ELSEVIER

177

PROGRESS IN BRAIN RESEARCH

Coma Science

Clinical and Ethical Implications

EDITED BY
STEVEN LAUREYS
NICHOLAS D. SCHIFF
ADRIAN OWEN

PROGRESS IN BRAIN RESEARCH

VOLUME 177

COMA SCIENCE: CLINICAL AND ETHICAL IMPLICATIONS

EDITED BY

STEVEN LAUREYS

Coma Science Group, Cyclotron Research Center and Department of Neurology, University of Liège, Liège, Belgium

NICHOLAS D. SCHIFF

Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY, USA

ADRIAN M. OWEN

MRC Cognition and Brain Sciences Unit, Cambridge, UK

This volume is an official title of

Coma and Consciousness Consortium funded by the James S. McDonnell Foundation and the European Cooperation in the field of Scientific and Technical Research (COST)

Action BM0605: Consciousness: A Transdisciplinary, Integrated Approach

ELSEVIER

AMSTERDAM – BOSTON – HEIDELBERG – LONDON – NEW YORK – OXFORD
PARIS – SAN DIEGO – SAN FRANCISCO – SINGAPORE – SYDNEY – TOKYO

Elsevier
360 Park Avenue South, New York, NY 10010-1710
Linacre House, Jordan Hill, Oxford OX2 8DP, UK
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands

First edition 2009

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-444-53432-3 (this volume)
ISSN: 0079-6123 (Series)

Printed and bound in Great Britain

09 10 11 12 13 10 9 8 7 6 5 4 3 2 1

List of Contributors

A. Arzi, Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel
P. Azouvi, AP-HP, Department of Physical Medicine and Rehabilitation, Raymond Poincare Hospital, Garches; University of Versailles-Saint Quentin, France; Er 6, UPMC, Paris, France
T. Bekinschtein, MRC Cognition and Brain Sciences Unit; Impaired Consciousness Research Group, Wolfson Brain Imaging Centre, University of Cambridge, UK
A. Belmont, AP-HP, Department of Physical Medicine and Rehabilitation, Raymond Poincare Hospital, Garches, France; Er 6, UPMC, Paris, France
J.L. Bernat, Neurology Department, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA
H. Blumenfeld, Department of Neurology; Departments of Neurobiology and Neurosurgery, Yale University School of Medicine, New Haven, CT, USA
M. Boly, Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège and CHU Sart Tilman Hospital, Liège, Belgium
M.-A. Bruno, Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège, Liège; Fund for Scientific Research – FNRS, Belgium
C. Buhmann, Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
A. Casali, Department of Clinical Sciences, University of Milan, Milan, Italy
C. Chatelle, Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège, Liège, Belgium
I. Chervoneva, Department of Pharmacology and Experimental Therapeutics, Division of Biostatistics, Thomas Jefferson University, Philadelphia, PA, USA
E. Chew, Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Network, Boston, MA, USA
N. Childs, Texas NeuroRehab Center, Austin, TX, USA
M.R. Coleman, Impaired Consciousness Research Group, Wolfson Brain Imaging Centre; Academic Neurosurgery Unit, University of Cambridge, Cambridge, UK
V. Cologan, Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium
D. Coughlan, Brain Injury Program, Braintree Rehabilitation Hospital, Braintree; Sargent College of Health and Rehabilitation Sciences, Boston University, Boston, MA, USA
B. Dahmen, Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium
A. Demertzi, Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège, Liège, Belgium
A. Dennison, Charlotte Institute of Rehabilitation, Carolinas Medical Center, Charlotte, NC
A.M. de Noordhout, Neurology Department, University of Liège, Centre Hospitalier Regional de la Citadelle, Liège, Belgium
M.C. Di Pasquale, Moss Rehabilitation Research Institute/Albert Einstein Healthcare Network, Philadelphia, PA, USA
B. Eifert, Fachkrankenhaus Neresheim Hospital, Neresheim, Germany
A.K. Engel, Department of Neurophysiology and Pathophysiology, Center of Experimental Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

D.J. Englot, Department of Neurology, Yale University School of Medicine, New Haven, CT, USA
J.J. Fins, Division of Medical Ethics, Weill Medical College of Cornell University, New York, NY, USA
D. Galanaud, Department of Neuroradiology, Pitié-Salpêtrière Hospital, Paris, France
J.T. Giacino, JFK Johnson Rehabilitation Institute; New Jersey Neuroscience Institute, Edison, NJ, USA
R. Goebel, Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands; Maastricht Brain Imaging Centre (M-BIC), Maastricht, The Netherlands
D. Golombek, Chronobiology Lab, University of Quilmes/CONICET, Buenos Aires, Argentina
O. Gosseries, Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium
S. Häcker, Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany
W. Hamel, Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
F. Hammond, Charlotte Institute of Rehabilitation, Carolinas Medical Center, Charlotte, NC
U. Hidding, Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
J. Hirsch, fMRI Research Center, Columbia University, New York, NY, USA
K. Kalmar, JFK Johnson Rehabilitation Institute; New Jersey Neuroscience Institute, Edison, NJ, USA
D.I. Katz, Brain Injury Program, Braintree Rehabilitation Hospital, Braintree, MA; Department of Neurology, Boston University School of Medicine, Boston, MA, USA
A. Kübler, Institute of Psychology I, Biological Psychology, Clinical Psychology and Psychotherapy, University of Würzburg, Würzburg, Germany; Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany
N. Lapitskaya, Neurorehabilitation Research Department, Hammel Neurorehabilitation and Research Centre, Hammel, Denmark; Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium
S. Laureys, Coma Science Group, Cyclotron Research Center and Neurology Department, University and University Hospital of Liège; Fund for Scientific Research – FNRS; University of Liège, Liège, Belgium
D. Ledoux, Coma Science Group, Cyclotron Research Center and Intensive Care Department, University of Liège, Liège, Belgium
N. Levy, Oxford Centre for Neuroethics, Littlegate House, Oxford, UK
D. Long, Bryn Mawr Rehabilitation Hospital, Malvern, PA, USA
D. Lulé, Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany; Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium
I. Lutte, Medico-legal Department, Faculty of Medicine, Université Libre de Bruxelles and Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium
S. Majerus, Center for Cognitive and Behavioral Neuroscience and Coma Science Group, University of Liège, Liège; Fund for Scientific Research – FNRS, Belgium
R. Malach, Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel
M. Massimini, Department of Clinical Sciences; Department of Neurophysiology, University of Milan, Milan, Italy
A. Maudoux, Coma Science Group, Cyclotron Research Centre, and ENT department, CHU Sart Tilman Hospital, University of Liège, Liège, Belgium
P. Maurer, Fachkrankenhaus Neresheim Hospital, Neresheim, Germany
W. Mercer, Texas NeuroRehab Center, Austin, TX, USA

C.K.E. Moll, Department of Neurophysiology and Pathophysiology, Center of Experimental Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
M.M. Monti, MRC Cognition and Brain Sciences Unit; Impaired Consciousness Research Group, Wolfson Brain Imaging Centre, University of Cambridge, UK
G. Moonen, Department of Neurology, CHU University Hospital, Liège, Belgium
D. Müller, Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
A. Münchau, Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
M. Nichols, Brain Injury Program, Braintree Rehabilitation Hospital, Braintree, MA, USA
J.F. Nielsen, Neurorehabilitation Research Department, Hammel Neurorehabilitation and Research Centre, Hammel, Denmark
Y. Nir, Department of Psychiatry, University of Wisconsin, Madison, WI, USA
Q. Noirhomme, Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium
P. Novak, Sunnyview Hospital and Rehabilitation Center, Schenectady, NY, USA
S. Ovadia, Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel
M. Overgaard, CNRU, Hammel Neurorehabilitation and Research Unit, Aarhus University Hospital, Hammel, Denmark
A.M. Owen, MRC Cognition and Brain Sciences Unit; Impaired Consciousness Research Group, Wolfson Brain Imaging Centre, University of Cambridge, UK
M. Papa, Medicina Pubblica Clinica e Preventiva, Second University of Naples, Naples, Italy
F. Pellas, Médecine Rééducative, Hôpital Caremeau, CHU Nîmes, Cedex, France
J.D. Pickard, Impaired Consciousness Research Group, Wolfson Brain Imaging Centre; Academic Neurosurgery Unit, University of Cambridge, UK
M. Polyak, Brain Injury Program, Braintree Rehabilitation Hospital, Braintree, MA, USA
L. Puybasset, Department of Anesthesiology-Reanimation, Pitié-Salpêtrière Hospital, Paris, France
J. Reithler, Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands; Maastricht Brain Imaging Centre (M-BIC), Maastricht, The Netherlands
A. Roche, Brain Injury Program, Braintree Rehabilitation Hospital, Braintree, MA, USA
D. Rodriguez-Moreno, fMRI Research Center, Columbia University, New York, NY, USA
M. Rosanova, Department of Clinical Sciences, University of Milan, Milan, Italy
J. Savulescu, Oxford Centre for Neuroethics, Littlegate House, Oxford, UK
N.D. Schiff, Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY, USA
C. Schnakers, Coma Science Group, Cyclotron Research Center and Neuropsychology Department, University of Liège, Liège, Belgium
A. Sharott, Department of Neurophysiology and Pathophysiology, Center of Experimental Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
A. Soddu, Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium; Medicina Pubblica Clinica e Preventiva, Second University of Naples, Naples, Italy
B. Sorger, Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands; Maastricht Brain Imaging Centre (M-BIC), Maastricht, The Netherlands; Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium
M. Stanziano, Medicina Pubblica Clinica e Preventiva, Second University of Naples, Naples, Italy
T. Taira, Department of Neurosurgery, Tokyo Women's Medical University, Shinjuku, Tokyo, Japan

G. Tononi, Department of Psychiatry, University of Wisconsin, Madison, WI, USA
L. Tshibanda, Coma Science Group, Cyclotron Research Center and Neuroradiology Department, University and University Hospital of Liège, Liège, Belgium
C. Vallat-Azouvi, UGECAM-antenne UEROS, Raymond Poincare Hospital, Garches, France; Er 6, UPMC, Paris, France
A. Vanhaudenhuyse, Coma Science Group, Cyclotron Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium
M. Westphal, Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
J. Whyte, Moss Rehabilitation Research Institute/Albert Einstein Healthcare Network, Philadelphia, PA, USA
R. Zafonte, Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Network, Boston, MA, USA
N.D. Zasler, Concussion Care Centre of Virginia, Ltd.; Tree of Life Services, Inc., Richmond, VA; Department of Physical Medicine and Rehabilitation, Virginia Commonwealth University, Richmond, VA; Department of Physical Medicine and Rehabilitation, University of Virginia, Charlottesville, VA, USA
A. Zeman, Cognitive and Behavioural Neurology, Peninsula Medical School, Exeter, UK
C. Zickler, Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany
S. Zittel, Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Foreword

Consciousness is the appearance of a world. In its absence there is no self, no environment, no pain, no joy; there is simply nothing at all. Following Thomas Nagel, without consciousness there is 'nothing like it is to be' (Nagel, 1974). Understanding the boundaries of consciousness is therefore of the highest clinical and ethical importance. The new enterprise of 'coma science' is at the very forefront of this mission, and the present volume — edited and in several chapters co-authored by the three pioneers of the field — represents an essential and timely contribution.

Coma science is perhaps the most dynamic yet empirically grounded sub-field within the rapidly maturing science of consciousness. It seeks to understand not only coma itself, but also the many differentiated varieties of impaired conscious level following brain injury, including the vegetative state, the minimally conscious state and the locked-in state. Its key objectives include: (i) reliable diagnosis of residual consciousness in patients unable to produce verbal or behavioural reports, (ii) establishing non-verbal or even non-behavioural means of communication where residual consciousness persists and ultimately (iii) delivering improved prognosis and even treatment, for example via novel applications of deep-brain stimulation or pharmacological intervention. More broadly, coma science provides an invaluable window into the mechanisms of consciousness in general, by revealing which structural and functional brain properties are either necessary or sufficient for the appearance of a world. As has often been the case in the history of science, the proper understanding of a natural phenomenon may be best pursued by examining those situations in which it is perturbed.

While the general goals of consciousness science carry substantial implications for our understanding of our place in nature, the specific objectives of coma science impose clear and present clinical and ethical challenges. Here are just of few of those discussed in the following pages: How is death to be defined (Bernat)? When should treatment be withheld, or applied more aggressively (e.g. Katz et al., Fins)? What is the quality of life like for patients (Azouvi et al., Lulé et al., Zasler, Lutte)? What are reliable criteria for residual consciousness, or for the capacity to suffer (e.g. Giacino et al., Coleman et al., Majerus et al., Boly et al., and others)?

These challenges cannot be relegated to the armchair. They arise on a daily basis at the patient's bedside, in the intensive care, neurology, neurosurgery or neurorehabilitation units, often with family members in attendance and sometimes with limited time for deliberation. Principled responses are urgently required, and this volume should be a primary port-of-call for their formulation. Its contents, collated and often co-written by Steven Laureys, Nicholas Schiff and Adrian Owen, span a remarkable range of issues relevant to coma science, all the while maintaining an impressive focus on the clinical and ethical implications they generate. A particularly worthwhile feature is the integration of novel theoretical approaches to consciousness. For example, both Massimini et al. and Boly et al. discuss how theories based on 'information integration' (Tononi, 2008) may be applied to clinical cases, potentially providing a means to assay residual consciousness without relying on indirect behavioural measures (Seth et al., 2008).

It is indeed by combining theory and practice, by integrating insights from philosophy to pharmacology to functional neuroimaging, and not least by conveying the excitement of real progress, that this volume belongs on the shelf not only of neurologists and ethicists, but also of every scientist interested in the neural basis of human consciousness.

