjunctiva was opened along the temporal limbus. A corneal incision was made and a viscoelastic fluid was injected into the anterior chamber to maintain it's depth and to protect the corneal endothelium. After a capsulorhexis of the anterior leaf of the lens' capsular bag the clear crystalline lens was removed in standard phacoemulsification procedure. An infusion cannula was inserted into the anterior chamber and the posterior leaf of the capsula was opened. The central vitreous was removed by a transplanar port-hole vitrectomy

(via corneal approach in the cat due to increased risk of scleral bleeding) and the globe was filled with Perfluordecalin (PFD) as vitreous substitute. Next, the corneal incision was enlarged, the anterior chamber filled again with viscoelastics and the prosthesis was carefully inserted into the anterior chamber. The corneal incision was sutured. With a small hook the microcable and the retina stimulator were pushed through the opening of the posterior capsula and placed onto the PFD surface. Thereafter, the receiver unit was carefully inserted into the capsular bag of the removed lens or into the sulcus ciliaris. The central aperture of the receiver unit allowed visual inspection of the retina so that manipulations within the posterior segment of the globe were possible with the receiver already in place (Fig. 2a). Then, the PFD was slowly removed and exchanged to balanced salt solution. Simultaneously the stimulator was placed onto the retinal surface in the region of the Area Centralis (AC). Finally, the stimulator was affixed with a titanium retinal tack at the appropriate location.

Biocompatibility of retina implants

To ensure the long term safety of the utilised materials, biocompatibility tests were conducted. Therefore retinal stimulators and microcontact foils were implanted by the above mentioned technique in rabbits (Fig. 3a, b). Clinical and electrophysiological data throughout 6 months of follow-up did not indicate any adverse effect of the surgery, the implant or the tack itself. Fluorescein angiography showed that the entire retina including the implantation area remained well perfused (Fig. 3c). No change in retinal architecture underneath the implant was found by light microscopy (Fig. 3d, e). In all cases the implant was stable at its original fixation area.

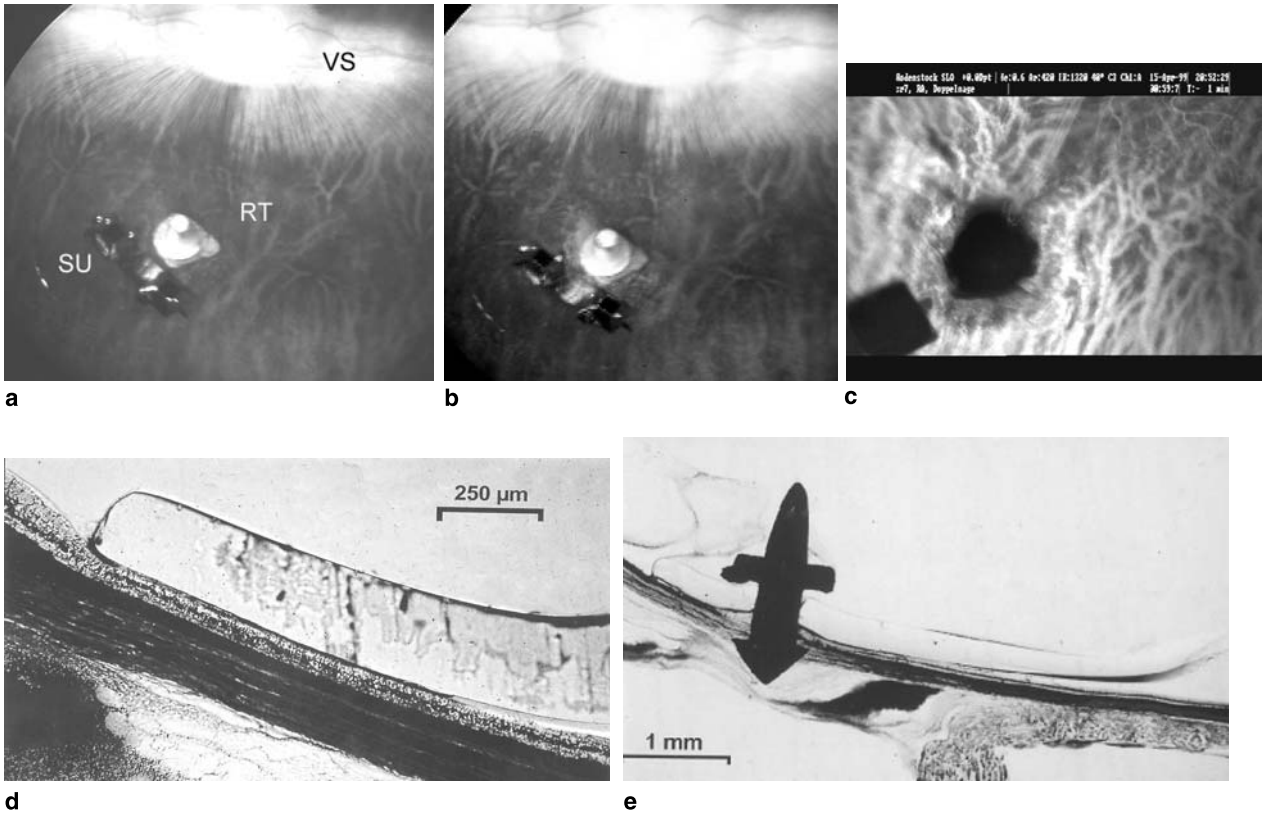

Fig. 3. Biocompatibility tests on the pin fixation of inactive retina stimulator micro contact foils. In rabbits vitrectomy (removal of the vitreous) was performed. Retinal tacks (*RT*) were inserted transretinal into the sclera to immobilise the retina stimulator (*RS*) close to the location of the visual streak (*VS*) (a). Follow up of six months after surgery showed no significant adverse affects to the retina (b). The RT and the RS remained firmly affixed to the retina throughout the follow-up period. Hypopigmentation of the retinal pigment epithelium was observed only around the site of retinal tack insertion. No fibrous encapsulation of the implant, intraocular inflammation or uncontrolled bleeding was visible. Fluorescein angiography showed that the entire retina including the area under the electrode array remained well perfused (c). Similarly, histologic evaluation revealed near total preservation of the retina underlying the electrode array (d, HE staining). The retinal tack proved to be biocompatible, producing only insignificant damage to the adjacent retina (e, HE staining)

Acute stimulation experiment with telemetrically driven retina implants

To evaluate the functional efficacy of the implant on spatial neuronal activation of the visual cortex upon telemetric stimulation, the technique of optical imaging of intrinsic signals was used. This technique reveals neuronal activity changes, both subthreshold and spike-related two-dimensionally and at high spatial resolution across large cortical regions [9]. Hereby, the shift in light absorption maxima is registered between oxygenated hemoglobin and deoxyhemoglobin as a parameter for glucose metabolism representing the grade of cortical activation.

After intraocular implantation of the retina implant device into the cat's eye, basic stimulation tests with recording of episcleral stimulus artefacts showed that the implant remained functional throughout surgery. A craniotomy was made over the central representation of the primary visual cortex in the hemisphere ipsilateral to the retinal implant. Cortical activity images were collected with a CCD camera and processed by special software. The prosthesis was wirelessly powered by magnetic coupling and maintained with stimulation data by an external Radiofrequency (RF) field. Two different stimulation protocols were used. For control, monocular (non-operated eye) visual stimuli were used and resulted in expected cortical activity patterns. In the test protocol, cortical activity was recorded before, during and after activation of the retina implant without visual stimulation (both eyes occluded). We found that telemetric stimulation of a single electrode pair gave rise to an increased activation of the visual cortex extending several millimetres parallel to the cortical surface (Fig. 4). Activation of a neighbouring electrode pair caused a predictable positional shift of the activated cortical zone [37]. This phenomenon is illustrated in Fig. 4 showing a case where nine electrodes of the implant were tested.

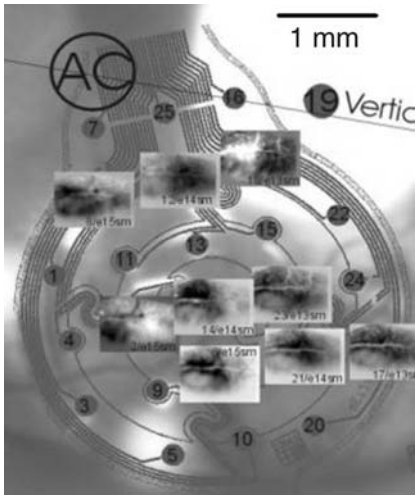

Fig. 4. Optical imaging of the visual cortex after electrical stimulation of the inner retina with a completely implanted retinal prosthesis in the cat. The figure shows a scheme of the electrodes overlying a fundus image. The electrode array was positioned in the lower nasal hemiretina of the left eye overlapping partially with the area centralis (*AC*). The electrodes are numbered 1–25. The nine small images outline the visual cortex with the region exposed for optical recording. Each photograph represents activity images during telemetric activation of the corresponding electrode pair. Dark zones represent strongly active regions and light zones represent less active regions. Each stimulation of a single electrode resulted in a predictable shift in the maximum of cortical activity

Discussion

Due to advances in the fabrication of flexible, highly integrated microsystems, the development of a visual prosthesis became a realistic option in the future treatment of currently untreatable conditions leading to blindness. We were able to demonstrate that a complex device for electrical stimulation of the inner retinal surface can be fabricated using hybrid and monolithic integration technologies even for the restricted space within the eye. This requires a highly dynamic collaboration of different specialists in engineering, micro technology, electronic engineering, neurophysiology and ophthalmology. As a first step toward the goal of a completely wireless human retina implant, the biocompatibility and the feasibility of surgically implanting an inactive electrode array in the vertebrate eye by modifying established ophthalmic surgical procedures were tested. The platinum and silicone arrays as well as the titanium tacks were biocompatible and the underlying retina showed insignificant damage and remaining perfusion. As a next step we could demonstrate that well defined cortical regions can be activated by epiretinal electrical stimulation from electrodes of a wireless and battery-less retinal prosthesis in an animal model. These tests not only comprised qualitative responses to electrical stimulation, but achieved cortical activation in the expected and retinotopically correct cortical area. A latero-medial shift of the peak of cortical activation was in line with the spatial separation of the retinal electrodes and the cortical magnification factor [37].

Future experiments are planned with more complex stimulus patterns. Chronic implantations to test long-term biocompatibility of materials, signal and energy transfer, and the stability of long-term electrical stimulation in terms of stimulation thresholds and retinotopy

will be conducted. Further steps in the development of implants will comprise a higher integration of electrical components, an increased number of electrodes up to patterns resembling ganglion cell density and the fabrication of 3D structured stimulation electrodes to optimise charge transfer to the tissue. A bi-directional data stream is desirable, allowing to read out functional parameters of the implant itself, like e.g. electric impedance of the electrodes or other information on the internal state of the implant. These data may modify its action and save energy by adapting stimulus currents for each single electrode. From the surgical aspect alternative fixation techniques should be discussed. In conclusion, there has been substantial progress toward an electronic retinal prosthesis. The proof of principle has been demonstrated, but further milestones in the development toward a human application are necessary.

Acknowledgements

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References

1. Alteheld N, Roessler G, Vobig M, Walter P (2004) The retina implant – new approach to a visual prosthesis. Biomed Tech (Berl) 49: 99–103
2. Baig-Silva MS, Hathcock CD, Hetling JR (2005) A preparation for studying electrical stimulation of the retina in vivo in rat. J Neural Eng 2: S29–S38
3. Bunker CH, Berson EL, Bromley WC, Hayes RP, Roderick TH (1984) Prevalence of retinitis pigmentosa in maine. Am J Ophthalmol 97: 357–365
4. Chowers I, Banin E (2003) Experimental therapeutic modalities for Retinitis pigmentosa. Harefuah 142: 277–280
5. Eckhorn R, Stett A, Schanze T, Gekeler F, Schwahn H, Zrenner E, Wilms M, Eger M, Hesse L (2001) Physiological functional evaluation of retinal implants in animal models. Ophthalmologe 98: 369–375
6. Eckmiller R (1997) Learning retina implants with epiretinal contacts. Ophthalmic Res 29: 281–289
7. Eckmiller R, Neumann D, Baruth O (2005) Tunable retina encoders for retina implants: why and how. J Neural Eng 2: 91–104
8. Feucht M, Laube T, Bornfeld N, Walter P, Velikay-Parel M, Hornig R, Richard G (2005) Development of an epiretinal prosthesis for stimulation of the human retina. Ophthalmologe 102: 688–691
9. Grinvald A, Shoham D, Shmuel A, Glaser DE, Vanzetta I, Shtoyerman E, Slovin H, Wijnbergen C, Hildesheim R, Sterkin A, Arieli A (1999) In-vivo optical imaging of cortical architecture and dynamics. In: Windhorst U, Johansson H (eds) Modern techniques in neuroscience research. Springer, Berlin, Heidelberg, pp 893–969
10. Gusseck H (2005) Retinal implants Patients' expectations. Ophthalmologe 102: 950–956
11. Hijazi N, Krisch I, Hosticka BJ (2002) Wireless power and data transmission system for a micro implantable intraocular vision aid. Biomed Tech (Berl) 47 Suppl 1: 174–175
12. Humayun MS, de Juan E (1998) Artificial vision. Eye 12: 605–607
13. Humayun MS, de Juan E Jr, Dagnelie G, Greenberg RJ, Propst RH, Philips DH (1996) Visual perception elicited by electrical stimulation of retina in blind humans. Arch Ophthalmol 114: 40–46
14. Humayun MS, de Juan E Jr, Weiland JD, Dagnelie G, Katona S, Greenberg R, Suzuki S (1999) Pattern electrical stimulation of the human retina. Vision Res 39: 2569–2576
15. Humayun MS, Prince M, de Juan E Jr (1999) Morphometric analysis of the extramacular retina from postmortem eyes with retinitis pigmentosa. Invest Ophthalmol Vis Sci 40: 143–148
16. Humayun MS, Weiland JD, Fujii GY, Greenberg R, Williamson R, Little J, Mech B, Cimmarusti V, Van Boemel G, Dagnelie G, de Juan E (2003) Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. Vision Res 43: 2573–2581
17. Kerdraon YA, Downie JA, Suaning GJ, Capon MR, Coroneo MT, Lovell NH (2002) Development and surgical implantation of a vision prosthesis model into the ovine eye. Clin Experiment Ophthalmol 30: 36–40
18. Laube T, Schanze T, Brockmann C, Bolle I, Stieglitz T, Bornfeld N (2003) Chronically implanted epidural electrodes in Gottinger minipigs allow function tests of epiretinal implants. Graefes Arch Clin Exp Ophthalmol 241: 1013–1019
19. Meyer JU, Stieglitz T, Scholz O, Haberer W, Beutel H (2001) High density interconnects and flexible hybrid assemblies for active biomedical implants. IEEE Trans Advanced Packaging 24: 366–374
20. Nadig MN (1999) Development of a silicon retinal implant: cortical evoked potentials following focal stimulation of the rabbit retina with light and electricity. Clin Neurophysiol 110: 1545–1553
21. Rizzo JF 3rd, Goldbaum S, Shahin M, Denison TJ, Wyatt J (2004) In vivo electrical stimulation of rabbit retina with a microfabricated array: strategies to maximize responses for prospective assessment of stimulus efficacy and biocompatibility. Restor Neurol Neurosci. 22(6): 429–443
22. Rizzo JF 3rd, Wyatt J, Humayun M, de Juan E, Liu W, Chow A, Eckmiller R, Zrenner E, Yagi T, Abrams G (2001) Retinal prosthesis: an encouraging first decade with major challenges ahead. Ophthalmology 108: 13–14
23. Rizzo JF, Wyatt J, Loewenstein J, Kelly S, Shite D (2003) Methods and perceptual thresholds for short-term electrical stimulation of human retina with microelectrode arrays. Invest Ophthalmol Vis Sci 44: 5355–5361
24. Rizzo JF, Wyatt J, Loewenstein J, Kelly S, Shite D (2003) Perceptual efficacy of electrical stimulation of human retina with a microelectrode array during short-term surgical trials. Invest Ophthalmol Vis Sci 44: 5362–5369
25. Santos A, Humayun MS, de Juan E Jr (1997) Preservation of the inner retina in retinitis pigmantosa: a morphometric analysis. Arch Ophthalmol 115: 511–515
26. Schanze T, Greve N, Hesse L (2003) Towards the cortical representation of form and motion stimuli generated by aretina implant. Graefes Arch Clin Exp Ophthalmol 241: 685–693
27. Schneider A, Stieglitz T (2004) Implantable flexible electrodes for functional electrical stimulation. Med Device Technol 15: 16–18
28. Sharma RK, Ehinger B (1999) Management of hereditary retinal degenerations: present status and future directions. Surv Ophthalmol 43: 427–444
29. Stieglitz T (2001) Implantable microsystems for monitoring and neural rehabilitation, part I. Med Device Technol 12: 16–18, 20–21
30. Stieglitz T, Beutel H, Keller R, Blau C, Meyer JU (1997) Development of flexible stimulation devices for a retina implant system. Proceedings of the 19th Annual International Conference

of the IEEE Engineering in Medicine and Biology Society, pp 2307–2310
31. Stieglitz T, Beutel H, Schuettler M, Meyer JU (2000) Micromachined, polyimide-based devices for flexible neural interfaces. Biomed Microdev 2: 283–294
32. Stieglitz T, Keller R, Beutel H, Meyer JU (2000) Microsystem integration techniques for intraocular vision prostheses using flexible polyimide-foils. Proceedings of the MICRO.tec September 25–27, 2000, Hannover/Germany, pp 467–472
33. Stieglitz T, Schuettler M, Koch KP (2004) Neural prostheses in clinical applications – trends from precision mechanics towards biomedical microsystems in neurological rehabilitation. Biomed Tech (Berl) 49: 72–77
34. Stieglitz T (2004) Considerations on surface and structural biocompatibility as prerequisite for long-term stability of neural prostheses. J Nanosci Nanotechnol 4: 496–503
35. Stone JL, Barlow WE, Humayun MS, de Juan E Jr, Milam AH (1992) Morphometric analysis of macular photoreceptors and ganglion cells in retinas with retinitis pigmentosa. Arch Ophthalmol 110: 1634–1639
36. Walter P, Heimann K (2000) Evoked cortical potentials after electrical stimulation of the inner retina in rabbits. Graefes Arch Clin Exp Ophthalmol 238: 315–318
37. Walter P, Kisvarday ZF, Gortz M, Alteheld N, Rossler G, Stieglitz T, Eysel UT (2005) Cortical activation via an implanted wireless retinal prosthesis. Invest Ophthalmol Vis Sci 46: 1780–1785
38. Walter P, Mokwa W (2005) Epiretinal visual prostheses. Ophthalmologe 102: 933–940
39. Walter P, Szurman P, Vobig M, Berk H, Lüdtke-Handjery HC, Richter H, Mittermayer C, Heimann K, Sellhaus B (1999) Successful long-term implantation of electrically inactive epiretinal microelectrode arrays in rabbits. Retina 19: 546–552
40. Wilms M, Eger M, Schanze T, Eckhorn R (2003) Visual resolution with epi-retinal electrical stimulation estimated from activation profiles in cat visual cortex. Vis Neurosci 20: 543–555
41. Yanai D, Lakhanpal RR, Weiland JD, Mahadevappa M, Van Boemel G, Fujii GY, Greenberg R, Caffey S, de Juan E Jr, Humayun MS (2003) The value of preoperative tests in the selection of blind patients for a permanent microelectronic implant. Trans Am Ophthalmol Soc 101: 223–228; discussion 228–230
42. Zrenner E (2002) Will retinal implants restore vision? Science 295: 1022–1025

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Motor cortex stimulation: role of computer modeling

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Summary

Motor cortex stimulation (MCS) is a promising clinical technique used to treat chronic, otherwise intractable pain. However, the mechanisms by which the neural elements that are stimulated during MCS induce pain relief are not understood. Neither is it known which of the main neural elements, i.e. cell bodies, dendrites or fibers are immediately excited by the electrical pulses in MCS. Moreover, it is not known what are the effects of MCS on fibers which are parallel or perpendicular to the cortical layers, below or away from the electrode. The therapy and its efficacy are less likely to be improved until it is better understood *how* it may work.

In this chapter, we present our efforts to resolve this issue. Our computer model of MCS is introduced and some of its predictions are discussed. In particular, the influence of stimulus polarity and electrode position on the electrical field and excitation thresholds of different neural elements is addressed. Such predictions, supported with clinical evidence, should help to elucidate the immediate effects of an electrical stimulus applied over the motor cortex and may ultimately lead to optimizations of the therapy.

Keywords: Neuromodulation; motor cortex stimulation; chronic pain; anode; cathode; neurostimulation; computer modeling.

Introduction

Electrical stimulation of the motor cortex was proposed in 1993 by Tsubokawa and his colleagues [23] as a treatment modality for chronic pain syndromes that were irresponsive to medications and for which other neuromodulative techniques were unsuitable or ineffective. Stimulation of the motor cortex gave better analgesic results than sensory cortex stimulation in Tsubokawa's series of patients. Since Tsubokawa's proposal, several centers have applied motor cortex stimulation (MCS) for chronic pain treatment. A total of about 350 patients have been reported world-wide until now [14]. Central and trigeminal chronic pain syndromes have been identified as main indications, but other pain syndromes such as phantom limb pain, brachial plexus injury, pain related to paraplegia and quadriplegia etc. have also shown responsiveness to MCS [3, 16]. Apart from chronic pain treatment, MCS has been used for the treatment of movement disorders [18]. In addition, an improvement in rehabilitation outcome has been reported when MCS was used concurrently with physical therapy in stroke patients [4].

Because the electrode is implanted epidurally (in the majority of cases), the brain is not exposed, resulting in little invasiveness of the surgical procedure and few complications [3, 16]. However, since the dura mater is not transparent, locating the central sulcus and motor cortex and subsequently mapping the topography of the motor cortex for each individual patient may be cumbersome and requires application of electrophysiological recording techniques (somatosensory evoked potentials, motor evoked potentials and electromyograms) and neuro-navigation (using CT-scans and fMRI) techniques [16, 26]. The use of these techniques is indispensable in order to ensure the positioning of the active contact(s) over the representation of the painful body area in the motor cortex; this is essential for the success of the therapy [15]. In most cases, the stimulation mode is bipolar across the central sulcus, with the cathode programmed on the motor cortex side at a stimulus amplitude at $\sim$50% of the motor threshold. The Resume^{TM} paddle with four contacts is most commonly used nowadays for chronic stimulation. The stimulus parameters (pulse duration, amplitude, frequency and cycling mode) are chosen for each patient empirically based on the subject's feedback on pain relief and side effects [3].

The mechanisms by which MCS induces pain relief are not known. PET studies showed that the neural

pathways descending to the thalamus and the brainstem as well as the cingulate gyrus and insula exhibit an increase in activity during MCS; these structures are known to be involved in pain perception and processing [5]. It is, however, unclear which neural elements *within* the motor cortex represent the input stage of the analgesic chain in MCS and are activated by stimulation. An increase of our knowledge on the neural elements which are immediately activated by a stimulus pulse will help us to determine stimulus parameters and to shorten the trial stimulation period and to optimize the electrode design. Several research centers have been performing computer modeling in order to explain the effects of neurostimulation. The focus of our group has been the modeling of clinical neuromodulation techniques. As a result, a model of spinal cord stimulation (SCS) has been developed and validated in the past. This modeling work helped to understand some mechanisms of SCS such as the influence of the electrical field on the stimulation of nerve fibers in the spinal cord region [8]. An increase of this knowledge led to a better understanding of which anatomical and electrode parameters are essential for the stimulation effects [10] and, consequently, to proposals for the optimization of electrode design [9] and ideas about new electrodes [11]. Using the same approach, we recently developed a model of MCS [12]. Although this modeling work is in an early stage and many parameters of the model are not well known, it can be expected that the model will give similar predictions as in SCS and that, consequently, proposals solutions can be suggested in order to improve efficacy of MCS. This chapter aims to introduce our MCS model and discuss its usefulness and the challenges that it faces.

Modeling methods

As in our SCS models, the MCS model consists of: 1) *3D volume conductor model* with a stimulating *electrode* and 2) *nerve fiber/neuron* models. These parts of the MCS model are only briefly described here. For detailed descriptions and explanations see our previous publication [12].

Volume conductor model

The precentral gyrus which hosts motor cortex on its superior and posterior aspect and the adjacent precentral and central sulci constitute the central part of the model (Fig. 1). A layer of cerebrospinal fluid (CSF) separates the cortical surface from the dura mater. In our model,

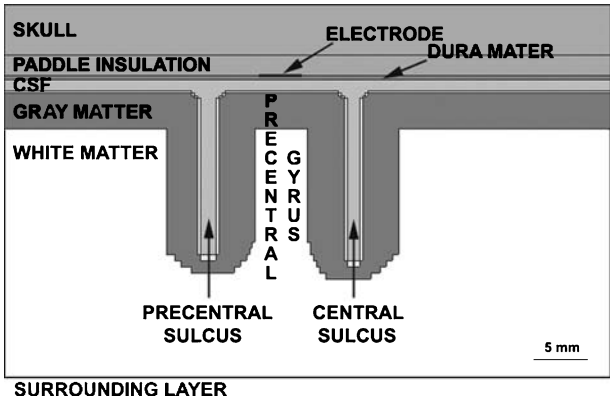

Fig. 1. Antero-posterior cross-section of the 3D volume conductor model. The anatomical compartments and the electrode contact are indicated. The cross-section was made through the center of the electrode

the dura is pressed towards the cortex by the implanted electrode paddle and the overlaying skull. The dimensions of the anatomical compartments were taken from the literature and our own measurements on cortical preparations. The thickness of CSF was set at 1.1 mm thus representing a value resulting from subtraction of the mean pre-implant CSF thickness (=3.1 mm) obtained from our measurements on MRI images and the thickness of the electrode paddle insulation (=2.0 mm). The values of electrical conductivity of the modeled tissues were obtained from literature and most of them were inherited from our SCS model.

The results presented in this chapter were obtained from models that had the electrode paddle orientated perpendicularly to the central sulcus; this is the orientation most commonly encountered in clinical practice. This is different from the models presented in our previous publication which had the electrode lead positioned in parallel to the central sulcus [12]. *Monopolar* stimulation with a single *cathode/anode* positioned over the center of the precentral gyrus or over the central sulcus was modeled. The potentials at the boundary of the model were set at 0 V (Dirichlet boundary condition); this boundary provides the return path for the stimulation current. The distribution of the *electrical field potentials* in the 3D space of the model, resulting from the applied stimulus pulse, was calculated by solving a discrete form of the Laplace equation using numerical techniques.

Nerve fibre/neuron models

The modeled neural elements are shown in Fig. 2. The neural elements designated with 'A' and 'E' represent the nerve fibers whose orientation is *parallel* to the

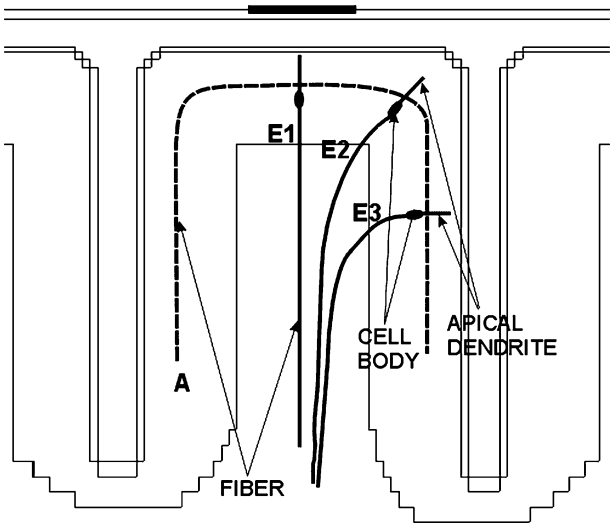

Fig. 2. Cortical neural element models. '*A*' fiber parallel to the cortical layers; '*E*' neurons perpendicular to the cortical layers; '*E1*' neuron on top of the precentral gyrus, '*E2*' neuron in the lip of the central sulcus, '*E3*' neuron in the anterior wall of the central sulcus. The cell bodies and apical dendrites of the '*E*' neurons are indicated

cortical layers and the neurons whose fibers are *perpendicular* to the cortical layers, respectively.

The electrical model of the fibers *parallel* to the cortical layers is the same as previously used in SCS and consists of nodal compartments with membrane kinetics as described by Wesselink *et al*. [25]. In an attempt to account for the presence of the *cell body* and *apical dendrite* in neurons *perpendicular* to the cortical layers, the fiber model has been expanded with 1 somatic and 15 dendritic compartments attached at the fiber end proximal to the electrode site. The additional compartments were considered to be passive and the membrane resistance was chosen in order to obtain a membrane time constant of 10 msecs; this has been based on measurements in pyramidal cell bodies [24]. The size of the cell body compartment was chosen such that its volume matched mean value measured by Rivara *et al*. in human Betz cells [22]. The diameter of the apical dendrite was set at 8 μm and its length at 1 mm. The axial direction of the cell body and dendrite coincided with the direction of the fiber (perpendicular to the cortical layers).

Simulations

The shape of the electrical potential field depends on the characteristics of the volume conductor (geometry and electrical conductivity of the anatomical compartments) and the position of the stimulating electrode in the model. Whether a given stimulus will stimulate a neural element depends on its position and orientation within the imposed potential field and its excitability (electrical and geometrical properties of the membrane compartments). The calculated stimulus-evoked potential field at the positions of the membrane compartments drives the membrane voltage behavior. The response of a neural element to this field was simulated by solving a system of differential equations that describe the membrane kinetics. In the simulations presented, the stimulus amplitude needed to excite the modeled neural elements (excitation threshold) was calculated. In addition, the site of stimulation, being either a fiber node or a somatic/dendritic compartment, was reported. The criterion of successful excitation was the occurrence of action potential (AP) generation and propagation.

Model predictions

In order to demonstrate what kind of predictions a MCS model can provide, the following results have been selected:

Electrode impedance and impressed current

When the electrode was shifted from a position over the precentral gyrus to a position over the central sulcus the electrode impedance decreased from 758 to 746 Ohms (1.5% change). With a voltage of 1 V applied to the electrode in both positions, a current of 1.32 and 1.34 mA, respectively, was calculated using Ohm's law. Therefore, the influence of the electrode position on the impedance and impressed current is negligible.

Iso-lines

Iso-potential lines (connecting points of equal potential) for anodal stimulation with the electrode centered over the precentral gyrus and over the central sulcus are shown in Fig. 3A and B, respectively.

Cathodal stimulation had the same distribution of the lines, but with a reversed polarity. Although the stimulus applied was equal in both cases and the same number of lines is shown for the same voltage range (0.45–0.8 V), the penetration of the lines into the precentral gyrus was remarkably different. When the electrode was positioned over the precentral gyrus the iso-lines were symmetrical with regard to the gyrus (Fig. 3A). With the electrode positioned over the central sulcus, a penetration of the iso-lines deep into the sulcus and sulci walls was observed (Fig. 3B). The direction and the density of the lines in the region where they overlap (anterior lip of the

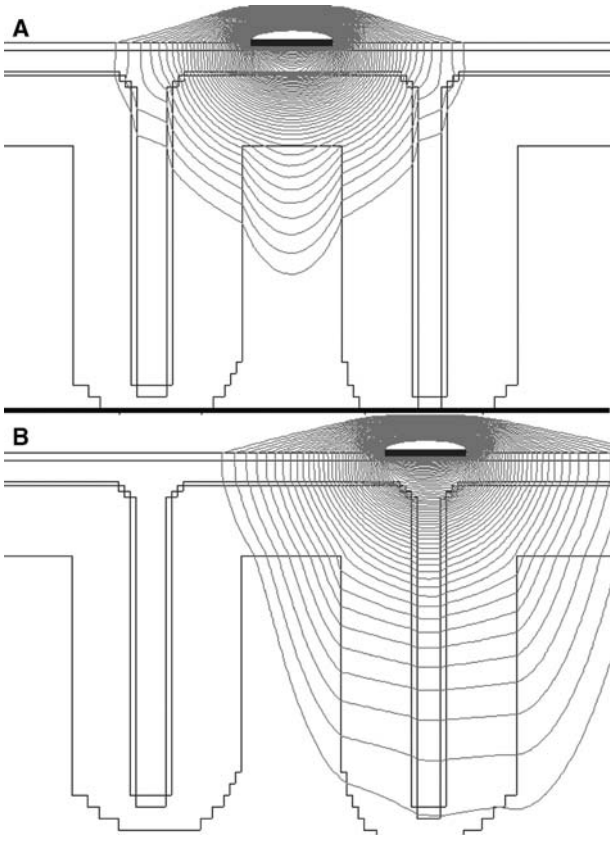

Fig. 3. Iso-potential lines in a plane through the center of the anode with the electrode over the precentral gyrus (A) and over the central sulcus (B). 150 iso-lines in the range 0.45–0.8 V are shown with the stimulus amplitude of 1 V. The outermost line connects the points having the potential 0.45 V. The increase in the potential value is ~2.3 mV (=0.35 V/149) for each inner line

sulcus) are different in Fig. 3A and B. Bearing in mind that the current density vectors are perpendicular to the iso-potential lines and the vector intensities are larger if the adjacent lines have a smaller spacing, the stimulation of those neural elements that extend perpendicularly to the iso-potential lines in the region of higher line density would be favored. Therefore, it is expected that *different* neural elements will be stimulated when the electrode is at one or the other position.

Excitation threshold voltages and sites of stimulation

Calculating the deflection of membrane potentials caused by a stimulus pulse of given amplitude is the most exact predictor of the response of the neural element. By varying the stimulus amplitude iteratively between two preset values and simulating the neural element responses for each stimulus, the amplitude needed to elicit an action potential was determined. A pulse amplitude up to 60 V and a pulse width of 210 μsec were used in all simulations. The excitation threshold voltages of the neural elements with fiber diameters varying between 5 and 15 μm are shown in Fig. 4 for the two electrode positions with stimuli of both polarities.

Cathode centered over the precentral gyrus

When a cathode was centered over the precentral gyrus, the fiber parallel to the cortical layers (Fig. 2, 'A') had the lowest threshold (Fig. 4a). The site of excitation was always at the node of Ranvier close to the center of the cathode. Assuming that the fiber diameter remains the same, the neurons in the wall and the lip of the sulcus (Fig. 2, 'E3' and 'E2') were excited at higher voltages. Their thresholds had similar values (Fig. 4a). The excitation always took place in the fiber, some nodes away from the cell body. The fiber of the neuron in the center of the gyrus (Fig. 2, 'E1') was always hyperpolarized by a cathodal stimulus and therefore these elements could not be excited.

Anode centered over the precentral gyrus

With an anode in the position over the precentral gyrus, the fiber parallel to the cortical layers ('A') and the neuron in the center of the gyrus ('E1') had comparable excitation thresholds when fibers of the same diameter were compared (Fig. 4b). The neurons in the sulcus wall and lip ('E3' and 'E2') were stimulated at significantly higher voltages. The threshold of the 'A' fiber was 2–3 times higher than in the cathodal stimulation. The site of excitation was located away from the center of the electrode, in the lip of the sulcus where the fiber orientation changes. For the 'E1' neuron, the excitation site was in the fiber at the 3rd–4th node away from the soma. The threshold to excite this neuron anodally was somewhat higher than the threshold to excite the 'A' fiber (of the same diameter) cathodally (compare Fig. 4a and b). The thresholds to excite 'E2' and 'E3' neurons were higher in anodal than in cathodal stimulation (see Fig. 4a and b), the difference being larger for the 'E3' neuron. The stimulation site of these neurons was always located at one of the nodes in the fiber, but further away from the cell body than in cathodal stimulation.

Cathode centered over the central sulcus

When the cathode was centered over the central sulcus, only the fiber parallel to the cortical layers ('A') could be excited. The threshold was slightly higher than in cathodal stimulation over the precentral gyrus

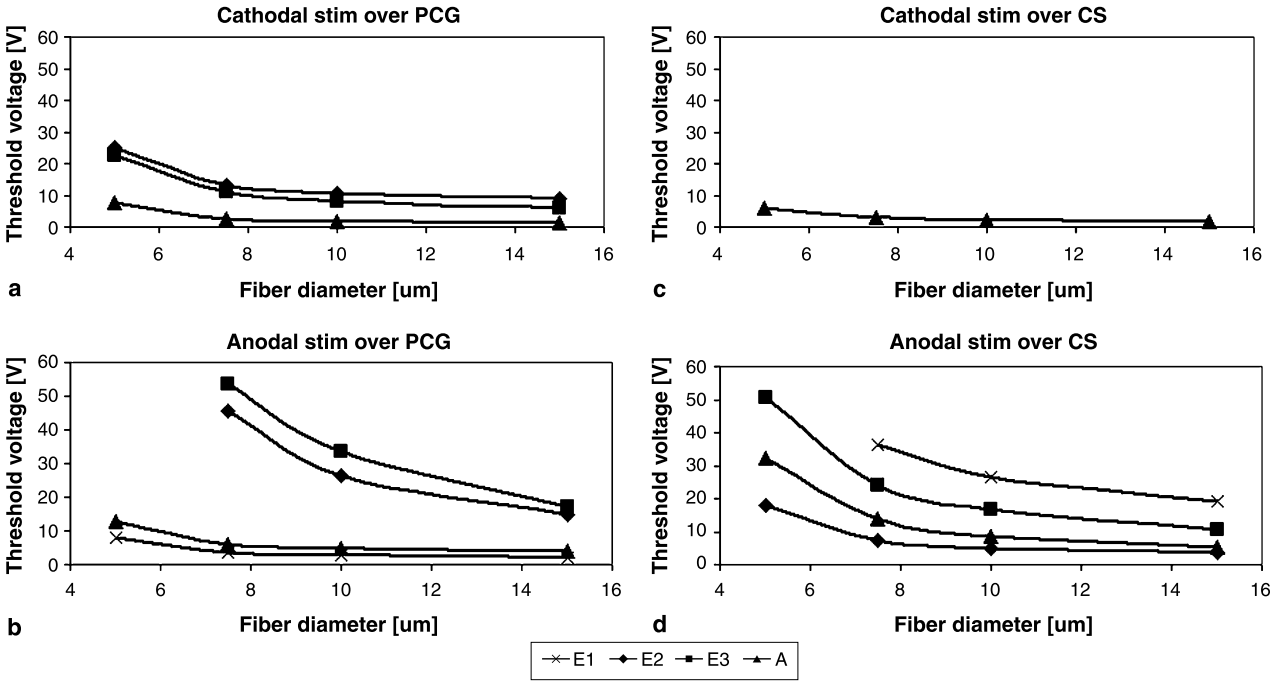

Fig. 4. Excitation threshold voltages for the modeled neural elements as a function of their fiber diameters. Results for the stimulation with the cathode (a) and anode (b) over the precentral gyrus and the cathode (c) and anode (d) over the central sulcus are shown. The legend explains the traces for the modeled neural elements and is valid for all four subfigures. Some of the data points are missing because the thresholds of maximum 60 V are shown

(compare Fig. 4a and c). The site of stimulation shifted along with the electrode and was at one of the nodes in the lip of the sulcus where the fiber changes its orientation. The fibers of the 'E' neurons were hyperpolarized and could not be excited within the simulated range of amplitudes (up to 60 V). Therefore, their threshold curves are missing in Fig. 4c. However, if the neuron 'E3' were displaced deeper in the sulcus it became excitable (results not shown).

Anode centered over the central sulcus

If anodal stimulation over the central sulcus was simulated, the neuron 'E2' had the lowest threshold, whereas neuron 'E1' had the highest value, but was still excitable. The thresholds to excite the neuron 'E3' and fiber 'A' were ranging in between, with 'E3' having the higher threshold (Fig. 4d). The site of action potential generation in the 'A' fiber was at the nodes near the bend of the fiber on the opposite side of the precentral gyrus. The 'E' neurons were stimulated at one of the nodes of the fiber. The site of stimulation roughly matched the site when the cathode over the precentral gyrus was used, thus it was closer to the cell body than in anodal stimulation over the precentral gyrus.

Discussion

In this chapter, our computer model of MCS has been introduced and explained. A number of model predictions have been shown in order to demonstrate what kind of results can be expected. The most important issues with respect to the validation and limitations of our results are described in the following sections.

Field iso-lines

As shown by the iso-lines, a change in the electrode position altered the shape of the electrical field but the electrode impedance was influenced only slightly. Therefore, impedance measurements cannot be used to control the position of the active electrode in respect to the central sulcus. In clinical practice, not only contacts anterior to the central sulcus are used, but also those in the vicinity or even posterior to the central sulcus [16]. Owing to the different shapes of the imposed electrical fields, the population of neural elements stimulated at applied voltage level can be different for the two electrode positions. In addition, programming a particular contact as an anode or a cathode can vastly influence the stimulation outcome.

Excitation thresholds

As shown in the Model Predictions, anodal stimulation over the precentral gyrus will preferably stimulate neurons perpendicular to the electrode in the convexity of the gyrus and nerve fibers parallel to the cortical layers. Cathodal stimulation with the same electrode will most easily stimulate nerve fibers parallel to the cortical layers. With the electrode centered on the central sulcus, cathodal stimulation will most easily stimulate nerve fibers parallel to the cortical layers (without stimulating perpendicular ones), whereas anodal stimulation will excite both neurons in the lip of the sulcus (nearly perpendicular to the electrode) and also nerve fibers parallel to the cortical layers. These comparative predictions were based on the assumption that the nerve fibers had the *same diameter*. To our knowledge, the diameters of human cortical nerve fibers (both efferents and afferents and their arborizations) are not well known. Better knowledge of the diameters of these nerve fiber types is essential in order to determine exactly which neural elements are excited at a given stimulus amplitude. Nerve fibers which are parallel to the cortical layers may have a diameter distribution different from the nerve fibers which are orientated perpendicular to the layers; moreover, it is likely that the diameters of the nerve fibers vary with cortical depth and with the position of the cell body in the motor cortex; these may vary not only between different body part representations but also between different positions within the same body part representation [22].

The modeling results are in accordance with the old experimental results on baboons and cats: anodal thresholds that evoke motor potentials are lowest [1, 7, 19, 20]. In those experiments, cathodal stimulation required a higher amplitude and induced more complex events with larger latencies, implying that presynaptic elements were stimulated. The results of cathodal stimulation can be explained from our results, namely by the stimulation of nerve fibers parallel to the cortical layers, which likely synapse with the dendritic trees of perpendicular neurons. Conversely, Hanajima *et al*. [6] found that cathodal stimulation needed less voltage to induce motor potentials in some cases of subdural stimulation of human motor cortex. The difference in results may be explained by the influence of the electrode position.

Site of excitation

With anodal stimulation, neurons perpendicular to the cortical layers were stimulated in the nerve fiber, several nodes distal to the cell body and thus likely to be located in the white matter. This is in accordance with conclusions based on measurements of the latencies of motor evoked potentials [1, 7, 19]. With cathodal stimulation, the site of stimulation was shifted closer to the cell body (provided that the neuron was stimulated). Our model confirmed that unlike anodal stimulation, cathodal stimulation may hyperpolarize the axon of a neuron perpendicular to the cortical layers and depolarize the dendrite especially when the neuron is perpendicular to the cathode [2]. Experiments based on the difference in chronaxie values between the soma-dendritic and axonal membrane [6, 17] and results on modeling stimulation of other parts of the central nervous system [13, 21] showed that axons and not cell bodies or dendrites are most likely excited by stimulation. Similarly, our modeling results show that generally, the depolarized part of the *axon* was the site of excitation. If no fiber part was depolarized (or depolarization was insufficient), depolarization of the dendrite did not result in action potential generation.

Model limitations

In order to draw conclusions from data such as in Fig. 4, it is essential to know the diameter of the nerve fibers as well as their location and orientation. The degree of myelination is unknown for certain fibers. The conductivities of several tissues are unknown (e.g. dura mater) and the transition between gray and white matter may not be as sharp as in our model. The thickness of the CSF layer separating the cortical surface from the dura below the electrode are still hard to assess due to artifacts in postoperative images and insufficient resolution. Furthermore, the nerve fiber model we used is a model of human myelinated sensory fiber whose characteristics may be different from the cortical nerve fibers. These are only a few challenges that our model faces. Due to uncertainties about some of these factors, the predicted excitation thresholds of several neuronal elements are beyond the output range of the pulse generators used and may be overestimated.

Usefulness of the model

So far, the terms ‘parallel’ and ‘perpendicular’ to the cortical layers were the only descriptions used when referring to the cortical nerve fibers. Parallel fibers may represent: a) bifurcations of either thalamo-cortical or cortico-cortical fibers, b) collaterals of descending

pyramidal tract fibers. On the other hand, nerve fibers perpendicular to the cortical layers may be either ascending thalamo-cortical fibers up to their branching point (in which case the termination with a cell body and dendrite is not valid) or descending fibers of either the pyramidal (cortico-spinal), cortico-thalamic tract or cortico-cortical tract. Understanding which cortical nerve fibers are actually represented by these models together with the model predictions of their excitation with different stimuli may help to elucidate the input elements of the pain relieving chain. Once the neural targets of chronic stimulation are better understood, modeling might also suggest improvements to optimize the therapy.

Future steps

In the future, present limitations of the model should be resolved, questions about the sensitivity of the model predictions with respect to CSF thickness, gray matter thickness, relative position and orientation of the neuronal elements, electrode size and spacing in bipolar/dual stimulation should be answered. Nevertheless, computer modeling is a theoretical and exact tool that can help to understand the neurophysiological phenomena taking place during MCS. This is an important step in the common goal to improve the therapy and establish it as an efficient treatment.