References

Nagel, T. (1974). What is it like to be a bat? *Philosophical Review*, *83*, 435–450.
Seth, A. K., Dienes, Z., Cleeremans, A., Overgaard, M., & Pessoa, L. (2008). Measuring consciousness: Relating behavioural and neurophysiological approaches. *Trends in Cognitive Sciences*, *12*(8), 314–321.
Tononi, G. (2008). Consciousness as integrated information: A provisional manifesto. *The Biological Bulletin*, *215*(3), 216–242.

Anil Seth
University of Sussex

Foreword

This is a strange and exciting time to be interested in how brains do minds. It is an exciting time, for not a week passes that yet another finding about how the brain works is published. There is a discernable sense of progress here, unfortunately amplified in the continued and already stale interest that the press and other media manifest towards anything neuroscientific.

It is a strange time too, at least for someone who's been around for quite a while. When I first became interested in cognitive psychology, about 25 years ago, almost nobody worked on consciousness per se. I was not either. Instead, I was focused on the mechanisms of implicit learning — what is it that we can learn without awareness? The first half of each of my lectures here and there about the topic was dedicated to pre-emptive precautionary arguments: It is a complex domain, our measures are uncertain and imprecise, some authors strongly disagree, there is ongoing controversy. Today, I hardly have to say anything at all about the existence of learning without awareness: It goes without saying that the phenomenon exists.

So that's a first strange turn of events: In the space of 25 years, not only does everybody agree that the brain can process information without consciousness, but also many even believe that whatever the brain does is better done without consciousness than with consciousness. The pendulum, however, always swings back, and it is not too difficult to imagine which way it will go next.

A second reason why these are strange times is that it feels like we are reinventing cognitive psychology all over again. Most imaging studies are replications of earlier behavioural findings. Likewise, most studies about consciousness are replications of earlier studies in which the infamous C word had been carefully blotted out in one way or another. And yet, there is also tremendous innovation in our methods, and in the way in which traditional questions in cognitive psychology are approached anew. It is a real joy to see an entire new generation of philosophers who know their empirical literature come up with new designs for testing out hypotheses that are informed by deep, substantive ideas about the mind. Likewise, it is sobering to see neuroscientists lose some of their arrogance and realise that their experiments are not, perhaps, as incisive as they had initially thought. It is only by striving to combine subjective and objective data that the field will make genuine progress. This is the only field in which I have witnessed genuine interdisciplinary progress.

A third reason that these are strange times is because, in what feels like an instant, we have moved from living in the present to living in the future. Nothing illustrates this better than this excellent volume, edited by Steven Laureys, Nicholas Schiff and Adrian Owen. How astonishing and unexpected it is that we can now use brain imaging to obtain subjective reports! What an incredible hope do brain–computer interfaces represent for people no longer able to control their environment! And how exciting is the possibility that deep-brain stimulation will perhaps offer a new potent form of therapy. These developments, at the border between clinical and fundamental neuroscience, were almost unthinkable just a few years ago. Crucially, such developments have both clinical and fundamental import. 'Coma science' is only beginning, and this volume will no doubt be remembered as its starting point.

Axel Cleeremans
Université Libre de Bruxelles
(Coordinator of the European Cooperation in the field of Scientific and Technical Research Action on 'Consciousness: A Transdisciplinary, Integrated Approach')

Preface

Understanding consciousness is one of the major unsolved problems in science. An ever more important method of studying consciousness is to study disorders of consciousness, such as brain damage leading to coma, vegetative states, or minimally conscious states. Following the success of the first Coma and Consciousness Conference held in Antwerp in 2004, satellite to the 8th Annual Meeting of the Association for the Scientific Studies of Consciousness (ASSC8), the 2nd Coma and Consciousness Conference, satellite to ASSC13, focused on the clinical, societal, and ethical implications of ''coma science.'' Held at the historic Berlin School of Mind and Brain of the Humboldt University in Berlin, 4–5 June 2009, the conference was a joint meeting of the European Cooperation in Science and Technology COST Action BM0605 ''Consciousness: A transdisciplinary, integrated approach''; the Coma and Consciousness Consortium — McDonnell Foundation Initiative Grant ''Recovery of consciousness after severe brain injury''; the European Union Specific Targeted Research Projects (STREP) ''Measuring consciousness: Bridging the mind-brain gap'' (Mindbridge); and the Marie Curie Research Training Network ''Disorders & coherence of the embodied self'' (DISCOS). The conference was endorsed by the European Neurological Society and co-funded by the Mind Science Foundation. It brought together a distinguished small group of neuroscientists and clinical investigators engaged in the study of coma and consciousness and mechanisms underlying large-scale cortical integration, state-of-the-art neuroimaging studies of sleep, anesthesia and patients with disorders of consciousness, and experts in the fields of the neurology of consciousness and ethics who addressed the larger context in which the emerging neuroscience will be received and integrated.

Recent studies have underscored that recovery of consciousness after severe brain injury remains poorly understood. Many of these investigations are very much in the public eye in part because of their relationship to controversies about end-of-life decisions in permanently unconscious patients (e.g., Terry Schiavo in the United States and Eluana Englaro in Italy recently), and the relationship to one of the major philosophical, sociological, political, and religious questions of humankind. The challenges are surprisingly difficult with a degree of diagnostic uncertainty that may range at the bedside in some patients from unconscious to fully aware, even for patients with no evidence of behavioral responsiveness. As measurements improve, behaviorally defined states from vegetative state (wakeful unawareness), minimally conscious state (at least some evidence of awareness), and up but not including patients in locked-in syndrome (full consciousness with virtually no motor control) will reveal subcategories of patients whose level of consciousness we cannot at present with confidence identify.

Although public interest is high, the broad needs for systematic research in this emerging area of knowledge is currently unmet. This volume focuses on our current understanding of the neuroanatomical and functional underpinnings of human consciousness by emphasizing a lesional approach offered via the study of neurological patients. Our intended goal aims at updating and advancing knowledge of diagnostic and prognostic methods, potential therapeutic strategies, and importantly identifying challenges for professionals engaged in the study of these patient populations. The selected contributors are all outstanding authors and undisputed leaders in their field.

The papers presented in this volume are likely to help form the scientific foundations for frameworks to systematically organize information and approaches to future clinical assessments of consciousness. The

interest of this is threefold. First, the exploration of brain function in disorders of consciousness represents a unique lesional approach to the scientific study of consciousness and adds to the worldwide effort to identify the ''neural correlate of consciousness.'' Second, patients with coma and related disorders of consciousness continue to represent a major clinical problem in terms of diagnosis, prognosis, and treatment. Third, new scientific insights in this field have major ethical, societal, and medico-legal implications, which are the topic of the last part of this book.

We thank ASSC13 organizers John-Dylan Haynes, Michael Pauen, and Patrick Wilken and our funding agencies including the James McDonnell Foundation, the European Commission, the Medical Research Council (UK), the National Institutes of Health, the Charles A. Dana Foundation, the Mind Science Foundation, the Belgian National Funds for Scientific Research and the University, and University Hospital of Liège in helping to make the conference and this book possible and hope that our joint efforts will ultimately improve the care and understanding of patients suffering from disorders of consciousness.

Steven Laureys (Liège)
Adrian Owen (Cambridge)
Nicholas Schiff (New York)
July 2009

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 1

The problem of unreportable awareness

Adam Zeman*

Cognitive and Behavioural Neurology, Peninsula Medical School, Exeter, UK

Abstract: We tend to regard consciousness as a fundamentally subjective phenomenon, yet we can only study it scientifically if it has objective, publicly visible, manifestations. This creates a central, recurring, tension in consciousness science which remains unresolved. On one 'objectivist' view, consciousness is not merely revealed but endowed by the process of reporting which makes it publicly accessible. On a contrasting 'subjectivist' view, consciousness, per se, is independent of the possibility of report, and indeed will always remain beyond the reach of direct observation. I shall explore this tension with examples drawn from clinical neurology, cognitive neuroscience and philosophy. The underlying aim of the paper is to open up the simple but profoundly difficult question that lurks in the background of consciousness science: what is it that are studying?

Keywords: consciousness; subjectivity; philosophy

Introduction

This paper will explore two ways of thinking about consciousness. The tension between them often lies in the background of discussions about consciousness, but is not always clearly articulated. The first, objective, conception tends to be adopted by neuroscientists with an interest in awareness; the second, subjective, view is closer to intuitive common-sense thinking, but is also familiar to doctors who care for patients with impairments of awareness. The first approach turns on the idea that the key to consciousness lies in complexity, especially in complex forms of neural processing which feed forward into action; the second holds fast to the thought that experience can take extremely simple forms, and need not give rise to action of any kind whatever. The first springs partly from a sense of wonder at the intricacies of the organ of experience, the brain, partly from a recognition that any *science* of consciousness must rely on observable manifestations of awareness, especially on forms of report; the second answers to the possibility that elements of experience may survive substantial damage to the brain, including damage to precisely those systems required for report. Reflection on these two conceptions prompts a simple but difficult question: do consciousness scientists know what we are studying yet?

In the next section of this paper ('Consciousness, complexity, control') I introduce the first of these two conceptions, explaining how it springs from contemporary brain research and meshes with some philosophical approaches to awareness. In 'Consciousness, simplicity, helplessness' I explain how the second conception arises from

*Corresponding author.
Tel.: 01392-406747; Fax: 01392-406767;
E-mail: adam.zeman@pms.ac.uk

DOI: 10.1016/S0079-6123(09)17701-4

intuitive ways of thinking about consciousness and comes naturally to doctors caring for patients with states of impaired awareness. I use a thought experiment to probe our intuitions about the minimum conditions for awareness. 'Which concept of consciousness?' examines some arguments for and against the two conceptions, and the implications of the second for the scope of a science of consciousness.

Consciousness, complexity, control

> Though it can be useful to speak of 'coding' and 'decoding'… we must be careful to avoid the conception that there is some final stage where the message [in the brain] is understood… The decoding is completed only by action… The brain is constantly making hypotheses that prepare for useful actions.
>
> J. Z. Young
>
> Perception is basically an implicit preparation to respond.
>
> Roger Sperry

The property of the brain most often emphasised in discussions of the neural basis of consciousness is its complexity. The brain contains of the order of 100,000 million neurons, of numerous varieties, and perhaps 1000 times as many synapses, utilising an extensive range of neurotransmitters and receptor molecules. This vast array of diverse parts is highly organised and widely integrated. Consider, for example the visual system: the neurons of primary visual cortex, like other cortical neurons, are organised in vertical columns; racking the microscope up from individual neurons to their functional groupings, ordered arrays of columns map the visual field, and set in train the parallel analysis of visual form, movement and colour; moving up one level further, this analysis is then carried forward in the 30 or so cortical visual areas which, we now know, are themselves organised into two major streams, an occipito-temporal stream concerned particularly with object identification and an occipito-parietal stream especially concerned with the visual guidance of action. Similar kinds of account, building from neurons, through their local networks, to cortical areas and extended cortical networks could be given for each of the other 'modules' of mental function — the sensory systems, language, memory, emotion, motivation, attention, executive function, praxis.

If this undeniable complexity is relevant to consciousness, *how* is it relevant? Not everything that happens in the brain appears to give rise to consciousness: what distinguishes the processes which do? The main candidates, in principle, are the amount of activity (e.g. the number of active neurons and the duration of their activity; Moutoussis and Zeki, 2002), its quality (e.g. the degree of neuronal synchronisation; Singer, 2009), its localisation (e.g. cortical vs. subcortical; Sahraie et al., 1997) and its connectivity or degree of integration (Laureys et al., 2000). While there is some experimental support for each of these candidates, the final proposal has received the widest interest. Its various versions have in common the basic idea that while much of the brain's modular activity proceeds unconsciously, it can be rendered conscious by an interaction with other systems which broadcast the activity more widely through the brain, organise action and allow report. I shall give examples of this line of thought from the work of Joseph LeDoux, Larrie Weiskrantz, Francis Crick and Cristof Koch, Antonio Damasio, Dan Dennett and Bernie Baars.

In The Emotional Brain, LeDoux (1998) reviews the brain mechanisms of emotion, especially fear. He notes that much of the brain activity which accompanies conscious emotion can occur unconsciously, for example stimuli presented too briefly for us to report them can bias later responses, and we are quite often unreliable witnesses to our own reasons for action. He explains these observations by way of the anatomy of emotion: there are direct subcortical routes, for example by which visual signals can reach the amygdala, the epicentre of fear signalling in the brain, bypassing the cortical visual areas on which conscious vision is thought to depend. So what determines when emotional

processing becomes conscious? LeDoux proposes a 'Simple Idea': 'a subjective emotional experience, like the feeling of being afraid, results when we become consciously aware than an emotion system in the brain, like a defence system, is active' — and this, LeDoux, suggests, occurs when information in the emotion system enters the working memory system based on lateral prefrontal cortex.

In Consciousness Lost and Found, Larry Weiskrantz (1997) develops a similar line of thought in the context of blindsight. Some patients with no conscious vision in a region of the visual field can, if pressed, make accurate guesses about the position, shape and direction of movement of objects of which they have no conscious perception at all. How can this be? Clearly the basic sensory ability on which visual discrimination depends is intact in patients with blindsight. But they have lost, as Wesikrantz puts it, 'the ability to render a parallel acknowledged commentary' — the ability to 'comment' on the discrimination they are manifestly capable of making. Weiskrantz very helpfully distinguishes two views of this commentary stage. The first is that it merely enables the acknowledgment of awareness, leaving open the question of how that awareness comes about, or what it consists in. He contrasts this 'enabling' view with a stronger alternative, which he favours, that the commentary 'is actually endowing: it is what is meant by saying that one is aware … the ability to make a commentary is what is meant by being aware and what gives rise to it'. Where does the commentary stage take place in the brain? At the time of writing of Consciousness Lost and Found Weiskrantz regarded this as an unsettled issue, but he suggests that the 'fronto-limbic complex' is likely to play a crucial role. As an aside, the distinction that Weiskrantz draws here between two views of the significance of report, corresponds to the distinction drawn by Ned Block between 'epistemic' and 'metaphysical' roles for 'cognitive access' in the detection of consciousness (Block, 2007).

The idea that much of the modular processing occurring in the brain proceeds subconsciously, and that consciousness requires a further interaction between cognitive modules, permitting action and report, was made starkly explicit in Crick and Koch's (1995) paper 'Are we aware of activity in primary visual cortex?'. They conclude, in this paper, that this is unlikely. They regard this as a testable, empirical claim, but in the course of the discussion state a revealing assumption: 'all we need to postulate is that, unless a visual area has a direct projection to at least one [frontal area], the activity in that particular visual area will not enter visual awareness directly, because the activity of frontal areas is needed to allow a person to report consciousness'. In other words, the ability to report consciousness, dependent upon frontal executive regions of the brain, is regarded as a prerequisite for consciousness. This is the clearest possible statement of Weiskrantz' second, stronger, version of this thesis: that the 'commentary stage' does not merely enable the acknowledgement of sensory awareness, but endows sensations with awareness.

This thesis is in keeping with the etymology of 'consciousness'. Its Latin root — 'cum-scio' — referred to knowledge that one shared with another or with oneself to knowledge that has been attended to, articulated, made explicit. It has some intuitive appeal: think of occasions when, for example you are eating something delicious but your attention is engaged on conversation or your thoughts: the moment that you become conscious of the taste is the moment that you realise 'goodness, this is a really dark, rich chocolate ice cream' — the consciousness and its articulation almost seem to be one and the same. The idea is echoed in information processing theories of consciousness. In the 'global workspace' theories of Bernard Baars (2002), and Stanislas Dehaene (Dehaene and Naccache, 2003), the contents of consciousness comprise those items that are currently being broadcast via the 'global workspace' throughout the modular sub-systems of the brain: in the words of Dan Dennett they express the 'cerebral celebrity' of the neural processes that have temporarily gained dominance over their competitors. Although expressed in different terms, Antonio Damasio's (2000) suggestion that consciousness arises when the representation of objects and events is married up to the representation of the organism

that represents them contains the same central thought: mere sensation, mere representation, is not enough for consciousness-some further recursive stage, of reflection, commentary, report, articulation is needed. The central place of communication — linked to report — in our thinking about consciousness is well illustrated by Adrian Owen's influential study (Owen et al., 2006) of a patient who appeared to be in the vegetative state: his demonstration that she could modulate her brain activity by following two contrasting instructions was widely accepted as proof of consciousness.

This line of thought among scientists interested in consciousness is in keeping with some philosophical approaches. David Rosenthal's well-known paper, Two Concepts of Consciousness (Rosenthal, 1986), contrasts two views which he characterises as Cartesian on the one hand, Aristotelian on the other. The Cartesian view is that consciousness is the mark of the mental: that is to say, only states of which we are conscious are mental. This view blocks any attempt to explain conscious states by way of mental states: such an attempt would be circular. The Aristotelian view is that 'the mental is somehow dependent upon highly organised forms of life, in something like the way in which life itself emerges in highly organised forms of material existence'. Such a view allows one 'to conceive of the mental as continuous with other natural phenomena', and at the same time opens up the possibility of explaining consciousness by way of mental states. Rosenthal's specific proposal, in the Aristotelian tradition, is that a conscious state is a mental state about which one is having the 'roughly contemporaneous thought that one is in that mental state': *that* thought is itself unconscious, explaining the fact that when we are conscious, for example that when we are looking at a red ball, we do not normally have the conscious thought 'I am looking at a red ball'. Thus consciousness in Rosenthal's theory is a matter of having a 'higher order' thought about an otherwise unconscious mental state. This view provides a philosophical echo of the proposals by LeDoux, Weiskrantz, Crick and Koch, Damasio, rooted in neuroscience. For the neuroscientists, contentful mental states become conscious when they gain access to brain systems linked to action and the possibility of report; for Rosenthal, mental states become conscious when they are the target of a higher-order thought.

These theories emphasising the cognitive and neural complexity of consciousness, and its close links with report, share some common ground with a more radical group of philosophical ideas, 'embodied' or 'enactive' theories that identify consciousness with skilful activity. These ideas, exemplified by the work of O'Regan and Noe (2001), advance on two fronts. First, focusing on visual experience, they question whether this is as we take it to be, arguing, on the basis of experimental evidence from change blindness and inattentional neglect, that our conscious visual representation of the world is relatively sparse. On this view, the *apparent* richness of our experience has two sources: the richness of the environment itself, and our finely honed, skilful, ability to find the details that we need just as and when we need them. The apparent presence of the visual world in our experience is therefore, at least in part, a 'presence in absence'. Second, developing this idea further, Noe and O'Regan reinterpret visual representations themselves in terms of visuomotor skills. To take an example from Noe's Action in Perception (Noe, 2004), he suggests that seeing a box involves possessing and exercising the practical knowledge which enables you to anticipate how its appearance will change as you move your eyes around it. The idea that seeing is a much more skilled, and in a sense more thoughtful, activity than we might suppose seems right. The science of vision is packed with illustrations of the basic truth that seeing is a highly active process. But it is natural to respond that while such activity and knowledge are surely involved in seeing the box, something else, the *seeing* itself, has been left out of account. Noe disputes this, with these riddling words: 'The content of experience is virtual *all the way in*.... Qualities are available in experience as possibilities, as potentialities, but not as givens. Experience is [the] process of navigating the pathways of these possibilities'. Subjective presence, on this view, is *always* 'presence in absence'.

Collectively, then, these theories emphasise the complexity of the cognitive and neural processes that underlie consciousness, underline the need for forms of processing that go beyond sensation to make experience explicit, and highlight their links with the control of action, in particular with report. In the work of theorists like Noe and O'Regan, the capacity for consciousness is reduced to our skilled ability to navigate networks of knowledge. These approaches make consciousness accessible to objective study: if consciousness has an intrinsic connection with action and report, then it is directly amenable to science. Alva Noe's courage seems to falter, for a moment, at the close of his book, when he acknowledges that perhaps, after all, there is a need for 'a smidgen … a spark' of consciousness to get his theory off the ground. The second section of this paper examines cases of neurological impairment, real and imagined, in some of which only 'a smidgen… a spark' of consciousness remains.

Consciousness, simplicity, helplessness

> How should these principles be entertained, that lead us to think all the visible beauty of creation a false imaginary glare?
>
> Bishop Berkeley

Neurologists often have to care for patients who are helpless, occasionally helpless to the point of complete or near complete paralysis. This is a relatively rare event but it occurs every month or so on a Neurology unit of any size, usually in the context of two disorders: the Guillain Barre and the locked-in syndromes. Guillain Barre syndrome (GBS) is an inflammatory disorder of nerves and nerve roots outside the brain and spinal cord. In severe cases the inflammation can temporarily block conduction in *all* the nerves which mediate voluntary action, preventing movement of the limbs, the face, the eyes and, critically for life, the muscles with which we breathe. A patient in this state is fully and unambiguously conscious, but in immediate need of life support. In the locked-in syndrome, a strategically placed stroke — or other form of injury — damages nerve fibres in the brain stem conveying signals from the hemispheres to areas of the brain stem and spinal cord which control movement: in this state, classically, vertical movements of the eyes and movement of the eyelids are spared, and these can be used for communication, because, just as in the GBS, the subject is fully aware. Occasionally patients paralysed for major surgery with a muscle relaxant fail to receive their anaesthetic: they lack even the tenuous channel of communication available to patients in the locked-in state. In each of these cases awareness survives paralysis. But this is no surprise and offers no really challenging counterexample to the proposals of Weiskrantz and others. These subject's difficulties in reporting their experiences at the time are simply due to a problem with the phone link to the outside world, so to speak: their cerebral hemisphere and cognitive abilities are perfectly intact, whatever havoc their situations may be wreaking lower down the neuraxis. Were Adrian Owen to interrogate them using fMRI he could readily set up an effective line of communication, revealing their unimpaired awareness.

But consciousness often also survives damage closer to the centre. It survives, for example the inactivation of declarative memory which occurs in transient global amnesia; the loss of language in dysphasia; the profound loss of motivation in catatonia. Laureys and Tononi (2009) in the concluding chapter of their recent survey of the neurology of consciousness suggest that it can also survive the loss of introspection, attention, of spatial frames of reference and of the sense of body. If it can survive so many losses, what are the minimal neurobiological foundations for consciousness? What is its sine qua non? This question is one we find ourselves asking sometimes at the bedside. Here is a patient who is giving no evidence of consciousness at all: but can be sure that he or she is unaware?

We do not yet know the minimum conditions for consciousness. A thought experiment might clarify our thinking on the subject. Its principle is that we shall, in imagination, strip away inessential psychological capacities, one by one, from healthy full-blown consciousness, to define the

bare minimum capacities required for experience of the simplest kind. If we accept that attention, introspection, language, motivation, the ability to form new long-term memories and a wide range of perceptual abilities are not required, what is? Well, at the very least, to achieve consciousness of the simplest kind, we might posit the need for a sensory system and an appropriate level of arousal.

Imagine that we could, or nature somehow had isolated the 'colour area' in the human visual system. Is it plausible that such an isolated system could have a visual experience? If it were genuinely isolated, most bets would be against any experience at all. For one thing it would lack the activation from the brain stem which is normally required to maintain the waking state; for another it would lack the re-entrant signals from other visual areas which may be required for conscious vision. So let's be generous and build these into our system. Now we have an isolated colour area, activated just as it would be in a normal, waking, seeing brain. And let us allow the visual input, say of a richly coloured abstract scene. The neurologically sophisticated among you will be feeling very uneasy: the brain is massively interconnected, and it is open to question whether the results of activity in 'isolated systems' can be sensibly discussed. But let us follow through the train of thought. It is plausible that one might be able to set up the neuronal conditions which occur in the visual system normally during the perception of a coloured scene. If, for the sake of argument, we could do so, in a system which, *ex hypothesi*, has no means of reporting its experience to others, or even to itself, would the resulting activity give rise to an experience?

Intuitions differ markedly about this. I personally find it plausible that the activity might give rise to an experience — although one has to remind oneself how limited the experience would be. A phrase of David Chalmers' (1996), 'unarticulated flashes of experience', comes to mind. Consciousness of this kind would lack any self-reference or personhood, any connection with associations which depend on a ready exchange with other areas of the brain, any linguistic dimension, any capacity to give rise to action or report. Would it be something or nothing?

If consciousness of this kind, unreportable in principle, is a possibility, a range of implications follows. But perhaps it is a will-o'-the-wisp, a beguiling illusion — or simply a pack of nonsense. Let us examine some reasonable objections to the idea that unreportable consciousness of this kind might occur, and then, if these objections are not fatal, take a look at its implications for a science of consciousness.

Which concept of consciousness?

An initial objection to the idea of 'unarticulated flashes of experience' is that they could not have evolved because they have no function. This objection, at least as I have framed it, holds no water. Evolution has endowed our bodies with many capacities which have no function: the highly evolved electrical behaviour of the heart, for example creates the capacity for a whole range of dysrhythmias which serve no evolutionary purpose but result from the intricate organisation of electrical pathways in the heart which normally do other things. A putative flash of experience in an isolated visual system would indeed serve no purpose, but it would exist, if it exists at all, as a by-product of a type of neural activity which evolved under a straightforward selection pressure for sight.

A second objection is obliquely related to the first. It is that these putative flashes of experience could not matter less, even if they occurred. Consider the analogy of our unremembered dreams. We know that four or five times each night, in the course of the cyclical alternation of dream states, we enter REM sleep. Sleepers woken in this phase of sleep reliably report dream narratives. Yet in the morning few of us remember more than a single dream, if that. Are we conscious of our dreams at the time, but subsequently amnesic for them, or unconscious of them all unless someone or something awakens us? The critic of our thought experiment who thinks that unarticulated flashes of experience would not matter even if they occurred is likely to feel that this question about our dreams is equally empty. *Who cares* whether or not we are conscious of our unremembered dreams?

There are two reasons why we should perhaps care. One is that some unremembered experiences are worth having — or not having — at the time. A real life example of an experience it may be worth not having is supplied by a study of an anaesthetic technique which achieved amnesia for the procedure but appeared to leave patients in pain during surgery, to judge by their responses to an experimenter at the time. The experimenter concluded that the technique achieved 'general amnesia' rather than 'general anaesthesia'. Would you be happy to undergo major surgery with the aid of this technique, or would you prefer to be as sure as possible that you were, strictly, unconscious? Whether, to press our thought experiment to the extreme once again, we can really make sense of the idea of isolated pain in a system which no longer has any resources to report or respond to or remember the pain afterwards is debatable — we will touch on this question below.

A second reason why we arguably should care about whether such flashes of experience could occur is that the practical consequences of an event may not exhaust our interest in it. If experience occurs in our hypothetical isolated visual system, that strikes me as an important fact about the universe. Another analogy may help. A practical neurologist, standing beside me at the bedside while I am wondering whether someone is or is not conscious might want to say — 'look, it doesn't matter, this patient's brain is so badly damaged that it could at best support only a glimmer of experience — so little as makes no difference'. I have sympathy with this view: consciousness is a matter of degree and some minimal varieties of awareness may not, in practice, be worth the costs of sustaining them. But for purposes of theoretical understanding of awareness and its mechanisms it remains important if they occur.