References

1. Amassian VE, Stewart M, Quirk GJ, Rosenthal JL (1987) Physiological basis of motor effects of a transient stimulus to cerebral cortex. Neurosurgery 20: 74–93
2. Basser PJ, Roth BJ (2000) New currents in electrical stimulation of excitable tissues. Annu Rev Biomed Eng 2: 377–397
3. Brown JA, Barbaro NM (2003) Motor cortex stimulation for central and neuropathic pain: current status. Pain 104: 431–435
4. Brown JA, Lutsep H, Cramer SC, Weinand M (2003) Motor cortex stimulation for enhancement of recovery after stroke: case report. Neurol Res 25: 815–818
5. Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, Convers P, Mauguiere F, Sindou M, Laurent B (1999) Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain 83: 259–273
6. Hanajima R, Ashby P, Lang AE, Lozano AM (2002) Effects of acute stimulation through contacts placed on the motor cortex for chronic stimulation. Clinical Neurophysiol 113: 635–641
7. Hern JEC, Landgren S, Phillips CG, Porter R (1962) Selective excitation of corticofugal neurons by surface anodal stimulation of the baboon's motor cortex. J Physiol 161: 73–90
8. Holsheimer J (2002) Which neuronal elements are activated directly by spinal cord stimulation. Neuromodulation 5: 25–31
9. Holsheimer J, Wesselink WA (1997) Optimum electrode geometry for spinal cord stimulation: the narrow bipole and tripole. Med Biol Eng Comput 35: 493–497
10. Holsheimer J, Struijk JJ, Tas NR (1995) Effects of electrode geometry and combination on nerve fiber selectivity in spinal cord stimulation. Med Biol Eng Comput 33: 676–682
11. Holsheimer J, Nuttin B, King GW, Wesselink WA, Gybels JM, de Sutter P (1998) Clinical evaluation of paresthesia steering with a new system for spinal cord stimulation. Neurosurgery 42: 541–549
12. Manola L, Roelofsen BH, Holsheimer J, Marani E, Geelen J (2005) Modelling motor cortex stimulation for chronic pain control: characteristics of the electrical field, activating function and nerve fibre responses. Med Biol Eng Comput 43: 35–343
13. McIntyre CC, Grill WM (1999) Excitation of central nervous system neurons by nonuniform electric fields. Biophys J 76: 878–888
14. Meyerson B (2005) Motor cortex stimulation – effective for neuropathic pain but the mode of action remains illusive. Pain 118: 6–7
15. Nguyen J-P, Lefaucheur J-P, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y (1999) Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomical data. Pain 82: 245–251
16. Nguyen J-P, Lefaucheur J-P, Keravel Y (2003) Motor cortex stimulation in Electrical stimulation and relief of pain. Pain research and clinical management, vol. 15. Elsevier Science
17. Nowak LG, Bullier J (1998) Axons but not cell bodies are activated by electrical stimulation in cortical gray matter. I. Evidence from chronaxie measurements. Exp Brain Res 118: 477–488
18. Pagni CA, Altibrandi MG, Bentivoglio A, Caruso G, Cioni B, Fiorella C, Insola A, Lavano A, Maina R, Mazzone P, Signorelli CD, Sturiale C, Valzania F, Zeme S, Zenga F (2005) Extradural motor cortex stimulation (EMCS) for Parkinson's disease. History and first results by the study group of the Italian neurosurgical society. Acta Neurochir Suppl 93: 113–119
19. Patton HD, Amassian VE (1953) Single- and multiple-unit analysis of cortical stage of pyramidal tract activation. J Neurophysiol 17: 345–363
20. Phillips CG, Porter R (1962) Unifocal and bifocal stimulation of the motor cortex. J Physiol 162: 532–538
21. Rattay F (1998) Analysis of the electrical excitation of CNS neurons. IEEE Trans Biomed Eng 45: 766–772
22. Rivara C-B, Sherwood CC, Bouras C, Hof PR (2003) Stereologic characterization and spatial distribution patterns of Betz cells in the human primary motor cortex. Anat Rec A Discov Mol Cell Evol 270: 137–151
23. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S (1993) Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 78: 393–401
24. Turner D, Schwartzkroin PA (1980) Steady-state electrotonic analysis of intracellularly stained hippocampal neurons. J Neurophysiol 44: 184–199
25. Wesselink WA, Holsheimer J, Boom HBK (1999) A model of the electrical behaviour of myelinated sensory nerve fibres based on human data. Med Biol Eng Comput 37: 228–235
26. Woolsey CN, Erickson TC, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg. 51: 476–506

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Computational models simulating electrophysiological activity in the basal ganglia

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Summary

Modeling of the basal ganglia has played a substantial role in gaining insight into the mechanisms involved in the computational processes performed by this elusive group of nuclei. Models of the basal ganglia have undergone revolutionary changes over the last twenty years due to the rapid accumulation of neuroscientific data. In this chapter, we present distinct modeling approaches that can be used to enhance our understanding of the functional dynamics of information processing within the basal ganglia, and their interactions with the rest of the brain. Specific examples of recently developed models dealing with the analysis of computational processing issues at different structural levels of the basal ganglia are discussed.

Keywords: Neuromodulation; basal ganglia; computer modeling; computational neuromodulation; computational neurobiology; computational neuroscience; neuroinformatics.

Introduction

The study of the brain is inevitably characterized by the complexity of structures and functions and the huge amounts of data produced. This, together with the evolution of computational algorithms and computational resources and the constant enhancement of data acquiring technologies make the development of models of the brain both a necessity and a cause. In what particularly concerns the basal ganglia, because of their broad diversity of neuron types and nuclei and their assumed role in several aspects of cognition and motion, they represent a very challenging and significant field of modeling effort. Especially during the last twenty years, a major progress in the understanding of the basal ganglia has been achieved, which has been accompanied by an increasing interest in computational modeling. Thus, various modeling approaches have been published considering various aspects of basal ganglia function. The qualitative information-flow (box-and-arrow) models of microcircuitry, of internal connectivity between basal ganglia nuclei and of their interactions with external brain structures have been useful for interpreting a wide range of experimental data and have guided much of the recent basal ganglia research [2, 16, 21, 31]. However, due to the rapidly increasing amount of available neuroscientific data, quantitative models of all aspects of basal ganglia biology are being developed. The models deal with computational issues at several structural levels of basal ganglia description, from the level of neuronal membranes to the system-level, where the nuclei that constitute the basal ganglia are acknowledged as a functional subsystem within the wider brain architecture. In this chapter, lower level, that is, cellular- and network-level models of the basal ganglia function are first presented, while particular emphasis is placed on the highest-level systems models that have sought to understand the computational role of the basal ganglia, as a whole.

Cellular-level models

At the cellular level, computational models of single neurons have been developed that try to capture the essential patterns of their behaviour. Usually, the models try to reproduce the firing rates and the shape of the action potential using ion channels. Every approach of this kind has its roots in the classic Hodgkin-Huxley model of the action potential [23]. The usual method is to represent different parts of a neuron by compartments, in which the membrane currents are examined.

In the basal ganglia, a wide range of different types of neurons exist. Each nucleus has specialized neurons and even in the same nucleus several types of neurons are present.

Striatal medium spiny neurons are the most extensively studied. Some experimentally observed non-linear characteristic behaviours of the medium spiny neurons of the striatum e.g., the general low firing frequency and the time-dependent increase in excitability, have been examined [30], by means of a set of voltage-gated potassium and sodium currents, based on the standard Hodgkin-Huxley modeling technique. The main conclusion of the model is that the kinetics of a potassium-current channel is the major reason for the observed behaviour of the medium spiny neurons. The hypothesis that striatal medium spiny neurons' activity depends on dopamine modulation has been also investigated [17], by means of a model that examines the modulation of voltage-dependent ionic currents through Hodgkin-Huxley based equations. The model leads to the conclusion that dopamine causes a bistability in the behaviour of the medium spiny neurons. Furthermore, the presence of two separate peaks in spike latency histograms, corresponding to a characteristic for the medium spiny neurons up or down state, has been demonstrated by the agreement between simulated and experimental data [27].

The dopaminergic neurons of the substantia nigra represent another pole of modeling attraction. The hypothesis that sodium dynamics drive the generation of a slow oscillation has been investigated with doubtful results by means of a multicompartmental model of a dopaminergic neuron [9]. The effects of pharmacological agents on the behaviour of the model have also been examined. A single compartment model of the dopaminergic neuron, defined by calcium dependent channels and a leak channel, has been presented, along with a multicompartmental model representing the dopaminergic neuron as a set of electrically coupled oscillators with different natural frequencies [42]. The latter model is able to take into account additional features of the dopaminergic neuron. Midbrain dopamine neurons have also been examined in a model that tries to understand the mechanisms underlying two types of calcium-dependent firing patterns that these cells exhibit in vitro [3].

A limited number of modeling approaches have been developed for neurons of the globus pallidus and the subthalamic nucleus. Concerning the globus pallidus, the hypothesis that dendritic sodium channels may facilitate the effect of excitatory inputs has been examined by means of a multicompartmental model [22]. The findings indicate a prominent role of the subthalamic nucleus in the control of globus pallidus activity. A computational model of the rat subthalamic nucleus projection neuron [15] has been developed using electrophysiological and morphological data. A restricted set of ion channels is used according to the Hodgkin-Huxley formulation. The model reveals that three channels have a primary role in distinguishing behaviours.

Network-level models

At the network level, the functional properties of small intra- and inter-nuclei circuits have been examined. Kotter and Wickens have modeled the interaction of glutamate and dopamine in the striatum [28]. They have constructed a network of biologically realistic striatal neurons that receive glutamatergic and dopaminergic synapses and have mutual inhibition connections between each other. Normal and parkinsonian conditions have been simulated and biological explanations of rigidity and akinesia have been given. A similar technique has been used for the development of a model of the neostriatum [20] that is based on anatomical facts such as the inhibitory lateral recurrent links between medium spiny neurons, the presence of inhibitory fast-spiking interneurons and gap junctions between them. The simulation results demonstrate selective abilities and suggest some crucial points for the mechanisms involved: First, the selection depends on the interaction strength between cell populations and on the gap junction weighting and further, the selection is achieved with low interneuron density.

The effect of local connectivity on striatal function has also been examined [41]. Various topologies have been considered and it has been shown that symmetric connectivity leads to stationary spatial activity while asymmetric connectivity produces slow traveling wave activity. The latter is assumed to have a link to the Huntington's disease. Gillies and Willshaw have stressed the importance of the intranuclear connectivity of the subthalamic nucleus in its functionality [14]. An overall suggestion is that this nucleus of the basal ganglia is likely to operate in switch- or pulse-like manner, while, under abnormal conditions, the interaction of the subthalamic nucleus and the external segment of the globus pallidus can produce oscillatory patterns of activity. The functioning of the loop between the subthalamic nucleus and the external segment of the globus pallidus is thought to be an essential and key factor in the overall

functioning of the basal ganglia. The functionality of the loop has been examined by a conductance-based computational model [38], where the cells of the nuclei are modeled as single compartments and their activation is described according to the Hodgkin-Huxley formalism. Various architectures are examined that lead to either rhythmic activity or irregular autonomous patterns of activity. The same loop is the subject of another computational modeling study [16], which reveals that the two nuclei can be switched between states of high and low activity or can generate oscillations consisting of bursts of high-frequency activity repeated at a low rate.

System-level models

The models of this category try to grasp the overall physiology of the basal ganglia. Single pathway models have been introduced, ranging from the hypothesis of maintained parallel segregation through each cortico-basal ganglionic-thalamo-cortical loop [2] to the hypothesis of complete convergence from each information source of the cortex to the basal ganglia [34]. In 1989, Albin *et al.* [1] proposed the famous "box-and-arrow" model of the basal ganglia connectivity and physiology (Fig. 1), which is known as direct and indirect pathways model and is still the most widely accepted and used assumption. However, obvious drawbacks of the model [33] have led to the consideration of more complex approaches that embody additional pathways [39]. All these models are called pathway models and they are rather qualitative since they do not define mathematically and/or computationally the firing mechanisms and the interaction among pathways. Nevertheless, they form the basis for the subsequent development of quantitative models. In contrast to the pathway models that are mainly based on anatomical considerations, the prominent system-level computational approaches are based on functional hypotheses about the basal ganglia's physiology. These models have generally considered high-level aspects of action selection, sequence generation, dimensionality reduction and reinforcement learning.

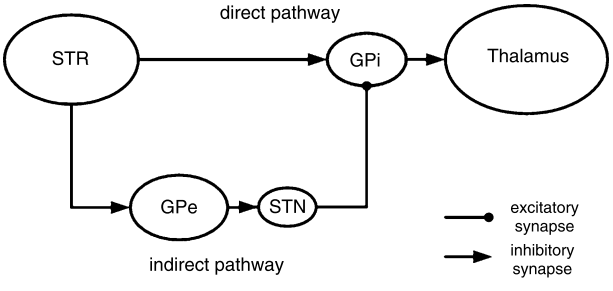

Fig. 1. Direct-indirect pathways model

Action selection

The observation that has led to the assumption of the action selection role of the basal ganglia is based on the direct pathway of the basal ganglia connectivity. According to that, when the striatal neurons fire, the pallidal neurons do not fire. Then, the corresponding thalamic neurons are released from inhibition. By that, it seems as if the striatum controls, or *selects*, through the internal segment of the globus pallidus, the activation of the thalamus [31]. Based on this idea, it has been demonstrated that the results of a series of psychological experiments can be explained by an action selection model [29].

Gurney *et al.* have extended the original idea and have presented extensive computational studies supporting the action selection hypothesis [18, 19]. The authors explain why behavioural action selection can be reduced to signal selection and then they quantify the latter process. Next, they formulate the core computational architecture, namely a specially organized neural network that implements signal selection. The original architecture of that neural network is then evolved by the incorporation of both assumptions and biological facts. The final form of the network's architecture points to a new functional architecture of the basal ganglia, which holds some resemblances to the classic direct-indirect pathways model but it is different in essence. It is divided into two pathways, the selection pathway and the control pathway. The architecture formulated in [18] is simulated in [19] using a computational network where the neurons are modeled as leaky integrators and their synapses as numerical weights. The network can finally demonstrate selective behaviour while an important side-result of the model is the role of the external pallido-subthalamic loop which seems to constrain the operating limits of the output nuclei, independently of the number of competing channels. When the loop is absent, the network's ability to select actions is ceased. Competition among active channels is generally a core idea in the action selection framework. This notion has also been used in a model [10] that consists of a number of different experts (adaptive modules) corresponding to the multiple parallel pathways of the basal ganglia. All the experts implement independent selection strategies. Action control is performed by selecting among the various possible actions proposed by each expert.

Sequence generation

According to the sequence generation hypothesis, the basal ganglia are thought to have a crucial role in the learning and reproduction of series of individual actions. Berns and Sejnowski [8] have implemented a form of ''loser-takes-all'' action selection mechanism in an anatomically inspired model that is used to simulate the learning and reproduction of sequences of actions. The model is comprised by processing units representing groups of neurons and connections between them according to the known basal ganglia connectivity. The hallmark of the model is the recurrent connection between the external globus pallidus and the subthalamic nucleus which acts as a short-term memory for action sequence generation. Mathematical equations rule the behaviour of the model: the neurons are modeled as leaky integrators and the learning process exercised by dopamine is hebbian. The simulation includes two phases, first learning of a sequence of actions and then reproducing it, when asked. Pathological conditions are emulated with specific changes in the values of some parameters.

In contrast to the previous model, Fukai [12] has assumed that the serial order of the sequence's components is stored in the cortex and is extracted by one class of striatal neurons by means of a ''winner-takes-all'' mechanism. Another class of striatal neurons retains the current component in the cortico-basal ganglionic-thalamic loop. The subthalamo-pallidal network is assumed to be useful in triggering the transition to the next component of the sequence. Beiser and Houk [7] have also supported the idea that the cortex stores the sequences and propose a cortical input classification role for the striatum. Wickens and Arbuthnott [40] have demonstrated how lateral inhibitory connections in the striatum can be the biological base for the generation of spatiotemporal patterns. On the other side, Dominey [11] has used different sub-networks to formulate a sequence generation mechanism. There, the striatum is thought to identify sequences instead of actions.

Dimensionality reduction

A whole different and radical assumption for the basal ganglia's physiology has started by the observation of the funnel-like view of the basal ganglia (Fig. 2a). This anatomical feature inspired the physiological hypothesis of dimensionality reduction. This is an engineering algorithm used to reduce the amount of data needed to represent a mathematical feature space (Fig. 2b). Under this assumption, the basal ganglia act as a central switch that

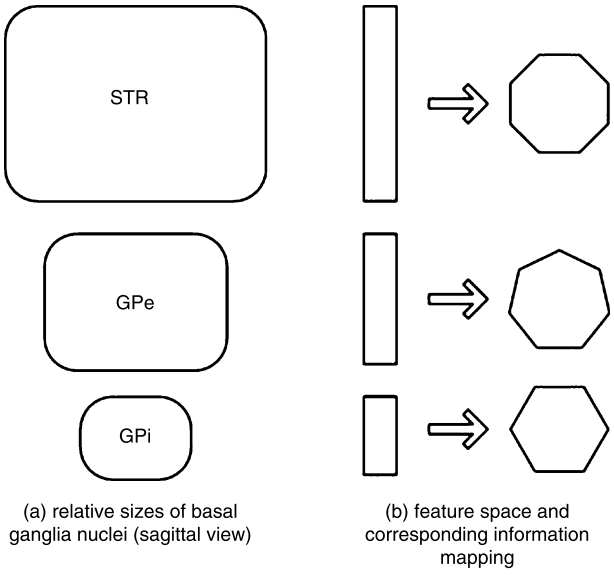

Fig. 2(a, b). Dimensionality reduction hypothesis for the basal ganglia

receives information from all the regions of the cortex and, after proper compression, transfer the information to the frontal cortex. Dimensionality reduction is performed by the basal ganglia in order to decrease the amount of information needed to encode activity patterns.

Bar-Gad *et al.* [4] have presented a neural network model that performs dimensionality reduction. The network has two layers, the input layer with N processing elements and the output layer with M processing elements, where typically $N > M$. A scalar reinforcement signal is present to modulate a hebbian learning rule. Lateral inhibitory synapses also exist. The network implements the well-known Principal Component Analysis (PCA) algorithm for dimensionality reduction, which determines the values of the weights. Finally, the network is capable of selecting the M most representative features out of the original N. The authors also present a more complex network architecture, which is more biologically plausible and can ultimately fit as an assumption for basal ganglia's physiology.

Reinforcement learning

The common feature of every basal ganglia physiological assumption is the role of dopamine in their functionality [21]. Dopamine is considered to modulate the cortico-striatal synapses and, thus, to biologically implement a learning scheme. It has been assumed that this scheme is reinforcement learning. Reinforcement learning uses the notion of reward to force the behaviour of the learning system to the desired direction. When the action undertaken by the system is positive (in some

sense) it produces high amount of reward. For the basal ganglia, the flow of dopamine is considered to be the reward. Based on this idea, several models of basal ganglia physiology have been proposed [5, 24]. The most widely used model is the actor-critic architecture [26]. This tries to solve the temporal credit assignment problem [5] rising because the consequences of actions are not immediately obvious in the biological system (the reward delays). The actor is the part of the basal ganglia that performs an action while the critic is another part that tries to predict the reward for this action and assign it to the actor before the actual reward comes [37]. An anticipated property of the dopaminergic system is that when the predicted reward is correct, there is no actual release of dopamine but in cases of false predictions, dopamine flow gives positive or negative response [32]. This observation is consistent with high-level behaviour.

Further, it has been shown that the actor-critic algorithm can be combined with various functional hypotheses about the basal ganglia. The implications of reinforcement in learning and reproduction of sequences of actions have been examined by a neural network implementation of an actor-critic architecture [36]. The network learns a pre-composed sequence of stimulus-action pairs with reinforcement learning according to the temporal difference algorithm. Then, the sequence can be reproduced at any time. The model suggests that the role of the critic can be played by the nigral dopaminergic neurons while the actor can be the striatum. Furthermore, goal-directed behaviour, which the basal ganglia are thought to contribute to, has been simulated by means of an actor-critic architecture. In a specially selected environment, it has been shown that the combination leads to better performance. Far from the actor-critic architecture, a computational model, considering the relation between dopamine and its receptors in the striatum, has tried to account for a range of experimental evidence suggesting that ventral striatal dopamine D2 receptor manipulation selectively modulates motivated behavior for distal versus proximal outcomes [35]. The model is based on the assumption that an animal builds an internal representation of action-outcome relationships. Based on these, an agent learns to maximize reward through trial-and-error interaction with its environment.

Concluding remarks

The structural complexity of the basal ganglia can foster important modeling approaches at every hierarchical level of description. Cellular-level models deal with the intrinsic properties of the various types of neurons of the basal ganglia. Significant attention has been paid on the striatal medium spiny neurons and the dopaminergic neurons of the substantia nigra. This is justified by the widely realized functional importance of the striatum and dopamine in the functionality of the basal ganglia. Network-level models have been presented, with the striatum being at the center of the related efforts. The models of this category are usually restricted into small circuits within the nuclei or between two adjacent nuclei.

System-level models of the basal ganglia are following four major hypotheses. The action selection assumption is relatively well-developed and widely supported. In many cases, it is based on the intrinsic properties of the striatum while it remains unclear how exactly the other nuclei of the basal ganglia contribute to this function. On the other hand, though the sequence generation hypothesis seems to be an extension of the action selection, it has been proved much more difficult to follow and there is no prominent modeling assumption to lead to clear conclusions. The assumption of dimensionality reduction seems very interesting because an efficient handling of the huge amount of information that flows among the various modules of the brain should be expected. Basal ganglia may be responsible for that, which might explain their central position and their vast innervations from the cortex. However, this function could even be considered to be complementary to others. Finally, reinforcement learning is the most concretely developed hypothesis and the models considering it are the most mature at this point.

Generally, the computational modeling of a biologically observed behaviour of the basal ganglia is useful in providing a mechanistic explanation that will possibly lead to further *in silico* experimentation that may reveal the role of hidden factors in the production of the behaviour or clarify the dependencies between them. However, the computational modeling of the brain function restricts the relationship of the hypothesis-model couple because of the necessity of biological plausibility in the construction of the latter. In almost every modeling approach that we presented about the physiology of the basal ganglia, a hypothesis preceded and then a model tried to confirm it. In low-level models, such as single-cell models, it is relatively easy to maintain some form of biological plausibility. Almost every approach is based on the classic Hodgkin-Huxley formulation, so the modeling procedure lies on the selection of the ionic

currents and their parameters. On the network- and system-levels, however, this is not the case. The computational hypotheses about the basal ganglia can be supported by approaches that are not necessarily based on known anatomical facts or on any anatomical facts whatsoever. Despite that, the retention of the biological plausibility is almost always favoured.

Finally, a key issue in computational modeling of the basal ganglia (and the brain in general) is the consistence between low- and high-level models. Low-level models must be capable of producing the functional characteristics of higher-level approaches when connected together. High-level models must be able to decompose their function in simpler modules that will correspond to lower-level unit function. Models, at any structural level, are expected to shed additional light on the mysterious and obscure functions of the basal ganglia in health and disease. These insights should in turn lead to experimental predictions, which, when proved or disproved, can then form the basis for better basal ganglia models.

References

1. Albin R, Young A, Penney J (1989) Functional anatomy of basal ganglia disorders. Trends Neurosci 12: 366–375
2. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9: 357–381
3. Amini B, Clark JW Jr, Canavier CC (1999) Calcium dynamics underlying pacemaker-like and burst firing oscillations in midbrain dopaminergic neurons: a computational study. J Neurophysiol 82: 2249–2261
4. Bar-Gad I, Morris G, Bergman H (2003) Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. Progr Neurobiol 71: 439–473
5. Barto AG (1995) Adaptive critics and the basal ganglia. In: Houk JC, Davis J, Beiser DG (eds) Models of informations processing in the basal hanglia. MIT Press, Cambridge MA, pp 215–232
6. Beiser DG, Hua SE, Houk JC (1997) Network models of the basal ganglia. Curr Opin Neurobiol 7: 187–190
7. Beiser DG, Houk JC (1998) Model of cortical-basal ganglionic processing: encoding the serial order of sensory events. J Neurophysiol 79: 3168–3188
8. Berns GS, Sejnowski TJ (1998) A computational model of how the basal ganglia produce sequences. J Cogn Neurosci 10: 108–121
9. Canavier CC (1999) Sodium dynamics underlying burst firing and putative mechanisms for the regulation of the firing pattern in midbrain dopamine neurons: a computational approach. J Comput Neurosci 6: 49–69
10. Chavarriaga R, Strosslin T, Sheynikhovich D, Gerstner W (2005) A computational model of parallel navigation systems in rodents. Neuroinformatics 3: 223–242
11. Dominey P (1995) Complex sensory-motor sequence learning based on recurrent state representation and reinforcement learning. Biol Cybern 73: 265–274
12. Fukai T (1999) Sequence generation in arbitrary temporal patterns from theta-nested gamma oscillations: a model of the basal ganglia-thalamocortical loops. Neural Networks 12: 975–987
13. Gillies A, Arbuthnott G (2000) Computational models of the basal ganglia. Mov Dis 15: 762–770
14. Gillies A, Willshaw D (2004) Models of the subthalamic nucleus. The importance of intranuclear connectivity. Med Eng Physics 26: 723–732
15. Gillies A, Willshaw D (2006) Membrane channel interactions underlying rat subthalamic projection neuron rhythmic and bursting activity. J Neurophysiol 95: 2352–2365
16. Gillies A, Willshaw D, Li Z (2002) Subthalamic-pallidal interactions are critical in determining normal and abnormal functioning of the basal ganglia. Proceedings of the Royal Society: Biological Sciences 269: 545–551
17. Gruber AJ, Solla SA, Surmeier DJ, Houk JC (2003) Modulation of striatal single units by expected reward: a spiny neuron model displaying dopamine-induced bistability. J Neurophysiol 90: 1095–1114
18. Gurney KN, Prescott T, Redgrave P (2001) A computational model of action selection in the basal ganglia. I. A new functional anatomy. Biol Cybern 84: 401–410
19. Gurney KN, Prescott T, Redgrave P (2001) A computational model of action selection in the basal ganglia. II. Analysis and simulation of behaviour. Biol Cybern 84: 411–423
20. Gurney KN, Overton PG (2004) A model of short and long range selective processing in neostriatum. Neurocomputing 58–60: 555–562
21. Gurney KN, Prescott T, Wickens J, Redgrave P (2004) Computational models of the basal ganglia: from robots to membranes. Trends Neurosci 27: 453–459
22. Hanson JE, Smith Y, Jaeger D (2004) Sodium channels and dendritic spike initiation at excitatory synapses in globus pallidus neurons. J Neurosci 24: 329–340
23. Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol 117: 500–544
24. Houk JC, Adams JL, Barto AG (1995) A model of how the basal ganglia generate and use neural signals that predict reinforcement. In: Houk JC, Davis JL, Beiser DG (eds) Models of information processing in the basal ganglia. MIT Press, Cambridge MA, pp 249–270
25. Itoh H, Aihara K (1999) Combination of actor-critic algorithm with the goal-directed reasoning. Proceedings of the 6th International Conference on Neural Information Processing, 777–782
26. Joel D, Niv J, Ruppin E (2002) Actor-critic models of the basal ganglia: new anatomical and computational perspectives. Neural Networks 15: 535–547
27. Kitano K, Cateau H, Kaneda K, Nambu A, Takada M, Fukai T (2002) Two-state membrane potential transitions of striatal spiny neurons as evidenced by numerical simulations and electrophysiological recordings in awake monkeys. J Neurosci 22: RC230
28. Kotter R, Wickens J (1998) Striatal mechanisms in Parkinson's disease: new insights from computer modeling. Artif Intell Med 13: 37–55
29. Kropotov JD, Etlinger SC (1999) Selection of actions in the basal ganglia-thalamocortical circuits: review and model. Int J Psychophysiol 31: 197–217
30. Mahon S, Deniau JM, Charpier S, Delord B (2000) Role of a striatal slowly inactivating potassium current in short-term facilitation of corticostriatal inputs: a computer simulation study. Learn Mem 7: 357–362
31. Mink JW (1996) The basal ganglia: Focused selection and inhibition of competing motor programs. Progr Neurobiol 50: 381–425

32. Montague PR, Dayan D, Sejnowski T (1996) A framework for mesencephalic dopamine systems based on predictive hebbian learning. J Neurosci 16: 1936–1947
33. Parent A, Levesque M, Parent M (2001) A re-evaluation of the current model of the basal ganglia. Parkinsonism Relat Dis 7: 193–198
34. Percheron G, Yelnik J, Francois C (1987) Spatial organization and information processing in the core of the basal ganglia. In: Carpenter MB, Jayaraman A (eds) The basal ganglia vol. II. Plenum Press, New York, pp 205–226
35. Smith AJ, Becker S, Kapur S (2005) A computational model of the functional role of the ventral-striatal D2 receptor in the expression of previously acquired behaviors. Neural Comput 17: 361–395
36. Suri RE, Schultz W (1998) Learning of sequential movements by neural network model with dopamine-like reinforcement signal. Exp Brain Res 121: 350–354
37. Suri RE (2002) TD models of reward predictive responses in dopamine neurons. Neural Networks 15: 523–533
38. Terman D, Rubin JE, Yew AC, Wilson CJ (2002) Activity patterns in a model for the Subthalamopallidal network of the basal ganglia. J Neurosci 22: 2963–2976
39. Wichmann T, DeLong MR (1996) Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 6: 751–758
40. Wickens J, Arbuthnott G (1993) The corticostriatal system on computer simulation: an intermediate mechanism for sequencing of actions. Prog Brain Res 99: 325–339
41. Wickens J, Kotter R, Alexander ME (1995) Effects of local connectivity on striatal function. Synapse 20: 281–298
42. Wilson CJ, Callaway JC (2000) Coupled oscillatory model of the dopaminergic neuron of the substantia nigra. J Neurophysiol 83: 3084–3100

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Computational perspectives on neuromodulation of aging

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Summary

Cognitive functions, such as memory, attention, and perception, decline with age. Besides other neuroanatomical changes, the level of dopamine also attenuates during aging. We review how computational modeling can provide insights in how these lifetime changes in dopamine levels are expressed at the behavioral level yielding a bridge across different levels. Results indicate that attenuation of dopamine lowers the signal to noise ratio providing a less distinctive neural representation, and detrimental cognitive performance.

Keywords: Dopamine; neuromodulation; noise; aging; cognitive functions; neural networks.

Introduction

An important goal in studies of cognitive aging is to link behavioural changes to underlying age-related modifications in the neural system. However, this endeavour is difficult because it is not clear how the behaviour typically found in older adults (cognitive impairments) relates to mechanisms at the neurological level. Here, we review how computational models may serve as a tool to study how changes at the neurobiological level can lead to a wide range of observable behaviour changes. In particular, we focus on how dopamine, a neuromodulator known to attenuate with age, influences performance. A link is made between attenuation of dopamine, increased internal neural noise, less distinct cortical representation, cognitive deficits, and increased intra- and inter-variability in cognitive tasks.

Aging is accompanied with a general decline in cognitive functions, involving episodic memory, working memory, prospective memory, inhibition, attention, executive functions, sensory perception, and sensorimotor skills [14, 18, 22, 42, 47]. Cross-sectional studies indicate that the decline in cognitive function starts as early as in the 20s and 30s and performance declines as much as a standard deviation at the age of 60, and two standard deviations at the age of 80 [33, 34]. However, longitudinal studies show that some of this decline can be attributed to a cohort-effect, and that performance in young and middle age groups are rather stable and that reliable and accelerated decline occurs for older age groups [49].

Among various neuromodulators (e.g., dopamine, serotonin, and catecholamine), dopamine is a particulary promising correlate for cognitive aging. During normal aging there is a 7–11% attenuation of dopamine D2 receptors per decade starting from an age of about twenty in extrastriatal regions [24] and in the nigrostriatal region [48]. Loss of D2 receptors has also been found in cortex [15] and striatum [21]. There is also more direct evidence that dopamine influence performance. Working memory function in old monkeys has been improved by drugs that facilitate dopaminergic modulation [2]. Response speed and reaction time variability has been associated with dopaminergic modulation in old rats [30]. Age-related attenuation in processing speed and episodic memory has been statistically related to decreased levels of striatal D2 receptors binding mechanism in humans [7, 17]. Finally, the prefrontal lobe has been implicated to play a significant role in the cognitive deficience in aging [47], and at the same time dopamine have been shown to modulate cortical representation, attention, and appropriate response to stimulus in the frontal lobe [1].

Modeling dopamine's impact on the signal-to-noise ratio

Neuromodulation can be modeled at different levels of detail. Detailed biological models offer fidelity to the

underlying biological system, but are often more difficult to connect to the behavioral level. A general feature of the dopaminergic system can be modulated without biological details by changing the gain parameter in the sigmoid function [37]. This parameter determines the responsiveness of a neuron to external inputs. Furthermore, it alters the signal-to-noise relation that is the output from a cell, given a certain input. This change in gain, in combination with a change in the negative bias term, captures the stimulus response pattern of the non-linear gain that is modulated by catecholamines [11]. Although, the impact of dopamine on cells has been modeled with other approaches, and with various levels of details [16], these models share the basic feature of tuning the signal-to-noise ratio.

Reducing the gain parameter in a neural network simulates attenuation of dopamine transmission associated with cognitive aging. This yields a more linear relationship between input and output of neural cells for an aging network, whereas young networks are characterized by a non-linear, threshold-like behavior. It is well known that non-linearity is a crucial mechanism necessary for solving certain problems in neural networks. For example, the simple logical function ''exclusive or'' (i.e., a function that is true if one, but not if both, inputs are active) requires non-linearity to be solved. Furthermore, non-linear activation function has been shown to be an essential mechanism to account for certain features of episodic recognition memory [38]. In particular, in the back-propagation algorithm, a decrease in the gain parameter is equivalent with either an increase in the initial weights or a decrease in learning rates [44]. This indicates that a low gain is associated with larger initial weights or more internal neural noise.

Simulations studies have further shown that lower levels of dopamine lead to a less distinct neural representation [25, 27]. A low distinct representation means that the neural units have a similar level of activity, whereas a distinct representation means that some units are highly active and other units are strongly inactivated. This may be linked to the hypothesis that older people process information less elaborative than young due to lower attentional resources [13]. In a simulation study, Li and Sikström in 2002 [27] investigated Stroop interference in aging, using a dual model resembling the Cohen *et al.* model [10]. Verbal and spatial memory was implemented in different input layers and the task demand, i.e. to attend to either verbal or spatial information, was controlled by units connected to the hidden layer. The results show that a reduced gain in the old network yielded an overlapping representation in the verbal and spatial representations, whereas the young network had distinct representation in either of these modules that depended on the task demands. These results are consistent with neuro-imaging data of young and olds, where young subjects have a more distinct neural representation compared to old. In spatial and working memory tasks, old participants had showed activity in both the left and right hemispheres, whereas young had a more lateralized activity pattern [8]. The view proposed here is complementary to the prevailing idea that increased bi-lateral activation is a way to compensate for neuro-cognitive deficits. Another study found that the sensorimotor neural representations in the pawn of rats are large and highly overlapping and associated with behavioral deficiencies compared to young rats [41].

Beyond influencing the noise level, the gain parameter also influences the performance variability. A change in the gain parameter, of a fixed size, influences the performance more when the gain parameter is small compared to when it is large. That is for large gains the activation function will approximate a threshold function and is little influenced by small changes, whereas for small gains the activation function is approximately linear, and a change in gain scales approximately linearly to the output. The probabilistic nature of transmitter release, and other noise in the neural system leads to changes in dopamine level. Thus, even if the stochastic fluctuations are of a similar magnitude for old and young networks, the overall impact of behavior will be larger for an old than a young network.

Consistent with this theoretical framework, age-related increase in cognitive variability within subjects has also been empirically found. Old rats with decreased dopamine density receptors in nigrostriatum show an increased reaction time variability and slower responses [30]. Furthermore, as aging progresses the variability also increases between individuals, for example individual differences in sensorimotor performance increase with age [26].

Stochastic resonance (SR) and dopamine

In a recent computational framework, dopamine and aging has been related to the phenomena of stochastic resonance [28]. Stochastic resonance (SR) is the empirical finding that a signal that is presented below the detection threshold, for example the threshold for generating action potentials in neural cells, can be detected

in presence of noise. Stochastic resonance is found in a variety of physical and neurobiological systems. In particular adding noise to a signal has been found to improve performance in sensory detection [12] and visual perception [39]. The enhancement of neural activity though SR has also been studied using fMRI [40].

Li *et al.* [28] investigated how noise influences performance in young and old adults. The reduction in dopamine with aging reduces the gain parameter in neural cells. Computational modeling shows that this reduction in gain modulates the SR-curve in several aspects. First, more noise is required for maintaining optimal performance. Second, the overall detection in the SR-curve is lower in old associated with a low gain in comparisons to young adults. Earlier studies using noise in tactile sensation and balance have provided indirect empirical support for these computational predictions in old [29] and young [12] adults in separate studies. A recent study directly compared young and old vibrotactile sensitivity and indeed found that old required more noise for optimal performance compared to young adults [46].

Excessive dopamine harms cognitive performance

Most research has emphasized that behavioral performance increases with the levels of dopamine; later research has shown that too much dopamine may also be harmful. Too high values of dopamine D1 receptors impair prefrontal memory performance [31]. Taken together with earlier findings of moderate dopamine levels, this indicates an inverted U-shaped curve of performance as a function of dopamine levels. Computational modeling of the dopamine levels in the back propagation algorithm show a similar pattern of results, where too low and too high gains show lower performance compared to a moderate gain. The low performance for too high gain can be related to a less distinct neural representation, where more units are more likely to be active for different stimulus. The mechanism accounting for this phenomenon is that the backpropagating algorithm scales the learning rate with the derivative of the sigmoid function, so that units for excessive high gains operates in a regime where this derivative is near zero, yielding a low learning rate. Looking at the entire lifespan there is also a U-shaped relation between age and performance where children, as well as old age adults, perform worse than young adults [19]. However, the role of neuromodulation in children is less known and further research is required before drawing firm conclusions.

Dopamine and the prefrontal cortex

Dopamine extrinsically modulates the prefrontal cortex though mesencephalic neurons (in ventral, tegmentum, and substantia nigra) in a diffuse manner [9]. Prefrontal dopamine levels increase during working memory task [45] and phasic burst of dopamine occurs following the onset of such task [35]. Blocking of dopaminergic input to the prefrontal cortex, or D1 receptors blocking within the prefrontal cortex, interferes with working memory performance [36]. The influence of dopamine on prefrontal cortex has been simulated in detailed neural networks models [16]. These simulations indicate that D1 modulation deepens and widens the basin of attraction of neural network while suppressing background activity. This leads to a more self-sustained activity that is persistent to noise and environmental distracters, which may enhance the ability to sustain attention to the current goal.

The computational role of dopamine in the prefrontal cortex during aging has been emphasized [5]. More specifically, it has been argued that successful performance is related to updating of contextual information and maintenance of the internal representation to exert control over thoughts and behavior. There are three main components in the model. First, active maintenance of context information is maintained though recurrent excitatory connections. These connections maintain the context even in absences of external inputs. Second, context serves as bias to either suppress or enhance competing inputs from the external stimuli. Third, the dopamine system serves as modulator of the contextual information maintained in the dorsolateral prefrontal cortex, thus acting as a gating mechanism. When the gate is open, which occurs during the phasic activity of the dopamine system, incoming information can gain access to the contextual information and update the current state of context representation. When the gate is closed the context is protected from interfering noise and irrelevant inputs. An important insight from this model is how a single model might subserve three different functions, which are typically regarded as being independent; namely attention, active memory, and inhibition. Attention, is maintained by projection of the contextual information, a process that otherwise typically is associated with working memory. In a similar way, the contextual representation suppresses irrelevant stimulus, and thus there is no active mechanism for inhibition. Context information is also used to maintain active memory from interfering following noise. In this framework, healthy cognitive aging can be simulated by impairing the dopa-

mine projections to the dorsolateral prefrontal cortex, which disrupts the contextual representation so that performance on attention, inhibition, and working memory are attenuated.

This model have been empirically tested in a continuous performance task where participants are required to respond 'X' when it is preceded by an 'A', but not when it is preceded by a 'B'. Using this task, the model has been validated on the neurobiological level by several findings. Consistent with the idea of maintaining context, the dorsolateral prefrontal cortex shows greater activity at long cue target delays during active maintenance, compared to short inter-trial intervals [6]. The performance on this task improved during administration of low-dose D-amphetamine, which acts as a stimulator for dopamine release [4]. Furthermore, the performance is differently affected by the delay between the cue and the target so that very old adults show a decline in performance of 'B'–'X' cue target pair with delay, whereas 'A'–'Y' improved. These results suggest that context representation, and maintaining of context, reflect dissociable cognitive functions that are differently affected by age.

Event related negativity and dopamine

When participants commit an error in a reaction time task and receive feedback an error-related negativity (ERN) is evoked in the event-related potentials (ERP) [20]. It has been proposed that the ERN functions as an evaluative control so that behavior is adapted following feedback. In a neurocomputational model Holroyd and Coles [23] suggested that phasic dopamine release may serve as a reward signal, so that ERN adapts behavior depending on predicted rewards. In particular the mesencephalic dopamine system increases the phasic responses if the rewards are better than predicted and attenuates if the rewards are worse than predicted. This is accomplished by using the temporal difference algorithm [43], a reinforcement learning rule for learning the earliest predictor of reward or punishment. The mesencephalic dopamine is projected to the anterior cingulated cortex (ACC) and is related to the ERN. Thus, if an error occurs dopamine is released in the ACC though mesencephalic projections activating a strong ERN leading to adaptive learning. The ERN has been found to be attenuated in old adults compared to control [3]. Nieuwenhuis *et al.* [32] applied the Holroyd *et al.* [23] model to account for the attenuated ERN in old adults. According to their framework, weaker phasic dopamine responses in old adults results in a smaller ERN.

Conclusion

Aging is associated with a number of neurophysiological and behavioral changes. For example the level of dopamine, among other neurophysiologic changes, attenuates across the adult lifespan. Behaviorally, aging is associated with loss in performance in various cognitive abilities, such as working memory, attention, sensorimotor integration, inhibition, executive function etc. A major goal in cognitive neuroscience is to achieve an understanding of the complex relation between the neurophysiological and the behavioral levels. Computational modeling using neural network is an essential tool in this enterprise, which may bridge the gap between these levels.

The modeling perspective has a number of advantages. First, computational modeling allows us to study the interaction between a large number of small low-level processing units and a global behavioral response. Second, modeling allows studying vastly complex systems. In particular neural network models are recurrent non-linear systems that behave in ordered but at the same time chaotic way. Characteristic of these chaotic systems is that it may not be possible to make prediction of particular events; nevertheless, emergent properties arise from neural networks that may be studied. Furthermore, even if the behavior of the system is very complex, the underlying rules that govern the system may be relatively simple and thus afford the possibility of being intellectually tractable. Third, the behavior arising from simulated neural networks yields behavioral predictions. These predictions are empirically testable so that the underlying modeling system can be confirmed or rejected. Fourth, although modeling may be seen as a method, the basic building blocks in the model may regarded as a theory of behavior. Fifth, successful models can be further tested by conducting computational lesioning studies were the results may be compared with an equivalent empirical lesioning studies. For example, a model that has been successful in describing behavioral data in young adults may be damaged by attenuation dopamine levels to provide prediction of old adult's behavior. Sixth, computational modeling should always be conducted in close mutual interaction with empirical studies. In the same way as modeling is driven by empirical data, empirical studies may also gain momentum by feedback from computational modeling.

Current literature on computational models of dopamine to account for the effect on cognitive aging is converging on a complex but coherent picture. Age-re-

lated decrease in dopamine levels alters the signal-to-noise ratio in neural cells, which can be simulated by decreasing the gain parameter in the sigmoid function in relatively abstract neural network models or by detailed biophysical models. The decrease in dopamine increases the internal neural noise resulting in cognitive deficits, for example lower and slower performance on episodic memory task. Beyond decreasing performance, computational modeling predicts an age-related increase in performance variability, both within participants and between participants. In addition, the neural representation becomes less distinct, leading to a diffuse pattern of neural activation as seen in bilateral activation in fMRI studies.

The mesencephalic sources of dopamine project mainly to the prefrontal cortex that is particularly important for maintaining attention on task related activities. Attenuation of these systems leads to poorer performance in go-nogo and Stroop tasks. Age-related decrease in dopamine is also expressed in stochastic resonance by the counterintuitive phenomenon that addition of moderate noise improves performance in threshold based systems. Modeling efforts predict that old networks require more noise for optimal performance, which later have been confirmed in studies using vibrotactile sensory systems. Computational modeling of reinforcement learning rules have also been applied to task with feedback and been linked to the Error-Related Negativity component of the ERP.

The examples listed above suggested that the last few years, we have witnessed a major progress in modeling of neuromodulation mechanisms in aging. This progress has been made possible by a tight connection between computational modeling on one hand and neurophysiology and behavioral data on the other hand. However, several challenges remain open in the field. This review has largely focused on age-related changes in dopamine; however, several other neurophysiologic changes occur across the lifespan. For example, changes in other neuromodulators, cell death, etc. Future computational studies should incorporate experimentally quantifiable measures of these age-related changes in their models so that main and interaction effects can be studied. Current neurocomputational models typically investigate the interaction of a few cortical regions. By incorporating larger structures computational models may gain in accuracy. Furthermore, new modeling efforts could gain considerably by constraints from multiple sources and techniques, for example by simultaneously accounting for evidence from fMRI, ERP, and single cell recordings. Collaborative research and computational modeling on multiple levels may bear intriguing results in the future.

References

1. Arnsten AFT (1998) Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn Sci 2: 436–447
2. Arnsten AFT, Cai JX, Murphy BL, Goldmanrakic PS (1994) Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys. Psychopharmacology 116: 143–151
3. Band GPH, Kok A (2000) Age effects on response monitoring in a mental-rotation task. Biol Psychol 51: 201–221
4. Braver TS (1997) Mechanisms of cognitive control: a neurocomputational model. Psychological Department, Carnegie Mellon University, Pittsburgh
5. Braver TS, Barch DM (2002) A theory of cognitive control, aging cognition, and neuromodulation. Neurosci Biobehav Rev 26: 809–817
6. Braver TS, Cohen JD (2001) Working memory, cognitive control, and the prefrontal cortex: computational and empirical studies. Cogn Process 2: 25–55
7. Bäckman L, Ginovart N, Dixon RA, Robins Wahlin T-B, Wahlin Å, Halldin C, Farde L (2000) Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am J Psychiatry 157: 635–637
8. Cabeza R (2002) Hemispheric asymmetry reduction in older adults: the Harold model. Psychol Aging 17: 85–100
9. Cass WA, Gerhardt GA (1995) In vivo assessment of dopamine uptake in rat medial prefrontal cortex: comparison with dorsal striatum and nucleus accumbens. J Neurochemistry 65: 201–207
10. Cohen JD, Dunba K, McClelland JL (1990) On the control of automatic processes: a parallel distributed processing model of the Stroop effect. Psychol Rev 97: 332–361
11. Cohen JD, Servan-Schreiber D (1992) Context, cortex, and dopamine: a connectionist approach to behavior and biology in Schizophrenia. Psychol Rev 99: 45–77
12. Collins JJ, Imhoff P, Grigg P (1996) Noise-enhanced tactile sensation. Nature 383: 770
13. Craik FIM (1983) On the transfer of information from temporary to permanent memory. Philos Trans R Soc Lond B 302: 341–359
14. Craik FIM, Salthouse TA (2000) The handbook of aging and cognition. NJ, Erlbaum
15. de Keyser J, Debacker JP, Vauquelin G, Ebinger G (1990) The effect of aging on the D1 dopamine receptors in the human cortex. Brain Res 528: 308–310
16. Durstewitz D, Seamans JK (2002) The computational role of dopamine D1 receptors in working memory. Neural Netw 15: 561–572
17. Erixon-Lindroth N, Farde L, Robins-Wahlin T-B, Sovago J, Halldin C, Bäckman L (2005) The role of the striatal dopamine transporter in cognitive aging. Psychiatry Res 138: 1–1
18. Ferrandez AM, Teasdale N (1996) Changes in sensory motor behavior in aging. New York, Elsevier Science
19. Fry AF, Hale S (2000) Relationship among processing speed, working memory, and fluid intelligens in children. Biol Psychol 54: 1–34
20. Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E (1993) A neural system for error detection and compensation. Psychol Sci 4: 385–390
21. Giorgi O, Calderini G, Toffano G, Biggio G (1987) D1 dopamine receptors labeled with ^{3}H-SCH 23390: decrease in the striatum of aged rats. Neurobiol Aging 8: 51–54

22. Hasher L, Zacks RT (1988) Working memory, comprehension and aging: a review and a new view. The psychology of learning and motivation. G. H. Bower. New York, Academic Press 22: 193–225
23. Holroyd CB, Coles MGH (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. Psychol Rev 109: 679–709
24. Kassinen V, Vilkman H, Hietala J, Nagren K, Helenius H, Olsson H, Farde L, Rinne JO (2000) Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. Neurobiol Aging 21: 683–688
25. Li S, Lindenberger U, Sikström S (2001) Aging Cognition: from neuromodulation to representation to cognition. Trends Cogn Sci 5: 479–486
26. Li S-C, Lindenberger U, Frensch PA (2000) Unifying cognitive aging: from neuromodulation to representation to cognition. Neurocomputing 32–33: 879–890
27. Li S-C, Sikström S (2002) Integrative neurocomputational perspectives on cognitive aging, neuromodulation, and representation. Neurosci Biobehav Rev 26: 795–808
28. Li S-C, von Oertzen T, Lindenberger U (in press) A neurocomputationtional model of stochastic resonance and aging
29. Liu W, Lipsitz LA, Montero-Odasso M, Bean J, Kerrigan DC, Collins JJ (2002) Noise-enhanced vibrotactile sensitivity in older adults, patients with stroke, and patients with diabetic neuropathology. Arch Phys Med Rehabil 83: 171–176
30. MacRae PG, Spirduso WW, Wilcox RE (1988) Reaction time and nigrostriatal dopamine function: the effect of age and practice. Brain Res 451: 139–146
31. Murphy BL, Arnsten AFT, GoldmanRakic PS, Roth RH (1996) Increased dopamine levels turnover in the prefrontal cortext impairs spatical working memory performance in rats and monkeys. Proc Natl Acad Sci USA 93: 1325–1329
32. Nieuwenhuis S, Ridderinkhof KR, Talsma D, Coles MGH, Holroyd CB, Kok A, Van der Molen MW (2002) A computational account of altered error processing in older age: dopamine and the error-related negativity. Cogn Affect Behav Neurosci 2: 19–36
33. Nilsson LG, Bäckman L, Erngrund K, Nyberg L, Adolfsson R, Bucht G, Karlsson S, Widing G, Winblad B (1997) The Betula prospective cohort study: memory, health, and aging. Aging Neuropsych Cogn 4: 1–32
34. Park DC, Lautenschlager G, Hedden T, Davison N, Smith AD, Smith PK (2002) Models of visuospatial and verbal memory across the adult life span. Psychol Aging 17: 299–320
35. Schultz W (1998) Predictive reward signal of dopamine neurons. J Neurosci Neurophysiol 80: 1–27
36. Seamans JK, Floresco SB, Phillips AG (1998) D1 receptor modulation of hippocampal-prefrontal cortical circuits integrating spatial memory with executive functions in the rat. J Neurosci 18: 1613–1621
37. Servan-Schreiber D, Printz H, Cohen J (1990) A network model of catecholamine effects: gain, signal-to-noise ratio, and behavior. Science 249: 892–895
38. Sikström S (2004) The variance reaction time model. Cogn Psychol 48: 371–421
39. Simonotto E, Riani M, Seife C, Roberts M, Twitty JD, Moss F (1997) Visual perception of stochastic resonance. Phys Rev Lett 78: 1186–1189
40. Simonotto E, Spano F, Riani M, Ferrari A, Levriero F, Pilot A, Renzetti P, Paodi R, Sardanelli F, Vitali P, Twitty J, Chiou-Tan F, Moss F (1999) fMRI studies of visual cortical activity during noise timulation. Neurocomputing 26–27: 511–516
41. Spengler F, Godde B, Dinse HR (1995) Effects on aging on topographic organization of somatosensory cortex. NeuroReport 6: 469–473
42. Stevens CF, Cruz LA, Marks LE, Lakatos S (1998) A multimodal assessment of sensory threshold in aging. J Gerontol 53B: 263–272
43. Sutton RS, Barto AG (1998) Reinforcement learning: an introduction. MIT Press, Cambridge, MA
44. Thimm G, Moerland P, Fiesler E (1996) The interchangeability of learning rate and gain in backpropagation neural networks. Neural computation 8: 451–460
45. Watanabe M, Kodama T, Hikosaka K (1997) Increase of extracellular dopamine in primate prefrontal cortex during a working memory task. J Neurophysiol 78: 2795–2798
46. Wells C, Ward LM, Chua R, Inglis JT (2005) Touch noise increases vibrotactile sensitivity in old and young. Psy Sci 16: 313–320
47. West RL (1996) An application of prefrontal cortex function theory to cognitive aging. Psychol Bull 120: 272–292
48. Wong DF, Young D, Wilson PD, Meltzer CC, Gjedde A (1997) Quantification of neuroreceptors in the living brain: III. D2-like dopamine receptors: theory, validation and changes during normal aging. J Cerebr Blood Flow Metab 17: 316–330
49. Zelinski EM, Stewart ST (1998) Individual differences in 16-year memory changes. Psychol Aging 13: 622–630

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Emerging applications

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The periaqueductal grey area and the cardiovascular system

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Summary

In this chapter, we report that blood pressure can be increased or decreased depending on whether an electrode is in ventral or dorsal PAG. We also describe that it is theoretically possible to treat orthostatic hypotension. These are exciting developments not only because they provide an example of direct *translational* research from animal research to humans but also because they highlight a potential for future clinical therapies. The control of essential hypertension without drugs is attractive because of the side effects of medication such as precipitation of heart failure [10]. Similarly, drug treatment of orthostatic hypotension cannot differentiate between the supine and standing positions and can therefore lead to nocturnal hypertension [22, 29]. A stimulator could be turned off at night or contain a mercury switch that reacts to posture.

Keywords: Neuromodulation; deep brain stimulation; DBS; periaquaductal grey area; periventricular grey area; cardiovascular system; orthostatic hypotension.

Introduction

The periaqueductal grey area (PAG) is well known to be important in the modulation of pain and is an area where deep brain stimulating electrodes are often placed for the treatment of chronic, intractable neuropathic pain [6, 16, 25]. However, in mammals, this region is known to be an important component in the *defence* reaction [7]. The *defence* reaction is an integrated response from the forebrain down to the cardiovascular system that is associated with survival in the wild [19]. For example, if escape from danger is a possibility, the response involves a 'fight or flight' reaction that includes raised blood pressure and heart rate, non-opioid mediated analgesia and emotional effects such as fear [9]. On the other hand, if escape is unlikely, the reaction consists of lowered blood pressure, opioid-mediated analgesia and 'passive' behaviour as well as fear [12, 21]. Electrical stimulation of the PAG in animals will elicit these *defence* reactions and thus, it is likely that stimulation of the same area in the human will affect not only the pain modulation pathways, but also the cardiovascular components of this system. As we have patients with electrodes implanted into the rostral part of the PAG, we are in an ideal position to study the effect of PAG stimulation in the human.

A limited amount of previous evidence exists to suggest that stimulation of the human PAG causes cardiovascular changes in humans [36]. Here, we characterise these effects in detail.

Alteration of blood pressure with PAG stimulation

We have shown that electrical stimulation of the human PAG alters blood pressure [17]. In this study of fifteen chronic neuropathic pain patients (17 electrodes), blood pressure and ECG were continuously measured in the laboratory whilst stimulation parameters were altered (either 10 or 50 Hz i.e. in the frequency range used to treat chronic pain). We found that cardiovascular responses to stimulation were consistent (on at least three occasions) for any pair of electrode contacts used. Overall, arterial blood pressure significantly decreased in seven pairs of electrode contacts in seven patients (significance was determined using one-way analysis of variance of blood pressure with time – ANOVA). Conversely, blood pressure significantly increased in six pairs of contacts. These results are summarised in Fig. 1.

The average reduction in SBP (for those in whom BP was reduced) was 14.2 ± 3.6 mmHg (range 7–25 mmHg), or 13.9%, after 300 s stimulation. Figure 1A shows that the drop in SBP is accompanied by a fall in diastolic

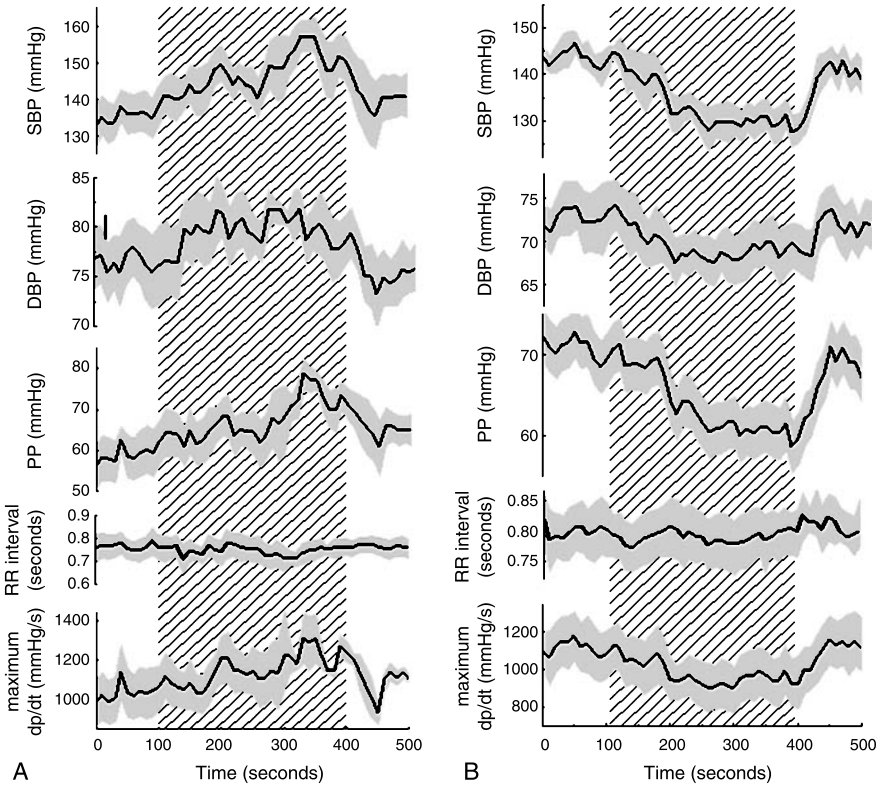

Fig. 1. (A) Changes in cardiovascular parameters associated with reduced blood pressure. *Patterned area* Period of stimulation. *Grey area* ± one standard error of the mean. *SBP* Systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *RR interval* time period between R waves on electrocardiogram, *dP/dt* change of systolic blood pressure with time. (B) Changes in cardiovascular parameters associated with increased blood pressure (see text for details)

BP (DBP) of 4.9 mmHg ± 2.9 ($p = 0.03$, single factor ANOVA, $n = 7$, range 1.5–9.3), equivalent to 6%. This implies a degree of peripheral vasodilatation. However, as the systolic drops more than the diastolic BP (leading to a reduction in pulse pressure), the mechanism is unlikely to be related simply to peripheral vascular changes. We therefore measured the change of SBP with time (maximum dP/dt i.e. the slope of the blood pressure curve). This is known to be a marker of cardiac contractility [8] as the harder the myocardium contracts, the steeper the slope of this curve. This revealed a mean reduction of 222 mmHg/s ± 126 (19.8%, $p = 0.06$). This is suggestive, but not absolute proof that the contractility of the myocardium was reduced. On the other hand, R–R interval (a measure of heart rate) did not change significantly throughout the stimulation period (mean change = 0.01s ± 0.04, range 0–0.08). As heart rate is controlled via the vagal nerve, this implies that there was no change in parasympathetic activity.

For those with an increase in BP, the mean rise in SBP was 16.73 mmHg ± 5.9 ($p < 0.001$, single factor ANOVA, $n = 6$, range 16–31 mmHg), equivalent to 16.4% at the end of a 400 s period where stimulation was started at 100 s (however, the maximum rise of 22.23 mmHg occurred just before this – see Fig. 1B). Stimulation parameters required to raise BP were the same as with the episodes of reduced BP (i.e. 10 Hz, 120 μs and up to 3.0 V), except that 50 Hz did not have the same effect in any patient. As with BP reduction, increases were accompanied by a smaller rise in DBP of 4.9 mmHg ± 2.8 or 6.4% ($p = 0.04$, single factor ANOVA, $n = 6$, range = 2.4–12.1 mmHg). There was also an increase in mean pulse pressure and again, the maximum rise of 17.33 mmHg occurred just before 400 s. Maximum dP/dt increased by 212 ± 97 mmHg/s ($p < 0.03$, single factor ANOVA). As with reduction in BP, there was no significant change in R–R interval. Thus, it appears that increasing BP is accompanied by a mirror of the changes that occur during reduction in BP.

Six control patients were investigated (six thalamic electrodes, one spinal cord stimulator). Despite extensive investigation using a variety of frequencies and voltages, as well as a variety of electrode contact configurations, we were unable to modulate the BP in any of these patients. In addition to the control electrodes that had no effect on BP, four patients with PVG electrodes (six electrodes in total) also had no effect.

Electrode location

Because blood pressure changes in animals depend on whether the electrode is in ventral or dorsal PAG, we

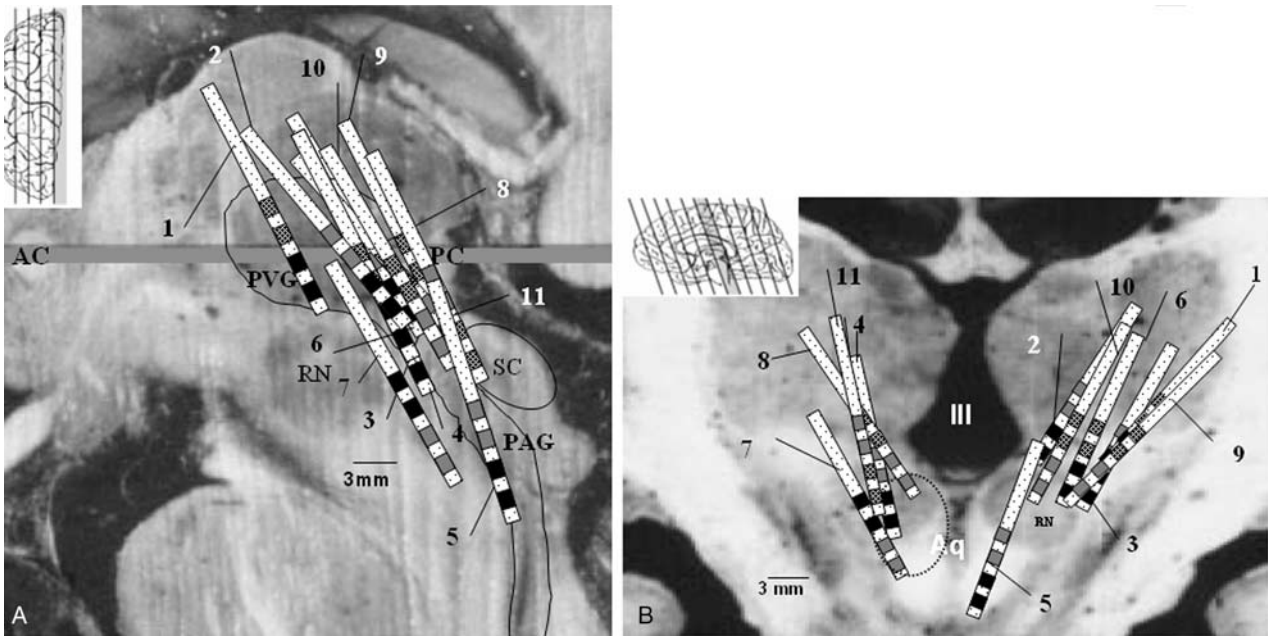

Fig. 2. (A) Sagittal positions of the electrodes in patients in whom there were changes in blood pressure. (B) Coronal positions. For clarity, patients with no changes are not shown. Note that patients *#1–7* all had reduction in BP (*black contacts*) and have the most ventral electrodes. Conversely, *#8–11* and the upper 2 contacts of *#1* and *#6* had a rise in BP (*patterned contacts*). Gray contacts are those that, when stimulated, had no effect on BP. *AC* Anterior commissure, *PC* posterior commissure, *PVG* periventricular gray, *PAG* periaqueductal gray, *SC* superior colliculus (the level of which is depicted by the dotted circle in 1B), *RN* red nucleus, *III* third ventricle, *Aq* aqueduct. Inset of A shows the AC–PC plane, inset of B shows the slice position

looked at electrode position. These were plotted on a brain atlas [23] using the post-operative MRI and a manipulation program (MRIcro version 1.38 build 1, Chris Rorden). The results are shown in Fig. 2. This shows that those electrodes that reduced blood pressure were placed ventrally, as compared to the dorsal electrodes that increased blood pressure. Patients with no blood pressure changes are not shown for clarity. However, we plotted electrode positions for five of these six electrodes (one had not had a post-operative scan). Four of the five electrodes were dorsal to the group that raised BP and were therefore probably outside the PAG/PVG. The remaining electrode was in mid-PVG.

Changes in BP were compared between the two groups of ventral and dorsal electrodes ($n = 8$ and 9, respectively – unlike the changes described above, this included all patients, even those without significant changes in BP). The mean peak change in SBP was -10.3 ± 2.8 mmHg for the ventral group and $+10.8 \pm 3.1$ mmHg for the dorsal group. Comparison using one way ANOVA showed significance ($p = 0.003$). Similarly, the mean peak change in DBP was -4.6 ± 1.2 and $+3.5 \pm 0.8$ mmHg, respectively ($p = 0.007$). Mean peak change in pulse pressure ranged from -8.6 ± 3.5 mmHg for the ventral to $+7.4 \pm 2.1$ mmHg for the dorsal group ($p = 0.01$). dP/dt ranged from -181.6 ± 28 mmHg/s for ventral and $+82 \pm 26$ mmHg/s for dorsal electrodes ($p = 0.007$). Comparison of RR interval between the two groups did not reveal any significant difference ($p = 0.13$).

Power spectral analysis of systolic blood pressure

It is possible to elucidate underlying mechanisms of blood pressure changes by looking at the dominant frequencies in the blood pressure wave-form [26]. Activity in the range just under 0.1 Hz is associated with activity of the sympathetic nervous system – a wave known as Meyer's wave [28, 13]. We, therefore, performed *autoregressive power spectral analysis* of the blood pressure waveform in all patients. Frequencies below 0.02 Hz were filtered out to remove the trend in the signal (see [33] for methodology). Figure 3A shows a typical example in a patient whose blood pressure could be increased or decreased depending on which contacts were used. It can be seen that with an increase in blood pressure, there was a large increase in the low frequency wave in the 0.1 Hz region. With a reduction in blood pressure, there was a corresponding decrease. This implies that increase in blood pressure is associated with an increase in sympathetic activity, and vice versa.

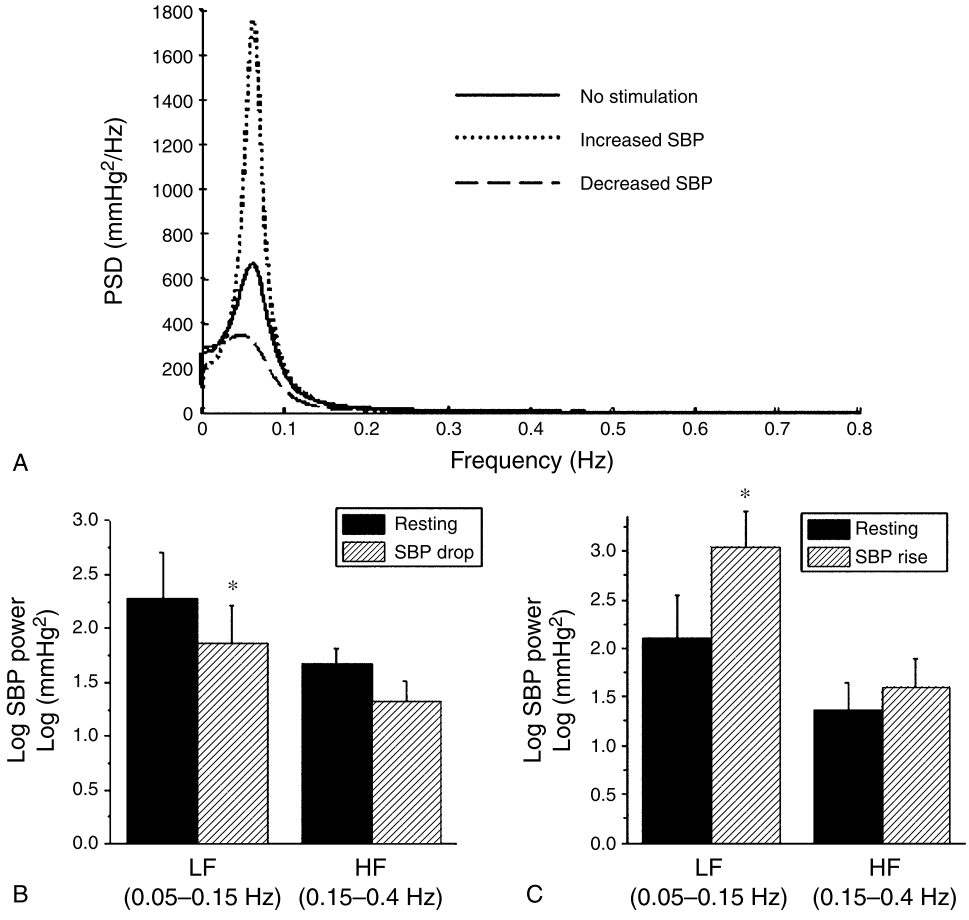

Fig. 3. Changes in low- and high-frequency power spectra of systolic blood pressure. (A) Example in one patient, in whom blood pressure could be increased or decreased, depending on which contacts were used. A change in the low-frequency component was associated with change in blood pressure, implying changes in sympathetic nervous system activity. (B, C) Changes for the groups in whom blood pressure decreased ($n = 7$) or increased ($n = 6$), respectively. Error bars denote ± 1 SEM

To look at the group results, we calculated the power of the low- and high-frequency components as the integral of the power spectra between 0.05 and 0.15 Hz and between 0.15 and 0.4 Hz. The logarithm of the low- and high-frequency power for the two groups of patients (blood pressure increase or decrease) ON and OFF stimulation were analysed using a paired *t*-test (Fig. 3C, D). This revealed that for the group as a whole, there was a change in low-frequency power spectra that corresponded to blood pressure changes. There were also changes in high-frequency power, but these were not significant (this may be due to small numbers).

Can we treat essential hypertension?

We have demonstrated that it is possible to increase or decrease blood pressure in humans with electrical stimulation of the PAG. Furthermore, the direction of blood pressure change can be controlled by placing the electrode in either ventral or dorsal PAG. Essential hypertension is a significant clinical problem that has a skewed distribution and can lead to stroke or myocardial infarction [2, 34]. Approximately, 3% of these patients are refractory to treatment [1]. Reducing blood pressure with deep brain stimulation is theoretically possible but in itself poses a risk; there is approximately one in three hundred risk of stroke as well as other less serious, but nevertheless troublesome complications such as infection and hardware problems [5]. Therefore it is unlikely that deep brain stimulation could be justified at the present time. As well as further elucidating the mechanisms of DBS on blood pressure, the risk of the procedure needs to be reduced for what is essentially a prophylactic operation. This may come about with advances in technology such as nanotechnology etc. that may lead to smaller, less invasive electrodes. However,

Gotoh *et al.* [15] have shown that it is theoretically possible to control blood pressure at a given value by altering electrical stimulation of cardiovascular centres in the medulla according to blood pressure measurements made via an arterial line. This shows proof of principle.

Can we treat orthostatic hypotension?

We have shown that we are able to *increase* as well as *decrease* blood pressure with PAG stimulation. This raises the possibility that we might be able to treat orthostatic or *postural* hypotension (OH). In the normal subject, assumption of an upright posture leads to pooling of venous blood in the lower extremities and splanchnic circulation [14]. The resulting decrease in venous return to the heart leads to a compensatory, centrally mediated increase in sympathetic and decrease in parasympathetic activity (known as the *baroreceptor reflex*). This activity usually results in a transient fall in systolic blood pressure of 5–10 mmHg, a small rise in diastolic blood pressure (5–10 mmHg) and a rise in heart rate of 10–25 beats per minute. In *orthostatic hypotension*, patients suffer troublesome low blood pressure on standing or symptoms of cerebral hypoperfusion [32]. It is present in up to 20% of people over 65 and its treatment may lead to troublesome raised blood pressure [29, 22]. Ascending projections of barosensitive adrenergic cells in the rostroventrolateral medulla project to PAG [18]. There is evidence that chemical stimulation of the PAG inhibits baroreflex vagal bradycardia in rats [20]. Thus it is conceivable that stimulation of this area in the

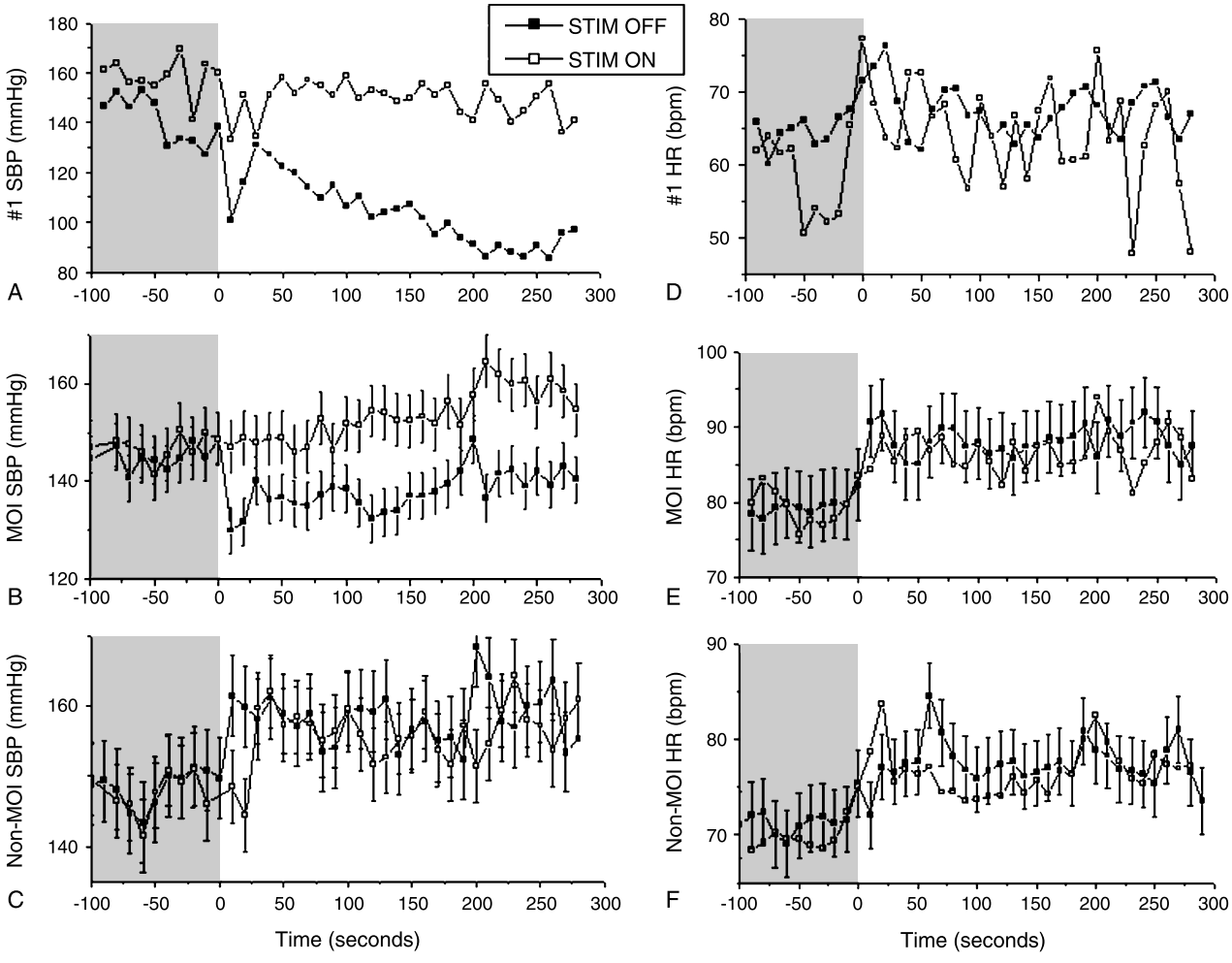

Fig. 4. Blood Pressure and Heart Rate changes on standing. (A–C) Mean changes in systolic blood pressure for subject #1, MOI group, and non-MOI group, respectively. (D–F) Changes in heart rate for the same groups. All traces include the mean of three sessions, averaged every ten seconds. *MOI* Mild orthostatic intolerance group, *nonMOI* no mild orthostatic intolerance group. *Grey area* Period when patient was sitting, *white area* (from 0 seconds) period of standing. ■ Stimulation 'OFF', □ stimulation 'ON'. Error bars show ±1 standard error of the mean

human may affect the baroreceptor reflex. We performed a study in eleven patients with PVG/PAG stimulators for neuropathic pain, in which we continuously recorded blood pressure while sitting for 100 s, followed by 280 s of standing. Subjects were grouped into three categories as follows; subject #1 had a history of orthostatic hypotension that had resolved after the stimulator was inserted (whilst it was on). The second group (five subjects) had *mild orthostatic intolerance* (MOI-group) that was defined as a fall in systolic blood pressure of >20 mmHg on standing, but no clinical symptoms. The third group (five subjects) had no significant postural effects on blood pressure (non-MOI group). We showed that stimulation in subject #1 significantly reduced the postural drop in blood pressure (from 28.2 to 11.1%, $p<0.001$, *t*-test) and in the MOI group, completely reversed it ($p<0.001$, *t*-test) (Fig. 4A, B). In the control group (non-MOI), there was no significant difference in blood pressure between the two groups (Fig. 4C).

Figure 4D–F shows that *absolute* heart rate changes on standing were not significantly altered with stimulation. However, Fig. 4D shows that with stimulation, the heart rate variability appears to be increased (there is a greater oscillation in heart rate with stimulation). To formally assess this, we looked at the power of RR interval spectra. The power of RR interval spectra in the high frequency band (0.15–0.4 Hz) has been shown to be a marker of cardiac vagal control [27, 31]. The low frequency band (0.04–0.15 Hz) has been associated with cardiac sympathetic activity, although it has been shown to be affected by *both* vagal and sympathetic nerves [4, 31]. Previous research has shown a reduction in both of these components of heart rate variability power with head up tilt in patients with autonomic neuropathy [37] compared to the increase in low-frequency power seen on standing in normal subjects [30]. We performed *auto-regressive power spectra analysis* of RR interval on all patients in the study. In the MOI and Non-MOI groups, baseline low-frequency power of RR interval significantly increased with stimulation (*t*-test, $p=0.021$ and $p<0.001$, respectively, Table 1). However, baseline high-frequency power in these groups was not significantly altered by the stimulation ($p>0.1$, *t*-test). In the MOI group and subject #1, the reduction in both low *and* high frequency power associated with standing was prevented with stimulation ($p=0.008$, *t*-tests, 'ON' vs. 'OFF'). These results suggest that stimulation may increase the cardiac sympathetic activity and enhance its response to standing.

Another way of elucidating mechanisms of the effects of stimulation on postural changes is to look at baroreflex sensitivity. In young and middle-aged healthy subjects, baroreflex sensitivity decreases on standing [11, 30, 35]. In autonomic neuropathy, such as that of diabetes, it has been shown that it is lower in the supine position and there is less further reduction on standing than in normal subjects [30]. We calculated the baroreflex sensitivity index from the transfer function of systolic blood pressure and RR interval signals using bivariate autoregressive modeling [3, 35]; $\mathrm{RR}(n) = \sum_{k=1}^{p} a_{11}(k)\mathrm{RR}(n-k) + \sum_{k=1}^{p} a_{12}(k)\mathrm{SBP}(n-k) + w(n)$. We showed that the baroreflex sensitivity in subject #1 (i.e. orthostatic hypotension) and MOI groups were similar to those with a mild autonomic neuropathy (Table 1). We also showed that stimulation significantly raises sensitivity in the sitting position (*t*-test, $p=0.018$, <0.001 and 0.002 for subject #1, MOI and

Table 1. *Changes in heart rate variability and baroreflex sensitivity while sitting and standing, with stimulation ON or OFF*

Group	Subject #1		MOI group		Non-MOI group	
Stimulation	OFF	ON	OFF	ON	OFF	ON
Low frequency (ms^2)						
Sitting	5.2	4.7	69.8 (1–285)	136.2* (1–474)	208.1 (81–330)	466.3* (298–489)
Standing	1.6	4.9	7.0 (0.1–20)	135.0* (1–520)	313.5 (63–603)	346.9* (86–636)
High frequency (ms^2)						
Sitting	6.9	7.4	176.0 (3–730)	182.1 (1–757)	224.6 (10–618)	341.4 (9–727)
Standing	4.2	7.6	122.4 (1–600)	181.8* (1–751)	247.5 (6–521)	464.6* (5–1280)
Baroreflex sensitivity index (ms/mmHg)						
Sit	3.6	11.1	6.6 (2.5–10.7)	8.6* (7.2–11.1)	9.9 (2.9–17.3)	15.3* (6.9–23.8)
Stand	0.13	5.41	0.7 (0.1–2)	4.3* (0.5–9.2)	4.5 (0.1–8.3)	14.7* (4.2–26)

MOI Mild orthostatic intolerance. Ranges shown in brackets. *Indicates significant difference between OFF and ON conditions within each group.

non-MOI groups, respectively) and reduces the magnitude of reduction on standing in orthostatic hypotension ($p = 0.024$ subject #1, $p < 0.001$, MOI). This suggests that the reversal of postural changes in blood pressure are associated with increased baroreceptor sensitivity.

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References

1. Alderman MH, Budner N, Cohen H, Lamport B, Ooi WL (1988) Prevalence of drug resistant hypertension. Hypertension 11: II71–II75
2. Almgren T, Persson B, Wilhelmsen L, Rosengren A, Andersson OK (2005) Stroke and coronary heart disease in treated hypertension – a prospective cohort study over three decades. J Intern Med 257: 496–502
3. Barbieri R, Bianchi AM, Triedman JK, Mainardi LT, Cerutti S, Saul JP (1997) Model dependency of multivariate autoregressive spectral analysis. IEEE Eng Med Biol Mag 16: 74–85
4. Berger RD, Saul JP, Cohen RJ (1989) Transfer function analysis of autonomic regulation. I. Canine atrial rate response. Am J Physiol 256: H142–H152
5. Beric A, Kelly PJ, Rezai A, Sterio D, Mogilner A, Zonenshayn M, Kopell B (2001) Complications of deep brain stimulation surgery. Stereotact Funct Neurosurg 77: 73–78
6. Bittar RG, Kar-Purkayastha I, Owen SL, Bear RE, Green A, Wang S, Aziz TZ (2005) Deep brain stimulation for pain relief: a meta-analysis. J Clin Neurosci 12: 515–519
7. Bittencourt AS, Carobrez AP, Zamprogno LP, Tufik S, Schenberg LC (2004) Organization of single components of defensive behaviors within distinct columns of periaqueductal gray matter of the rat: role of N-methyl-D-aspartic acid glutamate receptors. Neuroscience 125: 71–89
8. Brinton TJ, Cotter B, Kailasam MT, Brown DL, Chio SS, O'Connor DT, DeMaria AN (1997) Development and validation of a non-invasive method to determine arterial pressure and vascular compliance. Am J Cardiol 80: 323–330
9. Carrive P, Bandler R (1991) Control of extracranial and hindlimb blood flow by the midbrain periaqueductal grey of the cat. Exp Brain Res 84: 599–606
10. Cohen Solal A, Johnson N (2004) Prescription of betablockers in chronic cardiac failure: results of a national enquiry of cardiologists. Arch Mal Coeur Vaiss 97: 1236–1243
11. Cooper VL, Hainsworth R (2001) Carotid baroreceptor reflexes in humans during orthostatic stress. Exp Physiol 86: 677–681
12. Finnegan TF, Chen SR, Pan HL (2005) Effect of the {mu} opioid on excitatory and inhibitory synaptic inputs to periaqueductal gray-projecting neurons in the amygdala. J Pharmacol Exp Ther 312: 441–448
13. Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baselli G, Cerutti S, Lombardi F, Pagani M, Malliani A (1990) Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation 81: 537–547
14. Garas Z, Komor K (1971) Changes in the plasma volume in the erect position in hypertension. Comparative studies in the normotensive and hypertensive disease phase. Z Gesamte Inn Med 26: 199–202
15. Gotoh TM, Tanaka K, Morita H (2005) Controlling arterial blood pressure using a computer-brain interface. Neuroreport 16: 343–347
16. Green AL, Owen SLF, Davies P, Moir L, Aziz TZ (2005) Deep brain stimulation for neuropathic cephalalgia. Cephalalgia (in press)
17. Green AL, Wang S, Owen SLF, Xie K, Liu X, Paterson DJ, Stein JF, Bain PG, Aziz TZ (2005b) Deep brain stimulation can regulate arterial blood pressure in awake humans. Neuroreport 16: 1741–1745
18. Haselton JR, Guyenet PG (1990) Ascending collaterals of medullary barosensitive neurons and C1 cells in rats. Am J Physiol 258: R1051–R1063
19. Hunsperger RW (1956) Affective reaction from electric stimulation of brain stem in cats. Helv Physiol Pharmacol Acta 14: 70–92
20. Inui K, Nosaka S (1993) Target site of inhibition mediated by midbrain periaqueductal gray matter of baroreflex vagal bradycardia. J Neurophysiol 70: 2205–2214
21. Johnson PL, Lightman SL, Lowry CA (2004) A functional subset of serotonergic neurons in the rat ventrolateral periaqueductal gray implicated in the inhibition of sympathoexcitation and panic. Ann N Y Acad Sci 1018: 58–64
22. Kaplan NM (1993) The promises and perils of treating the elderly hypertensive. Am J Med Sci 305: 183–197
23. Mai JK, Assheuer J, Paxinos G (1998) Atlas of the human brain. Academic Press, San Diego, pp 79, 118
24. McGaraughty S, Farr DA, Heinricher MM (2004) Lesions of the periaqueductal gray disrupt input to the rostral ventromedial medulla following microinjections of morphine into the medial or basolateral nuclei of the amygdala. Brain Res 1009: 223–227
25. Owen SLF, Green AL, Stein JF, Aziz TZ (2005) Deep brain stimulation for the alleviation of post-stroke neuropathic pain. Pain (in press)
26. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E *et al* (1986a) Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 59: 178–193
27. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E *et al* (1986b) Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 59: 178–193
28. Pagani M, Montano N, Porta A, Malliani A, Abboud FM, Birkett C, Somers VK (1997) Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. Circulation 95: 1441–1448
29. Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS (1992) Orthostatic hypotension in older adults. The cardiovascular health study. CHS Collaborative Research Group. Hypertension 19: 508–519
30. Sanderson JE, Yeung LY, Yeung DT, Kay RL, Tomlinson B, Critchley JA, Woo KS, Bernardi L (1996) Impact of changes in respiratory frequency and posture on power spectral analysis of heart rate and systolic blood pressure variability in normal subjects and patients with heart failure. Clin Sci (Lond) 91: 35–43
31. Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ (1991) Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol 261: H1231–H1245

32. Schatz IJ, Bannister R *et al* (1996) Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. J Neurol Sci 144: 218–219
33. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 93: 1043–1065
34. Wang JG, Staessen JA, Franklin SS, Fagard R, Gueyffier F (2005) Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. Hypertension 45: 907–913
35. Wang S (2002) Multivariate and multidimensional signal analysis of cardiovascular time series. PhD Thesis
36. Young RF (1997) Brain Stimulation. In: North RB, Levy RM (eds) The neurosurgical management of pain. Springer, New York, pp 288–290
37. Zhang Y, Critchley LA, Tam YH, Tomlinson B (2004) Short-term postural reflexes in diabetic patients with autonomic dysfunction. Diabetologia 47: 304–311

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Therapeutic potential of computer to cerebral cortex implantable devices

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Summary

In this article, an overview of some of the latest developments in the field of cerebral cortex to computer interfacing (CCCI) is given. This is posed in the more general context of Brain-Computer Interfaces in order to assess advantages and disadvantages. The emphasis is clearly placed on practical studies that have been undertaken and reported on, as opposed to those speculated, simulated or proposed as future projects. Related areas are discussed briefly only in the context of their contribution to the studies being undertaken. The area of focus is notably the use of invasive implant technology, where a connection is made directly with the cerebral cortex and/or nervous system. Tests and experimentation which do not involve human subjects are invariably carried out *a priori* to indicate the eventual possibilities before human subjects are themselves involved. Some of the more pertinent animal studies from this area are discussed. The paper goes on to describe human experimentation, in which neural implants have linked the human nervous system bi-directionally with technology and the internet. A view is taken as to the prospects for the future for CCCI, in terms of its broad therapeutic role.

Keywords: Neuromodulation; brain-computer interface; biological systems; implant technology; feedback control.

Introduction

Much research is being carried out in which biological signals of some form are measured, are acted upon by some appropriate signal processing technique and are then employed either to control a device or as an input to some feedback mechanism [17, 21]. In most cases, electroencephalogram (EEG) signals are measured externally to the body, using externally adhered electrodes on the scalp [26] and are then employed as a control input. However, reliable interpretation of EEG data is extremely complex – partly due to both the compound nature of the multi-neuronal signals being measured and the difficulties in recording such highly attenuated signals in the first place. Recently, interest has grown in the use of real-time functional magnetic resonance imaging (fMRI) for applications such as computer cursor control. This typically involves an individual activating their brain in different areas by reproducible thoughts [28] or by recreating events [27]. Alternatively fMRI and EEG technologies can be combined so that individuals can learn how to regulate slow cortical potentials (SCPs) in order to activate external devices [12].

It is worth noting that external monitoring of neural signals, by means such as EEG analysis, currently leaves much to be desired. In almost all cases, the measuring techniques considerably restrict the user's mobility and, as is especially the case with fMRI, the situation far from presents a natural or comfortable setting. Such systems also tend to be relatively slow, partly because of the nature of recordings via the indirect connection, but also because it takes time for the individuals themselves to actually initiate changes in the signal. As a result of this, distractions, both conscious and sub-conscious, can result in false indicators, thus, preventing the use of such techniques for safety–critical and/or highly dynamic applications. Despite this, the method can enable some individuals who otherwise have extremely limited communication abilities to operate some local technology in their environment, and, in any case, it can serve as a test bed for a more direct and useful connection. The definition of what constitutes a cerebral cortex/computer interface (CCCI) or, even more so, a brain-computer interface (BCI) can be extremely broad. Indeed, a standard keyboard could be so regarded. It is clear however that various wearable computer techniques and virtual reality systems, e.g. glasses containing a miniature computer screen for a remote visual experience [15], are felt by some researchers to fit this category. Although certain body conditions, such as stress or alertness, can be

monitored in this way, the focus of this paper is on bidirectional CCCIs and is more concerned with a direct connection between the human and technology.