A third critical thought about these 'unarticulated flashes of experience' is that if consciousness is not an organisational property of the brain, a product of its supreme complexity, then where is the rot going to stop? If we allow an isolated colour area to be conscious, how about a single neuronal column? Or a single neuron? Or any isolated cell? This way panpsychism — and madness — seem to lie. Well, panpsychism has struck some thinkers as a plausible theory of mind. And, less exotically, many of us admit to uncertainties about which animals are conscious: you and I, of course; the chimp in the zoo, sans doute; your dog, sure; your goldfish, that spider up in the corner…? Most of us are prepared to live with doubt about which animals are conscious. But this thought experiment does open up the space of possibilities rather alarmingly. Perhaps we should look back at our main assumptions once again.

In doing so we are likely to encounter the fourth and most powerful objection to our thought experiment: that it stretches our concept of consciousness beyond any reasonable application. The notion of unreportable consciousness and our thought experiment depend upon a concept of consciousness which they confound: they undermine their own conceptual assumptions. This case could be argued in the following kind of way: we learn to ascribe consciousness to organisms whose behaviour reveals certain kinds of sensitivity to the environment and certain kinds of intelligible purpose. The isolated visual system has no means of revealing anything about its sensitivities and no means of generating purposes: it is therefore simply the wrong kind of thing to be conscious. As Clark and Kilverstein (Block, 2005) have written: '… we cannot make sense of the image of free-floating experiences, of little isolated islets of experience that are not even potentially available as fodder for a creatures' rational choices and considered actions'. Similarly, returning to the case of pain, it might be argued that it is the *essence* of pain that we strive to escape it — pain which is isolated from every means of response, and from the system which plots responses, just makes no sense.

Although this objection is strong, it is not immediately overwhelming. It would be if our ordinary concept of consciousness were so closely tied to the possibility of issuing a report — to another or to oneself — that unreportable consciousness is ruled out of consideration by logic alone. We can, of course, under ordinary circumstances, comment upon and report the contents of consciousness. But the claim that it is a logical condition of being conscious that the

contents of consciousness must be informing the 'enabled sweep of deliberate action and choices available to a reasoning subject' is open to question — perhaps the most difficult question raised so far.

Let me summarise the range of objections to the idea of unreportable experience. First it would have no function: this may be so, but is not a conclusive argument against its existence. Lots of things happen in our bodies which lack function. Second if it happened, it would not matter. This is debatable. It strikes many people that it might matter to the subject of experience at the time, and it would certainly matter in the sense that it would affect our understanding of what goes on in the universe. Third, if it can happen, it looks as if we will have difficulty in defining the range of conscious systems: but this is a familiar difficulty. Fourth, and most importantly, the idea relies on a concept that has lost its bearings and needs to be set back on track: the natural retort to this potentially powerful objection is that the idea of unreportable consciousness is a natural extension of our ordinary use of the concept of consciousness.

So much for the objections to the idea, and some responses. If, just for the sake of argument, we assume that the idea of unreportable consciousness is plausible, what follows?

The first consequence is that the science of consciousness is subject to an unmysterious constraint: it must rely on reports and indications of awareness which do not necessarily accompany the neural processes responsible for consciousness itself. In some cases it may be extremely difficult, even impossible, to decide whether a neural process is or is not associated with awareness. Although there is no necessary entailment, this epistemic limitation may flow from a more fundamental one — that the true target of the science of consciousness, awareness itself, is unobservable, as our everyday intuitions about consciousness suggest. These intuitions may well mislead us, but it is worth trying to spell them out.

We tend to regard awareness is a deeply private matter, inaccessible to observation by third parties (Zeman, 2005). On this intuitive view, awareness casts an 'inner light' on a private performance: in a patient just regaining awareness we imagine the light casting a faltering glimmer, which grows steadier and stronger as a richer awareness returns. We sometimes imagine a similar process of illumination at the phylogenetic dawning of awareness, when animals with simple nervous systems first became conscious. We wonder whether a similar light might one day come to shine in artificial brains. But, bright or dim, the light is either on or off: awareness is present or absent — and only the subject of awareness knows for sure. The light of awareness is invisible to all but its possessor.

If so the science of consciousness must reconcile itself to studying its object at one remove from the phenomenon itself. This is an everyday requirement in some areas of science: cosmologists build models of the first few seconds of the universe which they have no prospect of observing. Particle physicists famously work on a scale which defies direct observation in practice and principle. In the case of consciousness science it would follow that the best we can hope for is a comprehensive stock of correlations between the neural activity and behaviour that we can observe and the experiences that we cannot, indexed by reports.

Secondly the idea subverts some suppositions in consciousness science. It undermines the assumption, made by Crick and Koch (1995), that only brain regions with direct connections to the frontal lobes can mediate awareness, by underlining the distinction between the occurrence and the reporting of awareness. It raises the possibility that theories of consciousness which emphasise the importance of modular integration may to some extent be built on an artefact of observation, targeting the mechanisms of report and action rather than those of consciousness. Finally, it highlights the tricky question that lurks in the background of consciousness science: *what* do we think we are studying and seeking to explain?

Conclusion

This paper contrasts two ways of thinking about consciousness. They mirror the tension between objective and subjective characterisations of consciousness. One, currently popular in neuroscience,

emphasises the complexity of the brain, and the importance of modular integration, especially the type of modular integration which allows self-report, in the genesis of awareness. The strong version of this thesis regards self-report as the step which *endows* otherwise unconscious, modular, brain activity with consciousness — the step which creates consciousness. On this view, the study of self-report takes us to the heart of consciousness. The alternative view, which stems partly from clinical neurology, partly from our everyday conception of consciousness, emphasises the resilience of awareness in the face of damage to the brain. It raises the possibility that some types of brain activity might give rise to unreportable awareness and reminds us that, on our intuitive conception of consciousness, the target of study in consciousness science is unobservable. Resolving this tension is likely to require conceptual advances in both neuroscience and the philosophy of mind.

Acknowledgement

I am very grateful to Ned Block for helpful comments on this paper.

References

Baars, B. J. (2002). The conscious access hypothesis: Origins and recent evidence. *Trends in Cognitive Sciences*, *6*, 47–52.

Block, N. (2005). Two neural correlates of consciousness. *Trends in Cognitive Sciences*, *9*(2), 46–52.

Block, N. (2007). Consciousness, accessibility and the mesh between psychology and neuroscience. *Behavioural and Brain Sciences*, *30*, 481–548.

Chalmers, D. J. (1996). *The conscious mind*. New York: Oxford University Press.

Crick, F., & Koch, C. (1995). Are we aware of neural activity in primary visual cortex? *Nature*, *375*(6527), 121–123.

Damasio, A. (2000). *The feeling of what happens*. London: Vintage.

Dehaene, S., & Naccache, L. (2003). Towards a cognitive neuroscience of consciousness: Basic evidence and workspace framework. *Cognition*, *79*, 1–37.

Laureys, S., Faymonville, M. E., Luxen, A., Lamy, M., Franck, G., & Maquet, P. (2000). Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet*, *355*(9217), 1790–1791.

Laureys, S., & Tononi, G. (2009). The neurology of consciousness: An overview. In *The neurology of consciousness* (pp. 375–412). Amsterdam: Elsevier.

LeDoux, J. (1998). *The emotional brain*. London: Phoenix.

Moutoussis, K., & Zeki, S. (2002). The relationship between cortical activation and perception investigated with invisible stimuli. *Proceedings of the National Academy of Sciences, USA*, *99*, 9527–9532.

Noe, A. (2004). *Action in perception*. Cambridge, MA: MIT Press.

O'Regan, J. K., & Noe, A. (2001). A sensorimotor account of vision and visual consciousness. *Behavioral and Brain Sciences*, *24*(5), 939–973.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*(5792), 1402.

Rosenthal, D. M. (1986). Two concepts of consciousness. *Philosophical Studies*, *49*, 329–359.

Sahraie, A., Weiskrantz, L., Barbur, J. L., Simmons, A., Williams, S. C., & Brammer, M. J. (1997). Pattern of neuronal activity associated with conscious and unconscious processing of visual signals. *Proceedings of the National Academy of Sciences, USA*, *94*(17), 9406–9411.

Singer, W. (2009). Consciousness and neural synchronisation. In: *The neurology of consciousness* (pp. 43–52). Amsterdam: Elsevier.

Weiskrantz, L. (1997). *Consciousness lost and found*. Oxford: Oxford University Press.

Zeman, A. (2005). What in the world is consciousness? *Progress in Brain Research*, *150*, 1–10.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 2

How can we know if patients in coma, vegetative state or minimally conscious state are conscious?

Morten Overgaard*

CNRU, Hammel Neurorehabilitation and Research Unit, Aarhus University Hospital, Hammel, Denmark

Abstract: This paper examines the claim that patients in coma, vegetative state and minimally conscious state may in fact be conscious. The topic is of great importance for a number of reasons — not least ethical. As soon as we know a given creature has any experiences at all, our ethical attitude towards it changes completely. A number of recent experiments looking for signs of intact or partially intact cognitive processing in the various stages of decreased level of consciousness are reviewed. Whether or not vegetative or coma patients are in fact conscious is an empirical issue that we yet do not know how to resolve. However, the simple fact that this is an unresolved empirical issue implies that the standard behavioural assessment is not sufficient to decide what it is like to be these patients. In other words, different and more sophisticated methods are necessary. From a theoretical position, the paper moves on to discuss differences in validity between reports (e.g. verbal) and signals (e.g. brain activations) in the study of consciousness, and whether results from experiments on the contents of consciousness may be of any use in the study of levels of consciousness. Finally, an integrated approach is suggested, which does not separate research in level and content as clearly as in current practice, and which may show a path to improved paradigms to determine whether patients in coma or vegetative state are conscious.

Keywords: coma; vegetative state; minimally conscious state; consciousness; experience; neural correlates of consciousness

Introduction

This paper will consider the seemingly controversial hypothesis that patients in coma, vegetative or minimally conscious state (MCS) may in fact have conscious experiences. It is a typical opinion in current neuroscience that the absence of reports or clear neurophysiological markers of consciousness in these patient groups place the burden of proof lies with the claim that there is any conscious experience left in coma or the vegetative state (VS) (Giacino and Smart, 2007). However, since we have no certain neurophysiological or behavioural markers for the absence of consciousness either, one could — at least for the sake of the argument — take on the opposite stance without violating any logical imperatives; that is there is no claim necessitated by the reason that when a given individual cannot behave in certain ways (or behave at all), then that individual can have no subjective experiences.

The question is of great importance for a number of reasons. For instance, our ethical

*Corresponding author.
Tel.: +45 2078 3154;
E-mail: mortover@rm.dk

DOI: 10.1016/S0079-6123(09)17702-6

considerations are specifically directed at conscious beings. That is, we have no ethical problems cutting wood or kicking a football as we are convinced that these objects have no experience of pain. As soon as we know a given creature has any experiences at all, our ethical attitude towards it changes completely.

The patients

Three distinct ''stages'' of decreased consciousness have been described — coma, the VS and the MCS. The distinction between the stages is based on behavioural criteria. VS patients are generally thought to differ from comatose patients as coma patients can be aroused, yet they are believed to be equally unconscious (Schiff, 2005). MCS patients, however, are believed to have ''some'' or ''fluctuating'' consciousness. Other patients with severe brain injury who, however, are not in MCS, are typically believed to be ''more conscious'', yet in some cases ''less conscious'' than healthy people. Consciousness is thus considered gradual and not necessarily stable — and measurable by different aspects of overt behaviour.

Coma is generally believed to be a state of constant, continuous unconsciousness in which the eyes remain closed and the patient cannot be aroused. The eyes remain closed, there seems to be a total absence of voluntary behaviour or any kind of purposeful motor activity or expressive language ability, and no sleep/wake cycles can be identified. There seems to be a total absence of voluntary behaviour or any kind of purposeful motor activity or expressive language ability. The comatose state almost always resolves within 2–4 weeks, leading either to the patient's death or an improved level of consciousness.

The appearance of spontaneous eye opening marks the onset of VS. In VS, eyes are open but there is no evidence of sustained or reproducible purposeful behaviour, responses to sensory stimuli and no evidence of language comprehension. The term persistent vegetative state (PVS) refers to an ongoing VS lasting at least 1 month from the time of onset. When VS persists for one year after traumatic brain injury or three months following other types of brain injury, it is generally considered highly unlikely that the individual ever recovers there, seemingly, lost consciousness. Most research on patients with a reduced level of consciousness rests on the assumption that many of these patients, and certainly all of those in coma and VS, are fully unconscious. One central example is Laureys et al. (2000, see also Laureys, 1999) where brain activity recorded from a patient in VS was contrasted with that from healthy controls and, subsequently, with his own brain activity post-recovery. Analysis of cortico-subcortical coupling showed that, in contrast to when the patient was in VS, both healthy controls and the patient on recovery had a specific pattern of cortico-thalamic activity. This is in turn used to suggest that this pattern of coupling is part of the neural correlate of consciousness — given, of course, that the VS patients are in fact fully unconscious.

MCS is distinguished from VS by the presence of one or several signs of knowledge about self or the environment; for example the following of simple commands, recognizable verbal or gestural yes/no-responses (accurate or not) or movements that seem to be beyond mere reflexes. MCS typically occurs as a progression from VS, but may also be observed during the course of progressive decline in neurodegenerative diseases. Although MCS may involve reactions to emotional stimuli or reaching toward objects placed in the immediate visual field, the general assumption in neurological wards appears to be that these patients are ''less conscious'' than are healthy subjects. The assumption is not just they have decreased cognitive functions or, due to their impairments, are conscious of fewer things, but their consciousness itself is somehow diminished. Although one should think that such a claim should be supported by literature discussing what it is like to be in MCS (or, for that matter, in VS), this is extremely rare (see however Laureys and Boly, 2007). Instead, MCS is discussed in terms of behavioural and/or neurological signs only. Emergence from MCS is signalled by the recovery of some kind of meaningful interaction with the environment affording the assessment of higher cognitive functions.