In vivo studies

Non-human animal studies are often considered to be a pointer for what is potentially achievable with humans in the future. As an example, in one particular animal study the extracted brain of a lamprey, retained in a solution, was used to control the movement of a small wheeled robot to which it was attached [19]. The lamprey innately exhibits a response to light reflections on the surface of water by trying to align its body with respect to the light source. When connected into the robot body, this response was utilised by surrounding the robot with a ring of lights. As different lights were switched on and off, so the robot moved around its corral, trying to position itself appropriately. Meanwhile in studies involving rats, a group of rats were taught to pull a lever in order to receive a suitable reward. Electrodes were then chronically implanted into the rats' brains such that the reward was proffered when each rat thought (one supposes) about pulling the lever, but before any actual physical movement occurred. Over a period of days, four of the six rats involved in the experiment learned that they did not in fact need to initiate any action in order to obtain a reward; merely thinking about it was sufficient [2]. In another series of experiments, implants consisting of microelectrode arrays have been positioned into the frontal and parietal lobes of the brains of two female rhesus macaque monkeys. Each monkey learned firstly how to control a remote robot arm through arm movements coupled with visual feedback, and it is reported that ultimately one of the monkeys was able to control the arm using only brain derived neural signals with no associated physical movement. Notably, control signals for the reaching and grasping movements of the robotic arm were derived from the same set of implanted electrodes [3, 16]. Such promising results from animal studies have given the drive towards human applications a new impetus.

Human application

The more general class of brain-computer interfaces (BCIs) for humans, of one form or another, have been specifically developed for a range of applications including military weapon and drive systems, personnel monitoring and for games consoles. However, by far the largest driving force for BCI research to date has been the requirement for new therapeutic devices such as neural prostheses. The most ubiquitous sensory neural prosthesis in humans is by far the cochlea implant [7]. Here, the destruction of inner ear hair cells and the related degeneration of auditory nerve fibres results in sensorineural hearing loss. As such, the prosthesis is designed to elicit patterns of neural activity via an array of electrodes implanted into the patient's cochlea, the result being to mimic the workings of a normal ear over a range of frequencies. It is claimed that some current devices restore up to approximately 80% of normal hearing, although for most recipients it is sufficient that they can communicate to a respectable degree without the need for any form of lip reading. The typically modest success of cochlea implantation is related to the ratio of stimulation channels to active sensor channels in a fully functioning ear. Recent devices consist of up to 32 channels, whilst the human ear utilises upwards of 30,000 fibres on the auditory nerve. There are now reportedly over 10,000 of these prostheses in regular operation.

Historically, studies investigating the integration of technology with the human central nervous system have varied from merely diagnostic to the amelioration of symptoms [29]. In the last few years, some of the most widely reported research involving human subjects is based on the development of an artificial retina [20]. Here, small electrode arrays have been successfully implanted into a functioning optic nerve. With direct stimulation of the nerve it has been possible for the otherwise blind recipient to perceive simple shapes and letters. The difficulties with restoring sight are though several orders of magnitude greater than those of the cochlea implant simply because the retina contains millions of photodetectors that need to be artificially replicated. An alternative is to bypass the optic nerve altogether and use cortical surface or intracortical stimulation to generate phosphenes [4]. Unfortunately, progress in this area has been hampered by a general lack of understanding of brain functionality, hence, impressive and useful short-term results are still awaited. Electronic neural stimulation has proved to be extremely successful in other areas, including applications such as the treatment of Parkinson's disease symptoms. In Parkinson's disease, diminished levels of the neurotransmitter dopamine cause over-activation in the globus pallidus internus and the subthalamic nucleus, resulting in slowness, stiffness, gait difficulties and hand tremors. By implanting electrodes into the subthalamic nucleus to provide a constant stimulation pulse, the over-activity

can be inhibited allowing the patient, to all external intents and purposes, to function normally [18]. Meanwhile, ongoing research is investigating how the onset of tremors can be accurately detected in the initial stages such that merely a stimulation current burst is required rather than a constant pulsing [10]. Clearly, this has implications for battery inter-recharge periods as well as limiting the extent of in-body intrusive signalling.

In a more general sense, most invasive CCCIs monitor multi-neuronal intracortical action potentials, requiring an interface which includes sufficient processing in order to relate recorded neural signals with movement intent. Problems incurred are the need to position electrodes as close as possible to the source of signals, the need for long term reliability and stability of interface in both a mechanical and a chemical sense, and adaptivity in signal processing to deal with technological and neuronal time dependence. However, in recent years a number of different collective assemblies of microelectrodes have been successfully employed both for recording and stimulating neural activity. Although themselves of small scale, nevertheless high density connectors/transmitters are required to shift the signals to/from significant signal processing and conditioning devices and also for onward/receptive signal transmission. A line of research has centred around patients who have suffered a stroke resulting in paralysis. The most relevant to this paper is the use of a '3rd generation' brain implant which enables a physically incapable brainstem stroke victim to control the movement of a cursor on a computer screen [13, 14]. Functional magnetic resonance imaging (fMRI) of the subject's brain was initially carried out to localise where activity was most pronounced whilst the subject was thinking about various movements. A hollow glass electrode cone containing two gold wires and a neurotrophic compound (giving it the title 'Neurotrophic Electrode') was then implanted into the motor cortex, in the area of maximum activity. The neurotrophic compound encouraged nerve tissue to grow into the glass cone such that when the patient thought about moving his hand, the subsequent activity was detected by the electrode, then amplified and transmitted by a radio link to a computer where the signals were translated into control signals to bring about movement of the cursor. With two electrodes in place, the subject successfully learnt to move the cursor around by thinking about different movements. Eventually, the patient reached a level of control where no abstraction was needed – to move the cursor he simply thought about moving the cursor. Notably, during the period that the implant was in place, no rejection of the implant was observed; indeed the neurons growing into the electrode allowed for stable long-term recordings.

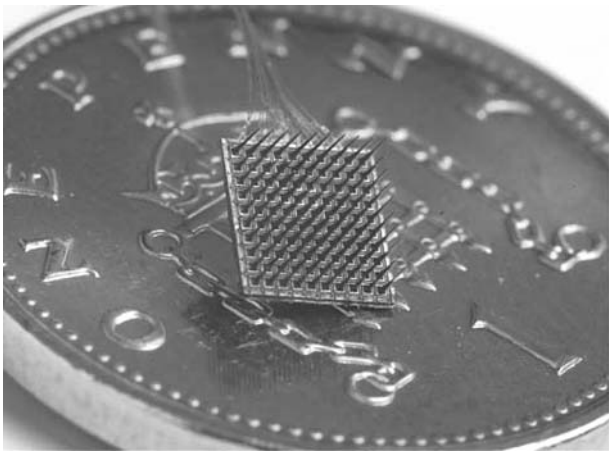

Fig. 1. A 100 electrode, 4×4 mm microelectrode array, shown on a UK 1 pence piece for scale

Some of the most impressive human research to date has been carried out using the microelectrode array, shown in Fig. 1. The individual electrodes are only 1.5 mm long and taper to a tip diameter of less than 90 microns. Although a number of trials not using humans as a test subject have occurred [1], human tests are at present limited to two studies. In the second of these, the array has been employed in a recording only role [5, 6, 8], most notably, recently as part of the 'Braingate' system. Essentially, activity from a few neurons monitored by the array electrodes is decoded into a signal to direct cursor movement. This has enabled an individual to position a cursor on a computer screen, using neural signals for control combined with visual feedback. The first use of the microelectrode array (Fig. 1) will be discussed in the following section as this has considerably broader implications, which extend the concept of therapy. A key selection point at the present time are what type of implant to employ, as several different possibilities exist, ranging from single electrode devices to multielectrode needles which contain electrode points at different depths to multielectrode arrays which either contain a number of electrodes which penetrate to the same depth (as in Fig. 1) or are positioned in a banked/sloped arrangement. A further key area of consideration is the exact positioning of a CCCI. In particular, certain areas of the brain are only really useful for monitoring purposes whilst others are more useful for stimulation. Actually deriving a reliable command signal from a collection of captured neural signals is not necessarily a simple task, partly due to the complexity of signals recorded and partly due to time constraints in dealing

with the data. In some cases, however, it can be relatively easy to look for and obtain a system response to certain anticipated neural signals – especially when an individual has trained extensively with the system. In fact, neural signal shape, magnitude and waveform with respect to time are considerably different to other signals picked up.

If a greater understanding is required of neural signals recorded then this will almost surely present a major problem. This is especially true if a number of simultaneous channels are being employed, each requiring a rate of digitization of (most likely) greater than 20 kHz in the presence of unwanted noise. For real time use, this data will also need to be processed within a few milliseconds (100 ms at most). Further, although many studies have looked into the extraction of command signals (indicating intent) from measured values, it is clear that the range of neural activity is considerable. Even in the motor area, not only are motor signals present but so too are sensory, cognitive, perceptual along with other signals, the exact purpose of which is not clear – merely classifying them as noise is not really sufficient and indeed, it can be problematic when they are repeated and apparently linked in some way to activity. It is worth stressing here, that the human brain and spinal cord are linking structures, the functioning of which can be changed through electronic stimulation such as that provided via a microelectrode array arrangement. This type of technology, therefore, offers a variety of therapeutic possibilities. In particular, the use of implanted systems when applied to spinal cord injured patients, in whom nerve function is disordered, was described [22] as having the following potential benefits (among others):

1. Re-education of the brain and spinal cord through repeated stimulation patterns.
2. Prevention of spinal deformity.
3. Treatment of intractable neurogenic and other pain.
4. Assisting bladder emptying.
5. Improving bowel function.
6. Treatment of spasticity.
7. Improvement of respiratory function – assisting coughing and breathing.
8. Reduction of cardiovascular maleffects.
9. Prevention of pressure sores – possibly providing sensory feedback from denervated areas.
10. Improvement and restoration of sexual function.
11. Improved mobility.
12. Improved capability in daily living, especially through improved hand, upper limb and truncal control.

Sensate prosthetics is another growing application area of neural interface technology, whereby a measure of sensation is restored using signals from small tactile transducers distributed within an artificial limb [7]. The transducer output can be employed to stimulate the sensory axons remaining in the residual limb which are naturally associated with a sensation. This more closely replicates stimuli in the original sensory modality, rather than forming a type of feedback using neural pathways not normally associated with the information being fed back. As a result, it is supposed that the user can employ lower level reflexes that exist within the central nervous system, making control of the prosthesis more subconscious.

One final noteworthy therapeutic procedure is functional electrical stimulation (FES), although it is debatable if it can be truly referred to as a BCI, let alone a CCCI, however it aims to bring about muscular excitation, thereby enabling the controlled movement of limbs. FES has been shown to be successful for artificial hand grasping and release and for standing and walking in quadriplegic and paraplegic individuals as well as restoring some basic body functions such as bladder and bowel control [11]. It must be noted though that controlling and coordinating concerted muscle movements for complex and generic tasks such as picking up an arbitrary object is proving to be a difficult, if not insurmountable, challenge.

In the cases described in which human subjects are involved, the aim on each occasion is to either restore functions since the individual has a physical problem of some kind or it is to give a new ability to an individual who has very limited motor abilities. In this latter case, whilst the procedure can be regarded as having a therapeutic purpose, clearly it is quite possible to provide an individual with an ability that they have in fact never experienced before. On the one hand, it may be that whilst the individual in question has never previously experienced such an ability, some or most other humans have – in this case it could be considered that the therapy is bringing the individual more in line with the ''norm'' of human abilities. It is though also potentially possible to give extra capabilities to a human, to enable them to achieve a broader range of skills – to go beyond the ''norm''. Apart from the, potentially insurmountable, problem of universally deciding on what constitutes the ''norm'', extending the concept of therapy to include endowing an individual with abilities that allow them to do things that a perfectly able human cannot do raises enormous ethical issues. Indeed, it could be considered

that a cochlea implant with a wider frequency response range does just that for an individual or rather an individual who can control the cursor on a computer screen directly from neural signals falls into this category. Hence, the possibilities of extended therapy, in an area that can be considered as augmentation, are enormous. In the next section, we consider how far things could be taken, by referring to relevant experimental results.

Extended therapy

The interface, through which a user interacts with technology, provides a distinct layer of separation between what the user wants the machine to do, and what it actually does. This separation imposes a considerable cognitive load upon the user that is directly proportional to the level of difficulty experienced. It appears that the main issue is interfacing the human motor and sensory channels with the technology. One solution is to avoid this sensorimotor bottleneck altogether by interfacing directly with the human nervous system. It is certainly worthwhile considering what may potentially be gained from such an invasive undertaking. Advantages of machine intelligence are for example rapid and highly accurate mathematical abilities in terms of 'number crunching', a high speed, almost infinite, internet knowledge base, and accurate long term memory. Additionally, it is widely acknowledged that humans have only five senses that we know of, whereas machines offer a view of the world which includes infra-red, ultraviolet and ultrasonic. Humans are also limited in that they can only visualise and understand the world around them in terms of a limited dimensional perception, whereas computers are quite capable of dealing with hundreds of dimensions. Also, the human means of communication, essentially transfering an electro-chemical signal from one brain to another via an intermediate, often mechanical medium, is extremely poor, particularly in terms of speed, power and precision. It is clear that connecting a human brain, by means of an implant, with a computer network could in the long term open up the distinct advantages of machine intelligence, communication and sensing abilities to the implanted individual.

As a step towards this more broader concept of human-machine symbiosis, in the first study of its kind, the microelectrode array (as shown in Fig. 1) has been implanted into the median nerve fibres of a healthy human individual in order to test *bidirectional* functionality in a series of experiments. A stimulation current directed onto the nervous system allowed information to be sent to the user, while control signals were decoded from neural activity in the region of the electrodes [9, 23]. In this way, a number of experimental trials were successfully concluded [24, 25]: In particular:

1. Extra sensory (ultrasonic) input was successfully implemented and made use of.
2. Extended control of a robotic hand across the internet was achieved, with feedback from the robotic fingertips being sent back as neural stimulation to give a sense of force being applied to an object (this was achieved between New York (USA) and Reading(UK)).
3. A primitive form of telegraphic communication directly between the nervous systems of two humans was performed.
4. A wheelchair was successfully driven around by means of neural signals.
5. The colour of jewellery was changed as a result of neural signals – as indeed was the behaviour of a collection of small robots.

In each of the above cases, it could be regarded that the trial proved useful for purely therapeutic reasons, e.g. the ultrasonic sense could be useful for an individual who is blind or the telegraphic communication could be very useful for those with certain forms of motor neuron disease. However, each trial can also be seen as a potential form of augmentation for an individual. The question then arises as to how far should things be taken? Clearly, extended therapy by means of CCCIs opens up all sorts of new technological and intellectual opportunities, however, it also throws up a raft of different ethical considerations that need to be addressed directly.

Conclusions

External input-output interfaces with human and animal brains have been studied for many years. These are sometimes referred to as brain-computer interfaces even though the interface is external to the body and its sensorimotor mechanism. Systems based on EEG output with external contact electrodes would appear to be the closest implemented technology to an actual BCI or CCCI. In this article, an attempt has been made to put such systems in perspective. Emphasis has been placed on CCCIs as can be obtained by means of implanted devices through invasive surgery. In particular, a number of recent trials in this area have clearly shown the possibilities of monitoring and stimulating brain functioning. Although there is no distinct dividing line, it is

quite possible to investigate CCCIs in terms of those employed for direct therapeutic means and those which can have a more extended therapeutic role to play.

It is clear that the interaction of electronic signals with the human brain can cause the brain to operate in a distinctly different manner. Such is the situation with the stimulator implants that are successfully used to counteract, purely electronically, the tremor effects associated with Parkinson's disease. Such technology can though potentially be employed to modify the normal functioning of the human brain and nervous system in a number of different ways. Perhaps, understandably invasive CCCIs are presently far less well developed than their external BCI counterparts. A number of animal trials have though been carried out and the more pertinent have been indicated here, along with the relevant human trials and practice. The potential for CCCI applications for individuals who are paralysed is enormous, in cases where cerebral functioning is assisted to generate functional command signals, despite the motor neural pathways being in some way impaired – such as in Lou Gehrig's disease. The major role is then either one of relaying a signal of intention to the appropriate actuator muscles or to reinterpret the neural signals to operate technology, thereby acting as an enabler. In these situations, no other medical ''cure'' is available, something which presents a huge driver for an invasive implant solution for the millions of individuals who are so affected. Clearly though, bidirectional signalling is important, not only to monitor and enact an individual's intent but also to provide feedback on that individual's resultant interaction with the real world. For grasping, walking and even as a defensive safety stimulant, feedback is vital. This article has therefore focussed on such studies.

Although most prevalent in the field of CCCIs, where invasive interfaces are employed in human trials, a purely therapeutic scenario exists, as was detailed in section 3. In a small number of instances, such as use of the microelectrode array as an interface, an individual has been given different abilities, something which opens up the possibilities of an extended view of therapy as was described in section 4. These latter cases, however, raise more topical ethical questions with regard to the need and use of a CCCI. What might be seen as a new means of communication for an individual with an extreme form of paralysis or a new sensory input for someone who is blind, opening up a new world for them, can also be seen as an unnecessary extra for another individual, even though it may provide novel commercial opportunities. Indeed, what is therapy for one person may be regarded as an upgrading/augmentation for another. Whilst there are still many technical problems to be overcome in the development of CCCIs, significant recent experimental results have indicated that a sufficient technological infrastructure now exists for further major advances to be made. Although a more detailed understanding of the underlying neural processes will be needed in the years ahead, it is not felt that this will present a major hold up over the next few years, rather it will provide an avenue of research. Many new results will shortly appear through trials and experimentation, possibly initially through animal studies, although it must be recognised that it is only through human studies that a full analysis can be made and all encompassing conclusions can be drawn. Nevertheless, the topic opens up various ethical questions that need to be addressed and as such, research in this area should only proceed in light of a pervasive ethical consensus.

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References

1. Branner A, Normann R (2000) A multielectrode array for intrafascicular recording and stimulation in the sciatic nerve of a cat. Brain Res Bull 51: 293–306
2. Chapin JK (2004) Using multi-neuron population recordings for neural prosthetics. Nat Neurosci 7: 452–454
3. Carmena J, Lebedev M, Crist R, O'Doherty J, Santucci D, Dimitrov D, Patil P, Henriquez C, Nicolelis M (2003) Learning to control a brain-machine interface for reaching and grasping by primates. Plos Biol 1: E2
4. Dobelle W (2000) Artificial vision for the blind by connecting a television camera to the visual cortex. ASAIO J 46: 3–9
5. Donoghue J (2002) Connecting cortex to machines: recent advances in brain interfaces, Nat Neurosci Suppl 5: 1085–1088
6. Donoghue J, Nurmikko A, Friehs G, Black M (2004) Development of a neuromotor prosthesis for humans. Chapter 63 in advances in clinical neurophysiology. Clin Neurophysiol Suppl 57: 588–602
7. Finn W, LoPresti P (eds) (2003) Handbook of Neuroprosthetic methods. CRC Press
8. Friehs G, Zerris V, Ojakangas C, Fellows M, Donoghue J (2004) Brain-machine and brain-computer interfaces. Stroke 35: 2702–2705
9. Gasson M, Hutt B, Goodhew I, Kyberd P, Warwick K (2005) Invasive neural prosthesis for neural signal detection and nerve stimulation. Proc Inter J Adapt Contr Sign Proc 19: 365–375

10. Gasson M, Yung S, Aziz T, Stein J, Warwick K (2005) Towards a demand driven deep brain stimulator for the treatment of movement disorders. Proc. 3rd IEE International Seminar on Medical Applications of Signal Processing, pp 16/1–16/4
11. Grill W, Kirsch R (2000) Neuroprosthetic applications of electrical stimulation. Assis Techn 12: 6–16
12. Hinterberger T, Veit R, Wilhelm B, Weiscopf N, Vatine J, Birbaumer N (2005) Neuronal mechanisms underlying control of a brain-computer interface. Eur J Neurosci 21: 3169–3181
13. Kennedy P, Bakay R, Moore M, Adams K, Goldwaith J (2000) Direct control of a computer from the human central nervous system. IEEE Trans Rehab Eng 8: 198–202
14. Kennedy P, Andreasen D, Ehirim P, King B, Kirby T, Mao H, Moore M (2004) Using human extra-cortical local field potentials to control a switch. J Neur Eng 1: 72–77
15. Mann S (1997) Wearable computing: a first step towards personal imaging. Computer 30: 25–32
16. Nicolelis M, Dimitrov D, Carmena J, Crist R, Lehew G, Kralik J, Wise S (2003) Chronic, multisite, multielectrode recordings in macaque monkeys. Proc Nat Acad USA 100: 11041–11046
17. Penny W, Roberts S, Curran E, Stokes M (2000) EEG-based communication: a pattern recognition approach. IEEE Trans Rehab Eng 8: 214–215
18. Pinter M, Murg M, Alesch F, Freundl B, Helscher R, Binder H (1999) Does deep brain stimulation of the nucleus ventralis intermedius affect postural control and locomotion in Parkinson's disease? Mov Disord 14: 958–963
19. Reger B, Fleming K, Sanguineti V, Simon Alford S, Mussa-Ivaldi F (2000) Connecting brains to robots: an artificial body for studying computational properties of neural tissues. Artif Life 6: 307–324
20. Rizzo J, Wyatt J, Humayun M, DeJuan E, Liu W, Chow A, Eckmiller R, Zrenner E, Yagi T, Abrams G (2001) Retinal prosthesis: an encouraging first decade with major challenges ahead. Opthalmology 108, No 1
21. Roitberg B (2005) Noninvasive brain-computer interface. Surg Neurol 63: 195
22. Warwick K (2004) I Cyborg, University of Illinois Press
23. Warwick K, Gasson M, Hutt B, Goodhew I, Kyberd P, Andrews B, Teddy P, Shad A (2003) The application of implant technology for cybernetic systems. Arch Neurol 60: 1369–1373
24. Warwick K, Gasson M, Hutt B, Goodhew I, Kyberd P, Schulzrinne H, Wu X (2004) Thought communication and control: a first step using radiotelegraphy. IEE Proc Commun 151: 185–189
25. Warwick K, Gasson M, Hutt B, Goodhew I (2005) An attempt to extend human sensory capabilities by means of implant technology. Proc. IEEE Int. Conference on Systems, Man and Cybernetics, Hawaii, pp 1663–1668
26. Wolpaw J, McFarland D, Neat G, Forheris C (1990) An EEG based brain-computer interface for cursor control. Electroencephalogr Clin Neurophysiol 78: 252–259
27. Xie S, Yang Z, Yang Y (2004) Brain-computer interface based on event-related potentials during imitated natural reading, Inter J Psychol Suppl 39: S138
28. Yoo S, Fairneny T, Chen N, Choo S, Panych L, Park H, Lee S, Jolesz F (2004) Brain-computer interface using fMRI: spatial navigation by thoughts. Neuroreport 15: 1591–1595
29. Yu N, Chen J, Ju M (2001) Closed-loop control of quadriceps/hamstring activation for FES-induced standing-up movement of paraplegics. J Musculoskel Res 5: 173–184

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Trimodal nanoelectrode array for precise deep brain stimulation: prospects of a new technology based on carbon nanofiber arrays

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Summary

Although deep brain stimulation (DBS) has recently been shown to be effective for neurological disorders such as Parkinson's disease, there are many limitations of the current technology: the large size of current microelectrodes (~1 mm diameter); the lack of monitoring of local brain electrical activity and neurotransmitters (e.g. dopamine in Parkinson's disease); the open-loop nature of the stimulation (i.e. not guided by brain electrochemical activity). Reducing the size of the monitoring and stimulating electrodes by orders of magnitude (to the size of neural elements) allows remarkable improvements in both monitoring (spatial resolution, temporal resolution, and sensitivity) and stimulation. Carbon nanofiber nanoelectrode technology offers the possibility of trimodal arrays (monitoring electrical activity, monitoring neurotransmitter levels, precise stimulation). DBS can then be guided by changes in brain electrical activity and/or neurotransmitter levels (i.e. closed-loop DBS). Here, we describe the basic manufacture and electrical characteristics of a prototype nanoelectrode array for DBS, as well as preliminary studies with electroconductive polymers necessary to optimize DBS *in vivo*. An approach such as the nanoelectrode array described here may offer a generic electrical-neural interface for use in various neural prostheses.

Keywords: Neuromodulation; bionanotechnology; carbon nanofibers; deep brain stimulation; nanoelectrode array; Parkinson's disease.

Introduction

High-frequency deep brain stimulation (DBS) of the thalamus, subthalamic nucleus, or basal ganglia has been demonstrated as an effective clinical technique for the treatment of medically refractory movement disorders, such as Parkinson's disease [25], essential tremor, and dystonia [4], as well as other neurologic and psychiatric disorders, e.g. epilepsy [11], obsessive-compulsive disorder (OCD) [8], and major depression [18]. However, the scientific understanding of its mechanisms of action is far behind the clinical applications [19]. Current techniques in DBS mainly use open-loop macroelectrodes as represented by Medtronic (Medtronic Inc., Minneapolis, MN, USA) devices. Such techniques emphasize the observation of the therapeutic effectiveness of DBS, which have several significant drawbacks:

1. Only open-loop stimulation is available, i.e. the electrical stimulation is constant and not influenced by the ongoing electrical activity of the brain. Details of improvements in terms of closed-loop DBS (utilizing feedback from continuous monitoring of brain electrical activity), which are currently in early clinical trials for the treatment of intractable epilepsy, are detailed elsewhere in this Volume. Generally it is difficult to separate the electrical recording from the interference of the stimulation current.
2. No monitoring of other likely relevant parameters (beyond brain electrical activity) is available. For example, in Parkinson's disease, it is likely that monitoring of dopamine levels would improve the ability to stimulate specific regions of the brain in a manner which takes into account the fluctuating dopamine levels in different regions (paralleled by fluctuating Parkinson's symptoms throughout the day). Other examples include intractable epilepsy (where monitoring glutamate and or GABA may assist in tailoring closed-loop DBS to seizure control) and mood disorders (where monitoring neurotransmitters such as serotonin may improve DBS efficacy).
3. The macroelectrode currently employed, 1.27 mm diameter (dia), is much too large to permit more than a few electrodes being implanted in a given patient's brain. Being able to stimulate multiple regions of the brain with a much larger number of electrodes (of necessity much smaller in size) is likely to improve neuromodulation for various disorders.

4. The size (circular contacts 1.27 mm in diameter by 1.5 mm in length) is orders of magnitude larger than the cells (neurons) and cell processes (axons and dendrites) being stimulated. Thus, anatomic precision of stimulation is lost.
5. The characteristics of the electrical-neural interface of the current macroelectrode for DBS are suboptimal. The transfer of charge from the electrode to the neural tissue can be vastly improved, with increase in both efficacy and safety.

These disadvantages may be solved by the introduction of new technologies and methods. We intend in this chapter to illustrate the potential of a close-loop multiplex system based on a novel nanoelectrode platform with triple modalities, e.g. microelectrical stimulation, microelectrical recording, and local neurotransmitter monitoring.

As discussed elsewhere in this volume, there are several hypotheses regarding the therapeutic benefit of DBS. One might expect, on basic physiological principles, that DBS results in *excitation* of the neural elements (axons and cell bodies) surrounding the tip of the electrode, and thus increases firing of the axons projecting away from the region stimulated. Indeed, DBS was first used to activate a descending pain inhibitory pathway originating in the periventricular gray [10]. Neural fiber bundles are excited at both low and high frequencies [3]. On the other hand, in all target nuclei so far stimulated, DBS effects mimic those of lesions made during thalamotomy, pallidotomy or even subthalamotomy, suggesting an *inhibition* of at least the neuronal network containing the target, if not of the target itself [3, 7].

Four general hypotheses for the mechanisms of DBS have been proposed [19]: (1) depolarization blockade; (2) synaptic inhibition; (3) synaptic depression, and (4) stimulation-induced modulation of pathologic network activity. In reality, the therapeutic mechanisms for DBS are likely a combination of all these hypotheses. Currently, many techniques are employed to validate these hypotheses, including neural modeling, neural recording, microdialysis, and imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) [19]. By combining results from several modalities, a more complete understanding of the effects of DBS can be developed.

The fundamental question for DBS is: ''What is being stimulated?'' Since the current intensity decreases with distance from the electrode tip, the types of neural elements excited will differ depending on their distance from the electrode [7]. The excitability of axons is much higher than cell bodies, and large myelinated axons are much more excitable than unmyelinated axons [24, 27]. Thus, the predominant effect of stimulation of brain nuclei is likely activation of large axons, both the projection neurons and the axons of the afferent inputs to the nucleus (as well as fibers of passage in or near the nucleus). In these cases, both orthodromic and antidromic action potentials would be evoked. The clinically observed effects could thus be due to activation of afferent inputs onto neurons in the nucleus, direct effects on the output neurons and/or effects mediated at other regions by means of initial antidromic activation of axons in the nucleus and then release of neurotransmitters from axon collaterals in other nuclei [7]. Since the nuclei are not homogeneous, stimulation effects are likely to differ depending on the electrode location within the nucleus.

The need for multimodal DBS

There are several reasons why a nano-sized, multimodal electrode array can represent a substantial advance in DBS:

1. For a closed-loop system in Parkinson's disease, monitoring dopamine levels in the basal ganglia – possibly in multiple locations – is very likely to be the best parameter to guide stimulation (e.g. of the STN).
2. Research on subthalamic nucleus (STN) DBS in a rat model, using microdialysis to measure GABA and glutamate (Glu) in the globus pallidus (GP) and the substantia nigra reticulata (SNr), found STN stimulation to increase Glu in the GP and SNr, but to increase GABA in the SNr only [33]. More recently, the same group has shown the effect of STN DBS to be stimulation frequency-dependent [34]. Optimizing the effect of STN DBS is likely to be achieved when neurotransmitter levels can be monitored rapidly and continuously along with STN stimulation.
3. It has been shown in rats that DBS results in Glu release [1], and in thalamic and subthalamic slices, that high frequency stimulation (HFS) releases both excitatory and inhibitory neurotransmitters (presumably Glu and GABA, respectively) [12, 13].
4. There is research evidence in both animals and humans, from both epilepsy and Parkinson's disease, that STN DBS may involve changes in cortical electrical activity, likely glutaminergically-mediated. A closed-loop system will likely need multiple multimodal arrays in both the cortical and STN loca-

tions, with neurotransmitter monitoring capabilities [2, 6, 30].

5. DBS for OCD, like DBS for epilepsy and other applications, is thought to work in part because of desynchronization of oscillatory neuronal activity [29]. It is suggested that the stimulating and recording electrodes in DBS for OCD may be in physically distant parts of the brain, e.g. the former in the nucleus accumbens and the latter in the orbitofrontal cortex [29]. Again, micro-sized electrodes with multimodal capabilities are likely to be optimal for such applications.

A potential closed-loop trimodal chip for DBS

Due to the complexity discussed above, multiplex electrodes that can perform precise microstimulation as well as multiple electrical recordings at subcellular sites such as cell bodies and axons are desirable for DBS. Stimulation may activate neuron terminals to release neurotransmitters such as dopaminergic, glutamatergic, and gamma-aminobutyric acid (GABA)ergic afferents, which may lead to excitatory or inhibitory postsynaptic neuron activities. Continuous monitoring of these neurotransmitters is also desirable for DBS. It is possible to integrate all three modalities into a close-loop electrode based on the carbon nanofiber (CNF) technology under development at NASA Ames as shown in Fig. 1.

As described in previous papers [14, 15], vertically aligned CNFs can be grown precisely on prepatterned microcircuits on a silicon (Si) wafer. Typically, multiplex individually addressed contact pads such as the 3×3 pattern can be fabricated using ultraviolet (UV) lithography and standard metallization techniques. The size of the contact pads can be varied from a few microns to macroscale. For DBS applications, the desired size is less than 20 microns, the size of the body of a neural cell, so that an individual cell or even a local node of Ranvier of myelinated axons can be directly excited by extracellular stimulation. The low limit is defined by the impedance of the electrode and the capability to deliver a current over the excitation threshold. The CNF array on a particular contact pad may be constructed into one of the two configurations for different modalities. In the first configuration, the CNF array remains as a three-dimensional (3D) open structure and serves as *microelectrical stimulating* and *microelectrical recording* electrodes. In the second configuration, the CNF array is embedded in insulating dielectrics such as SiO_2 leaving only the very end exposed. Such inlaid nanoelectrode array allows extremely sensitive *electrochemical recording* of the release of neurotransmitters in the local extracellular space. The principles of such device as a closed-loop trimodal chip and the potential benefits for DBS application are addressed in the following sections.

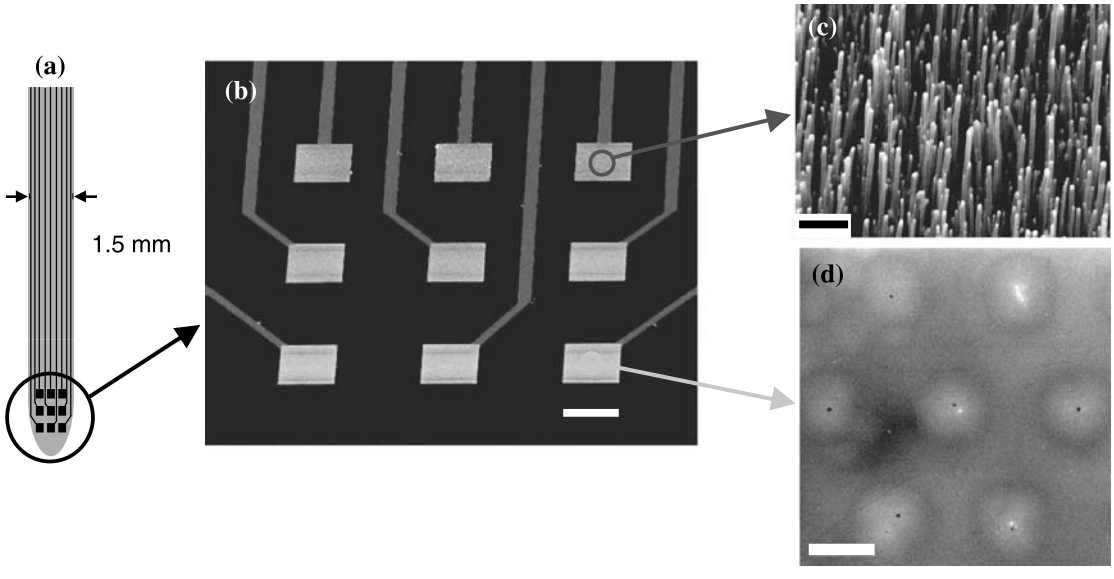

Fig. 1. (a) The schematic of an implantable close-loop trimodal chip for DBS. Scanning electron microscopy images of (b) a 3×3 CNF nanoelectrode array each with an independent metal contact line, (c) one of the microelectrodes configured with an open CNF array for *microelectrical stimulation* and *microelectrical recording*, and (d) an embedded low-density CNF array used for *electrochemical neurotransmitter recording*. The size of the microelectrode pads can be varied from a few microns to hundreds of microns. The scale bars in (b)–(d) are 200, 1, and 2 μm, respectively

Benefits for electrical stimulation and recording using CNF arrays

Properties of CNFs

Carbon nanotubes (CNTs) and CNFs belong to a family of materials that have attracted extensive interest in nanotechnology over the past 15 years. A CNT is a cylindrical form of carbon, configurationally equivalent to a two-dimensional graphene sheet rolled into a seamless tube [21]. A CNT consisting of a single graphene sheet, known as a single-walled carbon nanotube (SWCNT), can be as small as 0.7 nm dia and over tens of microns long. A multi-walled carbon nanotube (MWCNT) consists of a concentric cylindrical arrangement of multiple nanotubes with a typical wall separation of 0.34 nm around a central hollow core. The diameter can vary from a few nanometers to about 200 nm and the length can be hundreds of nanometers to tens of microns. CNF is a defective form of MWCNT, where the sidewalls are not perfectly parallel to the tube axis, resulting in a structure similar to a stack of cups [21]. Such defects were induced by the plasma enhanced chemical vapor deposition (PECVD) process. However, the PECVD process has the advantages of producing the free-standing vertically aligned structure as well as the low processing temperature which is compatible with microelectronic devices. These two advantages are the main reasons that we use CNF arrays for the current applications.

CNTs and CNFs have very strong mechanical strength: they can maintain the rigid fiber structure at high aspect ratio with the diameter reduced down to a few nanometers. The Young's modulus of CNTs is around 1 TPa and the maximum strain is about 10%, which is higher than any other material. The strength to weight ratio is about 500 times greater than that of aluminum. CNTs and CNFs have a very high electrical conductivity (orders of magnitude higher than electronic conductive polymers (ECPs)), i.e. close to the conductivity of metals. These superb mechanical and electrical properties are essential requirements for nanoscale elements of the implantable DBS devices.

3D electrical-neural interface

Since the brain consists of neurons and glial cells connected through the 3D neurite network, an efficient electrical neural interface needs to accommodate such complexity. Currently, used DBS electrodes are normally solid metal over 1 mm in size, where the electrical neural interface is essentially a 3D network on a solid plane. Efforts have been made to cover the solid surface with a porous hydrous metal oxide film [32] and fuzzy ECPs [5]. The vertically aligned CNF array as shown in Fig. 1c has a large open space between neighboring CNFs and thus would be ideal to create a 3D electrical-neural interface.

However, the CNF has a large surface to volume ratio. For any implantable application, the capillary force exerted by the physiologic solutions and pressure from the surrounding tissue would be tremendous. As shown in Fig. 2a, although CNFs have extremely high mechanical strength, the as-grown CNF array will collapse into microbundles after it is submerged into aqueous solution. This is exactly the reason why other materials were not able to be used to form a reliable 3D electrical-neural interface. With CNF array, the bunching problem can be solved by coating each CNF with a thin conformal ECP film. As shown in Fig. 2b, even a 20 nm polypyrrole (PPy) film can dramatically improve the mechanical strength of the CNF array so that the free-standing vertically aligned structure can be maintained in the water solutions [23]. PPy is one of the commonly used ECPs to improve the performance of implantable neural devices [5].

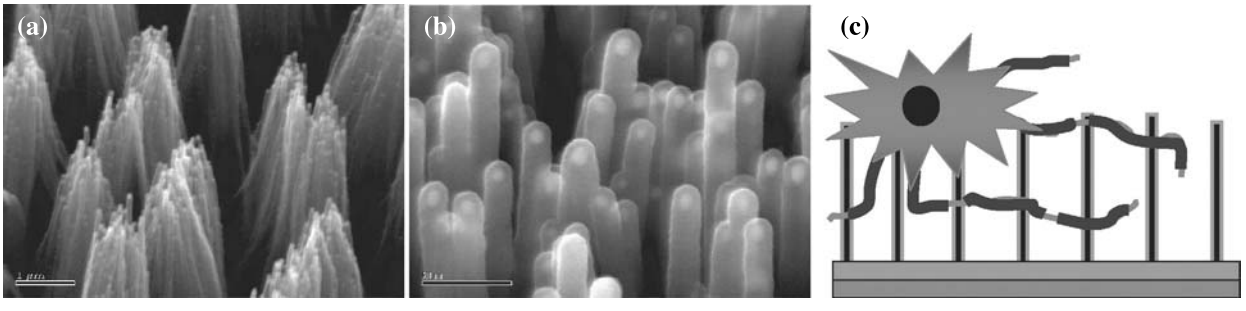

Fig. 2. Scanning electron microscopy images of (a) an as-grown CNF array after submerging into water solutions and (b) a similar CNF array after coated with a thin layer of polypyrrole film. (c) The schematic of the 3D electrical-neural interface. The scale bars in (a) and (b) are 1 μm and 500 nm, respectively

Figure 2c shows the schematic of how such a stable 3D structure may be used for high-efficacy stimulation. As reported before, in extracellular stimulation, the excitability of axons is much higher than cell bodies and large myelinated axons are much more excitable than unmyelinated axons [24, 27]. Extremely high stimulation efficacy can be achieved if one can bring the electrode close to the node of Ranvier of myelinated axons. This may be done with the vertically aligned CNF array as shown in Fig. 2c. Our preliminary data also show that CNFs can easily penetrate the membrane of the cell body without destroying its integrity. Hence it is possible to use CNF arrays for intracellular stimulation in the future.

Miniaturization and multiplexing

Ideally one would like to reduce the size of each contact pad below 20 μm, e.g. the size of the cell body, so that individual neuron can be excited. Many of such electrodes in a multiplex form for simultaneous stimulation and recording may map out the activity of the neural network. However, the reduction of the electrode size will increase the impedance of the electrode and limit the current that it can deliver to the brain to stimulate the neural network. Extensive efforts have been made to reduce the impedance by porous metal oxides [20, 32] and fuzzy ECPs [5]. The 3D CNF structure in Fig. 2b consists of a highly conductive and mechanically stable template on which an ECP film is coated. This improves both the electrical and mechanical properties of the fuzzy ECP structures on solid electrode surface [5]. A thin PPy film is able to add a pseudo capacitance over 1000 times higher than a solid electrode and thus dramatically decreases the impedance [23]. This makes it possible to decrease the electrode size to single neurons. The ECP coating may be also used as a media for surface modification to gain some advantages in multiplexing. Different electrodes can then be modified with different ligands to control the attachment of the type of cells, i.e. neurons vs. glial cells, or the subcellular entities such as the cell body or myelinated axons.

Potential for monitoring neurotransmitters

While the signal is transduced as electrical pulses inside a neuron, it is carried through the release of chemical messengers i.e. neurotransmitters, into the synapse between neurons as shown in Fig. 3. Most neurotransmitters are electrochemically active molecules (e.g. catecholamines such as dopamine), which can be directly measured with electrochemical sensors. Microelectrodes, where conductive microfibers are sealed in capillary glass tubes pulled down to about 10 microns in diameter, are commonly used to detect the changes of extracellular neurotransmitters in the brain as shown in Fig. 4. It has been reported that microfiber electrodes can measure subsecond processes with minimal tissue damage. In the past decade, microfiber electrodes have revealed invaluable information despite that the sensitivity and time-resolution barely meet the requirements for real-time measurements [31].

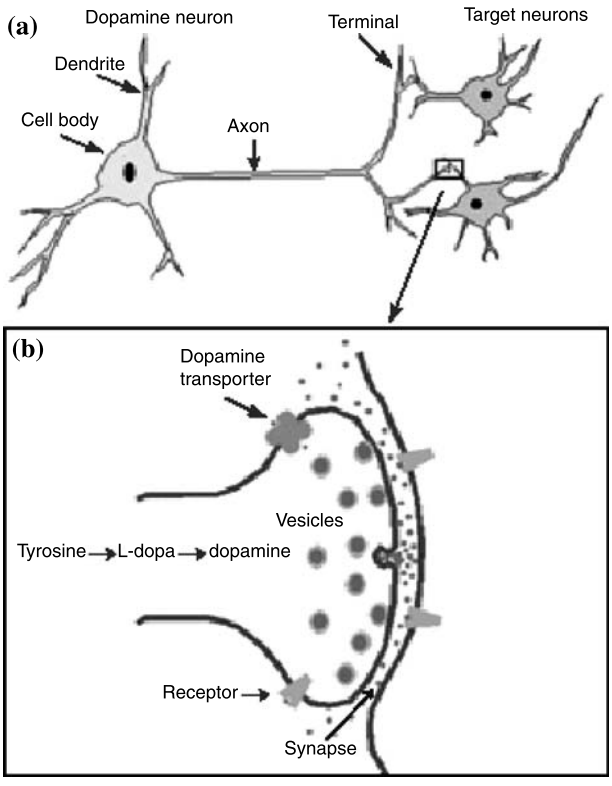

Fig. 3. Schematic of a dopaminergic neuron. (a) The dendrites of the dopaminergic neuron receive information from other cells. An action potential then propagates down the axon to the terminals, where neurotransmitters relay information to target cells. (b) Enlarged view of a dopamine terminal. Dopamine (grey circles) is synthesized from tyrosine and packaged into vesicles. In response to an action potential, vesicles release their contents into the synapse. Dopamine can then diffuse out of the synapse, to play a role in the interaction with receptors, or be taken up by the dopamine transporter (Adapted with permission from [31])

Among various neurotransmitters, dopamine has been most intensively studied due to the ease of detection as well as the biomedical importance. In particular, deficiency of dopamine in the basal ganglia is a well known finding in Parkinson's disease (PD). Dopamine neurotransmission in the rat brain has been studied using a

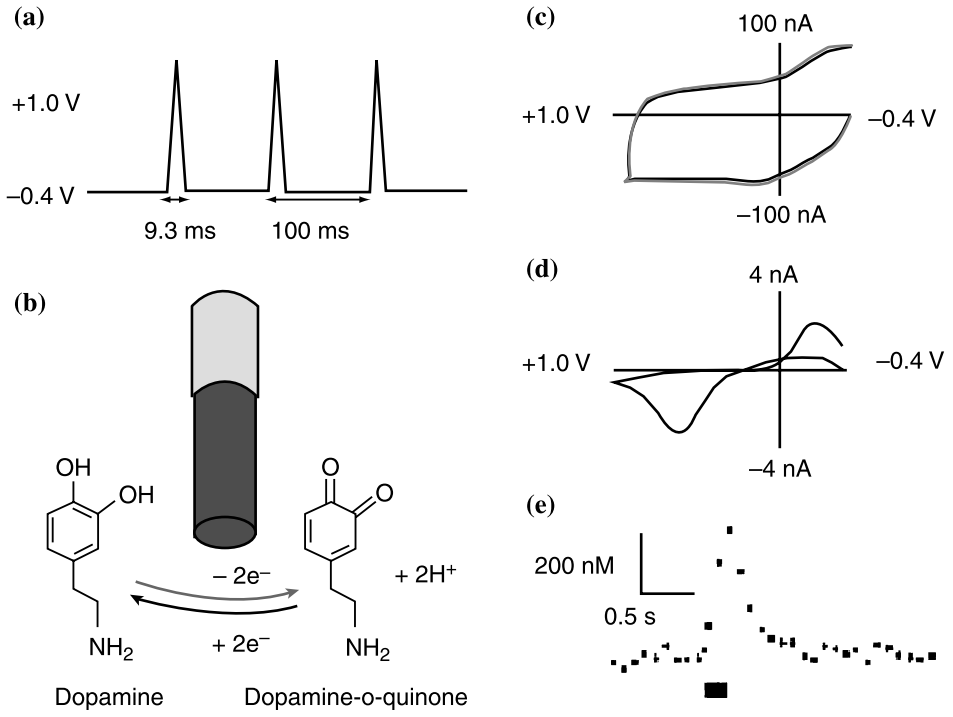

Fig. 4. FSCV with a carbon-fiber microelectrode for dopamine detection. (a) The electrode potential is scanned from −0.4 to +1.0 V and back every 100 ms at 300 V/s. (b) At the cylindrical carbon-fiber microelectrode, dopamine is oxidized to dopamine-o-quinone and then reduced back to dopamine. (c) A large background charging current at the electrode (black line) is produced. When dopamine is present (grey line), only small changes in the current are detected. (d) The characteristic chemical ''fingerprint'' cyclic voltammogram for dopamine is obtained by subtracting the black line from the red line in (c). (e) The current at the oxidation potential, converted to concentration using an in vitro calibration value, can be plotted versus time to monitor dopamine concentration changes after a short electrical stimulation (4 pulses delivered at 100 Hz, indicated by hash marks) (Adapted with permission from [31])

glass-encased carbon fiber microelectrode (>5 μm dia) [31]. Using fast-scan cyclic voltammetry (FSCV), the extracellular dopamine level can be monitored in temporal resolution down to ∼0.1 sec at a concentration down to 100 nM. Electrically evoked dopamine release was measured in brain slices, anesthetized rats and mice, and freely moving rats in real time. Naturally occurring dopamine pulse release in freely moving rats during behavioral situations was also measured, indicating that a behavioral stimulus can evoke a transient dopamine increase [26]. Dopamine acts as a reward for behavior that precedes its release, and subsequently it triggers pursuit of the same reward after its release. Correlation of dopamine signal with DBS is to be established in the future.