Such criteria for diagnosing hypothesised levels of consciousness do not stand without criticism. Taylor et al. (2007) have suggested that the requirements for reliable communication and functional object use confuse central aspects of the posttraumatic amnesia syndrome (PTA) with MCS. The loss of executive control during PTA may cause communicative difficulties so that an ''actual'' emergence from MCS goes unnoticed. But although the clinical criteria for establishing these supposedly distinguishable levels of consciousness are quite debated (see also Giacino and Smart, 2007), the robustness of the levels themselves, curiously enough, are uncritically accepted from research papers to neurological wards. This is particularly interesting as, in the absence of a verifiable or merely consensual operationalisation of consciousness, clinical assessment currently relies on the strictly pragmatic principle that people can only be considered to be unequivocally conscious if they can report that this is indeed the case. Thus, the discrimination between VS and MCS, and, in effect, the discrimination between states of conscious and unconscious being, depends upon such communication. Quite obviously, this approach is seriously flawed and represents a central, if not the crucial, problem in the study of decreased levels of consciousness.

Signs of consciousness?

A number of recent experiments have looked for signs of intact or partially intact cognitive processing in the various stages of decreased level of consciousness in the absence of any behavioural signals or communication. This has been done by looking for neural signals, such as event-related potentials (ERPs) or patterns of functional brain activation, typically associated with conscious cognitive processing in healthy individuals.

Some ERP studies have focussed on the P300 response, a positive wave elicited 300 ms after a stimulus, which is usually seen when a subject detects a ''surprising'' (unpredicted) stimulus in a train of other stimuli, for example in an ''oddball paradigm'' (Sutton et al., 1965). One sub-component of P300 is the P3b amplitude, which seems sensitive to the importance of the stimulus to the subject — for example the subject's own name (Perrin et al., 1999). Thus, P300 is typically associated with attentional discrimination, anticipation and emotional states. Signorino et al. (1997) used, in one experimental condition, a conventional auditory oddball paradigm and, in another, a paradigm in which the tones were coupled to emotional verbal stimuli. P300 responses were obtained in 36–38% of comatose patients in the first condition, and in 52–56% in the second. Other experiments have confirmed that emotional stimuli evoke a larger P300 than do meaningless stimuli (e.g. Lew et al., 1999), suggesting that even comatose patients process auditory stimuli to a semantic level. One study (Perrin et al., 2006) found that the patient's own name elicited stronger P3 responses in VS patients than do other names, and, interestingly, found no significant differences between VS and MCS patients in this regard. Obviously, this is of specific interest given the common conception that the difference between these patient groups marks the difference between being conscious and unconscious.

Other ERP studies have focused on the N400 potential. The N400 seems less related to focused attention and more related to verbal stimuli discordant to preceding verbal stimuli (Vanhaudenhuyse et al., 2008). Schoenle and Witzke (2004) presented different patient groups with semantically congruent and incongruent sentences while recording ERP and found an N400 response to incongruent words in 12% of the vegetative population, 77% in a population named ''near-VS'' and in 90% of a population with ''severe brain damage'' (probably MCS).

A number of brain imaging studies in VS patients have, in addition, shown that areas of the brain increase their metabolic activity in response to sensory stimuli — for example the auditory processing areas of such patients might be activated in response to hearing a familiar voice such as their name (Perrin et al., 2006).

Owen et al. (2006) used fMRI to study visual imagery in a patient fulfilling all the behavioural criteria for a diagnosis of VS. This 23-year-old

woman sustained a severe brain injury in a traffic accident. After an initial comatose state, she opened her eyes and demonstrated sleep–wake cycles. However, even during the waking periods, she was unresponsive to stimuli and did not manifest spontaneous intentional behaviour. In an experiment, the patient was asked to perform two mental imagery tasks — either to imagine visiting the rooms in her home or to imagine that she was playing tennis. Patterns of brain activation observed using fMRI during each task were indistinguishable from those recorded from a group of conscious control subjects.

It seems impossible to explain these results without accepting that this patient retained the ability to comprehend verbal instructions, to remember them from the time they were given (before scanning began) to the appropriate time during the scan itself, and to act on those instructions, thereby wilfully producing specific mental, or at least neural, states. It may be tempting to dismiss this as a simple case of error in the behavioural assessment of her as vegetative, but examination of the exhaustive case report reveals this as unlikely. Indeed, at testing, the patient exhibited no evidence of sustained or reproducible purposeful behaviours consistent with the criteria defining the MCS. The diagnosis of VS was thus entirely appropriate, given current criteria.

One way to oppose the view that this patient and, as a logical consequence, perhaps all other patients diagnosed as vegetative are in fact conscious, would be to argue that the neural activations only represent unconscious cognitive processes involved in the mental task. The fact that the healthy subjects had vivid experiences of their visual imageries would accordingly rely on other brain processes as those observed to be shared with the vegetative patient.

Whether or not this patient, or all patients in VS, is in fact conscious is an empirical issue that we yet do not know how to resolve. However, the simple fact that this is an unresolved empirical issue implies that the standard behavioural assessment is not sufficient to decide what it is like to be in VS. In other words, different and more sophisticated methods may be necessary.

Conscious states and conscious levels

There seem to be persuasive arguments indicating that patients with impaired consciousness are not merely able to passively receive external stimuli, but that they are able to perform distinctly different kinds of cognitive processing. Current debates about conscious and unconscious cognitive processing are centred on studies of conscious content rather than levels of consciousness. Even though this distinction is widespread, both in definitions and in actual research, it may not be fruitful as discussed in section below. For this reason, I will briefly summarise relevant discussions from the content approach to aid the ongoing debate about levels.

Studies of conscious content seek to identify those specific factors that make a subject conscious of something rather than something else (e.g. the taste of coffee or the visual impression of a tree). Typically, this is done by comparing brain states in conditions where a specific conscious content is present to conditions where it is absent. Studies of levels of consciousness also look for enabling factors (using the terminology of Koch, 2004) making it possible to be conscious at all. Here, differences between different states such as being awake, being in dreamless sleep or in a coma are typically compared.

The research strategy currently dominant in consciousness studies per se is the identification of neural correlates of consciousness (NCC). A term coined by David Chalmers (2000), the NCC for content consciousness is those minimally sufficient neural conditions for a specific (mostly representational) content. The basic methodology was set out early by Baars (1988) as a contrastive analysis between being conscious (i.e. having specific conscious content) and unconscious (i.e. having this content in an unconscious form), thus either identifying (a) equal levels of performance, accompanied by different degrees of awareness (e.g. blindsight), (b) changes in performance unaccompanied by changes in awareness (e.g. implicit learning) and (c) changes in awareness despite stimulation remaining constant (e.g. binocular rivalry). A classic example of subliminal abilities is the phenomenon of ''blindsight''.

Blindsight refers to the observations that at least some patients with lesions to the primary visual cortex resulting in blindness have nevertheless preserved such visual functions such as perception of movement direction (Weiskrantz et al., 1995), target detection (Pöppel et al., 1973) and spatial summation (Leh et al., 2006) even though they report to be fully blind in that part of the visual field corresponding to the location of the injury. As such, blindsight might be considered ''less interesting'' than subliminal perception in healthy subjects, as the phenomenon has so far only been studied in a few patients. However, in those patients, blindsight has proven so consistent and persuasive as an example of an almost unbelievable discrepancy between subjective report and behavioural reactions (such as the ability to discriminate) that many researchers see it as the primary source of evidence for subliminal processing. In 1986, however, Weiskrantz and co-workers found evidence which argues that blindsight should be subdivided into two ''types'' — type 1 and type 2. Type 1 blindsight patients are characterised, as above described, that is by preserved visual functions despite verbal reports of having no visual experiences. Type 2 blindsight patients report seeing after-images or ''shadows'' when presented with stimuli.

Ramsøy and Overgaard (2004) developed a new approach to introspective reports of conscious and unconscious processes. Subjects were here asked to create their own categories for subjective reports during long training sessions. They were asked what they were shown and how they experienced stimuli in terms of clarity. Here, stimuli were simple visual figures (triangles, circles or squares) presented in one of three possible colours (blue, green or red). In the study, subjects conformed to a four-point scale categorised as ''not seen'', ''weak glimpse'' (meaning ''something was there but I had no idea what it was''), ''almost clear image'' (meaning ''I think I know what was shown'') and ''clear image''. When subjects tried to use more than four categories in the scale, they found it confusing and quickly abandoned the extra categories. In the experiment, after the category-generating training process, subjects found the categories easy to use, and in free reports, they explained that the categories seemed very straightforward. Ramsøy and Overgaard showed that in an experimental design where one should expect to find subliminal perception, there was in fact none. In a later study using this scale (named Perceptual Awareness Scale, or PAS), two different report methods were compared directly to investigate subliminal perception (Overgaard et al., 2006). Again, it was found that PAS fully eliminated subliminal perception, which was otherwise heavily present using binary reports. Even more problematic for the concept of unconscious perception is a recent study by Overgaard et al. (2008) presenting a blindsight patient, GR, who exhibits the subliminal capabilities associated with blindsight using a dichotomous report. However, when the patient was asked to report using PAS, there was a significant correlation between correctness and consciousness in her ''blind'' field, just as in her ''healthy'' field. Essentially, these experiments indicate that subliminal perception at least in some cases is a methodological artefact based on flawed methods to study conscious states.

As argued by Overgaard and Timmermans (in press), subliminal perception may not be a real phenomenon at all. Instead, subliminal perception may be an artefact of (a) the result of objective measures that can be reduced to other behavioural measures and the a priori assumption of congruence between sensitivity and consciousness, and (b) crude subjective measures (e.g. dichotomous or arbitrary 10-point scales) which claim to measure subjectively conscious experiences, but that presumably do not succeed. The notion of ''unconscious cognitive processing'' has had a turbulent history in psychology, and it is, to say the least, an open question how to interpret the current status of concepts like ''unconscious'' and ''subliminal''.

Returning to the question of levels of consciousness, two things are suggested by this line of argument. First, the research discussed above indicates that we currently have no certain knowledge that totally unconscious cognitive processing exists — or, at least, how common unconscious processing is. This, in and of itself, casts further doubts on the interpretation of the

Owen et al. (2006) experiment that the vegetative patient had an ''unconscious version'' of the same cognitive process as the healthy subjects did. Secondly, it becomes evident that current methods used to study conscious content are intimately linked to introspective reports: How we ask subjects what they experience is crucial. Although it has been argued that there can be objective measures of consciousness (Persaud et al., 2007) that do not need to involve subjective reports at all, these suggestions are all methodologically flawed (Overgaard and Timmermans, in press). Arguing, say, that some objective method lends a ''more direct'' insight into the contents of consciousness than does a subjective report rests upon circularity (Overgaard, 2006). That is, associating a certain objective measure such as the ability to perform correct identifications of stimuli with consciousness is only possible based on empirical evidence, that is a correlation between this performance and the relevant conscious state. Since the conscious state cannot in itself be observed from the outside, the use of a subjective report about the relevant state seems the only possible methodology. Accordingly, no other kind of response can be a more reliable indication of a given conscious state than the subjective report itself. The objective performance correlated with the subjective report, given this correlation is perfect, is thus exactly as valid a measure of consciousness as the report itself.

Reports and signals

As argued above, the study of consciousness from a methodological point of view is a study of reports. Obviously, not all experiments are designed in such a way that it is practical — or possible — to use verbal reports with the explicit content ''I am now conscious of…''. In many cognitive psychology experiments, subjects are asked to press a button or give some sort of behavioural gesture to report. In other situations, we may have to suffice with bodily or behavioural signals which may be interpreted as signs of consciousness, such as increased arousal, reflexes or neural activations. To make correct use of these different types of data, however, we need a closer look at their respective validity.

There is, initially, an important distinction between reports and signals. A report is an intended communication from a conscious subject. That is, it involves a subject with metacognitive insight in their own conscious content and the intended, self-controlled giving of information about this content. A signal lacks this intention and is outside the control of the subject. A signal may be any kind of information obtained from the subject that previous research has indicated can be correlated with consciousness — typically, this will be data from technological measurement techniques such as brain scanners, EEG, eye tracking, galvanic skin response, or, more rarely, the observation of uncontrolled behaviours such as reflexes.

As already mentioned, consciousness is subjective. That is, we may have insight into the contents of our own consciousness, but no existing method lends such insight into the contents of the consciousness of other individuals. One may in fact argue that this will always be the case, in spite of any possible technological achievement, as any kind of representation of the experience of other people will always be perceived or looked at from one's own point of view, thus missing the very essence of what it is like to be this other subject. For this reason, reports are indirect evidence of a given conscious content. Nevertheless, they get us as close as we may come. Signals are even more indirect and much more dubious. First of all, even if a perfect correlation is established between a specific signal and a report, it is not possible to test the correlation in all possible situations. Thus, it is always an open possibility that the signal in some cases may fail as an indicator of consciousness. Following this reasoning, neither signals nor reports may count as measures of consciousness, but as indicators only.

When studying non-communicating patients, we only have signals. As hopefully is made clear from the discussion above, state of the art research and debate makes this a highly difficult yet not necessarily impossible situation. Although we at the present do not have a finished research paradigm to handle this situation, some pitfalls and possibilities can be identified.

Examining the central Owen et al. study, their findings are of no less interest in the light of the report–signal distinction, keeping in mind that the patient, as well as the healthy subjects, participated in cognitive tasks demanding voluntary control and insight into the contents of one's own consciousness. That is, in the experiment, the patient and the healthy subjects were both asked to sustain their visual imagery for approximately 30 s and to stop when requested to rest. Although this is far from any proof, it gives us reason to speculate that the patient could have reported the contents of her conscious state, were she physically able to, as insight and control are the essential features distinguishing reports from signals.