The challenges for realtime neurotransmitter recording during DBS lie in the extremely high requirements for both sensitivity (∼10 nM) and temporal resolution (<0.1 ms). The state-of-the-art technology using carbon fiber microelectrode does not meet these requirements even though it is much better that macroelectrodes. There have been long-standing interests to develop electrodes with smaller size – down to a few nanometers – for higher sensitivity and better temporal resolution. In previous studies [15], we have demonstrated that inlaid CNF nanoelectrode arrays as shown in Fig. 1d indeed provide much higher sensitivity (with the detection limit down to ∼10 nM) and potentially a submillisecond temporal resolution. This may be used for dopamine monitoring during DBS.

In the brain nuclei normally involved in DBS, glutamate and GABA are the relevant neurotransmitters. Glutamate is responsible for excitatory synaptic transmission, and GABA is for inhibitory synaptic transmission. It would be very useful to specifically measure all of these neurotransmitters simultaneously in the local area that is stimulated. Many studies have measured glutamate electrochemically using a glutamate oxidase modified electrode [35], where H_2O_2 generated by enzymatic oxidation of glutamate is measured and used as an indirect measure of glutamate concentration. This method can be applied to the inlaid CNF nanoelectrode array sensor. A glucose sensor with very similar mechanism has been recently demonstrated on such nano-

electrode arrays [16]. Current studies of GABA release during DBS mainly rely on microdialysis or HPLC in conjunction with electrochemical detectors. Certainly, GABA may be electrochemically detected either directly or through the enzymatic reaction in the future.

Future aspects of nanoelectrodes for neuromodulation and monitoring

The 3D structure of a CNF array is similar to the 3D fibrous network structure of extracellular matrix (ECM), which forms the necessary basement structure to support tissue growth. The surface of the CNF may be modified to induce the growth of neurites to form an interdigitized interface. Such interpenetration of the 3D solid-state structure into the 3D soft biological tissue would in principle form an improved electrical neural interface. Future work will focus on the biocompatibility and tissue engineering issues so that the CNF array can be optimized for implantable applications.

Biocompatibility and toxicity

With the rapid growth in bionanotechnology has come intense interest in the potential toxicity of implanted nanomaterials [28]. The main biocompatibility concern for CNTs and CNFs lies in the hydrophobic graphite basal plane-like structure of the sidewall that likely induces denaturation of biomolecules such as proteins when implanted in the human body. The resistance to degradation may also pose a problem in that these materials may accumulate in the human body. Carbon materials, however, are among the most commonly used biocompatible materials. The introduction of a biocompatible coating may further improve the biocompatibility. As shown in Fig. 2b, an ECP such as PPy coating can be applied to modify the surface properties of CNTs and CNFs as well as to improve the mechanical and electrical properties of the nanostructure. PPy is an FDA-approved biocompatible material for implantable devices. The ECP coating converts the hydrophobic sidewall into a hydrophilic surface. All CNTs and CNFs are encapsulated inside the ECP coating and are unlikely to come in contact with body fluids. During electrical stimulation, Cl^- ions can be loaded into the ECP film or released from the ECP film into the physiologic environment. These processes convert the electrical current in the solid-state circuit into ionic current in the body fluid. The major current carrier, Cl^- ion, is compatible with the physiologic environment, and thus can avoid the dramatic pH value change incurred with other metal or metal oxide electrodes [20]. The third toxicity concern is that the metal catalysts such as Ni, Co, and Fe used for CNT or CNF growth may dissolve into solution to reach a toxic metal ion concentration. This problem is normally solved by dissolving the metal catalysts away in strong acid solutions before coating with ECP films. No evidence of toxicity due to the trace metal residues has been observed, but it is worthy of further investigation.

Tissue engineering

CNTs and CNFs are a class of new materials which may provide many opportunities for implantable devices [9]. Studies have found that the fibrous template of CNTs and CNFs may promote the growth of neurites and boost neuronal network activity [17]. Research on optimizing tissue engineering and realizing the appealing concepts of 3D interfaces has just started. The small dimension of CNTs and CNFs minimizes tissue damage during implantation. However, these nanostructures are attached to a solid Si substrate which will unavoidably face the same problem as other solid electrodes. One advantage of the CNF array is that it can form an interface with open 3D structure between the tissue and solid substrate. The ECP coating further makes the electrode surface even softer and more compatible with the biological tissue. Anti-inflammatory drugs and neurochemicals such as nerve growth factors can be loaded in the ECP film, which are then released by tuning the electrode potential. These chemicals may reduce the lesion and enhance neuronal survival and/or regrowth near the implanted electrode arrays. The surface of the ECP film can be also covalently attached with proper ligands to regulate the relative growth rate of neurons and glial cells, which was recently found to be critical for a good electrical neural interface [22].

Conclusion

We have introduced a multiplex trimodal chip using CNF arrays as a 3D electrical-neural interface or electrochemical sensor. The unique mechanical, chemical, and electrical properties of the vertically aligned CNF array make it possible to reduce the size of the stimulating electrode for DBS to less than that of the cell body – so that individual cells may be excited by electrical stimulation at many sites. The open nanostructure also makes it possible to interdigitize with neurites and to deliver currents near the node of Ranvier of mye-

linated axons, which should have much higher excitation efficacy. In addition to monitoring local electrical activity, neurotransmitters such as dopamine, glutamate, and GABA may be detected and monitored in the nearby extracellular space. The 3D open structure, the ability to modify the surface chemistry, and controllable release of chemicals from the ECP coating are other attractive properties desired for implantable neural devices. In combination, these features should provide a much better understanding of the mechanisms of DBS as well as provide much more efficacious closed-loop DBS for applications such as movement disorders (e.g. Parkinson's disease), epilepsy, and depression. If successful, the techniques used for the multiplex trimodal nanoelectrode array described here may be generally applied to other neural prosthetic devices such as a generic electrical-neural interface.

Acknowledgement

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References

1. Anderson T, Hu B, Pittman Q, Kiss Z (2004) Mechanisms of deep brain stimulation: an intracellular study in rat thalamus. J Physiol 559: 301–313
2. Baker KB, Mongomery EB, Rezai A, Burgess R, Luders HO (2002) Subthalamic nucleus deep brain stimulation evoked potentials: physiological and therapeutic implications. Mov Disord 17: 969–983
3. Benabid AL, Benazzous A, Pollak P (2002) Mechanisms of deep brain stimulation. Mov Disord 17 Suppl 3: S73–S74
4. Coubes P, Roubertie A, Vayssiere N, Hemm S, Echenne B (2000) Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus. Lancet 355: 2220–2221
5. Cui X, Lee VA, Raphael Y, Wiler JA, Hetke JF, Anderson DJ, Martin DC (2001) Surface modification of neural recording electrodes with conducting polymer/biomolecules blends. J Biomed Mater Res 56: 261–272
6. Dinner DS, Neme S, Nair D, Mongomery EB, Baker KB, Rezai A, Luders HO (2002) Clin Neurophysiol 113: 1391–1402
7. Dostrovsky JO, Lozano AM (2002) Mechanisms of deep brain stimulation. Mov Disord 17 Suppl 3: S63–S68
8. Gabriels LA, Cosyns PR, Meyerson BA, Andreewitch S, Sunaert SG, Maes AF, Dupont PJ, Gybels JM, Gielen F, Demeulemeester HG (2003) Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. Neurosurgery 52: 1263–1274
9. Gheith MK, Sinani VA, Wicksted JP, Matts RL, Kotov NA (2005) Single-walled carbon nanotube polyelectrolyte multilayers and freestanding films as a biocompatible platform for neuroprosthetic implants. Adv Mater 17: 2663–2670
10. Gybels JM, Sweet WH (1989) Neurosurgical treatment of persistent pain. Physiological and pathological mechanisms of human pain. Pain and Headache 11: 1–402
11. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM (2002) Chronic anterior thalamus stimulation for intractable epilepsy. Epilepsia 43: 603–608
12. Lee K, Chang S-Y, Roberts DW, Kim U (2004) Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. J Neurosurg 101: 511–517
13. Lee KH, Hitti FL, Shalinsky MH, Kim U, Leiter JC, Roberts DW (2005) Abolition of spindle oscillations and 3-Hz absence seizure-like activity in the thalamus by using hig-frequency stimulation: potential mechanism of action. J Neurosurg 103: 538–545
14. Li J, Ng HT, Cassell A, Fan W, Chen H, Ye Q, Koehne J, Han J, Meyyappan M (2003) Carbon nanotube nanoelectrode array for ultrasensitive DNA detection. Nano Lett 3: 597–602
15. Li J, Koehne JE, Cassell AM, Chen H, Ng HT, Ye Q, Fan W, Han J, Meyyappan M (2005) Inlaid multi-walled carbon nanotube nanoelectrode arrays for electroanalysis. Electroanalysis 17: 15–27
16. Lin Y, Lu F, Tu Y, Ren ZF (2004) Glucose biosensors based on carbon nanotube nanoelectrode ensembles. Nano Lett 4: 191–195
17. Lovat V, Pantarotto D, Lagostena L, Cacciar B, Grandolfo M, Righi M, Spalluto G, Prato M, Ballerini L (2005) Carbon nanotubes substrates boost neuronal electrical signaling. Nano Lett 5: 1107–1110
18. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistent depression. Neuron 45: 651–660
19. McIntyre CC, Savasta M, Walter BL, Vitek JL (2004) How does deep brain stimulation work? Present understanding and future questions. J Clin Neurophysiol 21: 40–50
20. Merrill DR, Bikson M, Jefferys JGR (2005) Electrical stimulation of excitable tissue: design of efficacious and safe protocols. J Neurosci Methods 141: 171–198
21. Meyyappan M (2004) Carbon nanotubes: science and applications. CRC Press
22. Nam Y, Chang J, Khatami D, Brewer GJ, Wheeler BC (2004) Patterning to enhance activity of cultured neuronal networks. IEE Proc Nanobiotechnol 151: 109–115
23. Nguyen-Vu TDB, Chen H, Cassell AM, Andrews R, Meyyappan M, Li J (2006) Vertically aligned carbon nanofiber arrays; an advance toward electrical-neural interfaces. Small 2: 89–94
24. Nowak LG, Bullier J (1998) Axons, but not cell bodies, are activated by electrical stimulation in cortical gram matter I. Evidence from chronaxie measurements. Exp Brain Res 118: 477–488
25. Obeso JA, Olanow CW, Rodriguez-Oroz MC, Krack P, Kumar R, Lang AE (2001) Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 345: 956–963
26. Phillips PEM, Stuber GD, Heien MLAV, Wightman RM, Carelli RM (2003) Subsecond dopamine release promotes cocaine seeking. Nature 422: 614–618
27. Ranck JB (1975) Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 98: 417–440
28. Service RF (2005) Calls rise for more research on toxicology of nanomaterials. Science 310: 1609
29. Tass PA, Klosterkotter J, Schneider F, Lenartz D, Koulousakis A, Sturm V (2003) Obsessive-compulsive disorder: development of demand-controlled deep brain stimulation with methods from stochastic phase resetting. Neuropsychopharmacology 28: S27–S34

30. Usui N, Maesawa S, Kajita Y, Endo O, Takebayashi S, Yoshida J (2005) Suppression of secondary generalization of limbic seizures by stimulation of subthalamic nucleus in rats. J Neurosurg 102: 1122–1129
31. Venton BJ, Wightman RM (2003) Psychoanalytical electrochemistry: dopamine and behavior. Anal Chem 75: 414A–421A
32. Weiland JD, Anderson DJ (2000) Chronic neural stimulation with thin-film, iridium oxide electrodes. IEEE Trans Biomed Eng 47: 911–918
33. Windels F, Bruet N, Poupard A, Urbain N, Chouvet G, Feuerstein C, Savasta M (2000) Effects of high frequency stimulation of subthalamic nucleus on extracellular glutamate and GABA in substantia nigra and globus pallidus in the normal rat. Eur J Neurosci 12: 4141–4146
34. Windels F, Bruet N, Poupard A, Feuerstein C, Bertrand A, Savasta M (2003) Influence of the frequency parameter on extracellular glutamate and gamma-aminobutyric acid in substania nigra and globus pallidus during electrical stimulation of subthalamic nucleus in rats. J Neurosci Res 72: 259–267
35. You T, Niwa O, Kurita R, Iwasaki Y, Hayashi K, Suzuki K, Hirono S (2004) Reductive H_2O_2 detection at nanoparticle iridium/carbon film electrode and its application as l-glutamate enzyme sensor. Electroanalysis 16: 54–59

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Neural networks on chemically patterned electrode arrays: towards a cultured probe*

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Summary

One type of future, improved neural interfaces is the 'cultured probe'. It is a hybrid type of neural information transducer or prosthesis, for stimulation and/or recording of neural activity. It would consist of a micro-electrode array (MEA) on a planar substrate, each electrode being covered and surrounded by a local circularly confined network ('island') of cultured neurons. The main purpose of the local networks is that they act as bio-friendly intermediates for collateral sprouts from the in vivo system, thus allowing for an effective and selective neuron electrode interface. As a secondary purpose, one may envisage future information processing applications of these intermediary networks.

In this chapter, first, progress is shown on how substrates can be chemically modified to confine developing networks, cultured from dissociated rat cortex cells, to 'islands' surrounding an electrode site. Additional coating of neurophobic, polyimide coated substrate by tri-block-copolymer coating enhances neurophilic-neurophobic adhesion contrast. Secondly, results are given on neuronal activity in patterned, unconnected and connected, circular 'island' networks. For connected islands, the larger the island diameter (50, 100 or 150 μm), the more spontaneous activity is seen. Also, activity may show a very high degree of synchronization between two islands. For unconnected islands, activity may start at 22 days in vitro (DIV), which is two weeks later than in unpatterned networks.

Keywords: Live neural networks; neural network patterning; cultured neural probe.

Introduction

Efficient and selective electrical stimulation and recording of neural activity in peripheral, spinal or central neural pathways requires multielectrode arrays at micrometer or nanometer scale. At present, wire-arrays in brain, flexible linear arrays in the cochlea and cuff-arrays around nerve trunks are in experimental and/or clinical use. Two- and three-dimensional brush-like micro arrays and 'sieves', with around hundred electrode sites, have been proposed, fabricated in microtechnology and/or tested in a number of laboratories. As there are no 'blueprints' for the exact positions of fibres in a peripheral nerve, or motor neurons in a ventral root region, an insertable multielectrode has to be designed in a redundant way. Even then, the efficiency of a multielectrode will be less than 100%, as not every electrode will contact one neural axon or soma. Therefore, 'cultured probe' devices are being developed, based on cell-cultured planar MEA's (multi-electrode arrays) (Figs. 1 and 2). They may enhance efficiency and selectivity because neural cells have been grown over and around each electrode site as electrode-specific local networks. If, after implantation, collateral sprouts branch from a motor fibre (ventral horn area) and if they can each be guided and contacted to one specific 'host' island-network, a one-to-one, i.e. very selective and efficient stimulatory interface will result.

The islands perform the function of a bio-friendly surrounding for the sprouts, producing neuro-attractive proteins to guide the sprouts towards them. A number of aspects relevant to the successful development of a cultured probe have been studied in our group intensively during recent years. Among them are the electrical behaviour of the neuron-electrode contact [1, 3, 4], the capability to record and stimulate neuron activity of cells positioned on top of MEA-electrodes or closely beside them [2], and the chemical surface modification of flat substrates into neurophilic and neurophobic

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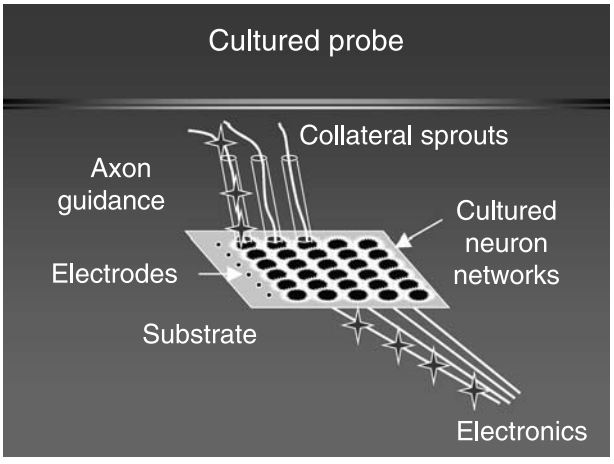

Fig. 1. Schematic impression of a 'cultured probe'-type of neural information transducer/prosthetic device. The black circular 'stand-alone-islands' are cultured neuronal networks, separated from each other, at and around each electrode, acting as bio-friendly hosts/attractors for the sprouts. The primary goal is selective stimulation of neuronal sprouts (motor fibers). The series of stars stand for information flow from one electronic stimulus channel to one neural fiber, via one electrode site

regions [11, 12]. In summary, these studies resulted in understanding of the neuron-electrode contact and the wave shapes of recorded action potentials, the discovery of a stimulation current 'window', and the discovery of chemical coatings suited for patterning of host islands. As stated, the local island networks serve only to provide a bio-friendly surrounding for the sprouts. However, it is well established that (large) developing cortical neuron networks will start to exhibit spontaneous activity after about one week in vitro. It has been shown that the patterns resemble those seen in vivo [7]. Recording of the firing activity of individual neurons has become established, since the pioneering work of Gross and Pine [8, 9], as a useful technique, as is also shown by Jimbo *et al.* [10] in a study of activity-dependent plasticity at the synaptic level. The question is whether smaller networks, like our islands, will become spontaneously active also. Is there a minimal network size?

In the following sections of this chapter we report latest progress regarding two of the aforementioned aspects: 1) enhanced neurophilic/neurophobic contrast and 2) spontaneous and synchronised activity of patterned host islands.

Enhanced neurophobic/neurophilic contrast

Essential properties of the probe are that cells must adhere to the surface of the substrate and develop into

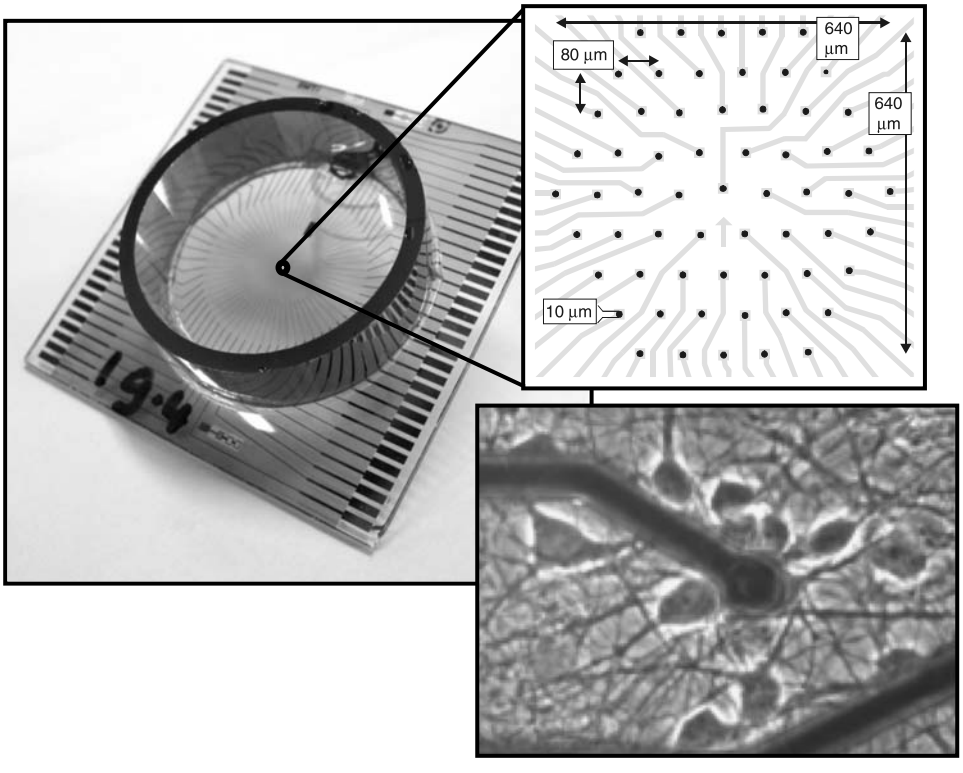

Fig. 2. MEA (multi-electrode array) device with culture dish (diameter 30 mm) on top. The MEA is based on a glass substrate (5×5 cm), it has 61 embedded electrodes. The 61 electrode tips (tip diameter 10 µm) lie in the center of the chamber (magnified in right-top figure). The figure right below shows a detail of one tip, surrounded by a 4 DIV (Days In Vitro) old developing cortical cell culture

networks of somata and outgrowing neurites/axonal fascicles, within a predefined area around the electrodes. The goal should be also to keep the networks flat and confined as long as possible, so to delay the natural tendency of neurons to aggregate, or island networks to become connected by 'neural cables'. For that, chemical modification of the substrate and electrode areas with various coatings, such as neurophilic polyethyleneimine (PEI) and neurophobic fluorocarbon (FC) monolayers is applied, to promote or inhibit adhesion of cells.

Then, one of the key problems in long-term neuronal patterning studies on MEAs is the biofouling of the background material with cell-adhesive proteins, which on turn promote the random overgrowth with neuronal tissue [6]. Polyethylene oxide (PEO)-coated surfaces are known for their ability to inhibit the adsorption of proteins and are promising alternatives as neurophobic background surfaces. The methods to fabricate PEO-coated surfaces can be divided in two different subgroups, e.g. covalent bonding of relatively short polyethylene oxide chains (PEO also termed poly-ethylene-glycol PEG) and adsorption of polyethylene oxide-polypropylenoxide (PEO-PPO) block-copolymers onto hydrophobic materials [13]. The advantage of covalent coupling of PEO chains to surfaces is the initial stability of the layer and the prohibited displacement of PEO by proteins in solution. However, the physiological environment in time could dissociate the chemical bonds between the PEO chains and the underlying substratum. Another important point is the fact that the chemistry involved should be transferable onto multi-electrode arrays, which are usually vulnerable to more laborious chemistry. For instance, cleaning of MEAs with aggressive acids before chemical modification is prohibited because the conductive metal leads would be dissolved. Therefore, it is relevant to test more simple modification routes as potential methods to be used on MEAs. Thus, adsorbed layers of PEO-PPO block-copolymers on hydrophobic surfaces were investigated as potential neurophobic background surfaces in patterning studies, over a time period of 30 days (commercially available PEO-PPO-PEO triblock copolymers, called Synperonics F108 and F127 were tried). Background adhesion results are shown over a period of 30 days for neurophobic Polyimide and Fluorocarbon coated surfaces, each supplemented by F108 or F127 Synperonics.

Spontaneous activity of patterned islands

It is well known that large unpatterned ('random') cultured networks of cortical neurons start to fire spontaneously after about a week in vitro. The implications of such firing for the proper functioning as host has to be considered. In first instance, the cultured probe is meant for stimulation purposes. In that case, electrodes deliver stimuli directly to the sprouts (antidromic propagation) and the activity of the network itself is of no importance (antidromic stimulation of sprouts by natural synaptic connections between axonal sprout and network is impossible). Secondly, if one would consider, for future two-way interface applications, the use of the cultured probe for recording purposes, the spontaneous activity of networks may seriously distort the information from the sprouts. For smaller networks, like the patterned islands of the cultured probe, it is not known yet what the minimum network size and cell density conditions are for the occurrence of spontaneous activity. It may be that small diameter islands show no activity at all. Therefore, it is very interesting to investigate whether the patterned islands of a cultured probe indeed show spontaneous activity. Part of this paper is devoted to that topic, to answer questions such as: do islands also become spontaneously active after a week ? With the same characteristics as unpatterned (random) networks? Is there a minimum diameter, above which networks become spontaneously active? If stand-alone networks become interconnected, do firing patterns synchronize?

Materials and methods

Cortical neuron isolation/culturing and MEA fabrication

Dissociated (Trypsin/EDTA) cortical neurons (1 day postnatal rats) were seeded onto patterned structures with a plating density of 5000 living cells/mm^2. Cells were allowed to adhere onto the surfaces during a time period of 4 hours. Samples were rinsed with NaCl (0.9%) solution to remove non-adherent cells. Neurons were cultured in chemically defined R12 medium (DMEM/HAM's F12, Gibco) without serum. The cultures were stored in a CO_2 incubator with a constant temperature of 37 °C, and a constant CO_2 level of 5%. The culture medium was refreshed half, 3 times a week.

In short, multi-electrode areas (MEAs) were fabricated from 5×5 cm glass plates with gold deposited tracks leading to 61 hexagonal ordered electrodes. MEAs were isolated with a sandwich layer of SiO_2–Si_3N_4–SiO_2 (ONO) using a plasma enhanced chemical vapor deposition (PECVD) process. Electrode tips were deinsulated with a Sulfur Hexafluoride 6 (SF_6) Reactive Ion Etching (RIE) technique and platinised to reduce the electrode impedance down to 200 kΩ at 1 kHz.

Neurophilic islands were created by PEI microstamping of circular patterns.

Recording of action potentials

Electrode signals were amplified, filtered between 0.3 and 6 kHz (first order) and captured by a 16-channel 12 bit National Instruments PCI-6023E Data Acquisition PC-card. The input range as well as the sampling frequency was software controlled by a Labview program. The real time data processing software reduced the data stream by rejection

of data which did not contain bioelectrical activity. Artefact rejection was severe: if activity is measured at the same time in different channels, the waveforms are rejected. In each channel, the rms noise level was constantly monitored and determined the setting of a level detector to detect spike activity. The threshold was set at 6 times the noise level (typically 7 μV rms). Each time bin of 10 ms with recorded activity was stored and analysed with Matlab computer software. Before further processing, wave shapes were classified to distinguish multi-unit from single unit activity [15].

Fabrication of neurophobic background materials

1) Polyimide: Polyimide (PI, Probimide 7510®, Arch Chemicals N.V., Zwijndrecht, Belgium) was spin-coated (4000 rpm, 30 s) onto 25 cm^2 glass plates (Glaverbel, Belgium). PI was diluted in n-methyl pyrolidon (1:1 v/v), dried on a hot plate (120 °C, 5 min), exposed to ultraviolet (UV)-light, and baked (300 °C, 90 min). Then plates were cut into square pieces of approximately 2.6 cm^2.
2) Plasma-coated Fluorocarbon (FC): In a reactive ion etching (RIE) system, spin-coated polyimide samples were treated with an etching CHF_3/O_2 plasma (25 sccm CHF_3, 5 sccm O_2, 150 mTorr and 2.1×10^{-1} W/cm^2) for 20 s, a depositing CHF_3 plasma (25 sccm CHF_3, 150 mTorr, and 2.1×10^{-1} W/cm^2) for 40 s, and a final depositing CHF_3 plasma treatment at 1.2×10^{-1} W/cm^2 for 8 min.
3) Synperonics F108 and F127: The triblock copolymers Synperonics F108 (EO_{127}–PO_{48}–EO_{127}; ICI, Holland BV, Rozenburg) and F127 (EO_{95}–PO_{62}–EO_{95}; ICI, Holland BV, Rozenburg) were dissolved in 0.1 M phosphate buffered saline (1% w/w) and adsorbed onto Polyimide- and Plasma-coated FC samples over a time period of 24 h. Subsequently, samples were rinsed twice with sterile water (Aqua Purificata, Bufa BV, Uitgeest, The Netherlands). Surfaces were dried by aspiration of residual water with a glass pipette connected to a vacuum pump.

Preparation of polydimethylsiloxane (PDMS) microstamps

Sylgard 184 silicone (Mavom bv, The Netherlands) was mixed with the curing agent in a 10:1 ratio. Air bubbles were removed from the mixture by evacuation with a water jet pump. Collapse of air bubbles was promoted by following a cycle of evacuation and pressure release for 6 times. A metal ring with an inner diameter of 4.3 mm (height 0.8 mm) was placed around the central area of a Polyimide mould containing 3 different regions of 20 microwells (12 um deep) with diameters of 50, 100, and 150 μm at the bottom. The spacing distance between the wells was fixed at 90 μm for all 3 regions. The ring was filled with the mixed silicone, covered with a 76 mm microscope slide, and crosslinked at room temperature in the mould for 4 days. Finally, stamps were carefully removed from the mould and stored in plastic tubes until use.

Quantification of background adhesion

Microphotographs were taken on 2 separate subsections of each pattern after 1, 4, 8, 15 and 30 days with a digital photo camera (AxioCam HR, Carl Zeiss, Germany) attached to an inverted phase contrast microscope (Nikon Diaphot-TMD, Tokyo, Japan). The images were first corrected for non-uniform illumination. Secondly, they were converted into black-and-white images by a threshold operation: white pixels for the cell areas, black for the background material. The calculated fraction F of white pixels in the image now represented a quantitative measure for the adhesion on the background material only

$$F = \frac{\text{Number of white pixels}}{\text{Number of white pixels} + \text{black pixels}}$$

Results

Improved neurophobic/neurophilic contrast

Figure 3 shows the results of cell adhesion in the neurophobic (called 'background') areas. It can be clearly observed that adhesion in the neurophobic regions decreases with time for poly-imid-only (first column), but remains equal or varies a bit for all other coating conditions. The only exception is the F108-FC coating, which shows an increase of cells in the neurophobic parts. The conclusion from Fig. 3 is that FC coating is better than PI coating, also after 30 days in vitro (DIV). Additional coating of PI or FC layers with triblock-copolymers synperonics F108 or F127, repels cells even better, as well for PI as for FC, but not after 30 days in the F108-FC case. Best results are obtained

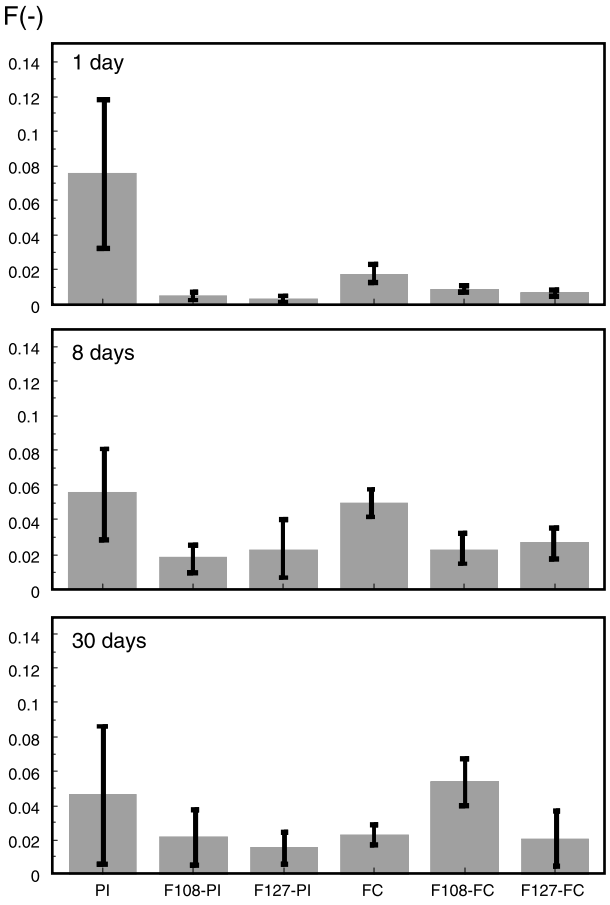

Fig. 3. Quantified background adhesion fraction *F* (see section II D) of neuronal tissue on 6 different background surfaces (neurophobic part) after 1, 8 and 30 days. Mean ± S.D. ($n = 6$). *PI* Poly-imid coating only; *F108-PI* superonics F108 coating on top of PI layer; *F127-PI* superonics F127 coating on top of PI layer; *FC* Fluoro carbon coating only; *F108-FC* superonics F108 coating on top of FC layer; *F127-FC* superonics F127 coating on top of FC layer

for the two coatings on the PI basic layer, with only a few % of neurophobic layer area taken by cells after 30 days, see Fig. 3. (full report is in Ref. [13]).

Table 1. *Cell coverage, network activity and connectivity for three island diameters*

Diameter PEI circles	50 µm	100 µm	150 µm
N (−) 1 day	16.4 ± 2.7 ($n = 20$)	45.6 ± 5.0 ($n = 20$)	81.2 ± 15.1 ($n = 20$)
$P_{AC\text{-}EL}$ (%) 8 days	0.7 ± 1.9 ($n = 7$)	2.8 ± 3.9 ($n = 7$)	10.7 ± 12.7 ($n = 7$)
$P_{COV\text{-}EL}$ (%) 8 days	70.0 ± 23.3 ($n = 6$)	93.6 ± 8.0 ($n = 6$)	93.6 ± 9.0 ($n = 6$)
N_C (−) active 8 days	– ($n = 0$)	6.0 ± 0.0 ($n = 3$)	3.5 ± 2.6 ($n = 7$)
N_C (−) non-active 8 days	2.0 ± 2.1 ($n = 36$)	2.9 ± 2.4 ($n = 34$)	2.7 ± 2.5 ($n = 31$)
$P_{AC\text{-}EL}$ (%) 15 days	0.8 ± 2.0 ($n = 6$)	5.0 ± 7.7 ($n = 6$)	10.0 ± 13.8 ($n = 6$)
$P_{COV\text{-}EL}$ (%) 15 days	64.2 ± 23.8 ($n = 6$)	93.3 ± 8.8 ($n = 6$)	95.8 ± 5.9 ($n = 6$)
N_C (−) active 15 days	– ($n = 0$)	6.0 ($n = 1$)	3.3 ± 2.2 ($n = 4$)
N_C (−) non-active 15 days	2.0 ± 2.0 ($n = 36$)	2.7 ± 2.4 ($n = 35$)	2.4 ± 2.3 ($n = 33$)

N The number of neurons adhering on microprinted PEI-circles with diameters of 50, 100, and 150 µm after 1 day. $P_{AC\text{-}EL}$ The percentage of corresponding electrically-active electrodes on MEAs after 8 and 15 days. $P_{COV\text{-}EL}$ The percentage of electrodes covered with neuronal cells on MEAs after 8 and 15 days. N_C The number of neuronal connections with the surrounding electrodes for electrically-active electrodes and non-active electrodes after 8 and 15 days.

Spontaneous activity of patterned islands

On 1 MEA, with unconnected islands, spike rates in a particular island were observed after 22 DIV. Neurons fired at a rate of 8 spikes/s at 22 DIV, and 4–5 spikes/s at 28 DIV. A second, more systematic, search for spontaneous activity in patterned, but connected, islands was done on 2 MEA's, each with 60 stamped circles of PEI, diameters 50, 100 ad 150 µm (20 each). Activity started at normal age, 8 DIV, and could last until the last observation day, 35 DIV. Almost no activity

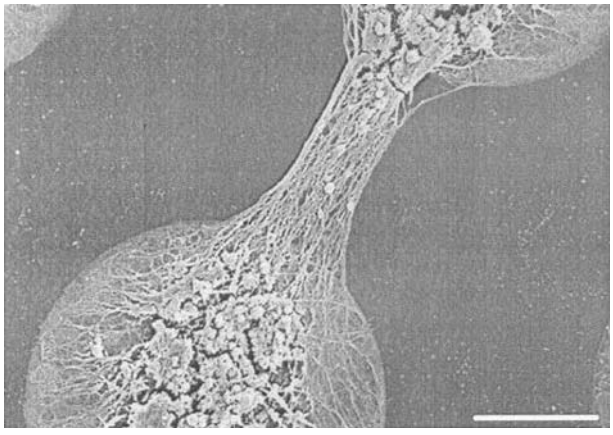

Fig. 4. Scanning electron micrograph of cortical neuronal tissue (30 days) present on a pattern of PEI circles microprinted onto FC. Diameter of the circular islands is 150 µm. Spacing distance between circles is 90 µm. Scaling bar = 50 µm. The micrograph shows a connected pair of islands in detail

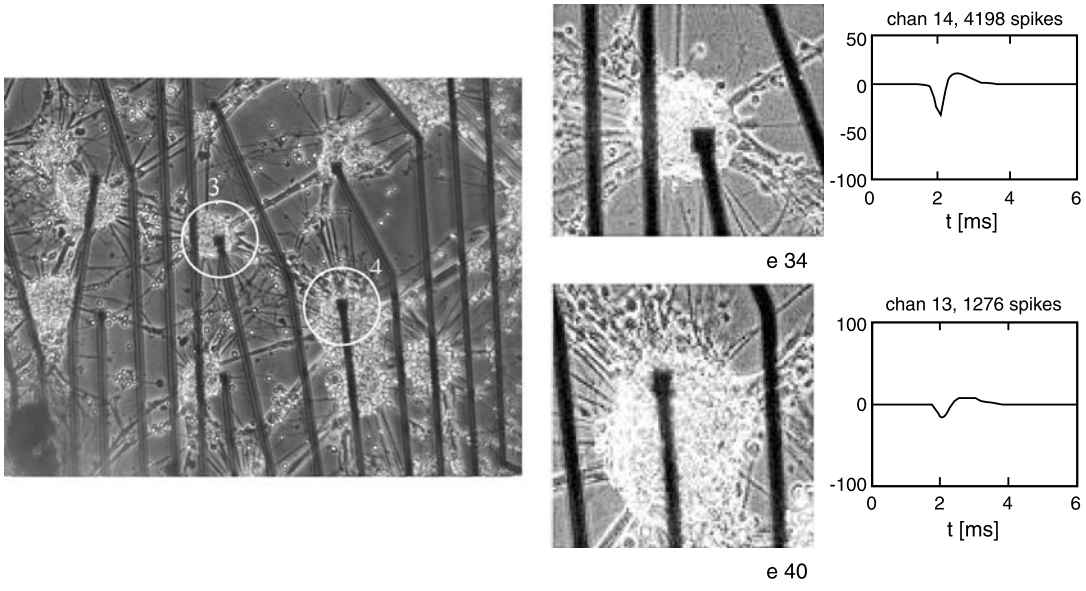

Fig. 5. Example of spontaneous bioelectrical activity from cortical neurons seeded onto a PEI-microprinted multi-electrode array (*12 DIV*). Two islands at electrodes 34 and 40 were spontaneously active after a week. Electrode separation is 190 µm. Islands became interconnected later and showed synchronized behaviour (Fig. 6). Details on the right show the two clusters and the derived averaged spike waveform (top: electrode 40, 4198 spikes. bottom: el. 34, 1276 spikes)

was seen for the 50 µm diameter islands. Five percent of the 100 µm diameter islands showed spontaneous activity and 10% of the 150 µm diameter islands. Spike rates were much higher than in the unconnected island, ranging from averages (±1 SD) of 17 (12), 302 (199), 229 (192), 95 (−) and 248 (−), at 8, 12, 14, 19 and 35 DIV, respectively (number of active electrodes/islands was 5, 3, 4, 1 and 1, respectively).

The experimental results are summarized in Table 1. On 150 µm PEI circles, the neuronal connectivity Nc between neuronal clusters (defined as the average number of surrounding electrodes, connected to a single PEI-coated island through neurite fascicles) was only slightly higher for N_c-active than for N_c non-active electrodes. However, on 100 µm circles the connectivity was significantly higher on the active electrodes. An example of connected clusters is given in Fig. 4. It shows the result of outgrowing neuronal tissue as observed after 30 days on a microprinted pattern of PEI circles onto FC. Cells initially migrated toward the center of the circles (not shown) and allowed free space for the outgrowth of neurites around the aggregates and within the borders of the PEI circles. The tissue on the two circles were interconnected by a bundle of neurites and/or axons.

Synchronized activity of patterned islands

Figure 5 gives a typical example of two connected islands at 12 DIV. They fired synchronously during periods of typically 120 s, with regular silent intervals between these 120 seconds-epochs. Figure 6 presents the spike rates of these islands, first as a spike rate plot

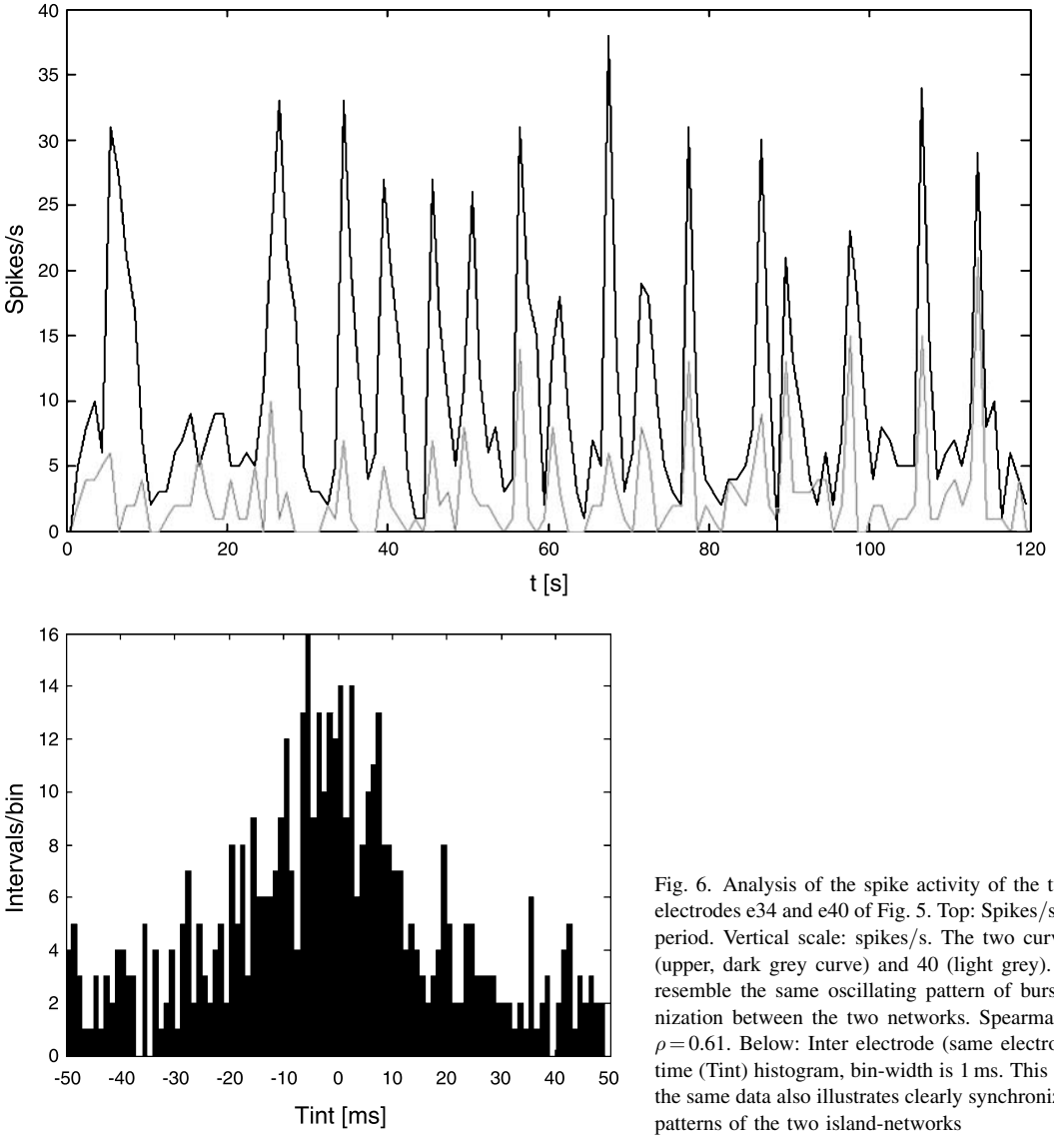

Fig. 6. Analysis of the spike activity of the two connected islands at electrodes e34 and e40 of Fig. 5. Top: Spikes/s during 120 s of bursting period. Vertical scale: spikes/s. The two curves are for electrode 34 (upper, dark grey curve) and 40 (light grey). The two curves clearly resemble the same oscillating pattern of bursts, pointing at synchronization between the two networks. Spearman correlation coefficient $\rho = 0.61$. Below: Inter electrode (same electrodes 34 and 40) interval time (Tint) histogram, bin-width is 1 ms. This second representation of the same data also illustrates clearly synchronization between the firing patterns of the two island-networks

over a time interval of 120 s, then as a inter-electrode interval histogram. It is clearly observed that the two clusters fire in a highly synchronized way, with periodic bursting. In the peaks, spike rates go up to 30 spikes/s in one channel, and about 20 spikes/s in the other.