The complexity of these issues is obviously difficult to handle — even for researchers specialising in these matters. Thus, there are conflations even in the foundational issues of how to interpret neural activations obtained from the patients. In the Owen et al. study, brain signals are used to discuss whether VS patients are conscious or not. This stands in clear contrast to the approach used in Laureys et al. (2000), where cortico-thalamic activations were suggested as parts of the NCC because VS patients are not conscious: Is the answer to the first question positive, the Laureys et al. approach is invalid. Is the Laureys et al. approach somehow shown valid, the Owen et al. study can no longer be interpreted to suggest that VS patients are conscious. At best, we may argue that Owen et al. have examined a very special and unique case story with no general implications.

As we have no prima facie reasons, nor any empirical evidence, to conclude that vegetative patients are not conscious, we should however at present avoid experiments accepting this as a background assumption. For this reason, at least until we have found a way to settle the issue whether patients in arguably reduced states of consciousness are in fact conscious, the whole contrastive approach to finding neural correlates to levels of consciousness is problematic — at least insofar as patients are involved in the research. For this reason, the approach of Owen et al. seems of exceptional value.

Future directions

Jakob Hohwy (2009) has recently argued that a specific conflation exists in those research paradigms looking for neural correlates of conscious contents and those looking for neural correlates of levels of consciousness. The content approach assumes that subjects are already conscious. That is, while the research goal seems to be finding the neural correlate of consciousness per se, experiments actually look for the neural correlate of the selection of specific mental content for conscious experience, rather than it not being selected, and, further, implied that the subject or animal under investigation is already in an overall conscious state. The approach assumes there are both conscious and unconscious contents in an otherwise conscious subject, and that something (in the brain) differentiates between the selection of content for consciousness. While these are questions that research may actually answer, the approach does not inform us what may be the neural correlates of being conscious at all — as this is already assumed and thus not a relevant variable in experiments.

With the other approach, looking specifically for conscious levels without studying conscious content, the idea is to intervene on a creature's overall conscious state in conditions where there is no conscious content at all. For instance, the philosopher John Searle (2004) insists in the primacy of consciousness. However, very few would agree with Searle that this viable reasoning is anything but theoretical speculation.

Justifiably, Hohwy suggests a combination of the two kinds of approaches, yet gives no exact suggestions how this could be done in real life. One approach that deserves special interest in this regard is the recent advances in neuroimaging attempting to decode a person's conscious experience based only on non-invasive measurements of their brain activity. Recent work (Haynes and Rees, 2006) demonstrates that pattern-based decoding of BOLD contrast fMRI signals acquired at relatively low spatial resolution can successfully predict the perception of low-level perceptual features. For example, the orientation, direction of motion and even perceived colour of

a visual stimulus presented to an individual can be predicted by decoding spatially distributed patterns of signals from local regions of the early visual cortex. Strikingly, despite the relatively low spatial resolution of conventional fMRI, the decoding of image orientation is possible with high accuracy and even from brief measurements of primary visual cortex (V1) activity.

Perceptual fluctuations during binocular rivalry can be dynamically decoded from fMRI signals in highly specific regions of the early visual cortex. This was achieved by training a pattern classifier to distinguish between the distributed fMRI response patterns associated with the dominance of each monocular percept. The classifier was then applied to an independent test dataset to attempt dynamic prediction of any perceptual fluctuations. Dynamic prediction of the currently dominant percept during rivalry was achieved with high temporal precision.

This approach holds out the promise of achieving important improvements in patients with claimed reduced levels of consciousness. Current experiments using ERP or fMRI, as reviewed above, investigate cognitive processes that may exist consciously as well as unconsciously. Thus, one may raise the criticism that we learn nothing of the patients' possible conscious contents with these approaches — we may in fact be studying cognitive processes that occur fully unconsciously. However, using a ''decoding approach'', one may decode neural patterns specific for conscious content (e.g. in a binocular rivalry paradigm) as verbally verified by healthy subjects able to report. If a strong report–signal correlation can be found, the experiment can be applied to comatose or VS patients looking for similar activations. Although such an approach, even with a 100% match between patients and controls, cannot be said to finally prove conscious experience in coma or VS, it will utilise the reflections above to get us as far as it has here been claimed possible.

Acknowledgment

Morten Overgaard was supported by The MindBridge project, co-funded by the European Commission under the Sixth Framework Programme, Contract No. 043457.

References

Baars, B. J. (1988). *A cognitive theory of consciousness*. Cambridge, NY: Cambridge University Press.

Chalmers, D. J. (2000). What is a neural correlate of consciousness? In T. Metzinger (Ed.), *Neural correlates of consciousness*. Cambridge, MA: MIT Press.

Giacino, J. T., & Smart, C. M. (2007). Recent advances in behavioral assessment of individuals with disorders of consciousness. *Current Opinion in Neurology*, *20*, 614–619.

Haynes, J., & Rees, G. (2006). Decoding mental states from brain activity in humans. *Nature Reviews Neuroscience*, *7*(7), 523–534.

Hohwy, J. (2009). The neural correlates of consciousness: New experimental approaches needed? *Consciousness and Cognition*, *18*(2), 428–438.

Koch, C. (2004). *The quest for consciousness: A neurobiological approach*. Englewood, CO: Robert and Company Publishers.

Laureys, S. (1999). Impaired effective cortical connectivity in vegetative state: Preliminary investigation using PET. *Neuroimage*, *9*, 377–382.

Laureys, S., & Boly, M. (2007). What is it like to be vegetative or minimally conscious? *Current Opinion in Neurology*, *20*, 609–613.

Laureys, S., Faymonville, M. E., Luxen, A., Lamy, M., Franck, G., & Maquet, P. (2000). Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet*, *355*, 1790–1791.

Leh, S., Johansen-Berg, H., & Ptito, A. (2006). Unconscious vision: New insights into the neuronal correlate of blindsight using diffusion tractography. *Brain*, *129*(7), 1822–1832.

Lew, H. L., Slimp, J., Price, R., Massagli, T. L., & Robinson, L. R. (1999). Comparison of speech-evoked vs. tone-evoked P300 response: Implications for predicting outcomes in patients with traumatic brain injury. *American Journal of Physical Medicine and Rehabilitation*, *78*(4), 367–371.

Overgaard, M. (2006). Introspection in science. *Consciousness and Cognition*, *15*, 629–633.

Overgaard, M., Fehl, K., Mouridsen, K., & Cleeremans, A. (2008). Conscious vision in blindsight revealed by subjective measures. *PLoS ONE*, *3*(8), 1–4.

Overgaard, M., Rote, J., Mouridsen, K., & Ramsøy, T. Z. (2006). Is conscious perception gradual or dichotomous? A comparison of report methodologies during a visual task. *Consciousness and Cognition*, *15*, 700–708.

Overgaard, M., & Timmermans, B. (in press). How unconscious is subliminal perception? In S. Gallagher & D. Schmicking (Eds.), *Handbook of phenomenology and the cognitive sciences*. Springer, London.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*(5792), 1402.

Perrin, F., Garcia-Larrea, L., Mauguiere, F., & Bastuji, H. A. (1999). A differential brain response to the subject's own name persists during sleep. *Clinical Neurophysiology*, *110*(12), 2153–2164.

Perrin, F., Schnakers, B. S., Schabus, M., Degueldre, C., Goldman, S., Brédart, S., et al. (2006). Brain response to one's own name in vegetative state, minimally conscious state and locked-in syndrome. *Archives of Neurology*, *63*, 562–569.

Persaud, N., Mcleod, P., & Cowey, A. (2007). Post-decision wagering objectively measures awareness. *Nature Neuroscience*, *10*(2), 257–261.

Pöppel, E., Held, R., & Frost, D. (1973). Residual visual function after brain wounds involving the central visual pathways in man. *Nature*, *243*, 295–296.

Ramsøy, T. Z., & Overgaard, M. (2004). *Introspection and subliminal perception, phenomenology and the cognitive sciences*, *3*(1), 1–23.

Schiff, N. D. (2005). Modeling the minimally conscious state: Measurements of brain function and therapeutic possibilities. *Progress in Brain Research*, *150*, 473–493.

Schoenle, P. W., & Witzke, W. (2004). How vegetative is the vegetative state? *Neurorehabilitation*, *19*, 329–334.

Searle, J. R. (2004). *Mind — A brief introduction*. Oxford: Oxford University Press.

Signorino, M., D'Acunto, S., Cercaci, S., Pietropaoli, P., & Angeleri, F. (1997). The P300 in traumatic coma: Conditioning of the odd-ball paradigm. *Journal of Psychophysiology*, *11*, 59–70.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. *Science*, *150*(700), 1187–1188.

Taylor, C., Aird, V., Tate, R., & Lammi, M. (2007). Sequence of recovery during the course of emergence from the minimally conscious state. *Archives of Physical Medicine and Rehabilitation*, *88*, 521–525.

Vanhaudenhuyse, A., Laureys, S., & Perrin, F. (2008). Cognitive event-related potentials in comatose and post-comatose states. *Neurocritical Care*, *8*, 262–270.

Weiskrantz, L. (1986). *Blindsight — A case study and implications*. Oxford: Oxford University Press.

Weiskrantz, L., Barbur, J. L., & Sahraie, A. (1995). Parameters affecting conscious versus unconscious visual discrimination with damage to the visual cortex (V1). *Proceedings of the National Academy of Sciences, USA*, *92*, 6122–6126.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 3

Contemporary controversies in the definition of death

James L. Bernat*

Neurology Department, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA

Abstract: Human death is a unitary phenomenon that physicians can determine in two ways: (1) showing the irreversible cessation of all brain clinical functions; or (2) showing the permanent cessation of circulatory and respiratory functions. Over the last 40 years the determination of human death using neurological tests (''brain death'') has become an accepted practice throughout the world but has remained controversial within academic circles. Brain death has a rigorous biophilosophical basis by defining death as the irreversible loss of the critical functions of the organism as a whole. The criterion best fulfilling this definition is the irreversible cessation of all clinical functions of the brain. Competing definitions, such as those within the higher brain, brain stem, and circulation formulations, all have deficiencies in theory or practice. Among physicians, the area of greatest controversy in death determination now is the use of circulatory–respiratory tests, particularly as applied to organ donation after circulatory death. Circulatory–respiratory tests are valid only because they produce destruction of the whole brain, the criterion of death. Clarifying the distinction between the permanent and irreversible cessation of circulatory and respiratory functions is essential to understanding the use of these tests, and explains why death determination in organ donation after circulatory death does not violate the dead donor rule.

keywords: definition of death; criterion of death; brain death; higher brain formulation; organism as a whole; organ donation after circulatory death

Introduction

Over the last half-century, the practice of determining death using neurological tests to show the irreversible cessation of clinical brain functions (known colloquially and medically as ''brain death'') has become accepted throughout the world. Although this practice was motivated by the intuitive belief that brain-dead patients were dead and by utilitarian needs to permit withdrawal of physiological support and multi-organ donation (Giacomini, 1997), the concept of brain death later was provided a biophilosophical foundation centered on a brain-based definition and criterion of death (Bernat, 2002).

By the turn of the 21st century, a durable consensus had emerged that brain-dead patients were legally and biologically dead (Capron, 2001). This consensus has permitted physicians in the United States and Canada, most of Europe, Australia, and in a number of countries in Asia,

*Corresponding author.
Tel.: 603-650-8664; Fax: 603-650-6233;
E-mail: bernat@dartmouth.edu

DOI: 10.1016/S0079-6123(09)17703-8

Africa, and Central and South America to use brain death as a legal determination of death. Although there remain minor variations in the performance of brain death tests among different countries (Haupt and Rudolf, 1999), they have become well-accepted and standard elements of medical practice around the world (Wijdicks, 2002). Comprehensive analyses of the concept, legality, and medical practice of brain death that were conducted in 1995 by the U.S. Institute of Medicine (Youngner et al., 1999) and during the last year by the U.S. President's Council on Bioethics (2009) found no justification to alter current American laws or medical practices.

Yet, despite this formidable medical, legal, and societal consensus, brain death remains controversial. Within academic circles, it continues to provoke opposition from some philosophers and other scholars who criticize it on conceptual grounds. Tellingly, this dispute plays out only within the pages of scholarly journals, in seminar rooms of colleges, and at academic conferences, and has had no impact on prevailing medical practices. Yet, if an observer were unaware of the global practice of brain death determination and judged its acceptance based solely on the output of currently published scholarly journal articles and academic conferences, she would reach the erroneous conclusion that the prevailing practice of brain death was an illogical and anachronistic activity supported by only a small minority of the professional and lay population.

Ironically, the topic of greatest current controversy in death determination has shifted from brain death to death declaration by showing cessation of circulation and respiration. This change in focus has been stimulated by the growing practice of organ donation after circulatory death (DCD), particularly physicians' need to know the precise moment the organ donor is declared dead, to permit timely organ recovery, and to respect the ''dead donor rule.'' DCD protocols also have raised important medical and social questions over how soon physicians can declare death once circulation and respiration have ceased permanently but before they have ceased irreversibly.

In this article, I present the standard biophilosophical analysis of death and describe the controversial issues raised by critics that center largely on the adequacy of the definition and criterion of death. I show that despite some admitted conceptual shortcomings, the formulation of whole-brain death remains the best criterion for the consensual concept of human death in our contemporary era in which technology can temporarily support or replace many visceral organ functions. I conclude by discussing the current issue of death determination using tests showing permanent cessation of circulation and respiration, and explain how refinements in this more traditional death determination also have been informed by the biophilosophical analysis of the definition and criterion of death.

The definition and criterion of death

To better understand the need to analyze the definition and criterion of death before physicians can design tests to determine death, let us consider the findings in a typical case of a brain-dead patient. A 44-year-old man suffered a spontaneous massive subarachnoid hemorrhage from a ruptured cerebral aneurysm. His intracranial pressure exceeded systolic blood pressure for over 12 h. Neurological examination showed a complete absence of all clinical brain functions. He had apnea, absence of all brain stem reflexes, and complete unresponsiveness to any stimuli. He had diabetes insipidus and profound systemic hypotension requiring vasopressor drugs to maintain his blood pressure. Brain MRI showed marked cerebral edema with bilateral uncal herniation. Intracranial blood flow was entirely absent by intravenous radionuclide angiography. While on the ventilator, his heart continued to beat, blood continued to perfuse visceral organs (but not his brain), his kidneys made urine, and his gastrointestinal tract absorbed nutrients provided medically through a nasogastric tube. Was he alive or dead?

He had some findings traditionally present in dead patients: he was apneic, motionless, utterly unresponsive, had no pupillary reflexes to light,

and had no neuroendocrine homeostatic control mechanisms. But he also had some findings seen in living patients: he had heartbeat and visceral organ circulation and functioning. But a physician's determination of whether he should be considered as alive or dead cannot be made until there is conceptual agreement on what it means to be dead when technology successfully supports some of his vital subsystems. In the pretechnological era, when one system vital to life stopped (heartbeat/circulation, respiration, or brain functions) the others stopped within minutes, so we did not have to address the question of whether a person was dead when only brain functions stopped. Now, technology has created cases in which brain functions can cease irreversibly but circulation and respiration can be mechanically supported. Now, we must analyze the nature of death to resolve the ambiguity of whether the ''brain dead'' person described in this case is truly dead.

In the earliest description of brain-dead patients, Mollaret and Goulon (1959) intuited that they were actually dead, claiming that they were in a state beyond coma (*le coma dépassé*). In the classic Harvard Medical School Ad Hoc Committee report that publicized the concept and established the term ''brain death'' (1968), the authors asserted that the patients were dead and therefore represented suitable organ donors. The first rigorous conceptual arguments showing why brain-dead patients should be considered dead were not offered until a decade later (Korein, 1978; Capron and Kass, 1978) and were refined and expanded further over the next several years (Bernat, et al., 1981, 1982; President's Commission, 1981). Jurisdictions within the United States began to incorporate brain death determination into death statutes in 1970 (Curran, 1971), even before a firm philosophical foundation justified doing so.

The analyses of death that have gained the greatest acceptance by other scholars begin conceptually with the meaning of death and progress to tangible and measurable criteria. Korein (1978) and Capron and Kass (1978) pointed out that agreement on a concept of death must precede the development of tests to determine it. My colleagues, Charles Culver and Bernard Gert, and I further developed their idea of hierarchies of analysis by fashioning a rigorous sequential analysis that incorporated the paradigm, definition, criterion, and tests of death (Bernat, et al., 1981, 1982). I refined this analysis in subsequent articles that I summarize here (Bernat, 1998, 2002, 2006a). This analysis is frequently regarded as the standard defense that brain death represents human death, even among those who disagree with it (Shewmon, 2009).

The first stage of analysis is to state and defend the preconditions of the argument or ''paradigm'' of death: that set of assumptions that frame the analysis by clarifying the goal and boundaries of the analysis. Agreement on these conditions is a prerequisite for further discussion. Much of the disagreement by other scholars with this account results from failure to accept one or more of the seven conditions of the paradigm.

1. The word ''death'' is a nontechnical word that we use correctly in ordinary conversation to refer to the cessation of life of a human being. The goal in an analysis should not be to redefine ''death'' by contriving a new or different meaning but to make explicit the implicit meaning of death that we all accept in our usage of ''death'' that has been made ambiguous by advances in life-support technology.
2. Death is a biological phenomenon. We all agree that life is a biological phenomenon; thus its cessation also is fundamentally biological. Death is an immutable and objective biological fact and is not a social contrivance. The focus of analyzing the definition and criterion of death is the ontology of death and not its normative aspects.
3. We restrict the analysis to the death of higher vertebrate species for whom death is univocal. We refer to the same phenomenon of ''death'' when we say our cousin died as we do when we say our dog died.
4. ''Death'' should be applied directly and categorically only to organisms. All living

organisms must die and only living organisms can die. When we say ''a person died,'' we refer to the death of the living organism that embodied the person, not that their organism continues to live but has ceased to have the attributes of personhood.

5. A higher organism can reside in only one of two states, alive or dead: no organism can be in both states simultaneously or in neither.
6. Death is most accurately represented as an event and not a process. If there are only two mutually exclusive underlying states of an organism (alive and dead), the transition from one state to the other, at least in theory, must be sudden and discontinuous, because there is no intervening state. However, because of technical limitations, the event of death may be determinable only in retrospect. Death is conceptualized most accurately as the event separating the true biological processes of dying and bodily disintegration.
7. Death is irreversible. If the event of death were reversible it would not be death but rather incipient dying that was interrupted and reversed.

A definition of death must reflect the concept that something fundamental and essential about the organism has changed irreversibly. We do not require the cessation of function of every cell, tissue, or organ to intuit death. The life and growth of some of a formerly living person's cells in a cell culture dish does not imply that she remains alive although part of her undoubtedly does. Similarly, the functioning of a single organ outside the body, such as a donated kidney that is being mechanically perfused and oxygenated awaiting transplantation, is not indicative of life of the organism. Respiration and circulation that are supported technologically after the brain has been destroyed allow many organs to continue functioning despite the loss of the life force driving them as well as the cessation of the overall interrelatedness and unity of the body. Such a preparation of mechanically functioning but nonintegrated bodily subsystems constitutes life of part of the organism but does not represent life of the overall organism any more than does the isolated functioning of its individual cells, tissue, or organs.

An adequate definition of death is the cessation of the critical functions of the organism as a whole. The biologist Jacques Loeb (1916) explained the concept of the organism as a whole. This concept does not refer to the whole organism (the sum of its parts) but to the integrated functioning and interrelatedness of its parts that create the unity of the organism. Contemporary biophilosophers use the mechanism of emergent functions to explain this concept more precisely (Mahner and Bunge, 1997). An emergent function is a property of a whole that is not possessed by any of its component parts, and that cannot be reduced to one or more of its component parts. A function is called an emergent function because it emerges spontaneously from the sum of its parts given the condition that the necessary parts (subsystems) are in place and functioning normally. The ineffable phenomenon of human consciousness is the most exquisite example of an emergent function. The organism as a whole is the set of critical emergent functions of the organism.

The irreversible loss of the organism's critical emergent functions produces loss of the functioning of the organism as a whole and represents the death of the organism. The organism's individual subsystems that remain functioning as a result of mechanical support do not represent life of the organism because their interrelatedness, wholeness, and unity have ceased forever. The cessation of the organism as a whole is the most precise conceptualization of death in our technological era in which physicians are capable of providing visceral organ support, transplantation, and advanced critical care.

The criterion of death best satisfying this definition is the irreversible cessation of all clinical brain functions. This criterion is known as the ''whole-brain'' criterion of death because it requires cessation of all clinically measurable brain functions including those executed by the brain stem, diencephalon, thalamus, and cerebral hemispheres. The functions generated and organized within these structures are necessary and

sufficient for the critical emergent functions of the organism and thus are necessary and sufficient for the organism as a whole. Death of the organism requires their irreversible cessation.

In past analyses of the unity and interrelatedness of the subsystems of the organism, my colleagues and I stressed that functions of the whole brain provided the integration of the parts that created the whole. Subsequently, critics pointed out that the brain was not the only organ responsible for integration, and that structures such as the spinal cord contributed significantly to the organism's integration of its parts into a whole (Shewmon, 2004). In their recent report, the President's Council on Bioethics (2009) accepted the coherence of the formulation of whole brain death but concluded that Shewmon's integration criticism was justified. As a result, they proposed an alternative explanation of why brain death satisfies the definition of death as the loss of the organism as a whole. They concluded that the cessation of clinical brain functions caused ''the inability of the organism to conduct its self-preserving work.'' This conceptualization emphasized the cessation of the organism's principal functions that made it an organism. Shewmon recently analyzed the President's Council's alternative justification and found it wanting (Shewmon, 2009).

Physicians have devised tests to show that the criterion of death has been fulfilled. Two sets of tests for death reflect the two basic clinical circumstances: resuscitation or no resuscitation. If positive-pressure ventilation is not used or planned, physicians can use the permanent cessation of circulation and respiration to declare death because the brain will be destroyed by ischemic infarction within a sort time once its circulation has ceased. If positive-pressure ventilation is being used, physicians must directly measure brain functions to assess death (''brain death''). Bedside clinical and laboratory tests to determine brain death have been standardized and subjected to evidence-based analysis. Their description is clinically crucial but is beyond the scope of this article. These tests and procedures have been critically reviewed (Wijdicks, 2001; Bernat, 2009).

Alternative formulations of death

Critics of either the whole-brain criterion of death or of all brain-based concepts of death have offered alternative analyses. The earliest criticism accepted the theory of brain death but argued that criterion of death should not be cessation of all clinical functions of the entire brain but only those of the cerebral hemispheres. This argument holds that the cerebrum imparts the characteristics that distinguish humans from other species and the more primitive brain structures that are shared with other species are not relevant. Robert Veatch claimed that death should be defined uniquely for human beings as ''the irreversible loss of that which is considered to be essentially significant to the nature of man.'' He rejected the idea that death should be related to an organism's loss of the capacity to integrate bodily function'' because ''man is, after all, something more than a sophisticated computer'' (Veatch, 1975, 1993). A reasonable application of the higher brain formulation would define as dead patients who had irreversibly lost consciousness such as those in a vegetative state. Several other scholars concurred with this concept that became known as the higher brain formulation of death (Gervais, 1986).

The higher brain formulation is an inadequate construct of death because it violates the first principle of the paradigm by not attempting to make explicit the ordinary concept of death. Instead, it redefines death by declaring as dead brain-damaged patients who are universally regarded as alive. A clear example of a patient satisfying the higher brain formulation would be a patient in an irreversible vegetative state. Despite loss of awareness and many features of personhood, these patients are regarded as alive throughout the world (Bernat, 2006b). Because many people would prefer to die if they were ever in such a state, the proper place of the higher brain formulation is in determining grounds to permit cessation of life-sustaining therapy.

Another critique of the criterion of whole-brain death is the British formulation of brain stem death. Under the intellectual leadership of Christopher Pallis, the practice of brain stem death in the United Kingdom requires the cessation of

only brain stem functions (Pallis, 1995). In these cases, examiners cannot test cerebral hemispheric function and cannot use confirmatory tests showing cessation of intracranial blood flow (Kosteljanetz et al., 1988). This circumstance creates the possibility of retained awareness despite other evidence of brain stem failure (Ferbert et al., 1988). This serious flaw is uncompensated for by any unique benefit of the brain stem formulation. Yet, because most whole-brain functions can be shown to be absent when all brain stem functions are absent, the whole-brain and brain stem formulations usually yield the same results. The sole exception is the case of a primary brain stem catastrophe in which the patient could be declared dead in the brain stem formulation but not in the higher brain formulation.

Several scholars have argued that no single criterion of death can be determined because death is not a discrete event but rather is an ineluctable process within which it is arbitrary to stipulate the moment that death has occurred. Linda Emanuel (1995) made this argument and offered a scenario of a patient gradually dying over many months from progressive multi-organ failure. Although this claim appears plausible in some cases of gradual dying, it errs by confusing the state of an underlying organism with our technical ability to determine that state. Simply because we may not always be able to detect the moment the organism changes from alive to dead, or we may be able to detect the transition only in retrospect — as in a brain death determination — does not necessarily mean that the point of death does not exist or is arbitrary. Death is not a process but is the event separating the process of dying from the process of bodily disintegration.

Other scholars argue that alive and dead are not always distinctly separable states and that some organisms (such as brain-dead patients) can reside in an in-between state that is neither alive nor dead but has elements of both. Halevy and Brody (1993) made this argument employing the mathematical theory of fuzzy sets. They claimed that physical or biological phenomena do not always divide themselves neatly into sets and their complements. They asserted that the event of death is such an example and therefore it is impossible to identify a unitary criterion of death. However, this claim confuses our ability to identify an organism's biological state and the nature of that underlying state. The paradigm made clear that life and death are the only two underlying states of an organism and there can be no in-between state because the transition from one state to the other must be sudden and discontinuous. Using the terminology of fuzzy set theory, it is most accurate biologically to view alive and dead as mutually exclusive (nonoverlapping) and jointly exhaustive (no other) sets thereby permitting a unitary criterion of death.

Some scholars claim that death is not an immutable biological event but is a social contrivance that varies among societies and cultures (Miles, 1999). The most libertarian among them go so far as to claim that because death is a socially determined event, individuals in a free society should be permitted to stipulate their own criterion of death based on their personal values (Veatch, 1999). These claims err in rejecting the paradigm requirement that death (like life) is fundamentally a biological, not a social, phenomenon. We all agree that customs surrounding death and dying have important and cherished social, legal, religious, and cultural aspects, which vary among societies. But Veatch and Miles err by failing to restrict their philosophical consideration to the ontogeny of death rather than to its normative issues.

A few philosophers argue that there are two kinds of death: death of the human organism and death of the person (McMahan, 1995; Lizza, 2005). These scholars claim that they are not using ''person'' metaphorically and assert that the death of a person is separate from that of the death of the human organism embodying the person. This nonbiological dichotomy and dualism violates the paradigm requirement that death is fundamentally a biological phenomenon that refers to the demise of the human organism that embodied a person.