Discussion

Activity in patterned MEA's will be briefly compared to unpatterned (random) network activity, as reported in Ref. [14]. In the latter, activity starts around one week after seeding, i.e. 7 DIV. Spike rate, summed over all 61 electrodes, develops gradually from zero to 32 spikes/s between 9 and 42 DIV. This implies a maximum of about 0.5 spikes/s per electrode, at 42 DIV. However, in time, and per electrode, spike rate may differ considerably, for example 22 spikes/s was observed maximally, in one electrode (lasting a few days). Comparing unpatterned networks with patterned islands, activity seems to start at the same age, 7–8 DIV. The variability in the random networks, and absence of statistics sofar in the unconnected island case, makes it hard to draw a comparison. A cautious observation may be that the spike rate in unconnected islands is in the same range as in the random network, i.e. 4–8 spikes/s at 22–28 DIV. It is, however, clear that the connected clusters fire at a very high spike rate, much higher than that observed in the unpatterned network [14].

Another comparison can be made with regard to the probability that spontaneous firing develops in unpatterned large networks and in patterned ones. In unpatterned networks, it was found [14] that 16 out of 24 experiments (each consisting of 7 cultured MEA's) were selected (on several grounds, but not presence/absence of activity) for longitudinal measurements. A number of 47 (40%) out of this set of 112 cultures (i.e. 112 MEA's with 60 electrodes each) exhibited spontaneous activity at 7 and 8 DIV, of which 16 had 4 or more active electrode sites. This means that 60% had no active electrodes at all, 26% ($n = 31$) showed activity at less than 4 electrodes, and 14% ($n = 16$) at 4 or more electrodes. So, one can estimate conservatively that the average probability that an electrode is active is in the order of one percent (under the assumption that the electrodes behave 'independently', so we do not consider the bursting periods, in which many of the available electrodes show activity). Clearly, this percentage is of the same order or lower as found for the patterned islands, as we saw in Table 1, i.e. 2.8 and 10.7% for the 100 and 150 μm islands, respectively, at 8 DIV. However, as the number of elements in each sample is only 7 and the standard deviations are considerable (Table 1), these figures are only indicative.

The start of activity at diameter 100 μm and onwards in circular islands probably indicates a minimum number of neurons needed to develop spontaneous activity. However, also other variables will play an essential role in that process, like number and density of synaptic connections and density of cells. Control of local density was done by Chang *et al.* [15] on hippocampal neurons showing that alternating line patterning (40 μm wide lines) of substrates gave control over local density of neurons, 100–500 cells/mm^2, and did enhance the activity compared to randomly plated networks with about the same density. The data give some indication that small islands, diameter 50 μm, develop hardly any spontaneous activity. This may be advantageous for the use of a cultured probe as a recording device. As stated in the introduction, for the stimulatory use of a cultured probe, spontaneous activity is unimportant as long as axonal sprouts grow from the host tissue towards the implant. Other types of cultured probes may do the reverse, i.e. 'send out' axons to the host tissue. In that case, spontaneous activity of the intermediate cultured networks is undesirable.

References

1. Buitenweg JR, Rutten WLC, Marani E (2003) Geometry based finite-element modeling of the electrical contact between a culture neuron and a microelectrode. IEEE Trans Biomed Eng 50: 501–510
2. Buitenweg JR, Rutten WLC, Marani E, Polman SKL, Ursum J (2002) Extracellular detection of active membrane currents in the neuron-electrode interface. J Neurosci Methods 115: 211–221
3. Buitenweg JR, Rutten WLC, Marani E (2002) Extracellular stimulation window explained by a geometry-based model of the neuron-electrode contact. IEEE Trans Biomed Eng 49: 1591–1600
4. Buitenweg JR, Rutten WLC, Marani E (2002) Modeled channel distributions explain extracellular recordings from cultured neurons sealed to microelectrodes. IEEE Trans Biomed Eng 49: 1580–1591
5. Ruardij TG, Goedbloed MH, Rutten WLC (2000) Adhesion and patterning of cortical neurons on polyethylenimine and fluorocarbon-coated surfaces. IEEE Trans Biomed Eng 47: 1593–1599
6. Ruardij TG, Goedbloed MH, Rutten WLC (2003) Long-term adhesion and survival of dissociated cortical neurons on miniaturized chemical patterns. Med Biol Eng Comp 41: 227–232
7. Corner MA, Ramakers GJA (1992) Spontaneous firing as an epigenetic factor in brain development – physiological consequences of chronic tetrodotoxin and picrotoxin exposure in cultured rat neocortex neurons. Dev Brain Res 65: 57–64
8. Gross G (1979) Simultaneous single unit recording in vitro with a photoetched laser deinsulated gold multielectrode surface. IEEE Trans Biomed Eng 26: 273–278
9. Pine J (1980) Recording action potentials from cultured neurons with extracellular microcircuit electrodes. J Neurosci Meth 2: 19–31

10. Jimbo Y, Tateno T, Robinson HPC (1999) Simultaneous induction of pathway-specific potentiation and depression in networks of cortical neurons. Biophys J 76: 670–678
11. Corey JM, Wheeler BC, Brewer GJ (1996) Micrometer resolution silane-based patterning of hippocampal neurons: critical variables in photoresist and laser ablation processes for substrate fabrication. IEEE Trans Biomed Eng 43: 944–955
12. Ruardij TG, van den Boogaart MAF, Rutten WLC (2002) Adhesion and growth of electrically-active cortical neurons on polyethyleneimine patterns microprinted on PEO-PPO-PEO triblockcopolymer-coated hydrophobic surfaces. IEEE Trans Nanobiosci 1: 1–8
13. van Staveren GW, Buitenweg JR, Heida T, Rutten WLC (2002) Wave shape classification of spontaneous neuronal activity in cortical cultures on micro-electrode arrays. Proceedings second joint IEEE-EMBS/BMES conference, Houston USA, ISBN: 0-7803-7613-7 CD-ROM
14. van Pelt J, Wolters PS, Corner MA, Rutten WLC, Ramakers GJA (2004) Long-term characterisation of firing dynamics of spontaneous bursts in cultured neural networks. IEEE Trans Biomed Eng 51: 2051–2062
15. Chang JC, Brewer GJ, Wheeler BC (2001) Modulation of neural network activity by patterning. Biosens Bioelectr 16: 527–533

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Brain-computer interface: a reciprocal self-regulated neuromodulation

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Summary

Brain-computer interface (BCI) is a system that records brain activity and process it through a computer, allowing the individual whose activity is recorded to monitor this activity at the same time. Applications of BCIs include assistive modules for severely paralyzed patients to help them control external devices or to communicate, as well as brain biofeedback to self regulate brain activity for treating epilepsy, attention-deficit hyperactivity disorder (ADHD), anxiety, and other psychiatric conditions, or to enhance cognitive performance in healthy individuals. The vast majority of BCIs utilizes non-invasive scalp recorded electroencephalographic (EEG) signals, but other techniques like invasive intracortical EEG, or near-infrared spectroscopy measuring brain blood oxygenation are tried experimentally.

Keywords: Neuromodulation; brain-computer interface; neurofeedback; EEG; near-infrared spectroscopy; seizures; paralysis.

Introduction

Human brain activity has fascinated not only the neuroscientists but also science fiction novelists and cinematographers. The former typically try to understand how the mind really works whereas the latter two typically fulfill the human fantasy to control others' minds or extend one's own mind capacity. *Applied neuroscience* is a field that merges the wish to extend our mind's capacity with the knowledge we have already acquired on how the brain works. Brain-computer interfaces (BCIs) are two such applications that attempt to improve paralyzed individuals' capacity to communicate and to control external devices, as well as to help individuals with or without pathology to exercise control on their own brains.

BCIs take advantage of technology to record brain activity directly from the brain. During the first international meeting for BCI technology that took place in June of 1999 at the Rensellaerville Institute near Albany, New York, BCI was defined as "*. . . a communication system that does not depend on the brain's normal output pathways of peripheral nerves and muscles*" [29]. Two major functional signals are recorded from the brain, electrical activity and metabolism or blood flow. Electrical activity can be recorded either invasively with implanted electrodes from single neurons (intracellular) and multiple neurons (extracellular), or non-invasively from the scalp, via electroencephalography (EEG). Metabolism and blood flow can be recorded with various techniques, including positron emission tomography (PET), single-photon emission tomography (SPECT), functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy (nIRS), with various degrees of invasiveness. A major restriction of BCIs is that the technology used must record and analyze brain signals fast enough for reasonable speed of communication or control. Other restrictions include cost, size, invasiveness, and mobility of the equipment used.

Neuromodulation

Neuromodulation is a general term that refers to the alteration of activity in the central, peripheral, or autonomic nervous systems. A very close and related term, neurostimulation is most commonly used to emphasize the stimulation of nerves by injecting automated electrical control signals. Usually there is an one-way communication between devices based on this technology and the nervous system. On the contrary, BCI establishes a two-way communication with emphasis on the extraction, recording, and analysis of the signal from the nervous system. Depending on the kind of feedback that the system provides to the user, the modification of the neural activity is usually done interactively.

Assistive applications for computer control in rehabilitation

Non-invasive EEG-controlled computer operations

Non-invasive EEG-controlled computer operations use scalp electrodes that record the summed activity of thousands of neurons. Signals are amplified and then digitized with analog-to-digital (A/D) converters. Scalp-recorded EEG signals vary in frequency from under 1 to more than 50 Hz [19]. With the use of analog filters or complex mathematical algorithms like the Fast-Fourier Transformation (FFT) for digital signals we can isolate the amplitudes or other characteristics of limited frequency bands that typically represent different brain functions [19]. For example, the ''alpha'' EEG rhythm is recorded over the occipital cortex in the range of 8–12 Hz, and is usually seen when individuals close their eyes. It is presumed that this rhythm reflects temporary inactivity or idling of a cortical area that is ready to be active again.

Since the 1970's, several published studies have shown the ability to learn, via operant conditioning, how to self-regulate the EEG in the alpha, theta, ''sensorimotor'' (sensory motor rythm (SMR), 12–15 Hz), and ''beta'' (15–30 Hz) frequency bands, as well as direct current (DC) voltage below 1 Hz, called ''slow cortical potentials (SCPs) (for a review, see 16). These observations have led to two different applications: brain self-regulation (EEG biofeedback, also neurofeedback, discussed later) [16], and non-invasive BCI for control and communication in patients with severe or total motor paralysis (''locked-in syndrome'') due to severe neuromuscular disorders, such as amyotrophic lateral sclerosis, brainstem stroke, and spinal cord injury [11].

The ''Thought Translation Device'' (TTD) is an EEG non-invasive BCI for communication via self-regulation of slow cortical potentials (SCPs) in severely paralyzed patients [11]. Patients learn to control a cursor in a computer screen and this may be used to control external devices (e.g., turn lights on/off), or to communicate verbally with the Language Support Program (LSP) [21]. Electrodes are placed on the scalp over the vertex (Cz in the International 10–20 system) and EEG is recorded against mastoid reference. The signal is digitally filtered and amplitude and polarity (positive vs. negative) of SCPs control the screen cursor. In the LSP, letters and symbols are presented in a dichotomous manner, in groups and subgroups, so the patient can select one of two. To increase typing speed, the software includes ''smart'' spelling by suggesting frequently used words form a dictionary. For the same reason, the thought translation device (TTD) can also be used to select from a menu of standard expressions or commands.

These investigators have shown that patients with late-stage amyotrophic lateral sclerosis were able to learn control of this BCI after 3–8 weeks of training [12]. Moreover, they showed that healthy individuals could control such BCIs with auditory feedback alone, although with less accuracy than with visual feedback [8]. Still, this may be the only solution to paralysed patients with visual impairments. One problem with severely paralysed patients is the uncertainty regarding their cognitive awareness, since they may appear as being in a vegetative state. For this reason, Hinterberger and associates [9] incorporated in the TTD a diagnostic tool using evoked-response potentials (ERPs) of the EEG, and were able to classify two out of five severely brain-injured patients in persistent vegetative state (previously diagnosed as unresponsive) as trainable for the TTD.

Others have shown BCI control driven by different EEG frequencies. McFarland and associates [14] showed that trainees were able to control a BCI by manipulating amplitude of either alpha (or in this case ''mu'', since this 8–12 Hz activity is recorded over the sensorimotor cortex) or beta (18–25 Hz) frequency bands. Adding more variables to control, such as more frequency bands or more scalp areas, may increase the complexity of control possible in BCIs. Alternatively, combining more EEG variables in multivariate linear algorithms has been shown to improve BCI control accuracy [15].

Invasive EEG-controlled computer operations

Non-invasive recording of the EEG signal proved important for the initial development of BCIs but according to Donoghue it has several limitations. In particular ''*it is impossible for these BMIs to obtain a direct readout of movement intent because neural spiking that carries this information is lost by averaging and filtering across the scalp* [5]''. Most important, ''*EEG as control signals are slow to engage or modulate (over 1 second), they require mental concentration to the exclusion of other activities and continuous control beyond 1 dimension is difficult to achieve* [23]''. As an alternative technology, direct brain-machine interfaces are based on the implantation of intracortical electrode arrays. Such an array had been implanted in the motor cortex area in a Macaca mulatta monkey [30]. In the first trial, the monkey controlled the position of a cursor on a video monitor using its hand to

track a continuously moving visual target. In subsequent trials, hand control of the cursor was substituted with neural control to test the reconstruction of hand trajectory. The experiment showed that the neural output from the motor cortex can be used to control a computer cursor almost as effectively as a natural hand.

In June 2004, a 4×4 mm, 100-channel sensor was implanted on the surface of the motor cortex, in the precentral gyrus immediately posterior to the superior frontal sulcus [18]. The surgical procedure consisted of an incision and 3 cm diameter craniotomy located above the right primary motor cortex. The patient was a 25 year-old quadriplegic ventilator-dependent male who was unable to move either upper extremity due to a C4 spinal cord injury; he is actively participating in a pilot study of the BrainGate system at the Sargent Rehabilitation Center. Using the BrainGate system, the participant gained control of a computer interface, with no special training, and managed to operate the cursor while performing other voluntary motor tasks, e.g. the patient was able to have full control over a TV while having a discussion with a nearby attendant.

Therapeutic applications

Brain biofeedback

Neurofeedback (NF; also *EEG Biofeedback*) is a technique that helps individuals self-regulate their EEG activity based on operant-conditioning. It utilizes the same principles and technology that BCIs use to record and analyze cortical electrical activity, but instead of being used for communication or control of external utilities it feeds the analyzed information back to the individual, in order to control the very source that produced the signal. NF is based on the principle that brain function can be self-regulated and altered with appropriate exercise in a similar fashion that muscle exercise can reshape a muscle. Just like body-building uses mirrors to provide information about muscle activity, NF uses BCIs as brain mirrors to make individuals aware of specific brain functions and their direction.

NF was found and developed by independent researchers for the treatment of different disorders. Sterman and his colleagues are responsible for developing a NF protocol to treat epilepsy by increasing 12–15 Hz activity over their rolandic cortex [24], whereas Rockstroh and associates have developed an alternative protocol for the same purpose by suppressing negative SCPs [22]. Lubar and colleagues have found a NF protocol to treat Attention Deficit Hyperactivity Disorder (ADHD) by suppressing theta activity and increasing SMR or low beta [13], whereas Heinrich and colleagues have recently developed an alternative ADHD protocol by augmenting negative SCPs [7]. Peniston and Kulkosky [20] have shown amplitude increases in the alpha (8–13 Hz) and theta (4–7 Hz) frequency bands to assist in the treatment of alcoholism, whereas Hardt and Kamiya [6] illustrated the potential of increasing alpha amplitude to reduce anxiety. Other researchers have also shown the potential of NF to enhance cognitive performance in healthy adults [27].

NF is being used worldwide to either treat neurological and psychological disorders, or to expand the cognitive potential of healthy individuals. Routine conditions treated with NF include ADHD, anxiety, epilepsy, and addictive disorders, whereas traumatic brain injury (TBI), learning disabilities, depression, and schizophrenia are currently being investigated as potential candidates (see review by Monastra, 2003).

The rationale for the development of NF protocols has been based upon EEG and neuroimaging research on correlates of brain pathology (ADHD, depression, TBI); accidental discovery (epilepsy); or neurophysiological correlates of cognitive states (anxiety, substance abuse). Sometimes more than one NF protocols are found effective for the same syndrome (see above). Some propose the comparison of patients' EEG to normative EEG databases in order to individualize NF according to each patients' abnormalities [25]. This is partly based on the rationale that identical symptoms may be due to different underlying primary pathologies, like for example attentional problems being due to ADHD or depression. However, EEG abnormality does not equal pathology, just as normal EEG does not guarantee healthy brain function. Therefore, caution and experience must be applied in such decisions, just as with any other medical or psychological treatment. A combination of standardized protocol, EEG normative database comparison, experience, and expert consultation will maximize the probability of treatment success.

NF sessions last for approximately one hour, including preparation and cleaning, 20–40 min of NF, and are usually administered twice per week. The number of sessions needed for treatment varies substantially from individual case to case, depending among other things on the condition being treated, the client's learning success, and the severity of the condition. Sterman [24] reports having used 25 sessions to treat epileptic seizures, Lubar [13] suggests that 40–80 sessions are

needed to treat ADHD, whereas improvement of patients with anxiety disorders have been reported with only 8 NF sessions (see 17, for a review).

Clinical efficacy of NF varies among studies, but epilepsy and ADHD seem to have the strongest experimental support, with anxiety and substance abuse following, and depression, schizophrenia, TBI, learning disabilities, Tourette's and chronic fatigue syndromes, and autism being under investigation [16]. Long term-effects of NF have been reported after six-month and up to 10-year post-treatment follow-ups [16, 13]. However, NF is not considered a panacea or sufficient treatment for all symptoms of the conditions treated, and other concurrent forms of care are recommended, including psychotherapy, family therapy, group support, and medication, whenever needed [13]. The existing research suggests that NF is a promising technique to treat a number of disorders. However, there is need for more research to further support the specificity of NF versus placebo, as well as the specificity of EEG frequency and scalp location to maximize or even attain therapeutic results.

Lubar [13] reports more than 1200 organizations worldwide (including private clinics and research centers/laboratories) applying NF for ADHD alone, based on information from NF equipment manufactures. There are several professional organizations that promote education and research on NF, including the International Society for Neuronal Regulation and its chapters worldwide (iSNR, www.isnr.org), the Association for Applied Psychophysiology and Biofeedback (AAPB, www.aapb.org), the Electroencephalography and Clinical Neuroscience Society (ECNS, www.ecns.com), and the Biofeedback Society of California (BSC, www.biofeedbackcalifornia.org) based in the U.S., as well as the Society for Applied Neuroscience (SAN, www.applied-neuroscience.org) based on Europe. Additionally, the Biofeedback Certification Institute of America (BCIA, www.bcia.org) tests and certifies clinicians who provide NF services to the public.

Research applications

(NIRSI)-driven BCIs & biofeedback

Recent attempts investigate the possibility to control BCIs via hemodynamic self-regulation. A non-invasive and inexpensive technology to measure cerebral blood flow (CBF) is using near-infra-red spectroscopy imaging (NIRSI), also referred to as *hemoencephalography* (HEG) [26]. Developed in the late 1970's [10], this technique uses near-infra-red light transmitters and respective sensors placed on the scalp, and can record blood oxygenation changes approximately 1–1½ cm under the scalp [1]. In contrast to light of different wavelengths, nIR light can pass through living tissue for short distances and be differentially absorbed and reflected back by different concentrations of oxy- and deoxy-hemoglobin. The rationale for using nIRS in BCIs is that nIRS self-regulation is faster to learn than EEG, and thus reduces patient frustration and possible withdrawal [3]. A few case studies have shown that HEG-biofeedback training to increase blood oxygenation in prefrontal cortex may improve sustained attention in children and adults with various pathologies including ADHD, stroke, depression, and TBI [26] or reduce migraines [2]. However, since these were not controlled studies, more systematic research has to follow to illustrate the potential of this method.

fMRI biofeedback

Others have shown the possibility to feedback blood oxygen level-dependent (BOLD) response with fMRI, with a delay of less than 2 s from image acquisition. Weiskopf and associates successfully trained an individual to self-regulate BOLD of the rostral-ventral and dorsal part of the anterior cingulate cortex (ACC) [28]. In a controlled study, deCharms and colleagues showed that volunteers who got fMRI feedback (but not others who did not get such feedback) were able to learn enhanced voluntary control over the somatomotor cortex [4].

Conclusions

BCIs show great potential in medical applications. Severely paralyzed "locked-in" patients can use BCIs to control their environment and communicate with others, a radical change in their life quality. Self-regulation of brain function with NF provides a very promising alternative for the treatment of psychiatric and neurological disorders such as epilepsy, ADHD, and anxiety, as well as the opportunity for healthy individuals to improve their cognitive performance. Researchers are currently investigating new applications for BCIs, such as treatment of depression or TBI, new technologies for BCIs like nIRS, implanted EEG electrodes, or even fMRI biofeedback, that will expand or improve current applications. Improved BCIs will provide better control accuracy, more complex communication, faster learning, and benefit for a broader patient range. However, it is

a complex field that requires combined efforts and serious further research. As experts in this field note, ''BCI development depends on close interdisciplinary cooperation between neuroscientists, engineers, psychologists, computer scientists, and rehabilitation specialists'' [29].

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References

1. Benaron DA, Kurth CD, Steven JM, Delivoria-Papadopoulos M, Chance B (1995) Transcranial optical path length by near infra-red phase-shift spectroscopy. J Clin Monit 11: 109–117
2. Carmen JA (2004) Passive infrared hemoencephalography: four years and 100 migrains. J Neurother 8: 23–52
3. Coyle S, Ward T, Markham C, McDarby G (2004) On the suitability of near-infrared (NIR) systems for next-generation brain-computer interfaces. Physiol Meas 25: 815–822
4. deCharms RC, Christoff K, Glover GH, Pauly JM, Whitfield S, Gabrieli JD (2004) Learned regulation of spatially localized brain activation using real-time fMRI. Neuroimage 21: 436–443
5. Donoghue JP (2002) Connecting cortex to machines: recent advances in brain interfaces. Nature Neurosci Suppl 5: 1085–1088
6. Hardt JV, Kamiya J (1978) Anxiety change through electroencephalographic alpha feedback seen only in high anxiety subjects. Science 201: 79–81
7. Heinrich H, Gevensleben H, Freisleder FJ, Moll GH, Rothenberger A (2004) Training of slow cortical potentials in attention-deficit-/hyperactivity disorder: evidence for positive behavioral and neurophysiological effects. Biol Psychiatry 55: 772–775
8. Hinterberger T, Neumann N, Pham M, Kubler A, Grether A, Hofmayer N, Wilhelm B, Flor H, Birbaumer N (2004) A multimodal brain-based feedback and communication system. Exp Brain Res 154: 521–526
9. Hinterberger T, Wilhelm B, Mellinger J, Kotchoubey B, Birbaumer N (2005) A device for the detection of cognitive brain functions in completely paralyzed or unresponsive patients. IEEE Trans Biomed Eng 52: 211–220
10. Jobsis FF (1977) Noninvasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198: 1264–1267
11. Kubler A, Kotchoubey B, Hinterberger T, Ghanayim N, Perelmouter J, Schauer M, Fritsch C, Taub E, Birbaumer N (1999) The thought translation device: a neurophysiological approach to communication in total motor paralysis. Exp Brain Res 124: 223–232
12. Kubler A, Neumann N, Kaiser J, Kotchoubey B, Hinterberger T, Birbaumer NP (2001) Brain-computer communication: self-regulation of slow cortical potentials for verbal communication. Arch Phys Med Rehabil 82: 1533–1539
13. Lubar JF (2003) Neurofeedback for the management of attention-deficit disorders. In: Schwartz MS, Andrasik F (eds) Biofeedback: a practitioner's guide. The Guilford Press. New York, pp 409–437
14. McFarland DJ, Sarnacki WA, Vaughan TM, Wolpaw JR (2005) Brain-computer interface (BCI) operation: signal and noise during early training sessions. Clin Neurophysiol 116: 56–62
15. McFarland DJ, Wolpaw JR (2005) Sensorimotor rhythm-based brain-computer interface (BCI): feature selection by regression improves performance. IEEE Trans Neural Syst Rehabil Eng 13: 372–379
16. Monastra VJ (2003) Clinical applications of electroencephalographic biofeedback. In: Schwartz MS, Andrasik F (eds) Biofeedback: a practitioner's guide. The Guilford Press, New York, pp 438–463
17. Moore NC (2000) A review of EEG biofeedback treatment for anxiety disorders. Clin Electroencephalogr 31: 1–6
18. Mukand J, Williams S, Shaikhouni A, Morris D, Serruya M, Donoghue J (2004) Feasibility study of a neural interface system for quadriplegic patients. Presented at the 65th Annual Assembly of the American Academy of Physical Medicine & Rehabilitation, October 2004, Phoenix, Arizona
19. Niedermeyer E (1999) The normal EEG of the waking adult. In: Niedermeyer E, Lopes da Silva F (eds) Electroencephalography: basic principles, clinical applications, and related fields. Williams & Wilkins, Baltimore, pp 76–92
20. Peniston EG, Kulkosku PJ (1989) Alpha-theta brainwave training and beta endorphin levels in alcoholics. Alcoholism Clin Exp Res 13: 271–279
21. Perelmouter J, Kotchoubey B, Kubler A, Taub E, Birbaumer N (1999) A language support program for thought-translation-devices. Automedica 18: 67–84
22. Rockstroh B, Elbert T, Birbaumer N, Wolf P, Dutchting-Roth A, Recker M, *et al* (1993) Cortical self-regulation in patients with epilepsies. Epilepsy Res 14: 63–72
23. Serruya MD, Donoghue JP (2003) Design principles of a neuromotor prosthetic. In: Horch KW, Dhillon GS (eds) Device in neuroprosthetics: theory and practice. Imperial College Press, London, pp 1158–1196
24. Sterman MB (2000) Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. Clin Electroencephalogr 31: 45–55
25. Thatcher R (1999) EEG database-guided neurotherapy. In: Evans JR, Abarbanel A (eds) Introduction to quantitative EEG and neurofeedback. Academic Press, San Diego, pp 29–65
26. Toomim H, Mize M, Kwong CK, Toomim M, Marsh R, Kozlowski G, Kimball M, Remond A (2004) Intentional increase of cerebral blood oxygenation using hemoencephalography (HEG): an efficient brain exercise therapy. J Neurotherapy 8: 5–22
27. Vernon D, Egner T, Cooper N, Compton T, Neilends C, Sheri A, Gruzelier J (2003) The effect of training distinct neurofeedback protocols on aspects of cognitive performance. Int J Psychophysiol 47: 75–85
28. Weiskopf N, Veit R, Erb M, Mathiak K, Grodd W, Goebel R, Birbaumer N (2003) Physiological self-regulation of regional brain activity using real-time functional magnetic resonance imaging (fMRI): methodology and exemplary data. Neuroimage 19: 577–586
29. Wolpaw JR, Birbaumer N, Heetderks WJ, McFarland DJ, Peckham PH, Schalk G, Donchin E, Quatrano LA, Robinson CJ, Vaughan TM (2000) Brain-computer interface technology: a review of the first international meeting. IEEE Trans Rehabil Eng 8: 164–173
30. Wu W, Black MJ, Gao Y, Bienenstock E, Serruya M, Donoghue JP (2002) Inferring hand motion from multi-cell recordings in motor cortex using a Kalman filter. SAB'02-Workshop on Motor Control in Humans and Robots, on the Interplay of Real Brains and Artificial Devices, August 10, Edinburgh, Scotland (UK), pp 66–73

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Cicerone: stereotactic neurophysiological recording and deep brain stimulation electrode placement software system

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Summary

Stereotactic neurosurgery and neurophysiological microelectrode recordings in both humans and monkeys are typically done with conventional 2D atlases and paper records of the stereotactic coordinates. This approach is prone to error because the brain size, shape, and location of subcortical structures can vary between subjects. Furthermore, paper record keeping is inefficient and limits opportunities for data visualization. To address these limitations, we developed a software tool (Cicerone) that enables interactive 3D visualization of co-registered magnetic resonance images (MRI), computed tomography (CT) scans, 3D brain atlases, neurophysiological microelectrode recording (MER) data, and deep brain stimulation (DBS) electrode(s) with the volume of tissue activated (VTA) as a function of the stimulation parameters. The software can be used in pre-operative planning to help select the optimal position on the skull for burr hole (in humans) or chamber (in monkeys) placement to maximize the likelihood of complete microelectrode and DBS coverage of the intended anatomical target. Intra-operatively, Cicerone allows entry of the stereotactic microdrive coordinates and MER data, enabling real-time interactive visualization of the electrode location in 3D relative to the surrounding neuroanatomy and neurophysiology. In addition, the software enables prediction of the VTA generated by DBS for a range of electrode trajectories and tip locations. In turn, the neurosurgeon can use the combination of anatomical (MRI/CT/3D brain atlas), neurophysiological (MER), and electrical (DBS VTA) data to optimize the placement of the DBS electrode prior to permanent implantation.

Keywords: Neuromodulation; movement disorders; Parkinson's disease; neurostimulation; electrical stimulation; electrode; stereotactic neurosurgery; surgical planning.

Stereotactic neurosurgery and deep brain stimulation

Stereotactic neurosurgery has been used in research for over one hundred years and it has gained acceptance into clinical practice since the 1950s [15]. The precision of target localization using stereotactic frames has improved since the inception of image-guided (MRI and CT) methods based on internal landmarks [17, 22, 27]. However, even with the increased accuracy of image-guided stereotactic targeting, it is often necessary to use neurophysiological microelectrode recordings (MER), and electrical stimulation to confirm and further explore the target [12, 13, 18, 26, 30]. In turn, stereotactic neurosurgical procedures typically require the integration of anatomical, neurophysiological, and electrical data to enable the neurosurgeon to make the most informed decisions possible.

Stereotactic neurosurgery is particularly relevant to deep brain stimulation (DBS). Over the last two decades DBS has evolved from a highly experimental technique to a well established therapy for a range of medically refractory neurological disorders [2]. To date, the most effective application of DBS technology is for the treatment of movement disorders. Surgical interventions for movement disorders have a long history, beginning with early studies that used lesions to eliminate activity in localized brain regions. Surgeons using stimulating/recording electrodes for target confirmation during ablative surgery found that high-frequency stimulation ($\sim$100 Hz) of the brain had behavioral outcomes similar to lesioning [3]. This realization transformed the world of functional neurosurgery, and DBS has become the surgical intervention of choice for Parkinson's disease (PD), essential tremor, and dystonia. In addition, DBS shows promise in the treatment of other neurological disorders such as epilepsy, obsessive-compulsive disorder, Tourette's syndrome, and depression. Currently the most common DBS procedures are for PD and they depend on precise localization and electrode insertion into the globus pallidus internus (GPi) or subthalamic

nucleus (STN), small structures deep within the basal ganglia.

In current clinical practice, MRI-based surgical navigation systems are used in concert with stereotactic frame systems to target the nucleus of interest and select the initial electrode trajectory for DBS surgeries [7–10, 16, 21, 28, 29]. The anatomical target is identified by direct visualization of the nucleus in the MRI and/or a brain atlas co-registered with the MRI [24]. The stereotactic coordinates of the anatomical target are calculated relative to the fiducial markers of the stereotactic frame present in the image. In turn, the mechanical adjustments of the frame system can be calibrated to enable a surgical trajectory that follows the desired path [26]. Many believe that accurate placement of DBS electrodes for a maximal therapeutic outcome requires neurophysiological definition of the anatomical borders of the nucleus and identification of areas where stimulation causes side effects [23, 25]. Therefore, the target area is commonly explored with several microelectrode penetrations during which extracellular unit recording and microstimulation data are collected.

The final DBS electrode placement is selected after a review of the gathered anatomical and neurophysiological data. This crucial decision is often based on paper records which are inefficient and limit opportunities for data visualization. Traditional 2D brain atlases are typically used to estimate electrode position with respect to the anatomy by superimposing the atlas over plots of the microelectrode recording data. However, these atlas slices are not customized to each patient and they are often spaced at large and irregular intervals, so the closest available slice may not accurately capture the neuroanatomy of the given electrode trajectory. This is especially true when the surgical trajectory is at an oblique angle relative to the sagittal and coronal planes used in 2D brain atlases. More importantly, the fundamental purpose of DBS is to modulate neural activity with applied electric fields, but current neurosurgical navigation systems do not allow for visualization of the spread of stimulation.

To address these limitations, we developed the Cicerone software system for stereotactic neurosurgical planning, neurophysiological data collection, and deep brain stimulation visualization. This research tool integrates the vast array of data used in the implantation of DBS electrodes, with the goal of improving the therapeutic outcome of the surgery. Cicerone provides interactive 3D visualization of co-registered MRI/CT images, subject-specific 3D anatomical brain atlas, and neurophysiological data from microelectrode recordings. Furthermore, it displays predictions of the volumes of tissue that would be activated by DBS for any given electrode position and orientation in the brain. Cicerone can be used to define a pre-operative target location and trajectory for the DBS electrode placement and help select the location on the skull for burr hole (in humans) or chamber (in monkeys) placement. Intra-operatively, Cicerone allows entry of the microdrive coordinates and MER data, enabling real-time interactive visualization of the electrode location in 3D relative to the surrounding anatomy. In addition, the user can simultaneously visualize the DBS electrode and its predicted stimulating effects in relation to the neuroanatomy and neurophysiology. In turn, stereotactic placement of the DBS electrode can be optimized prior to permanent implantation with the combination of anatomical, neurophysiological, and electrical data.

Cicerone was developed to integrate the various data sets used in our scientific analysis of human and monkey DBS research studies. The human and monkey versions of Cicerone are conceptually similar, but due to differences in the surgical procedures they have been developed as two separate software applications. Both systems were written using VTK (Visualization Toolkit; Kitware, Clifton Park, NY) and Tcl/Tk (Tool Command Language; http://tcl.sourceforge.net) making them portable across platforms, including Windows. Version 1.0 of Cicerone is self-contained on a single CD, and auto-installs on a PC similar to any traditional Windows software. Cicerone is currently a research tool and not commercially available or intended for clinical use outside of IRB approved studies. Individuals interested in using Cicerone in their own research are encouraged to contact CCM.

Human Cicerone

The Cicerone system was developed to address three issues. First, improve the intra-operative management of MER data. Second, provide the neurosurgeon with the ability to interactively visualize the stimulating influence of the DBS electrode in the target location before permanent implantation. Third, provide a common visualization platform to simultaneously analyze the anatomical (MRI/CT/3D brain atlas), neurophysiological (MER), and electrical (DBS VTA) data pertinent to the surgery.

In general, the MRI/CT scans with the stereotactic fiducial makers necessary for a human DBS procedure are acquired on the day of the surgery. Therefore, we

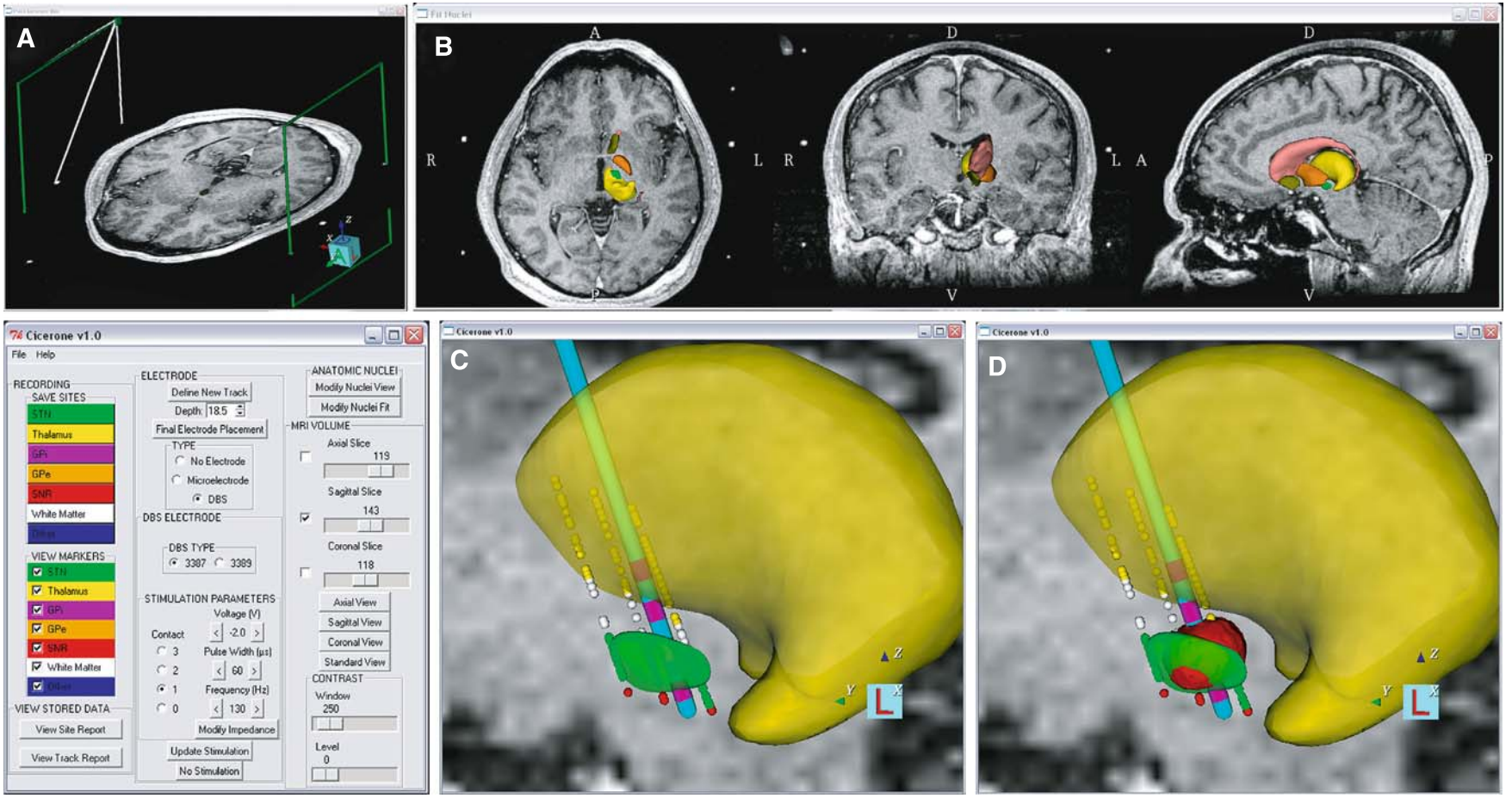

Fig. 1. Human Cicerone graphical user interface. (A) The green localizer box is manipulated to coincide with the stereotactic frame fiducial markers in the MRI. (B) A 3D brain atlas is customized to the subject's MRI with interactive scaling and translation. (C) Microelectrode recording data (*yellow dots* thalamus; *white dots* white matter; *green dots* STN; *red dots* SNr) and the DBS electrode position (*blue shaft with pink contacts*) can be viewed in stereotactic space with the MRI and anatomical nuclei (*yellow volume* thalamus; *green volume* STN). (D) Theoretical predictions of the volume of tissue that would be activated by DBS (*red volume*) can be visualized with any electrode position/trajectory and a range of stimulation parameter settings

developed our human Cicerone system to directly read in and interact with DICOM imaging data via a simple user interface; thereby decreasing the time needed to set up the system. When the user starts the program, they are prompted to enter any necessary patient/study identification data. Next, they navigate to the appropriate directory and load the patient's DICOM imaging data. A fundamental requirement of any stereotactic neurosurgical navigation system is the definition of a common coordinate system. In turn, the user must position a virtual replica of the frame fiducial system within the context of the MRI; thereby defining the stereotactic coordinate system relative to the imaging data (Fig. 1A). Version 1.0 of Cicerone has been designed to work with the Leksell stereotactic frame (Elekta Corp., Stockholm, Sweden). Following definition of the stereotactic frame coordinate system in the MRI, the user is prompted to select the right or left side of the brain for analysis. The user then orients the MRI along the midline using coronal and axial views, and defines the anterior commissure (AC) and posterior commissure (PC) in the image. The next step in the process consists of scaling and positioning 3D anatomical representations of nuclei of interest (e.g. subthalamic nucleus, globus pallidus, thalamus, etc.) (Fig. 1B). The anatomical nuclei are originally positioned within the context of the MRI based on the definition of the AC and PC. However, the user has the option to translate and/or scale the anatomical nuclei along the anterior/posterior, dorsal/ventral, and medial/lateral axes to enable the most accurate match possible with the MRI (Fig. 1B).

Once the Cicerone anatomical model has been defined relative to the MRI and stereotactic coordinate system, a preliminary target location and trajectory for the DBS electrode can be defined. This information can be used in conjunction with additional neurosurgical navigation systems and the stereotactic frame system to define the mechanical parameters of the frame apparatus (e.g. arc angle, collar angle, etc.). After a burr hole has been placed, the microdrive attached to the frame, and a cannula inserted along the initial trajectory to a specified depth above the target (15 mm at our institution), Cicerone can be used to visualize and record MER data (Fig. 1C). The user has the opportunity to identify each encountered cell as belonging to various anatomical nuclei and notes can be entered describing various electrophysiological characteristics (somatotopy, firing properties, background activity, etc.). The microelectrode recording (or stimulation) locations are displayed as small spheres and color-coded according to their user defined characteristics (Fig. 1C). The user can pan/zoom/rotate the view, adjust the display properties of the 3D brain atlas, and scroll through the MRI in three orthogonal planes. The recording markers and brain atlas can also be viewed in 2D, one slice at a time, which is sometimes preferable to a 3D view.

The fundamental advance of Cicerone over previous neurosurgical navigation software systems is the ability to predict the volume of tissue activated (VTA) by DBS for a given electrode position and stimulation parameter setting (Fig. 1D). This offers a great potential benefit to clinicians and researchers, enabling them to anticipate stimulation effects before the actual electrode implantation. The user can plan the electrode trajectory to achieve the desired interaction between the VTA, MER data, and 3D neuroanatomy (Fig. 1D). The computational details of generating VTA predictions are presented in our previous publications [4–6, 20]. Briefly, Cicerone employs pre-compiled solutions of the response of multicompartment cable models of myelinated axons to electric fields generated by finite element models of DBS electrodes. The theoretical VTA predictions used in Cicerone explicitly account for the effects of electrode capacitance, electrode impedance, and the stimulation parameter settings (contact, voltage, pulse width, frequency) [4–6] (Fig. 1D).

Simultaneous interactive visualization of the anatomical, neurophysiological, and electrical data pertinent to the DBS surgery allows definition of an optimal placement for the permanent DBS electrode. In turn, the stereotactic coordinates of the Cicerone-derived optimal placement can be applied to the surgical frame and the DBS electrode can be implanted. Once the user has finished their data entry and analysis, the stereotactic coordinate system transfer functions, brain atlas scaling/positioning, MER data, and DBS electrode placement are saved to a text file that can be re-imported into the program at a later time or stored to a central database.

Monkey Cicerone

The laboratory of Jerrold Vitek pioneered a parkinsonian non-human primate model of DBS that represents a powerful tool for experimental investigation on the therapeutic mechanisms of DBS [8, 14]. However, neurosurgical navigation systems customized for non-human primates are effectively non-existent. Therefore, we developed a monkey version of Cicerone (Fig. 2). It provides the same general features as the human version; however, differences in the stereotactic frame systems

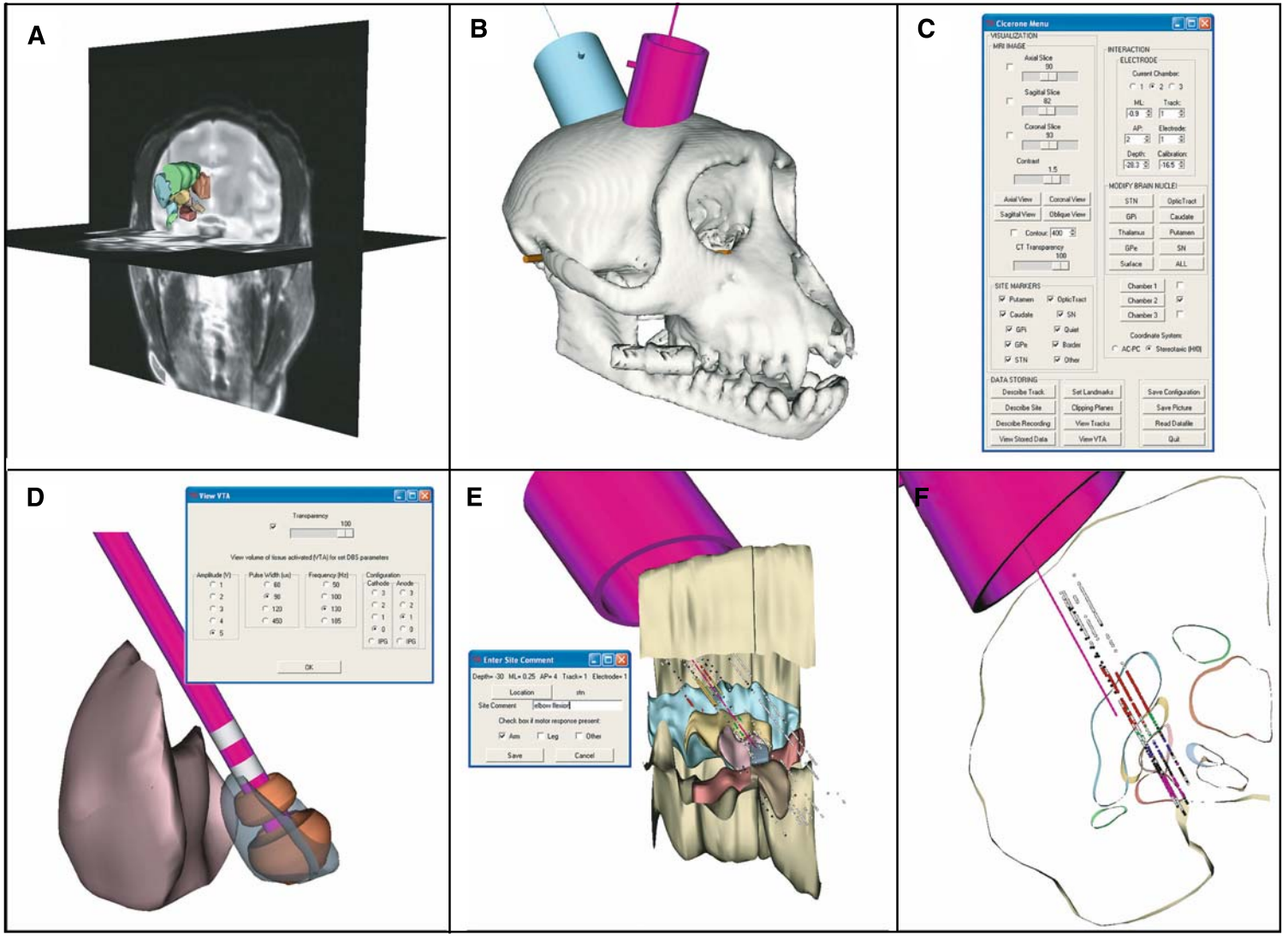

Fig. 2. Monkey Cicerone graphical user interface. (A) A 3D brain atlas is customized to the subject's MRI either by warping or linear scaling. (B) The contour of the skull is extracted from the CT data and co-registered with the MRI and 3D atlas. Electrode chambers are interactively positioned in the stereotactic coordinate system, defined by the ear bars and orbital bars. (C) Cicerone's main menu provides functions for image and data manipulation. (D) Orange ellipsoids inside the STN represent theoretical volume of tissue activated for the given DBS electrode position and stimulation parameters. (E) The user can enter information about each microelectrode recording site. The site markers are rendered in 3D with respect to the surrounding neuroanatomy. (F) Recording data and neuroanatomy can also be visualized in 2D, slice by slice

and surgical procedures require several differences in the software set-up. In monkey stereotactic neurosurgery, it is common to use a head frame and an atlas referenced to the orbitomeatal plane. This plane is defined by the interaural line (line between tips of the earbars) and the inferior orbital ridges. The origin is defined as the midpoint of the interaural line and the orbitomeatal plane (Frankfurt zero). For use in primate research, a CT is needed to visualize the skull and the external landmarks (ear canals and orbital ridges) so that the stereotactic head frame can be registered with the internal brain structures. The MRI is used to customize the 3D brain atlas and to locate internal landmarks on the CT. The MRI and CT are co-registered in Analyze 6.0 (AnalyzeDirect, Lenexa, KS) and imported into Cicerone as VTK volume files. Using the skull rendering extracted as a contour from the CT data, the user can position ear bars and orbital ridge bars to define the orbitomeatal plane (Fig. 2B). Cicerone enables the user to switch from the 'AC-PC coordinate system' to the 'stereotactic coordinate system' (i.e. orbitomeatal plane). When moving to the 'stereotactic coordinate system', rotation around mediolateral axis is performed so that the orbitomeatal plane is horizontal and the origin is shifted to Frankfurt zero.

The 3D brain atlas for non-human primates used in Cicerone was created from the University of Washington digital atlas of the longtailed macaque (*Macaca fascicularis*) brain [18] (Fig. 2A). A subject specific 3D brain atlas is constructed by warping 2D digitized atlas templates to the corresponding MRI slices using Edgewarp [1, 19]. Edgewarp applies a nonlinear warping function to atlas templates based on manual landmark selection. The warped atlas slices are converted into 3D volumes using the graphical modeling program Rhinoceros v 3.0 (McNeal & Associates, Seattle, WA). The customized 3D atlas is imported into Cicerone based on its registration with the MRI (Fig. 2A). Cicerone provides tools to interactively position up to three recording chambers on the animal's skull (Fig. 2B). This makes it possible to ensure, prior to surgery that the electrodes can reach the desired target areas and that the chambers and electrodes will not interfere with each other once placed on the skull. The user can also evaluate several chamber shapes to find the one that best fits the skull contour in a chosen location. The chamber placement coordinates provided by Cicerone can be applied directly to the stereotactic head frame. Cicerone's algorithm for coordinate calculation is designed for use with Kopf frame (model 1430 and electrode manipulator model 1460; David Kopf Instruments, Tujunga, CA). After the chamber placement surgery, it is advisable to perform another CT scan to verify the chamber position and angle on the skull.

During neurophysiologic data recording, the monkey and human versions of Cicerone are effectively the same. The user can interactively view the electrode position within the 3D anatomical environment by entering microdrive coordinates into Cicerone (Fig. 2C), MER data can be displayed (Fig. 2E and F), and DBS electrode positions can be evaluated with VTA predictions (Fig. 2D). One difference is the DBS electrode design used in the monkey. Our experimental monkey DBS electrodes are approximately one half the size of human DBS electrodes [8, 14]. In turn, the monkey Cicerone system has been customized to account for VTAs generated by monkey DBS electrodes (Fig. 2D). And similar to human Cicerone, the stereotactic coordinate system transfer functions, brain atlas scaling/positioning, MER data, and DBS electrode placement data are saved to a text file that can be re-imported into the program at a later time or stored to a central database.

Conclusions

The Cicerone software system represents the first neurosurgical navigation system to integrate electrically accurate predictions of neurostimulation-generated by DBS electrodes. In addition, it allows the neurosurgeon to simultaneously visualize the anatomical (MRI/CT/3D brain atlas), neurophysiological (MER), and electrical (DBS VTA) data pertinent to the implantation of DBS electrodes. Therefore, pre/intra-operative optimization of the stereotactic trajectory and placement of the DBS electrode can be performed with results derived from theoretical characterization of the stimulating effects of DBS and patient-specific characterization of the brain region targeted for implantation. Further, Cicerone provides a platform for integrated analysis of the interaction between the neuroanatomy, neurophysiology, neurostimulation, and behavioral outcomes of DBS.

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Conflict of interest statement

CRB and CCM are shareholders in IntElect Medical Inc., license holder for the neurostimulation prediction, optimization, and visualization intellectual property utilized in Cicerone.

References

1. Bookstein FL (1990) Morphometrics. In: Toga AW (ed) Three-dimensional neuroimaging. Raven Press, New York
2. Benabid AL (2003) Deep brain stimulation for Parkinson's disease. Curr Opin Neurobiol 13: 696–706
3. Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J (1987) Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 50: 344–346
4. Butson CR, Maks CB, McIntyre CC (2006) Sources and effects of electrode impedance during deep brain stimulation. Clin Neurophysiol 117: 447–454
5. Butson CR, McIntyre CC (2005) Tissue and electrode capacitance reduce neural activation volumes during deep brain stimulation. Clin Neurophysiol 116: 2490–2500
6. Butson CR, McIntyre CC (2006) Role of electrode design on the volume of tissue activated during deep brain stimulation. J Neural Eng 3: 1–8
7. D'Haese PF, Cetinkaya E, Konrad PE, Kao C, Dawant BM (2005) Computer-aided placement of deep brain stimulators: from planning to intraoperative guidance. IEEE Trans Med Imaging 24: 1469–1478
8. Elder CM, Hashimoto T, Zhang J, Vitek JL (2005) Chronic implantation of deep brain stimulation leads in animal models of neurological disorders. J Neurosci Methods 142: 11–16
9. Finnis KW, Starreveld YP, Parrent AG, Sadikot AF, Peters TM (2003) Three-dimensional database of subcortical electrophysiology for image-guided stereotactic functional neurosurgery. IEEE Trans Med Imaging 22: 93–104
10. Gibson V, Peifer J, Gandy M, Robertson S, Mewes K (2003) 3D visualization methods to guide surgery for Parkinson's disease. Stud Health Technol Inform 94: 86–92
11. Gironell A, Amirian G, Kulisevsky J, Molet J (2005) Usefulness of an intraoperative electrophysiological navigator system for subthalamic nucleus surgery in Parkinson's disease. Stereotact Funct Neurosurg 83: 101–107
12. Hamani C, Richter EO, Andrade-Souza Y, Hutchison W, Saint-Cyr JA, Lozano AM (2005) Correspondence of microelectrode mapping with magnetic resonance imaging for subthalamic nucleus procedures. Surg Neurol 63: 249–253
13. Hariz MI, Fodstad H (1999) Do microelectrode techniques increase accuracy or decrease risks in pallidotomy and deep brain stimulation? A critical review of the literature. Stereotact Funct Neurosurg 72: 157–169
14. Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL (2003) Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci 23: 1916–1923
15. Housepian EM (2004) Stereotactic surgery: the early years. Neurosurgery 55: 1210–1214
16. Lehman RM, Micheli-Tzanakou E, Zheng J, Hamilton JL (1999) Electrophysiological recordings in pallidotomy localized to 3D stereoscopic imaging. Stereotact Funct Neurosurg 72: 185–191
17. Laitinen LV (1985) CT-guided ablative stereotaxis without ventriculography. Appl Neurophysiol 48: 18–21
18. Magnin M, Jetzer U, Morel A, Jeanmonod D (2001) Microelectrode recording and macrostimulation in thalamic and subthalamic MRI guided stereotactic surgery. Neurophysiol Clin 31: 230–238
19. Martin RF, Bowden DM (2000) Primate brain maps: structure of the macaque brain. Elsevier, Amsterdam
20. McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL (2004) Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. Clin Neurophysiol 115: 589–595
21. Nowinski WL, Belov D (2003) The Cerefy Neuroradiology Atlas: a Talairach-Tournoux atlas-based tool for analysis of neuroimages available over the internet. Neuroimage 20: 50–57
22. Patel NK, Heywood P, O'Sullivan K, Love S, Gill SS (2002) MRI-directed subthalamic nucleus surgery for Parkinson's disease. Stereotact Funct Neurosurg 78: 132–145
23. Priori A, Egidi M, Pesenti A, Rohr M, Rampini P, Locatelli M, Tamma F, Caputo E, Chiesa V, Barbieri S (2003) Do intraoperative microrecordings improve subthalamic nucleus targeting in stereotactic neurosurgery for Parkinson's disease? J Neurosurg Sci 47: 56–60
24. Richter EO, Hoque T, Halliday W, Lozano AM, Saint-Cyr JA (2004) Determining the position and size of the subthalamic nucleus based on magnetic resonance imaging results in patients with advanced Parkinson disease. J Neurosurg 100: 541–546
25. Romanelli P, Heit G, Hill BC, Kraus A, Hastie T, Bronte-Stewart HM (2004) Microelectrode recording revealing a somatotopic body map in the subthalamic nucleus in humans with Parkinson disease. J Neurosurg 100: 611–618
26. Starr PA (2002) Placement of deep brain stimulators into the subthalamic nucleus or globus pallidus internus: technical approach. Stereotact Funct Neurosurg 79: 118–145
27. Starr PA, Vitek JL, DeLong M, Bakay RA (1999) Magnetic resonance imaging-based stereotactic localization of the globus pallidus and subthalamic nucleus. Neurosurgery 44: 303–313
28. St-Jean P, Sadikot AF, Collins L, Clonda D, Kasrai R, Evans AC, Peters TM (1998) Automated atlas integration and interactive three-dimensional visualization tools for planning and guidance in functional neurosurgery. IEEE Trans Med Imaging 17: 672–680
29. Teijeiro J, Macias RJ, Morales JM, Guerra E, Lopez G, Alvarez LM, Fernandez F, Maragoto C, Garcia I, Alvarez E (2000) Personal-computer-based system for three-dimensional anatomic-physiological correlations during stereotactic and functional neurosurgery. Stereotact Funct Neurosurg 75: 176–187
30. Zonenshayn M, Rezai AR, Mogilner AY, Beric A, Sterio D, Kelly PJ (2000) Comparison of anatomic and neurophysiological methods for subthalamic nucleus targeting. Neurosurgery 47: 282–292

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StimExplorer: deep brain stimulation parameter selection software system

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Summary

StimExplorer is a Windows-based software package intended to aid the clinical implementation of deep brain stimulation (DBS) technology. StimExplorer uses detailed computer models to provide a quantitative description of the 3D volume of tissue activated (VTA) by DBS as a function of the stimulation parameters and electrode location within the brain. The stimulation models are tailored to the individual patient by importing their magnetic resonance imaging (MRI) data and interactively scaling 3D anatomical nuclei to fit the patient anatomy. The user also inputs the DBS electrode orientation, location, and impedance data. The software then provides theoretically optimal stimulation parameter suggestions, intended to represent the start point for clinical programming of the DBS device. The software system is packaged into a clinician-friendly graphical user interface that allows for simultaneous interactive 3D visualization of the MRI, anatomical nuclei, DBS electrode, and VTAs for a wide range of stimulation parameter settings (contact, impedance, voltage, pulse width, and frequency). The goals of the StimExplorer system are to educate clinicians on the impact of stimulation parameter manipulation, and improve therapeutic outcomes by providing quantitative anatomical and electrical information useful for customizing DBS to individual patients.

Keywords: Neuromodulation; movement disorders; Parkinson's disease; Neurostimulation; electrical stimulation; electrode; magnetic resonance image; diffusion tensor image.

Deep brain stimulation

The realization that chronic high-frequency electrical stimulation generates clinical benefits analogous to those achieved by surgical lesioning has transformed the use of functional neurosurgery for the treatment of movement disorders. Deep brain stimulation (DBS) is an established therapy for essential tremor [3], Parkinson's disease (PD) [18], and dystonia [23]. In addition, DBS shows promise in the treatment of other neurological disorders such as epilepsy, obsessive-compulsive disorder, Tourette's syndrome, and depression. However, the clinical successes of DBS are tempered by our limited understanding of the effects of DBS on the nervous system. Converging theoretical [12, 13] and experimental results [1, 9] suggest that the therapeutic mechanisms of DBS may rely on activating axons surrounding the electrode, resulting in an override of pathological neural activity patterns [8, 16, 20]. However, no quantitative measures of the size and shape of the 3D volume of axonal activation generated by DBS currently exist within the clinical arena.

DBS parameter selection

The clinical outcomes of DBS are a testament to the efficacy of the current technology and programming strategies. DBS for movement disorders can provide more than 50% improvement in clinical ratings of motor symptoms in appropriately selected patients [26]. However, programming DBS devices for maximal clinical benefit can be a difficult and time-consuming process that typically requires a highly trained and experienced individual to achieve acceptable results. It has been found that the total time spent programming the stimulator and assessing DBS patients ranged from 18 to 36 hours per patient [10]. One current limitation in DBS programming is that these procedures are typically done with no visual reference of the electrode location in the anatomy, or current spread as it depends on the stimulation parameters. While guidelines exist on stimulation parameter settings that are typically effective [24], it is infeasible to clinically evaluate each of the thousands of stimulation parameter combinations that are possible. As a result, the therapeutic benefit achieved with DBS is strongly dependent on the intuitive skill and experience of the clinician performing the programming. In addition, application of DBS technology to disorders such as epilepsy, dystonia and obsessive-compulsive disorder

are especially problematic because the beneficial effects of stimulation can take weeks to months to manifest. Further, it remains unclear what stimulation paradigms are optimal for these different disorders. Therefore, synergistic combination of clinical experience and scientific characterization of the effects of DBS on the nervous system should enable more efficacious application of DBS technology to patients.

The fundamental purpose of DBS is to modulate neural activity with applied electric fields, but most clinicians implementing DBS technology do not have a quantitative understanding of the effects of manipulating the various stimulation parameters on the neural response to the stimulation. To address this limitation, we developed detailed computational models that accurately estimate the volume of tissue activated (VTA) by DBS as a function of the stimulation parameters (contact, impedance, voltage, pulse width, frequency) and electrode location in the brain [4–6, 13]. However, the computational power and computer science skills necessary to effectively implement such models are not available to most clinicians. Therefore, we developed a Windows-based, clinician-friendly software package we call StimExplorer that is intended to aid the post-operative programming of DBS technology.

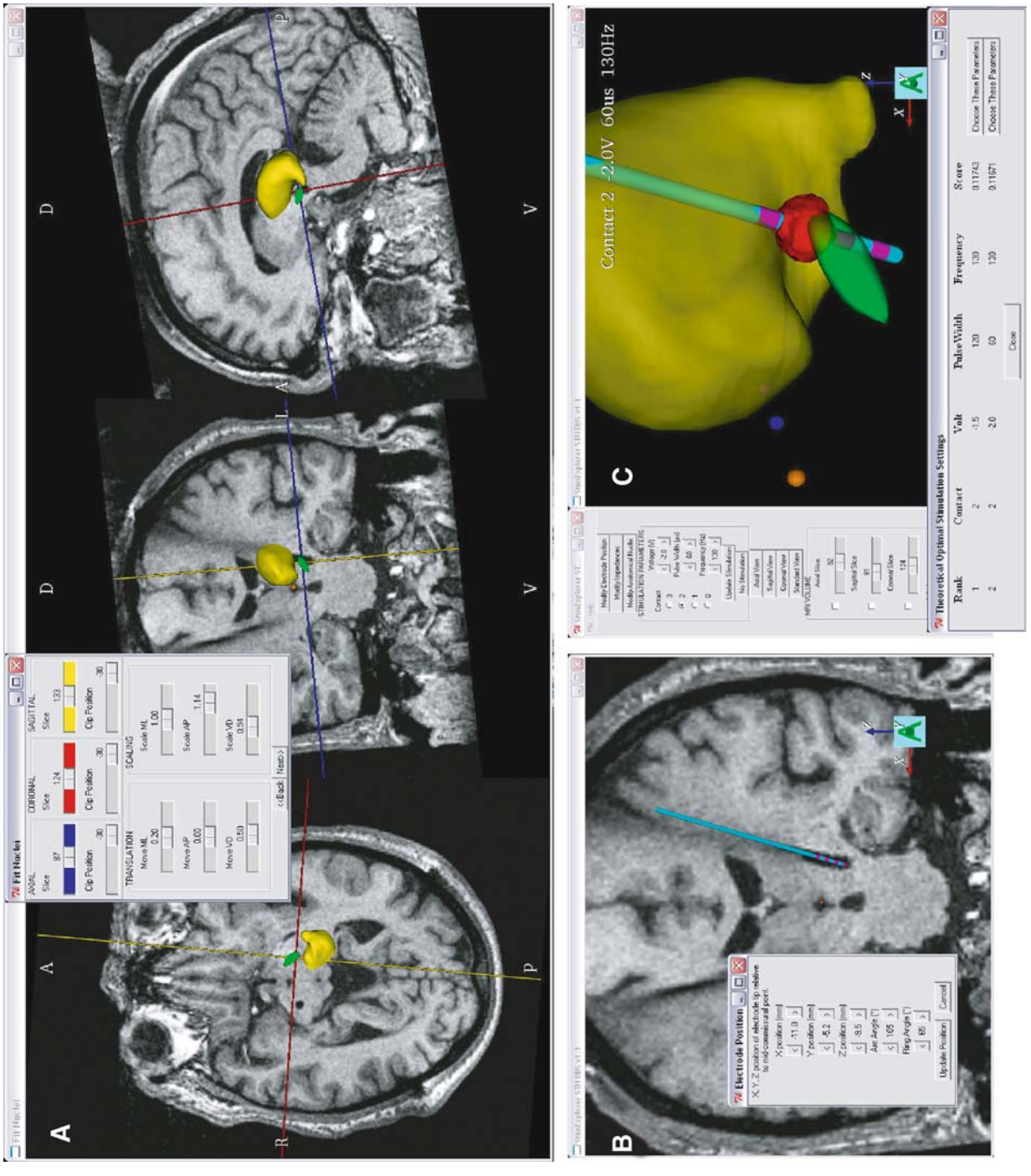
StimExplorer system

The purpose of the StimExplorer system is to integrate our theoretical understanding of the effects of DBS into clinically useful tools for the analysis and customization of stimulation parameters for individual patients (Fig. 1). Our patient-specific models of DBS consist of three fundamental components: 1) Anatomical Model, 2) Electrical Model, and 3) Stimulation Prediction. These three components are co-registered within a common coordinate and visualization system to enable analysis of the position of the electrode in the brain and the VTA generated by DBS as a function of the stimulation parameters. A fully functional StimExplorer system (version 1.1) currently exists for DBS of the subthalamic nucleus (STN). StimExplorer systems for pallidal and thalamic DBS are nearing completion. StimExplorer was written using VTK (Visualization Toolkit; Kitware, Clifton Park, NY) and Tcl/Tk (Tool Command Language; http://tcl.sourceforge.net). Version 1.1 of StimExplorer is self-contained on a single DVD, and auto-installs on a PC similar to any traditional Windows software. StimExplorer is currently a research tool and not commercially available or intended for clinical use outside of IRB approved studies. Individuals interested in using StimExplorer in their own research are encouraged to contact CCM.

The anatomical model developed for each patient in StimExplorer is created from pre- and/or post-operative anatomical magnetic resonance imaging (MRI) data. When the user starts the StimExplorer program they are presented with the option of using a patient MRI data set or an atlas brain. If the user selects the option of a patient MRI data set, they navigate to the directory containing the DICOM files of interest, and load the images into StimExplorer. The user is prompted to select the right or left side of the brain for analysis. The user then orients the image along the midline, using coronal and axial views of the MRI, and defines the anterior commissure (AC) and posterior commissure (PC) in the image. The next step in the process consists of scaling and positioning 3D anatomical representations of the various nuclei of interest (thalamus, subthalamic nucleus, pallidum, etc) (Fig. 1A). The anatomical nuclei are originally positioned within the context of the MRI based on the definition of the AC and PC. However, the user has the option to translate and/or scale the anatomical nuclei along the anterior/posterior, dorsal/ventral, and medial/lateral axes to enable the most accurate match possible with the MRI (Fig. 1A).

Once the anatomical model has been customized to the individual patient, the user must define the position and orientation of the DBS electrode in the brain (Fig. 1B). During the patient customization of the anatomical model, the user defined the AC/PC plane as well as the sagittal and coronal planes perpendicular to the AC/PC plane. In turn, StimExplorer defines a coordinate system with the mid-commissural point (MCP) as the origin, the X-axis representing medial/lateral, the Y-axis representing anterior/posterior, and the Z-axis representing dorsal/ventral. To define the electrode position,

Fig. 1. StimExplorer graphical user interface. (A) After aligning the image data set and defining AC/PC, volumetric representations of the anatomical nuclei of interest are translated and scaled to best fit the patient MRI. In this example, axial, coronal, and sagittal views are displayed with the thalamus (*yellow volume*) and subthalamic nucleus (*green volume*). (B) The position of the DBS electrode (*blue shaft and pink contacts*) in the brain is defined relative to the mid-commissural point and it can be interactively positioned within the MRI. (C) Following definition of the patient anatomy, electrode position, and impedance of each contact, theoretically optimal stimulation parameters are calculated and displayed. The VTA (*red volume*), for the theorectially optimal or any other stimulation parameter setting, is displayed with the anatomical volumes and/or MRI in an interactive 3D visualization window


A
B
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Electrode Position
Theoretical Optimal Stimulation Settings
Contact 2 -2.0V 60us 130Hz

the user inputs the X, Y, and Z location of the electrode tip relative to MCP (Fig. 1B). To define the electrode orientation, the user inputs the electrode trajectory angles relative to the sagittal and coronal planes (Fig. 1B). The angles are labeled as arc (angle relative to sagittal plane) and collar (angle relative to the coronal plane) to provide loose correspondence to the angles utilized in the stereotactic surgical frame. If a post-operative MRI is available, the user can interactively place the DBS electrode in the electrode artifact of the image data set (Fig. 1B).

The electrical model utilized in the StimExplorer system is derived from our previous work characterizing the electric field generated by DBS and neural response to applied electric fields [4–7, 13]. The foundation of the electrical model is a high-resolution diffusion tensor MRI brain atlas [25]. The electric field generated by DBS is dependent on the stimulus waveform, electrode capacitance, electrode impedance, electrode geometry (monopolar/bipolar), and the electrical conductivity of the surrounding tissue medium. Diffusion tensor imaging (DTI) characterizes the diffusion behavior of water in tissue on a voxel-by-voxel basis [2]. Conductivity and diffusion in biological media are related by mutual restriction of the ionic and water mobility by the geometry of the medium [22]. In turn, we utilize DTI for estimating the inhomogeneous and anisotropic electrical conductivity of the tissue medium surrounding the STN, thereby allowing for the generation of anatomically and electrically accurate models of the electric field generated by DBS electrodes [4, 13].

The development of detailed models of the electric field and neural response generated by DBS requires a number of advanced computational tools, including finite element models (FEM), multi-compartment cable neuron models, and workstation computers capable of running the simulations. It is unrealistic to expect a traditional clinician to have these tools at their disposal. Therefore, we designed the StimExplorer system to embody these advanced computational tools in a Windows software application by using pre-compiled solutions from our supercomputer simulations.

All of the DBS VTA calculations utilized in StimExplorer were performed on an 8 processor SGI (Silicon Graphics Inc., Mountain View, CA) Prism with 36 GB of shared memory. The conductivity tensors from the voxel-based DTI data were dynamically mapped to individual elements in a tetrahedron-based 3D FEM of the electrode and surrounding tissue medium [4, 13]. The FEM solutions generated a potential distribution (V_e) in the tissue medium that depended on the stimulus waveform, stimulus amplitude, electrode capacitance, electrode impedance, and electrode contact selected. The neural response to extracellular stimulation can be accurately predicted using the second spatial derivative of the extracellular potential distribution along a given neural process ($\partial^2 V_e/\partial x^2$) [7, 15, 19]. Therefore, we performed thousands of simulations of axonal activation with DBS electrodes to develop quantitative relationships that describe the threshold $\partial^2 V_e/\partial x^2$ for axonal activation as a function of distance from the DBS electrode [7, 13, 14]. These relationships were developed for a range of stimulation parameters applicable to DBS. In turn, we calculated the $\partial^2 V_e/\partial x^2$ within the context of our human DBS FEM and defined 3D surfaces that encompassed the volume where $\partial^2 V_e/\partial x^2$ was suprathreshold for axonal activation for the given stimulation parameters (contact, impedance, voltage, pulse duration, frequency). In turn, each electrode position, electrode orientation, and stimulation parameter setting has a unique VTA that can be displayed in StimExplorer (Fig. 1C).

Each VTA prediction included in StimExplorer was generated within the context of the DTI brain atlas; however, the anatomical geometry of each patient is unique. To addresses this issue, StimExplorer uses a series of transfer functions to appropriately visualize the VTA predictions within the context of the given patient's MRI. These transfer functions are defined by the translation and scaling of the anatomical nuclei to fit the patient's neuroanatomy. Therefore, once the user has customized the anatomical nuclei to the patient and placed the DBS electrode, they can simultaneously visualize the MRI, anatomical nuclei, DBS electrode, and VTAs for a wide range of stimulation parameter settings (Fig. 1C). In addition, the user can pan/zoom/rotate the view, adjust the display properties of the 3D brain atlas, and scroll through the MRI in three orthogonal planes.

Several studies have determined that clinically effective STN DBS for PD is typically achieved with electrode contacts located at or near the dorsal border of the STN [17, 21]. Based on these results and our own clinical evaluations of stimulation prediction with our models, we defined a 3D target VTA for STN DBS for PD. Our target VTA for version 1.1 was an ellipsoid that contained the dorsal STN and the fields of Forel. For each electrode position and orientation option provided in StimExplorer, we employed a volume-based optimization algorithm to define stimulation parameter settings representative of the theoretically optimal VTA [11] (Fig. 1C). This theoretically optimal VTA is provided to

the clinician as a suggested starting point for the DBS programming process. StimExplorer also provides the ability to visualize the VTA for any range of stimulation parameter settings for additional clinical analysis (Fig. 1C). Once the user has customized the StimExplorer system to an individual patient, they can save the MRI orientation, anatomical nuclei scaling, DBS electrode placement, and stimulation parameter settings to a file. The user can then revisit any given patient with StimExplorer by simply loading the appropriate file when starting the program.

Conclusions

StimExplorer uses pre-compiled results from our supercomputer simulations of the neural response to DBS that explicitly account for the effects of electrode capacitance, electrode impedance, electrode placement, and the 3D tissue electrical properties of the human brain. The stimulation results are coupled to 3D anatomical models of nuclei surrounding the electrode, and enable the clinician to interactively evaluate the effects of electrode location and stimulation parameter adjustments on the VTA. To customize the StimExplorer system to an individual patient, the user inputs MRI data, electrode position and orientation information, as well as the impedance of each electrode contact. Definition of a target VTA for DBS of the given anatomical nucleus and disease state allows StimExplorer to provide suggested theoretically optimal stimulation parameter settings for a given patient's implanted electrode. This theoretically optimal setting can represent the start point of clinical programming of the DBS device, thereby focusing the clinical customization of DBS to an anatomically and electrically logical parameter space. The intended benefits of using the StimExplorer system are decreased time and effort needed to adjust the stimulation parameters to achieve the desired clinical results from the therapy. In addition, StimExplorer may decrease the level of intuitive skill necessary to perform DBS programming, provide a teaching tool on the effects of DBS, and enable a degree of standardization in programming practices across centers.

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Conflict of interest statement

CRB and CCM are shareholders in IntElect Medical Inc., license holder for the neurostimulation prediction, optimization, and visualization intellectual property utilized in StimExplorer.

References

1. Anderson ME, Postupna N, Ruffo M (2003) Effects of high-frequency stimulation in the internal globus pallidus on the activity of thalamic neurons in the awake monkey. J Neurophysiol 89: 1150–1160
2. Basser PJ, Mattiello J, LeBihan D (1994) MR diffusion tensor spectroscopy and imaging. Biophys J 66: 259–267
3. Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, Payen I, Benazzouz A (1996) Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 84: 203–221
4. Butson CR, Hall J, Henderson JM, McIntyre CC (2004) Patient-specific models of deep brain stimulation: 3D visualization of anatomy, electrode and volume of activation as a function of the stimulation parameters. Soc Neurosci Abstr 30: 1011.11
5. Butson CR, Maks CB, McIntyre CC (2006) Sources and effects of electrode impedance during deep brain stimulation. Clin Neurophysiol 117: 447–454
6. Butson CR, McIntyre CC (2005) Tissue and electrode capacitance reduce neural activation volumes during deep brain stimulation. Clin Neurophysiol 116: 2490–2500
7. Butson CR, McIntyre CC (2006) Role of electrode design on the volume of tissue activated during deep brain stimulation. J Neural Eng 3: 1–8
8. Grill WM, Snyder AN, Miocinovic S (2004) Deep brain stimulation creates an informational lesion of the stimulated nucleus. Neuroreport 15: 1137–1140
9. Hashimoto T, Elder CM, Okun MS, Patrick SK, Vitek JL (2003) Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. J Neurosci 23: 1916–1923
10. Hunka K, Suchowersky O, Wood S, Derwent L, Kiss ZH (2005) Nursing time to program and assess deep brain stimulators in movement disorder patients. J Neurosci Nurs 37: 204–210
11. McIntyre CC, Butson CR, Maks CB, Noecker AM (2006) Optimizing deep brain stimulation parameter selection with detailed models of the electrode-tissue interface. 28th Int Conf IEEE-EMBS, New York
12. McIntyre CC, Grill WM, Sherman DL, Thakor NV (2004a) Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition. J Neurophysiol 91: 1457–1469
13. McIntyre CC, Mori S, Sherman DL, Thakor NV, Vitek JL (2004b) Electric field and stimulating influence generated by deep brain stimulation electrodes. Clin Neurophysiol 115: 589–595
14. McIntyre CC, Richardson AG, Grill WM (2002) Modeling the excitability of mammalian nerve fibers: influence of after potentials on the recovery cycle. J Neurophysiol 87: 995–1006
15. McNeal DR (1976) Analysis of a model for excitation of myelinated nerve. IEEE Trans Biomed Eng 23: 329–337
16. Montgomery EB, Baker KB (2000) Mechanisms of deep brain stimulation and future technical developments. Neurol Res 22: 259–266
17. Nowinski WL, Belov D, Pollak P, Benabid AL (2005) Statistical analysis of 168 bilateral subthalamic nucleus implantations by means of the probabilistic functional atlas. Neurosurgery 57: 319–330
18. Obeso JA, Olanow CW, Rodriguez-Oroz MC, Krack P, Kumar R, Lang AE (2001) Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 345: 956–963

19. Rattay F (1986) Analysis of models for external stimulation of axons. IEEE Trans Biomed Eng 33: 974–977
20. Rubin JE, Terman D (2004) High frequency stimulation of the subthalamic nucleus eliminates pathological thalamic rhythmicity in a computational model. J Comput Neurosci 16: 211–235
21. Saint-Cyr JA, Hoque T, Pereira LC, Dostrovsky JO, Hutchison WD, Mikulis DJ, Abosch A, Sime E, Lang AE, Lozano AM (2002) Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. J Neurosurg 97: 1152–1166
22. Tuch DS, Wedeen VJ, Dale AM, George JS, Belliveau JW (2001) Conductivity tensor mapping of the human brain using diffusion tensor MRI. Proc Natl Acad Sci 98: 11697–11701
23. Vidailhet M, Vercueil L, Houeto JL, Krystkowiak P, Benabid AL, Cornu P, Lagrange C, Tezenas du Montcel S, Dormont D, Grand S, Blond S, Detante O, Pillon B, Ardouin C, Agid Y, Destee A, Pollak P (2005) Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. N Engl J Med 352: 459–467
24. Volkmann J, Herzog J, Kopper F, Deuschl G (2002) Introduction to the programming of deep brain stimulators. Mov Disord 17 Suppl 3: 181–187
25. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S (2004) Fiber tract-based atlas of human white matter anatomy. Radiology 230: 77–87
26. Walter BL, Vitek JL (2004) Surgical treatment for Parkinson's disease. Lancet Neurol 3: 719–728

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Connections of the basal ganglia with the limbic system: implications for neuromodulation therapies of anxiety and affective disorders

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Summary

The basal ganglia are best known for their role in motor planning and execution. However, it is currently widely accepted that they are also involved in cognitive and emotional behaviors. Parts of the basal ganglia play a key role in reward and reinforcement, addictive behaviors and habit formation. Pathophysiological processes underlying psychiatric disorders such as depression, obsessive compulsive disorder and even schizophrenia involve the basal ganglia and their connections to many other structures and particularly to the prefrontal cortex and the limbic system. In this article, we aim, on the basis of current research, to describe in a succinct manner the most important connections of the basal ganglia with the limbic system which are relevant to normal behaviors but also to psychiatric disorders. Currently, we possess sufficiently powerful tools that enable us to modulate brain networks such as cortex stimulation (CS) or deep brain stimulation (DBS). Notably, neuromodulation of basal ganglia function for the treatment of movement disorders has become a standard practice, which provides insights into the psychiatric problems that occur in patients with movement disorders. It is clear that a sound understanding of the currently available knowledge on the circuits connecting the basal ganglia with the limbic system will provide the theoretical platform that will allow precise, selective and beneficial neuromodulatory interventions for refractory psychiatric disorders.

Keywords: Basal ganglia; limbic system; neural networks; neuromodulation; neuroanatomy.

Introduction

The basal ganglia consist of four main nuclei: the neostriatum or dorsal striatum, consisting of the caudate nucleus and the putamen, the globus pallidus, the subthalamic nucleus, and the substantia nigra. In addition, certain thalamic relay nuclei, mainly of ventral and central complexes, as well as the pedunculopontine nucleus are generally included as components of the basal ganglia [28]. The dorsal striatum is a separate entity from the ventral part which is named ventral striatum. The concept of the ventral striatum was introduced in order to include in an integrated system the ventral extension of the striatum, the nucleus accumbens, the medial and ventral portions of the caudate, the putamen, the striatal cells of the olfactory tubercule, and the anterior perforate substance. The putamen and the globus pallidus arise at the junction of the diencephalon and telencephalon and both constitute the lenticular nucleus. The globus pallidus is subdivided into an external (GPe) and an internal (GPi) segment. The ventral pallidum is located ventral to the anterior commissure and extents rostral in vicinity with the ventral striatum from which it receives its inputs [51, 104].

The subthalamic nucleus (STN) arises from the lateral hypothalamic cell column of the diencephalon [99] in a region located under the thalamus and above the mesencephalon [140]. The substantia nigra is a mesencephalic structure that on the basis of cytoarchitectonic and chemical criteria comprises two main subdivisions, the pars compacta (SNc) and the pars reticulata (SNr). It extends between the subthalamic region, where it is located beneath the STN, and the mesencephalon where it lies along the dorsal aspect of the base of the cerebral peduncle [148].

Although the basal ganglia are best known for their participation in motor planning end execution, their involvement in cognitive and emotional behaviors is now well accepted. Middleton and Strick [91], reported that about one-third of the total output from the basal ganglia is directed to the medial and lateral area 9, dorsal and ventral area 46 and lateral area 12 of the prefrontal cortex. It has been suggested that the ventral regions of the basal ganglia play a key role in reward and reinforcement, [38, 42, 120, 129] and are also important in the

development of addictive behaviors and habit formation. Thus, diseases affecting mental health including schizophrenia and obsessive compulsive disorder (OCD) are in relevance with the pathophysiology of these structures [66, 75, 127].

Connectivity and functional properties of basal ganglia

The main information to the basal ganglia system arises from the cerebral cortex [69]. Fronto-striatal inputs form a functional gradient from the ventromedial through dorsolateral striatum, with the medial and orbital prefrontal cortex terminating in the ventromedial part and the motor cortex terminating in the dorsolateral region. Other cortical areas, including the temporal lobe, project throughout wide areas of the striatum sharing characteristics of the functional gradient of the frontal lobe: inferior temporal areas terminate in the more ventral parts of the caudate nucleus, than the superior temporal gyrous [151]. The ventral part of the striatum also receives a prominent projection from the amygdale [121] and hippocampus [46].

Striatal information is transferred to the GPi [22, 53, 111, 150], and SNr [14, 83, 107] then to ventral anterior and ventral lateral (VA/VL) nuclei of the thalamus [30, 106, 109] and from there to the frontal cortex [5], supplementary motor area (SMA) for pallidal output [62], and dorsolateral prefontal cortex for nigral output [61]. This corticocortical loop passes through the "direct pathway" of the basal ganglia circuitry as modeled by Albin and colleagues in 1989 [1]. The "indirect pathway" in this model, involves the GPe, then the STN, and from there the GPi and the substantia nigra pars reticulata. The striatum [55, 60] and to a lesser degree, the globus pallidus [63] and STN [44, 52, 54] receive a major dopaminergic input from the substantia nigra pars compacta. This control is essential to balance the activity of the direct and indirect pathways [1, 29, 59, 145]. Both direct and indirect circuits modulate input to the thalamus. Direct and indirect pathways modulate circuit activities in response to different inputs. Dysfunction in

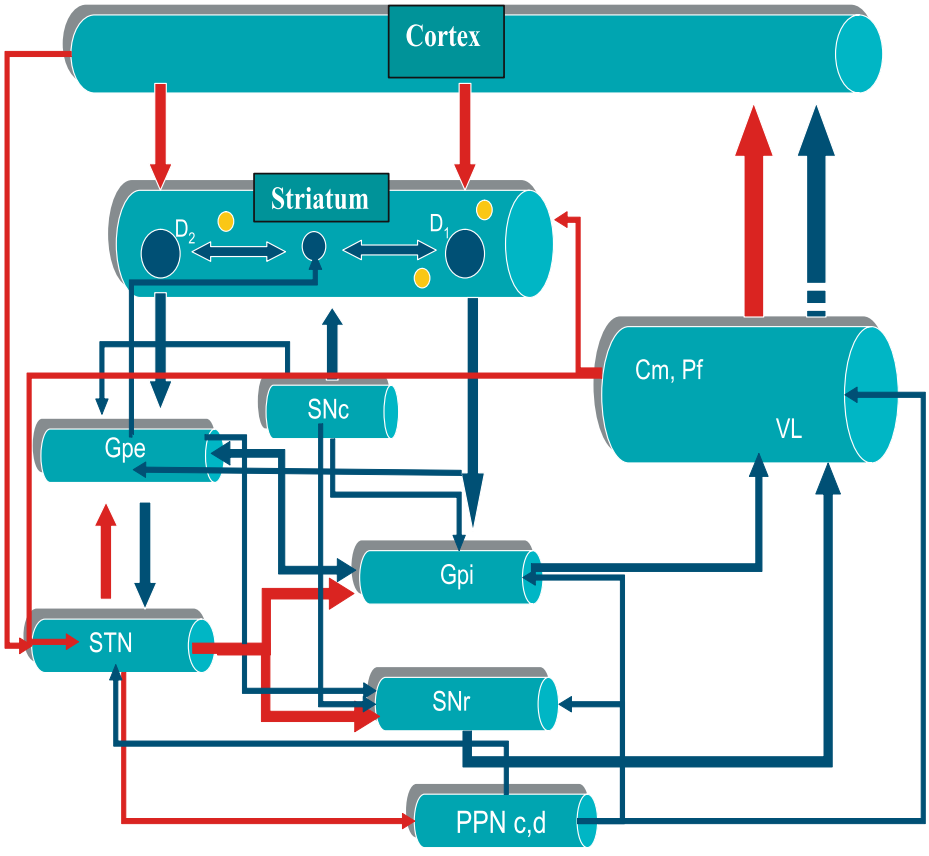

Fig. 1. Schematic diagram of the functional anatomy and connectivity of basal ganglia (see text for references). *GP* Globus pallidus; *STN* subthalamic nucleus; *PPN* penduculopontine nucleus; centromedian (*Cm*), parafascicular (*Pf*), ventrolateral (*VL*) thalamic nuclei; *SN* substantia nigra; with red excitatory connections, blue inhibitory connections

the direct circuit causes abnormal thalamic inhibition, whereas indirect circuit dysfunction leads to disinhibition and thalamic overactivity. Finally the pedunculopontine nucleus has prominent projections to the basal ganglia, mainly the pars compacta of the substantia nigra and the STN [77–79]. It receives its principal input from the GPi. Each set of circuits is present in each hemisphere (Fig. 1).

Limbic component of the basal ganglia

As noted, the origins of the limbic structural concept go back to Broca in 1878 [18] and, more recently, to MacLean [84, 85]. It has become obvious from the key functional studies of Kluver and Bucy [72], and the theoretical anatomical presumptions of Papez [103] that the limbic system plays a major role in emotional and motivational activity and other basic psychological functions of the brain. The limbic system comprises both cortical and subcortical systems including the hippocampal formation, amygdaloid complex of nuclei, hypothalamus, nucleus accumbens, certain parts of subthalamic nucleus, ventral pallidum, cingulate cortex, ventral tegmental area, major areas of the prefrontal cortex and limbic midbrain areas. The term ‘‘limbic brain’’ encompasses these formations and their distributions to forebrain, midbrain and hypothalamus. In particular, it also encompasses significant medial components of the midbrain including the nucleus raphé dorsalis, nucleus raphé medianus, central gray, and dorsal and ventral nuclei of Gudden. These formations are strongly interconnected, usually by reciprocal pathways, e.g., reciprocal limbic forebrain/limbic midbrain loops [97] showed that large areas of the midbrain and posterior midline brainstem receive especially strong limbic forebrain projections, hence the term ‘‘limbic midbrain area’’ (Fig. 2).

Many motivated goal-directed behaviors are thought to be regulated by glutamate projections that originate in limbic frontal cortical regions (collectively anterior ‘‘limbic forebrain’’), including the basolateral amygdala, the hippocampal formation and the medial prefrontal cortex, which converge on spiny neurons of the nucleus accumbens [56]. The output of nucleus accumbens is conveyed through projections to the ventral pallidum, which is likely responsible for motor execution of these goal-directed behaviors. Thus, it has been postulated that the nucleus accumbens (ventral striatum) is an interface between limbic and motor systems [49, 57, 68, 94, 98].

Various studies have revealed that dopamine innervation of the nucleus accumbens is related to reinforcement, choice and reward [20, 116, 128] as well as actions of addictive drugs and aspects of schizophrenia [65, 70, 147]. Drug-seeking behavior appears to depend upon glutamate transmission in the nucleus accumbens [31, 132, 147]. Normally, descending projections from the prefrontal cortex to nucleus accumbens, as well as other limbic regions, exert inhibitory control over reward-seeking behaviors. Existing data support the involvement

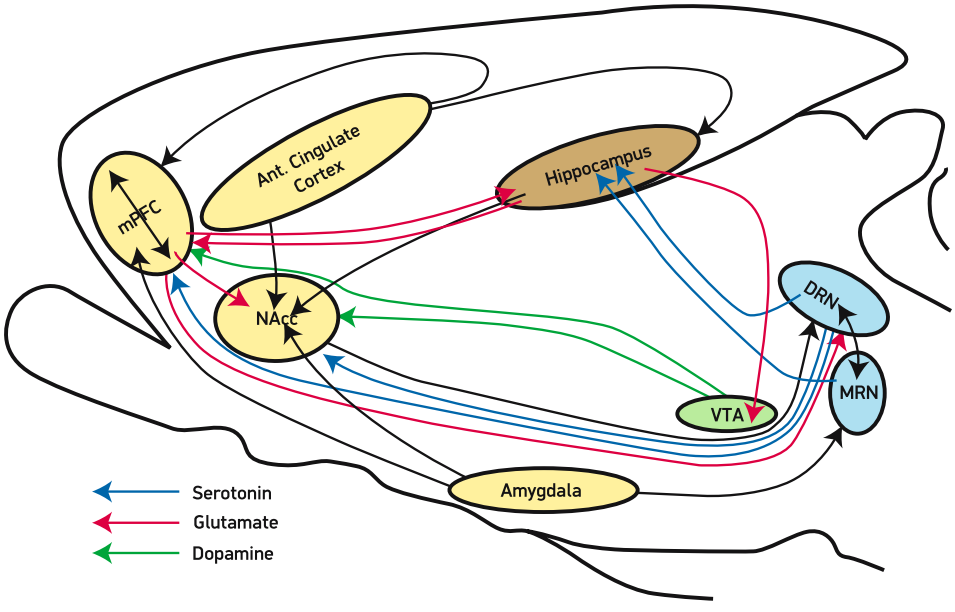

Fig. 2. Neuronal systems of the limbic forebrain interconnected with multiple limbic areas in cortical and subcortical level (*limbic midbrain*). Note the key role of nucleus accumbens (*NAcc*). *VTA* Ventral tegmental area; *DRN* dorsal raphe nucleus; *MRN* median raphe nucleus (*Adopted with permission from Morgane et al., ref. 95*)

of nucleus accumbens in behavioral inhibition, including both impulsive and compulsive forms of responding [21]. Ventral striatum (nucleus accumbens) implication in OCD has been suggested by many investigators [23, 100, 133, 140, 142]. Breiter *et al.* examined the effects of cocaine infusion in cocaine addicts on magnetic resonance imaging (MRI) signal change in comparison to saline infusion [16]. They found activation in a distributed circuit that included cortical and subcortical regions. There was observed a strong activation in regions of the ventral striatum which includes the caudate, putamen and the nucleus accumbens. Activation in this latter region is consistent with a large corpus of nonhuman data demonstrating the critical role played by the mesolimbic dopaminergic pathway in positive affect and addictive behaviors [73, 74, 137]. In the first functional MRI (fMRI) study of the effects of nicotine on regional brain activation in cigarette smokers, it was also found that activation of the nucleus accumbens does occur during infusion of nicotine compared with saline. Davidson and Irwin [27], in a positron emission tomography (PET) study, described that when they used pleasant and unpleasant pictures during an extended picture paradigm, they observed activation in a region including the nucleus accumbens during the picture-induced positive affect. Recently, it has been observed a remarkable improvement of OCD in two patients who underwent subthalamic nucleus deep brain stimulation (STN-DBS) for advanced Parkinson's disease [86].

In addition, data from various sources support the view that like striatum, both STN and GP are involved not only in motor control but also in cognitive, emotional and motivational processes sharing certain ''limbic'' characteristics. This notion is in consistency with reports that relevant anatomo-functional subdivisions are present also at the pallidal level: the sensorimotor area which is located ventrolateraly, the associative region which is located dorsomedially and the limbic part that extends to anterior and ventromedial pallidum. The GPi projects also via collaterals, to the central part of the thalamic complex (centromedian, intralaminar, and parafascicular nuclei) [40, 43, 76, 112, 122, 123]. The regions of the pallidum that receive sensory-motor inputs from the striatum project to the ventrolateral thalamic nucleus, those that receive afferent inputs from association areas of the striatum project to the ventral anterior and mediodorsal thalamic nuclei, and those that receive inputs from limbic striatal regions project to the mediodorsal nucleus and the lateral habenular nucleus [40, 106]. All these functional territories of the pallidal complex correspond to the respective sensorimotor, associative and limbic of the above mentioned corticostriatal circuits [50, 55, 110].

The subthalamic nucleus (STN) is a good target for symptomatic improvement of advanced Parkinson's disease motor deficits by high frequency DBS [12, 13, 71, 81], and is involved also in cognitive and emotional functions [6, 7]. STN has been implicated in improvement of depression but also induction of apathy and aggressive behavior [11, 124]. It seems that the functional characteristics of STN can be seen in the context of the same compartmentalization of neostriatum and globus pallidus. STN receives pallidosubthalamic projections originating in the limbic regions of the GPe in topographically arranged fashion with the sensorimotor part of the STN occupying the dorsolateral half, the associative part its medioventral half and the limbic part the most anterior and medioventral portion [67]. It seems also that the subthalomopallidal projections share the same topographical and functional characteristics.

Emotion, anxiety and basal ganglia function

Functional and structural changes have been observed in frontal cortical regions such as orbital (OrC) and medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC) insular cortex (InC), as well as in subcortical regions, which receive inputs from the above cortical areas; similar changes have also been noted in amygdala (Am), thalamus (Th), ventral striatum (VeS) and pallidum (VeP), and all have been implicated in the pathophysiology of mood and behavioral disorders (depression, anxiety, OCD, mania, bipolar disorder, and addiction) [33, 35, 37, 82, 89, 95]. Further support for the hypothesis that frontal-subcortical pathways are involved in the aforementioned pathological conditions is revealed from animal models [80] along with advances in functional neuroimaging [32, 34] in human subjects. In addition, regional neuroimaging and neuropathological abnormalities seen in primary mood disorders are found in the regions implicated in depression, neurodegenerative diseases, and syndromes like Parkinsonism, Huntington's disease, Tourrette's syndrome, Wilson's disease [47, 88, 92, 117, 118, 120, 143], and cerebrovascular disease [135].

Obsessive-compulsive disorder (OCD) is a chronic anxiety disorder characterized by recurrent, intrusive, and distressing thoughts (obsessions), together with repetitive ritualistic cognitive and physical activities (compulsions). The clinicopathological, functional and

structural imaging studies support the involvement of frontal-subcortical circuit structures in the pathogenesis of OCD. Patients with OCD have difficulty in inhibiting irrelevant information, like obsessive thoughts and impulses and reduced ability to selectively attend to relevant information, while simultaneously ignoring irrelevant competing information (gating) [4, 24, 25]. The critical process of gating has been linked to frontal-striatal function [64, 113]. Impaired frontal-striatal function is considered to be of etiological importance in the affective, behavioral, and cognitive characteristics of OCD [127]. Neurobiological models suggest that OCD is characterized by excessive activity in frontal-striatal circuits of the brain, with hyperactivity observed in orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus, and caudate [9, 17, 115, 126]. F18 fluoro-2-deoxyglucose positron emission tomography (PET) studies demonstrate abnormally increased activity in orbitofrontal cortex and caudate regions in patients with OCD [9, 10]. These areas show increased functional activity when OCD symptoms are provoked. The anterior cingulate gyrus, which has limbic connections and close associations with the orbitofrontal cortex, also exhibits increased activity in studies of OCD [8]. When patients are treated with serotonin reuptake inhibitors, the functional activity in the orbitofrontal cortex and caudate nucleus declines towards normal. Patients with OCD show decreased right caudate and left orbitofrontal region functional activity also following behavioral therapy techniques including methods of exposure and response prevention [130]. PET studies also suggest altered cortical-subcortical interactions in Gilles de la Tourette (GTS) syndrome. Patients with GTS show increased metabolism in the frontal motor regions and decreased glucose utilization in paralimbic prefrontal cortex and the ventral striatum [15]. Dopamine (DA) dysfunction in the caudate nucleus is thought to mediate ideational and motor symptoms of GTS.

Depression has been observed in patients with lesions in the frontal cortex and the caudate nucleus. Functional imaging studies in patients with Alzheimer's disease and depression show decreased metabolism in the orbitofrontal and dorsolateral prefrontal cortices. Similarly, depression in Parkinson's disease, Huntington's disease and epilepsy are correlated with reduced metabolic activity in the orbitofrontal cortex and the caudate nucleus [87, 88]. Depression may follow strokes in the dorsolateral prefrontal area and the basal ganglia. Recently, a model for depression has been proposed involving dysfunctional coordination of limbic-cortical pathways. In this model, a dorsal compartment composed of superior limbic structures is thought to regulate attentional and cognitive symptoms of depression including apathy, psychomotor retardation, impaired attention and executive dysfunction. A ventral compartment formed of limbic, paralimbic and subcortical structures is proposed to mediate the vegetative and somatic aspects of depression, such as sleep, appetite and endocrine disturbances. Rostral cingulate area has a regulatory role for the interactions between the two compartments. Dysfunction of this coordinating area may result in disintegrated mood, cognitive, somatic and autonomic responses [141].

A core feature of depression is a pervasive absence of behavioral incentive. This is clinically manifested by apathy, anhedonia, amotivation, and loss of interest in hobbies, socialization, work, food, and sex. These symptoms appear to be phenomenologically related to the putative functions of the mesolimbic dopaminergic projections from the ventral tegmental area (VTA) into the ventral mPFC, amygdala, and ventral striatum [41, 138]. These projections are thought to subserve a 'reward-related system' that mediates hedonia, motivation, behavioral reinforcement and psychomotor activity [39, 58, 101, 134]. DA release into the ventral striatum modulates afferent synaptic transmission from non-dopaminergic projections into the ventral striatum, PFC, amygdala, hypothalamus, and other limbic structures that may play more critical roles in *maintaining* behavioral reinforcement [41, 93, 102, 134]. The anhedonia, amotivation and psychomotor slowing of depression, and the euphoria, hypermotivational state and psychomotor restlessness of mania, have led to the hypothesis that mesolimbic DA function is decreased and increased, respectively, in the depressed and manic phases of bipolar disorder (BD) [41, 138, 146]. This hypothesis is corroborated by pharmacological evidence and cerebrospinal fluid (CSF) DA metabolite concentrations [139, 146]. Anhedonia is also evident in depressive syndromes arising secondary to conditions such as Parkinson's disease or cocaine abstinence (in cocaine-dependent individuals) that are putatively associated with deficits of DA function [41, 144]. Moreover certain ''atypical'' antipsychotic drugs included risperidone, a mixed 5HT2/D2 receptor antagonist, with beneficial effects in the negative symptoms of schizophrenia seems to continually increase the dopamine turnover in PFC [136].

Substance abuse and addiction have also been associated with neurobiological alterations in the thalamus, orbitofrontal cortex and limbic parts of basal ganglia. The mesocorticolimbic dopaminergic system has been

the main focus of research in the neurobiology of addiction. Important structures in the drug reward circuit are the ventral tegmental area, frontal cortex, nucleus accumbens and amygdala. The anterior cingulate and amygdala link substance addiction to motivational and reward systems in the brain. Neurochemical changes in these areas by chronic drug exposure lead to neuroadaptations underlying the substance addiction [19].

Functional territories of the basal ganglia from the emotional and behavioral perspectives

It has been proposed [3] that the basal ganglia participate in five defined frontal-subcortical parallel circuits. They are named according to their function or site of origin in the cortex: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and a limbic circuit originating in the anterior cingulate cortex. In this scheme, each circuit remains segregated as it passes through the relay nuclei of the basal ganglia and has no interaction with the others circuits [2, 3]. Today, even though zones of overlap exist between adjacent regions, the basal ganglia system is more often subdivided into three functional territories: 1. *sensorimotor territory* (the putamen) receiving bilateral projection from the motor cortex, and projecting back to motor cortices (primary motor cortex, supplementary motor association (SMA) and premotor cortex), 2. *associative territory* (the dorsolateral caudate nucleus) receiving homolateral projections from the frontal (dorsolateral), parietal, temporal, and occipital cortices and projecting to the prefrontal cortex, [48] and 3. *limbic territory* (ventral striatum) projecting to the anterior cingulate cortex and medial orbitofrontal cortices [105, 108]. The projections from each level are progressively connected to smaller areas as they proceed from cortical to subcortical structures, but each circuit is preserved as a largely distinct anatomical structure, consistent with its functional segregation. These territories process motor, cognitive, and emotional or motivational information, respectively.

It has been hypothesized that emotion and behavior are subserved by two interacting systems [114]. First, a ventral system, including the amygdala, insula, ventral striatum, and ventral prefrontal regions (rostral ACC, VLPFC, OFC), is mainly important for the identification of the emotional significance of a stimulus and the generation of an autonomic, unconscious emotional response. Second, a dorsal system, consisting of the parahippocampal gyrus and dorsal regions of the frontal cortex (dorsal ACC, aPFC, DLPFC, and medial PFC), is engaged in additional regulation of the initial emotional response by combining cognitive and emotional input. These territories can be best seen within the context of the frontal lobe functional compartmentalization [26].

Five corticostriatal circuits with pallido-subthalamic and thalamic relays, including that of parietal and temporal origin, have been implicated in mood and anxiety disorders (Fig. 3). In addition to these closed frontal-

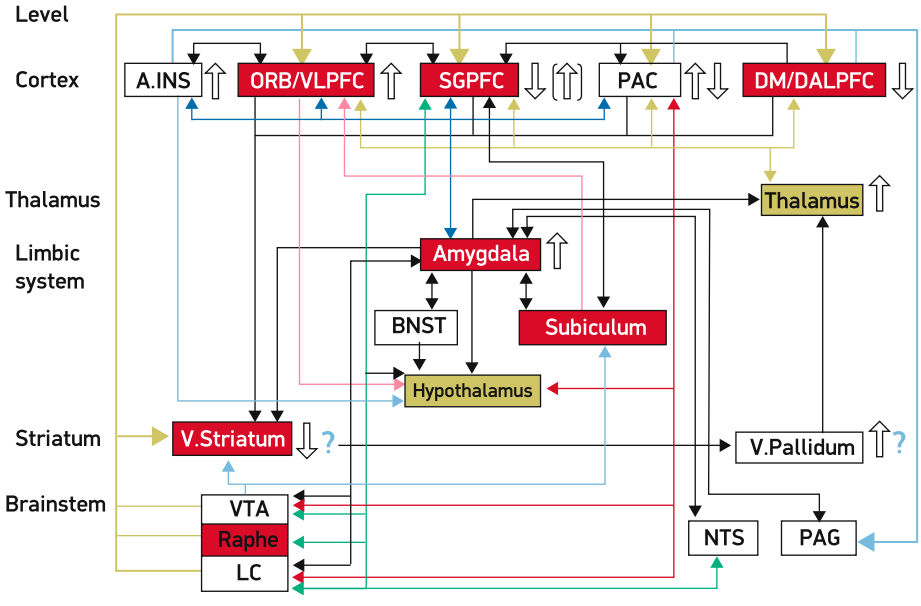

Fig. 3. Anatomical circuits implicated by neuroimaging and neuropathological studies in familial mood and anxiety disorders. *PFC* Prefrontal cortex; *Orb* orbital; *VL* ventrolateral; *SG* subgenual; *PAC* pregenual anterior cingulated; *DM* dorsomedial; *DAL* dorsal anterolateral, *NTS* nucleus tractus solitarious; *VTA* ventral tegmental area; *LC* locus ceruleus; *BSTN* bed nucleus of stria terminalis (*Adopted with permission from Drevets, ref. 33)*

subcortical loops, there are open connections of the circuits that integrate information from anatomically distant but functionally related brain areas. The open afferent and efferent connections mediate coordination between functionally similar areas of the brain and the frontal-subcortical circuits. These circuits are described below.

1. *The dorsolateral prefrontal* circuit originates in Broadmann's areas 9 and 10 on the lateral surface of the anterior frontal lobe and projects to the dorsolateral head of the caudate nucleus. Neurons from this site project to the lateral part of the mediodorsal globus pallidus interna and rostrolateral substantia nigra pars reticulata as the direct pathway. The fibers from the basal ganglia project to parvocellular portions of the ventral anterior and mediodorsal thalamus. The mediodorsal thalamus sends fibers back to the origin of the circuit in the dorsolateral frontal cortex. In addition major cortical afferents to the dorsolateral frontal-subcortical circuit are Broadman area 46 and parietal area 7a [131]. They are also strongly interconnected with each other. Area 7a has a role in visual processing. There are also minor afferents to limbic structures. Main efferents of dorsolateral prefrontal circuit are to Broadmann areas 46 and 8, which comprise the frontal eye fields. The dorsolateral prefrontal circuit is involved mainly in executive function. It includes abilities to solve complex problems like learning new information, planning ahead, activating remote memories, regulating actions according to the environmental stimuli, shifting behavioral sets appropriately, generating motor programs and temporal ordering of recent events.
2. *The lateral orbitofrontal circuit* originates in Broadmann's areas 10 and 11 and sends fibers to the ventromedial caudate nucleus. Neurons form this region of the caudate project to the medial part of the mediodorsal globus pallidus internus and to the rostromedial substantia nigra pars reticulata. Fibers from substantia nigra and globus pallidus connect to the ventral anterior and mediodorsal thalamus. The circuit then is closed by fibers projecting back to the orbitofrontal cortex from thalamus. In addition, the orbitofrontal subcortical circuit receives open afferents from the superior temporal cortex, substantia nigra, dorsal raphe and midbrain tegmentum. These afferents share a heteromodal sensory and paralimbic component.
3. *The medial division of the orbitofrontal circuit* originates in the gyrus rectus and the medial orbital gyrus of Broadmann's area 11 [90]. The projections go to medial aspects of the accumbens, to medial ventral pallidum and reach the mediodorsal thalamic nucleus. Among all three circuits, the medial part of the orbitofrontal circuit also has the strongest association with amygdala. The amygdala sends efferents to the brainstem and hypothalamus, allowing the medial orbitofrontal circuit to participate in modulation of endocrine, autonomic and involuntary behavioral responses. The orbitofrontal circuit connects the frontal monitoring systems to the limbic system. Dysfunction of the circuit is characterized by personality change including behavioral disinhibition and emotional liability.
4. *The anterior cingulate circuit* originates in the anterior cingulate cortex (Broadmann's area 24a–c). The neurons project to ventral striatum, which includes the ventromedial caudate, ventral putamen, nucleus accumbens and olfactory tubercle and which also receives input from medial orbitofrontal cortex, limbic and paralimbic cortices, hippocampus, amygdala entorhinal cortex, and superior and inferior temporal cortices [96]. Projections from the ventral striatum pass to the rostromedial globus pallidus internus, ventral pallidum and rostrodorsal substantia nigra. The ventral pallidum connects to the ventral anterior nucleus of the thalamus [51]. The anterior cingulate circuit is closed with projections from ventral anterior thalamus back to the anterior cingulate cortex. Limbic system connections involve both the anterior cingulate and medial frontal regions. The anterior cingulate circuit also receives major afferents from the perirhinal area and hippocampus and sends efferents to substantia nigra, lateral hypothalamus and subthalamic nucleus. While the orbitofrontal cortex mediates information concerning the internal environment, the anterior cingulate circuit facilitates the intentional selection of environmental stimuli based on their internal relevance [141]. The anterior cingulate mediates motivated behavior; dysfunction associated with lesions in this area reflects decreased motivation (akinetic mutism, aboulia, apathy).
5. *The subgenual prefrontal circuit* involves Broadmann area 24 and 25 and projects to medial caudate nucleus, nucleus accumbens, medial parts of GPi, medial thalamic nuclei, amygdale (lateral parvocellular, basal accessory and magnocellular basal nuclei) [45], lateral hypothalamus and brainstem; it has been suggested to play an heuristic role in pathological guilt and anxiety in depression and in the rapid shifts between euphoria and anger in mania [36].

Limbic-basal ganglia networks and neuromodulation

In the previous sections, we attempted to describe in a concise way important information on the connections of the basal ganglia with the limbic system. A sound understanding of the currently available knowledge on the circuitry connecting the basal ganglia with the limbic system can provide the theoretical platform that will allow very precise and highly selective neuromodulatory interventions for refractory psychiatric disorders. Currently, DBS or cortical stimulation techniques allow us minimally invasive, safe and reversible procedures in the nervous system. Advanced neuroimaging can verify postoperatively whether the electrodes have been inserted in the ideal location in order to have the best possible effect. This methodology has the potential not only to improve the lives of patients suffering from neuropsychiatric conditions but also to promote research, provide insights and enhance our understanding of the neural systems whose activities underlie and subserve normal behavior. Once we acquire a better understanding, it would be easier to hypothesize how the deregulation or loss of ''autoregulation'' of these networks can lead to psychiatric disorders. Therefore, it is important that we acquire a refined knowledge of neurochemical anatomy and develop detailed concepts on anatomical models. These could be subjected to computerised processing in order to develop sophisticated computer models of relevant neuronal circuits. These models may help us ultimately to develop and test hypotheses about the networks and their relay structures where neuromodulatory interventions using electrical stimulation methods would be beneficial. Recently, we proposed one such a hypothesis [125]; this field is certainly going to expand by the theoretical approaches, concepts and hypotheses that will be proposed by many neuroscientists and related investigators.

The relationships of the basal ganglia with the limbic system are metaphorically, the relationships of ''motion'' with ''emotion''. This topic is currently the new frontier of neuromodulation. The anatomical interrelationships of the basal ganglia with the limbic system and their role in the mechanisms of depression or OCD can be studied well not only when we face these conditions as separate clinical entities but also when these disorders occur in the context of chronic pain, dystonia, Parkinson's disease, epilepsy, Gille de la Tourette syndrome, etc. It becomes increasingly clear that we can learn a lot about psychiatric disorders by studying psychiatric problems occurring in the context of the aforementioned conditions which are treatable by DBS.

References

1. Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends Neurosci 12: 366–375
2. Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 13: 266–271
3. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9: 357–381
4. Bannon S, Gonsalvez CJ, Croft RJ, Boyce PM (2002) Response inhibition deficits in obsessive-compulsive disorder. Psychiatry Res 110: 165–174
5. Barbas H, Haswell H, Dermon CR (1991) Diverse thalamic projections to the prefrontal cortex in the rhesus monkey. J Comp Neurol 313: 65–94
6. Baron MS, Witchmann T, Ma D, DeLong MR (2002) Effects on transient focal inactivation of the basal ganglia in parkinsonian primates. J Neurosci 22: 592–599
7. Baunez C, Robbins TW (1997) Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. Eur J Neurosci 9: 2086–2099
8. Baxter LR (1991) PET studies of cerebral function in major depression and obsessive-compulsive disorder: emerging prefrontal cortex consensus. Ann Clin Psychiatry 3: 103–109
9. Baxter LR Jr (1992) Neuroimaging studies of obsessive compulsive disorder. Psychiatr Clin North Am 15: 871–884
10. Baxter LR, Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE (1987) Local cerebral glucose metabolic rates in obsessive-compulsive disorder: a comparison with rates in unipolar depression and normal controls. Arch Gen Psychiatry 44: 211–218
11. Bejjani BP, Houeto JL, Hariz M, Yelnik J, Mesnage V, Bonnet AM, Pidoux B, Dormont D, Cornu P, Agid Y (2002) Aggressive behavior induced by intraoperative stimulation in the triangle of Sano. Neurology 59: 1425–1427
12. Benabid AL, Pollak P, Gross C *et al* (1993) Stimulation of subthalamic nucleus acutely changes clinical status in Parkinson's disease. Soc Neurosci Abstr 19: 1052
13. Benazzouz A, Cross C, Feger J (1993) Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. Eur J Neurosci 5: 382–389
14. Bolam JP, Powell JF, Totterdell S, Smith AD (1981) The proportion of neurons in the rat neostriatum that project to the substantia nigra demonstrated using horseradish peroxidase conjugated with wheat germ agglutinin. Brain Res 220: 339–343
15. Braun AR, Randolph C, Stoetter B (1995) The functional neuroanatomy of Tourette syndrome. Neuropsychopharmacology 9: 277–291
16. Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE (1997) Acute effects of cocaine on human brain activity and emotion Neuron 19: 591–611
17. Breiter HC, Rauch SL, Kwong KK, Baker JR, Weisskoff RM, Kennedy DN, Kendrick AD, Davis TL, Jiang A, Cohen MS, Stern CE, Belliveau JW, Baer L, O'Sullivan RL, Savage CR, Jenike MA, Rosen BR (1996) Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. Arch Gen Psychiatry 53: 595–606
18. Broca P (1878) Anatomie comparee des circonvolutions cerebrales: Le grand lobe limbique et la scissure limbique dans la serie des mammife. Res Rev Anthropol 1: 385–498
19. Capote HA, Flaherty L, Lichter D (2001) Addictions and frontal subcortical circuits. In: Lichter D, Cummings JL (eds) Frontal

subcortical circuits in psychiatric and neurological disorders. Guilford Press, New York, pp 231–259
20. Cardinal RN, Howes NJ (2005) Effects of lesions of the nucleus accumbens core on choice between small certain rewards and large uncertain rewards in rats. BMC Neuroscience 6: 37
21. Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ (2001) Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science 292: 2499–2501
22. Chang HT, Wilson CJ, Kitai ST (1981) Single neostriatal efferent axons in the globus pallidus: a light and electron microscopic study. Science 213: 915–918
23. Charney DS (2003) Neuroanatomical circuits modulating fear and anxiety behaviors. Acta Psychiatr Scand Suppl 417: 38–50
24. Cohen Y, Lachenmeyer JR, Springer C (2003) Anxiety and selective attention in obsessive-compulsive disorder. Behav Res Ther 41: 1311–1323
25. Coles ME, Heimberg RG (2002) Memory biases in the anxiety disorders: current status. Clin Psychol Rev 22: 587–627
26. Cummings JL (1995) Anatomic and behavioral aspects of frontal subcortical circuits. Ann NY Acad Sci 769: 1–13
27. Davidson RJ, Irwin W (1999) The functional anatomy of emotion and affective style. Trends Cogn Sci 3: 11–21
28. De Jong MR (2000) The basal ganglia. In: Kandel JH, Schwartz JH, Thomas MJ (eds) Principles of Neural science. McGrow-Hill, New York, NY, pp 853–867
29. DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13: 281–285
30. DeVito JL, Anderson ME (1982) An autoradiographic study of the efferent connections of the globus pallidus in Macaca mulatta. Exp Brain Res 46: 107–117
31. DiCiano P, Cardinal RN, Cowell RA, Little SJ, Everitt BJ (2001) Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of Pavlovian approach behavior. J Neurosci 21: 9471–9477
32. Drevets WC (2000) Neuroimaging studies of mood disorders. Biol Psychiatry 48: 813–829
33. Drevets WC (2001) Neuroimaging and neuropathological studies in depression: implications for the cognitive-emotional features of mood disorders. Cur Opin Neurobiol 11: 240–249
34. Drevets WC, Todd RD (1997) Depression, mania and related disorders. In: Guze SB (ed) Adult psychiatry. Mosby Press, St Louis MO, pp 99–141
35. Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992) A functional anatomical study of unipolar depression. J Neurosci 12: 3628–3641
36. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, Raichle ME (1997) Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386: 824–827
37. Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, Mathis CA (2001) Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. Biol Psychiatry 49: 81–96
38. Everitt BJ, Robbins TW (1992) Amygdala-ventral striatal interactions and reward-related processes. In: Angleton JP (ed) The amygdala: neurobiological aspects of emotion, memory and mental dysfunction. Wiley-Liss, New York, pp 401–429
39. Everitt BJ, Cador M, Robbins TW (1989) Interactions between the amygdala and ventral striatum in stimulus-reward associations: studies using a second-order schedule of sexual reinforcement. Neuroscience 30: 63–75
40. Fenelon G, Percheron G, Yelnik J (1990) Topographic distribution of pallidal neurons projecting to the thalamus in macaques. Brain Res 520: 27–35
41. Fibiger HC (1991) The dopamine hypothesis of schizophrenia and mood disorders. In: Willner P, Scheel-Kruger J (eds) The mesolimbic dopamine system: from motivation to action. Wiley, New York, pp 615–638
42. Fibiger HC, Phillips AG (1986) Reward, motivation, cognition: psychobiology of mesotelencephalic dopamine systems. In: Mountcasle VB, Plum F, Geiger SR (eds) Handbook of physiology. Section I: the nervous system. American Physiological Society Bethesda, MD, pp 647–674
43. Francois C, Percheron G, Parent A, Sadikot AF, Fenelon G, Yelnik J (1991) Topography of the projection from the central complex of the thalamus to the sensorimotor striatal territory in monkeys. J Comp Neurol 305: 17–34
44. Francois C, Savy C, Jan C, Tandé D, Hirsch EC, Yelnik J (2000) Dopaminergic innervation of the subthalamic nucleus in the normal state, in MPTP-treated monkeys and in Parkinson's disease patients. J Comp Neurol 425: 121–129
45. Friedman LJ, Insel TR, Smith Y (2000) Subcortical projections of area 25 (subgenual cortex) of the macaque monkey. J Comp Neurol 421: 172–188
46. Fudge JL, Kunishio K, Walsh C, Richard D, Haber SN (2002) Amygdaloid projections to ventromedial striatal subterritories in the primate. Neurosci 110: 257–275
47. Ghika J (2000) Mood and behavior in disorders of the basal ganglia. In: Bogousslavsky J, Cummings JL (eds) Behavior and mood disorders in focal brain lesions. Cambridge University Press, New York, pp 122–201
48. Goldman-Rakic PS (1988) Topography of cognition: parallel distributed networks in primate association cortex. Annu Rev Neurosci 11: 137–156
49. Groenewegen HJ, Uylings HBM (2000) The prefrontal cortex and the integration of sensory, limbic and autonomic information. Prog Brain Res 126: 3–28
50. Haber SN, Lynd E, Klein C, Groenewegen HJ (1990) Topographic organization of the ventral striatal efferent projections in the rhesus monkey: an anterograde tracing study. J Comp Neurol 293: 282–298
51. Haber SN, Lynd-Balta E, Mitchell SJ (1993) The organization of the descending ventral pallidal projections in the monkey. J Comp Neurol 329: 111–128
52. Hassani OK, Francois C, Yelnik J, Feger J (1997) Evidence for a dopaminergic innervation of the subthalamic nucleus in the rat. Brain Res 749: 88–94
53. Hazrati LN, Parent A (1992) The striatopallidal projection displays a high degree of anatomical specificity in the primate. Brain Res 592: 213–227
54. Hedreen JC (1999) Tyrosine hydroxylase-immunoreactive elements in the human globus pallidus and subthalamic nucleus. J Comp Neurol 409: 400–410
55. Hedreen JC, DeLong MR (1991) Organization of striatopallidal, striatonigral and nigrostriatal projections in the macaque. J Comp Neurol 304: 569–595
56. Heidbreder CA, Groenewegen HJ (2003) The medial prefrontal cortex in the rat: evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. Neurosci Biobehav Rev 27: 555–579
57. Heimer L (2003) A new anatomical framework for neuropsychiatric disorders and drug abuse. Am J Psychiatry 160: 1726–1739
58. Heimer L, Alheid GF (1991) Piecing together the puzzle of basal forebrain anatomy. In: Napier TC, Kalivas PW, Hanin I (eds) The basal forebrain. Plenum Press, New York, pp 1–42
59. Hirsch EC, Perier C, Orieux G, Francois C, Feger J, Yelnik J, Vila M, Levy R, Tolosa ES, Marin C, Trinidad HM, Obeso JA, Agid Y (2000) Metabolic effects of nigrostriatal denervation in basal ganglia. Trends Neurosci 23: S78–S85

60. Hornykiewicz O (1973) Dopamine in the basal ganglia. Its role and therapeutic implications (including the clinical use of L-dopa). Br Med Bull 29: 172–178
61. Ilinsky IA, Jouandet ML, Goldman-Rakic PS (1985) Organisation of the nigrothalamocortical system in the rhesus monkey. J Comp Neurol 236: 315–330
62. Inase M, Tokuno H, Nambu A, Akazawa T, Takada M (1996) Origin of thalamocortical projections to the presupplementary motor area (pre-SMA) in the macaque monkey. Neurosci Res 25: 217–227
63. Jan C, François C, Yelnik J, Tandé D, Agid Y, Hirsch EC (2000) Dopaminergic innervation of the pallidum in the normal state, MPTP-treated monkeys and Parkinsonian patients. Eur J Neurosci 12: 4525–4535
64. Jentsch JD, Taylor JR (2001) Impaired inhibition of conditioned responses produced by subchronic administration of phencyclidine to rats. Neuropsychopharmacology 24: 66–74
65. Joseph MH, Datla KP, Young AMJ (2003) The interpretation of the measurement of nucleus accumbens dopamine by in vivo dialysis: the kick, the craving or the cognition? Neurosci Biobehav Rev 27: 527–541
66. Kalivas PW, Churchill L, Klitenic MA (1993) The circuitry mediating the translation of motivational stimuli into adaptive motor response. In: Kalivas PW, Barnes CD (eds) Limbic motor circuits and neuropsychiatry. CRC Press, Boca Raton, FL, pp 237–275
67. Karachi C, Yelnik J, Tande D, Tremblay L, Hirsch E, Francois C (2005) The pallidosubthalamic projection: an anatomical substrate for non-motor functions of the subthalamic nucleus in primates. Mov Disord 20: 172–180
68. Kelley AE (1999) Neural integrative activities of nucleus accumbens subregions in relation to learning and motivation. Psychobiology 27: 198–213
69. Kemp JM, Powell TPS (1970) The cortico-striate projection in the monkey. Brain 93: 525–546
70. Kiyatkin EA, Stein EA (1995) Fluctuations in nucleus accumbens dopamine during cocaine self-administration behavior: an in vivo electrochemical study. Neuroscience 64: 599–617
71. Kleiner-Fisman G, Fisman DN, Sime E, Saint-Cyr JA, Lozano AM, Lang AE (2003) Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson's disease. J Neurosurg 99: 489–495
72. Kluver H, Bucy PC (1938) An analysis of certain effects of bilateral temporal lobectomy in the rhesus monkey, with special reference to ''psychic blindness''. J Physiol (London) 5: 33–54
73. Koch M, Schmid A, Schnitzler H-U (1996) Pleasure-attentuation of startle is disrupted by lesions of the nucleus accumbens. NeuroReport 7: 1442–1446
74. Koob GF (1992) Neurobiological mechanisms of cocaine and opiate dependence. In: O'Brien CP, Faffe JH (eds) Addictive states. Raven Press, New York, NY, pp 171–191
75. Koob GF, Nestler EJ (1997) The neurobiology of drug addiction. J Neuropsychiatry Clin Neurosci 9: 482–497
76. Lapper SR, Bolam JP (1992) Input from the frontal cortex and the parafascicular nucleus to cholinergic interneurons in the dorsal striatum of the rat. Neuroscience 51: 533–545
77. Lavoie B, Parent A (1994) Pedunculopontine nucleus in the squirrel monkey: cholinergic and glutamatergic projections to the substantia nigra. J Comp Neurol 344: 232–241
78. Lavoie B, Parent A (1994) Pedunculopontine nucleus in the squirrel monkey: distribution of cholinergic and monoaminergic neurons in the mesopontine tegmentum with evidence for the presence of glutamate in cholinergic neurons. J Comp Neurol 344: 190–209
79. Lavoie B, Parent A (1994) Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by anterograde tract-tracing methods. J Comp Neurol 344: 210–231
80. LeDoux JE (2000) Emotion circuits in the brain. Annu Rev Neurosci 23: 155–184
81. Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, Perret JE, Benabid AL (1995) Effects on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 345: 91–95
82. Litvan I (2001) Personality and behavioral changes with frontal subcortical dysfunction. In: Lichter D, Cummings JL (eds) Frontal subcortical circuits in psychiatric and neurological disorders. Guilford Press, New York, pp 151–162
83. Lynd-Balta E, Haber SN (1994) Primate striatonigral projections: a comparison of the sensorimotor-related striatum and the ventral striatum. J Comp Neurol 345: 562–578
84. MacLean PD (1949) Psychosomatic disease and the ''visceral brain'': recent developments bearing on the Papez theory of emotion. Psychosom Med 11: 338–353
85. MacLean PD (1954) The limbic system and its hippocampal formation. J Neurosurg 11: 29–44
86. Mallet L, Mesnage V, Houeto JL, Pelissolo A, Yelnik J, Behar C, Gargiulo M, Welter ML, Bonnet AM, Pillon B, Cornu P, Dormont D, Pidoux B, Allilaire JF, Agid Y (2002) Compulsions, Parkinson's disease, and stimulation. Lancet 360: 1302–1304
87. Mayberg HS (1994) Frontal lobe dysfunction in secondary depression. J Neuropsychiatry Clin Neurosci 6: 428–442
88. Mayberg HS, Starkstein SE, Sadzot B, Preziosi T, Andrezejewski PL, Dannals RF, Wagner HN, Robinson RG (1990) Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. Ann Neurol 28: 57–64
89. McGaugh JL (2002) Memory consolidation and the amygdala: a systems perspective. Trends Neurosci 25: 456–461
90. Mega MS, Cummings JL, Salloway S, Malloy P (1997) The limbic system: an anatomic, phylogenetic and clinical perspective. J Neuropsychiatry Clin Neurosci 9: 315–330
91. Middleton F, Strick P (2002) Basal-ganglia 'projections' to the prefrontal cortex of the primate. Cerebral Cortex 12: 926–935
92. Mindham RHS (1970) Psychiatric symptoms in parkinsonism. J Neurol Neurosurg Psychiatry 33: 181–191
93. Mogenson GJ, Brudzynski SM, Wu M, Yang CR, Yim CCY (1993) From motivation to action: a review of dopaminergic regulation of limbic-nucleus accumbens-ventral pallidum-pedunculopontine nucleus circuitries involved in limbic motor integration. In: Kalivas PW, Barnes CD (eds) Limbic motor circuits and neuropsychiatry. CRC Press, Boca Raton, FL, pp 237–287
94. Mogenson GJ, Jones DL, Yim CY (1980) From motivation to action: functional interface between the limbic system and the motor system. Prog Neurobiol 14: 69–97
95. Morgane PJ, Galler JR, Mokler DJ (2005) A review of systems and networks of the limbic forebrain/limbic midbrain. Prog Neurobiol 75: 143–160
96. Nakano K, Kayahara T, Ushiro H, Hasegawa Y (1995) Some aspects of basal ganglia-thalamocortical circuity and descending outputs of the basal ganglia. In: Segawa M, Nomura Y (eds) Age-related dopamine-dependent disorders. Monogr Neural Sci, Karger, Basel 14: 134–146
97. Nauta WJH (1958) Hippocampal projections and related neuronal pathways to the mid-brain in the cat. Brain 81: 319–340
98. Nauta WJH, Domesick VB (1981) Ramifications of the limbic system. In: Matthysse S (ed) Psychiatry and the biology of the human brain. Elsevier, New York, pp 165–188
99. O'Rahilly R, Muller F (1994) The embryonic human brain. Wiley-Liss, New York

100. Okun MS, Bowers D, Springer U, Shapira NA, Malone D, Rezai AR, Nuttin B, Heilman KM, Morecraft RJ, Rasmussen SA, Greenberg BD, Foote KD, Goodman WK (2004) What's in a ''smile?'' Intra-operative observations of contralateral smiles induced by deep brain stimulation. Neurocase 10: 271–279
101. Olds J, Milner P (1954) Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 47: 419–429
102. Ongur D, Price JL (2000) The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex 10: 206–219
103. Papez JW (1937) A proposed mechanism for emotion. Arch Neurol Psychiatry 38: 725–743
104. Parent A (1986) Comparative neurobiology of basal ganglia. John Willey & Sons, New York, NY
105. Parent A (1990) Extrinsic connections of the basal ganglia. Trends Neurosci 13: 254–258
106. Parent A, De Bellefeuille L (1982) Organization of efferent projections from the internal segment of globus pallidus in primate as revealed by fluorescence retrograde labeling method. Brain Res 245: 201–213
107. Parent A, Hazrati LN (1994) Multiple striatal representation in primate substantia nigra. J Comp Neurol 344: 305–320
108. Parent A, Hazrati LN (1995) Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Rev 20: 91–127
109. Parent A, Mackey A, Smith Y, Boucher R (1983) The output organization of the substantia nigra in primate as revealed by a retrograde double labeling method. Brain Res Bull 10: 529–537
110. Parent A, Bouchard C, Smith Y (1984) The striatopallidal and striatonigral projections: two distinct fiber systems in primate. Brain Res 303: 385–390
111. Parent A, Smith Y, Filion M, Dumas J (1989) Distinct afferents to internal and external pallidal segments in the squirrel monkey. Neurosci Lett 96: 140–144
112. Parent M, Levesque M, Paren A (2001) Two types of projection neurons in the internal pallidum of primates: single-axon tracing and three-dimensional reconstruction. J Comp Neurol 439: 162–175
113. Passingham RE (1996) Attention to action. Philos Trans R Soc Lond B Biol Sci 351: 1473–1479
114. Phillips ML, Drevets WC, Rauch SL, Lane R (2003) Neurobiology of emotion perception I: the neural basis of normal emotion perception. Biol Psychiatry 54: 504–514
115. Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, Fischman AJ (1994) Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. Arch Gen Psychiatry 51: 62–70
116. Redgrave P, Prescott TJ, Gurney K (1999) Is the short-latency dopamine response too short to signal reward error? Trends Neurosci 22: 146–151
117. Ring HA, Bench CJ, Trimble MR, Brooks DJ, Frackowiak RS, Dolan RJ (1994) Depression in Parkinson's disease. A positron emission study. Br J Psychiatry 165: 333–339
118. Robbins AH (1976) Depression in patients with Parkinson's disease. Br J Psychiatry 128: 141–145
119. Robbins TW, Sahakian BJ (1983) Behavioural effects of psychomotor stimulant drugs: clinical and neuropsychological implications. In: Ceese I (ed) Stimulants: neurochemical, behavioral, and clinical perspectives. Raven Press, New York, pp 301–338
120. Robbins TW, Cador M, Taylor JR, Everit BJ (1989) Limbic-striatal interactions in reward-related processes. Neurosci Beobehav Rev 13: 155–162
121. Russchen FT, Bakst I, Amaral DG, Price JL (1985) The amygdalostriatal projections in the monkey. An anterograde tracing study. Brain Res 329: 241–257
122. Sadikot AF, Parent A, François C (1992) Efferent connections of the centromedian and parafascicular thalamic nuclei in squirrel monkey: I. A PHA-L study of subcortical projections. J Comp Neurol 315: 137–159
123. Sadikot AD, Parent A, Smith Y, Bolam JP (1992) Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. J Comp Neurol 320: 228–242
124. Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE (2000) Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 123: 2091–2108
125. Sakas DE, Panourias IG (2006) Rostral cingulate gyrus: a putative target for deep brain stimulation in treatment-refractory depression. Med Hypoth 66: 491–494
126. Saxena S, Rauch SL (2000) Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am 23: 563–586
127. Saxena S, Brody AL, Schwartz JM, Baxter LR (1998) Neuroimaging and frontalsubcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl 35: 26–37
128. Schultz W (1997) Dopamine neurons and their role in reward mechanisms. Curr Opin Neurobiol 7: 191–197
129. Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275: 1593–1599
130. Schwatz JM, Stoessel PW, Baxter LR, Martin KM, Phelps ME (1996) Systematic cerebral glucose metabolic rate changes after successful behavior modification treatment of obsessibe – compulsive disorder. Arch Gen Psychiatry 53: 109–113
131. Selemon LD, Goldman-Rakic PS (1985) Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. J Neurosci 5: 776–794
132. Sesack SR, Pickel VM (1992) Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J Comp Neurol 320: 145–160
133. Shapira NA, Okun MS, Wint D, Foote KD, Byars JA, Bowers D, Springer US, Lang PJ, Greenberg BD, Haber SN, Goodman WK (2006) Panic and fear induced by deep brain stimulation. J Neurol Neurosurg Psychiatry 77: 410–412
134. Spanagel R, Weiss F (1999) The dopamine hypothesis of reward: past and current status. Trends Neurosci 22: 521–527
135. Starkstein SE, Robinson RG (1989) Affective disorders and cerebral vascular disease. Br J Psychiatry 154: 170–182
136. Stathis P, Antoniou K, Papadopoulou-Daifotis Z, Rimikis M, Varonos D (1996) Risperidone: a novel antipsychotic with many atypical properties. Psychopharmacology 127: 181–186
137. Stein EA, Pankiewicz J, Harsch HH, Cho JK, Fuller SA, Hoffmann RG, Hawkins M, Rao SM, Bandettini PA, Bloom AS (1998) Nicotine-induced limbic cortical activation in the human brain: a functional MRI study Am J Psychiatry 155: 1009–1015
138. Swerdlow NR, Koob GF (1987) Dopamine, schizophrenia, mania, and depression: toward a unified hypothesis of cortico-striatothalamic function. Behav Brain Sci 10: 197–245
139. Tanda G, Carboni E, Frau R, Di Chiara G (1994) Increase of extracellular dopamine in the prefrontal cortex: a trait of drugs with antidepressant potential? Psychopharmacology 115: 285–288
140. Tass PA, Klosterkotter J, Schneider F, Lenartz D, Koulousakis A, Sturm V (2003) Obsessive-compulsive disorder: development of

demand-controlled deep brain stimulation with methods from stochastic phase resetting. Neuropsychopharmacology 28 Suppl 1: S27–S34
141. Tekin S, Cummings JL (2002) Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. J Psychosom Res 53: 647–654
142. van Kuyck K, Demeulemeester H, Feys H, De Weerdt W, Dewil M, Tousseyn T, De Sutter P, Gybels J, Bogaerts K, Dom R, Nuttin B (2003) Effects of electrical stimulation or lesion in nucleus accumbens on the behaviour of rats in a T-maze after administration of 8-OH-DPAT or vehicle. Behav Brain Res 140: 165–173
143. Vandewalle V, van der Linden C, Groenewegen HJ, Caemaert J (1999) Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus [letter]. Lancet 353: 724
144. Volkow ND, Fowler JS, Wolf AP, Schlyer D, Shiue CY, Alpert R, Dewey SL, Logan J, Bendriem B, Christman D *et al* (1990) Effects of chronic cocaine abuse on postsynaptic dopamine receptors. Am J Psychiatry 147: 719–724
145. Wichmann T, DeLong MR (1993) Pathophysiology of parkinsonian motor abnormalities. Adv Neurol 60: 53–61
146. Willner P (1995) Dopaminergic mechanisms in depression and mania. In: Bloom FE, Kupfer DJ (eds) Psychopharmacology: the fourth generation of progress. Raven Press, New York, pp 921–932
147. Wise RA, Newton P, Leeb K, Burnette B, Pocock D, Justice JB (1995) Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. Psychopharmacology 120: 10–20
148. Yelnik J (2002) Functional anatomy of the basal ganglia. Mov Disord 17 Suppl: S15–S21
149. Yelnik J, Percheron G (1979) Subthalamic neurons in primates: a quantitative and comparative analysis. Neuroscience 4: 1717–1743
150. Yelnik J, François C, Percheron G, Tandé D (1996) A spatial and quantitative study of the striatopallidal connection in the monkey. Neuroreport 7: 985–988
151. Yeterian EH, Pandya DN (1998) Corticostriatal connections of the superior temporal region in rhesus monkeys. J Comp Neurol 399: 384–402

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