A small group of scholars holds that any definition of death is impossible. In a metaphysical argument, Linda Emanuel (1995) claimed ''there is no state of death … to say 'she is dead' is meaningless because 'she' is not compatible with

'dead.'" This argument exemplifies the futility of pursuing concepts to such a metaphysical depth of linguistic analysis that they lose all clinical and practical reality because everyone, including Emanuel, knows that there is a state of being dead. Winston Chiong (2005) constructed an argument based on Wittgenstein's writings on the philosophy of language to claim that defining death is impossible linguistically. Yet despite this limitation, he supported a whole-brain criterion of death, a fact indicating that, despite his inability to define death, he could still conceptualize it and measure it. Alan Shewmon and Elisabeth Shewmon (2004) argued that all attempts to formally define death are futile because death is an "ur-phenomenon" that is "… conceptually fundamental in its class; no more basic concepts exist to which it can be reduced. It can only be intuited from our experience of it…" These abstract linguistic critiques underscore the difficulty in formally defining death but do not negate the importance of the effort to make our consensual concept of death more explicit.

Alan Shewmon (1997, 1998, 2001, 2009) has championed a position to which several other scholars have subscribed, completely rejecting a brain-based concept of death in favor of one based on the cessation of systemic circulation. Shewmon, formerly one of the staunchest defenders of brain death, changed his position (Shewmon, 1997) as a result of influence of the writings of Joseph Seifert (1993), his realization that the brain was not the only integrating system in the body, and his observations on several cases of alleged brain death that troubled him (Shewmon, 1997). Shewmon noted that some unequivocally brain-dead patients, as a consequence of heroic technological virtuosity, were able to have their systemic circulation and visceral organ function continued for months, and in one remarkable case for years, (Repertinger et al., 2006), and that some brain-dead patients could gestate a fetus or grow (Shewmon, 1998). He argued that it was simply counterintuitive to any concept of death that a dead person could do any of these things (Shewmon, 2001). Shewmon concluded that a brain-dead person is profoundly disabled but that no organism is dead until its systemic circulation ceases. This position has been called the circulation formulation.

Shewmon and his followers demonstrated some of the conceptual weakness of the whole-brain formulation and offered a plausible alternative. But the circulatory formulation is unnecessarily conservative, and it fails for reasons opposite to those that weaken the higher brain formulation. The higher brain formulation provides conditions that are necessary but not sufficient for death whereas the circulation phenomenon provides conditions that are sufficient but not necessary for death. The cessation of the organism as a whole requires only that all clinical brain functions cease, not all visceral organ functions. The proper place of the circulation formulation should be not in requiring the cessation of systemic circulation but only the absence of brain circulation. When the brain is totally deprived of circulation, all of its functions cease irreversibly satisfying the criterion of death.

An early and enduring criticism of brain death was the claim that it violated religious doctrines. Although in the early days of the brain death debate, Veith et al. (1977) argued that brain death was consistent with the world's major religious belief systems, there remains an active controversy about it within a few religions. Currently, brain death is accepted uniformly by Protestant denominations, it was accepted formally by Roman Catholicism in 2000 (Furton, 2002), it is accepted by Reform and Conservative Judaism but remains the subject of a rabbinic debate within Orthodox Judaism (Rosner, 1999), and is accepted in some Islamic and Hindu countries. I have addressed this topic in greater detail elsewhere (Bernat, 2008b).

Determining death using circulatory–respiratory tests

Physicians determine death using two testing methods: (1) in the absence of respiratory support, by showing the permanent cessation of circulation and respiration; and (2) in the presence of respiratory support, by showing the irreversible cessation of clinical brain functions ("brain

death''). It is clear that the first and far more common testing method is a valid procedure to determine death only because it leads to fulfilling the criterion of death, the irreversible cessation of clinical brain functions. Within an hour of the total cessation of systemic circulation, the brain is totally destroyed from lack of circulation.

Until recently, relatively little attention has been paid to the exact procedures for determining permanent cessation of circulation and ventilation. Once heartbeat and respiration ceased and the patient had failed cardiopulmonary resuscitation (CPR) or was not a resuscitation candidate, the patient was simply declared dead. Now, however, the growing practice of DCD has required physicians to exercise greater precision in this determination (Steinbrook, 2007). As was true for brain death four decades ago, the technology of organ transplantation has forced physicians to be more precise in defining and determining death.

Protocols permitting DCD require physicians to carefully observe patients who have been removed from life-sustaining therapy for cessation of respiration and circulation, and then wait an interval of time to prove that these functions will not restart spontaneously (''auto-resuscitation'') before declaring death (Bernat et al., 2006). This ''death watch'' period varies among hospitals from 2 to 10 min and must be of sufficient duration to prevent auto-resuscitation. The elimination of possible auto-resuscitation is essential for death determination using circulatory–respiratory testing. However, because the auto-resuscitation database is comprised of relatively few patients (DeVita et al., 2000), prudent physicians require a longer interval of asystole than the longest reported interval of auto-resuscitation.

As I have argued in detail elsewhere, the issue of the moment when death is determined using circulatory–respiratory tests turns on the distinction between the irreversible cessation of circulatory and respiratory functions and their permanent cessation (Bernat, 2006c). An ''irreversible'' cessation of functions means that they *cannot* be restored using known technology. A permanent cessation of functions means that they *will not* be restored because auto-resuscitation cannot occur and CPR will not be performed. Functions that cease permanently quickly and inevitably cease irreversibly. Therefore, it is inconsequential if physicians declare death at the point they cease permanently compared to the point they cease irreversibly as long as no therapeutic intervention (such as CPR) interferes with the process. The process becomes irreversible once the brain has been completely destroyed by lack of circulation.

In ordinary medical practice, physicians declare death at the point that respiration and circulation cease permanently but before they cease irreversibly (Bernat, 2006c). A physician called to the bedside to declare death of a terminally ill, hospitalized patient who was expected to die and had a Do-Not-Resuscitate order determines only that circulation and respiration have ceased permanently. Declaration of death at this time was reasonable because the physician knew that patients dying in this circumstance did not auto-resuscitate and that CPR would not be conducted. Earlier death determination is socially desirable so physicians and families are not required to await complete brain destruction that is the hallmark of irreversibility.

Statutes of death generally require the irreversible cessation of circulation and respiration. Yet the medical practice standard of death always has been their permanent cessation. This apparent mismatch has little significance in ordinary death determination because the rapid and inevitable progression from permanent to irreversible produces no difference in outcome. This perfectly contingent relationship makes the permanent loss of function a valid surrogate indicator for the irreversible loss of function.

The asymmetry between the requirement for demonstrating irreversibility of clinical brain functions in brain death but only permanence of cessation of circulatory and respiratory function in circulatory–respiratory death may seem peculiar but is simply a consequence of the timing of each determination. Brain death determinations are conducted in retrospect to prove that an irreversible cessation of all clinical brain functions has occurred previously. Obviously, the event of death had occurred earlier but that fact could not be proved until direct neurological testing had

been performed (Lynn and Cranford, 1999). By contrast, most circulatory–respiratory death determinations are conducted in prospect: once a determination is made that circulation and respiration have ceased permanently there is inescapable proof that all brain functions will cease irreversibly in the immediate future.

The difference between a permanent and irreversible loss of circulation and respiration is inconsequential in most death determinations using circulatory–respiratory tests not in a donation circumstance. But it becomes a more consequential issue in DCD because of the question of whether the organ donation satisfies the dead donor rule (DDR). The DDR originated in the Uniform Anatomical Gift Act, a law that has been accepted in every state in the United States. The DDR is the ethical axiom of multi-organ transplantation that requires that a multi-organ donor must first be dead prior to organ donation so that the donation does not kill the donor (Robertson, 1999).

Whether DCD respects or violates the DDR is a debatable question with plausible arguments on both sides (Bernat, 2006c). The most reasonable position is that DCD death determination does not violate the DDR because it is conceptually and practically identical to physicians' death determinations using circulatory–respiratory tests in circumstances not involving organ donation. But if one held that DCD did violate the DDR, it would constitute a justified violation because by preventing the donation from killing the donor, it satisfies the spirit of the DDR. Once circulation has ceased permanently, the brain is gradually destroyed by lack of circulation causing hypoxic-ischemic neuronal destruction. The subsequent recovery of organs for transplantation has no impact whatsoever on this inevitable process so it neither causes nor accelerates the death of the donor. Therefore, DCD does not constitute a violation of the DDR and, in any event, respects the spirit of the DDR.

Future directions

Debates over the definition of death continue to occupy scholarly attention within the academy but a durable worldwide consensus has emerged among physicians and societies that brain death is biological and legal death. It therefore seems unlikely that the eloquent, impassioned, and partially correct arguments opposing brain death will gain sufficient traction to change medical practices or laws. The recent in-depth review of the arguments opposing brain death by the President's Council on Bioethics (2009) rejected them and found no justification for changing prevailing laws on or practices of brain death. Ironically, medical attention now has moved away from brain death to attempting to clarify and tighten the standards for the circulatory–respiratory tests of death.

Future efforts need to be directed toward justifying standards and encouraging uniform practices of the circulatory–respiratory tests for death. The ad hoc nature of current testing in which hospitals create their own death determination standards is not adequate. The U.S. Health Resources and Services Administration (HRSA) Division of Transplantation, the agency that provides much of the funding for experimental DCD protocols, recently convened an expert multidisciplinary panel to address optimal DCD death determination standards and to apply them to innovative DCD protocols. Their report is expected in late 2009 or early 2010.

The effort to standardize the determination of brain death is equally important (Choi et al., 2008), especially in light of the disturbing evidence of wide variability of brain death determination procedures in the United States, even among leading neurological institutions (Greer et al., 2008). A multi-society task force should be impaneled to issue uniform evidence-based standards for brain death determination in adults and children (Bernat, 2008a). These efforts to improve the uniformity of both the circulatory–respiratory and brain death determinations should be formulated on the basis of a coherent biophilosophical analysis of the definition and criterion of death.

References

Ad Hoc Committee. (1968). A definition of irreversible coma: Report of the Ad Hoc Committee of the Harvard Medical

School to examine the definition of brain death. *Journal of the American Medical Association*, *205*, 337–340.
Bernat, J. L. (1998). A defense of the whole-brain concept of death. *Hastings Center Report*, *28*(2), 14–23.
Bernat, J. L. (2002). The biophilosophical basis of whole-brain death. *Social Philosophy & Policy*, *19*(2), 324–342.
Bernat, J. L. (2006a). The whole-brain concept of death remains optimum public policy. *The Journal of Law, Medicine & Ethics*, *34*, 35–43.
Bernat, J. L. (2006b). Chronic disorders of consciousness. *Lancet*, *367*, 1181–1192.
Bernat, J. L. (2006c). Are donors after cardiac death really dead? *Journal of Clinical Ethics*, *17*, 122–132.
Bernat, J. L. (2008a). How can we achieve uniformity in brain death determinations? *Neurology*, *70*, 252–253.
Bernat, J. L. (2008b). Ethical issues in neurology. In (3rd ed., pp. 266–269). Philadelphia, PA: Lippincott, Williams & Wilkins.
Bernat, J. L. (2009). Brain death. In S. Laureys & G. Tononi (Eds.), *The neurology of consciousness: Cognitive neuroscience and neuropathology* (pp. 151–162). Amsterdam: Elsevier-Academic Press.
Bernat, J. L., Culver, C. M., & Gert, B. (1981). On the definition and criterion of death. *Annals of Internal Medicine*, *94*, 389–394.
Bernat, J. L., Culver, C. M., & Gert, B. (1982). Defining death in theory and practice. *Hastings Center Report*, *12*(1), 5–9.
Bernat, J. L., D'Alessandro, A. M., Port, F. K., Bleck, T. P., Heard, S. O., Medina, J., et al. (2006). Report of a national conference on donation after cardiac death. *American Journal of Transplantation*, *6*, 281–291.
Capron, A. M. (2001). Brain death — Well settled yet still unresolved. *The New England Journal of Medicine*, *344*, 1244–1246.
Capron, A. M., & Kass, L. R. (1978). A statutory definition of the standards for determining human death: An appraisal and a proposal. *University of Pennsylvania Law Review*, *121*, 87–118.
Chiong, W. (2005). Brain death without definitions. *Hastings Center Report*, *35*(6), 20–30.
Choi, E. K., Fredland, V., Zachodni, C., Lammers, J. E., Bledsoe, P., & Helft, P. R. (2008). Brain death revisited: The case for a national standard. *The Journal of Law, Medicine and Ethics*, *36*, 824–836.
Curran, W. J. (1971). Legal and medical death — Kansas takes the first step. *The New England Journal of Medicine*, *284*, 260–261.
DeVita, M. A., Snyder, J. V., Arnold, R. M., & Siminoff, L. A. (2000). Observations of withdrawal of life-sustaining treatment from patients who became non-heart-beating organ donors. *Critical Care Medicine*, *28*, 1709–1712.
Emanuel, L. L. (1995). Reexamining death: the asymptotic model and a bounded zone definition. *Hastings Center Report*, *25*(4), 27–35.
Ferbert, A., Buchner, H., Ringelstein, E. B., & Hacke, W. (1988). Isolated brainstem death. Case report with demonstration of preserved visual evoked potentials (VEPs). *Electroencephalography and Clinical Neurophysiology*, *69*, 13–23.
Furton, E. J. (2002). Brain death, the soul, and organic life. *National Catholic Bioethics Quarterly*, *2*, 455–470.
Gervais, K. G. (1986). *Redefining death*. New Haven, CT: Yale University Press.
Giacomini, M. (1997). A change of heart and a change of mind? Technology and the redefinition of death in 1968. *Social Science and Medicine*, *44*, 1465–1482.
Greer, D. M., Varelas, P. N., Haque, S., & Wijdicks, E. F. (2008). Variability of brain death determination guidelines in leading U.S. neurological institutions. *Neurology*, *70*, 284–289.
Halevy, A., & Brody, B. (1993). Brain death: Reconciling definitions, criteria, and tests. *Annals of Internal Medicine*, *119*, 519–525.
Haupt, W. F., & Rudolf, J. (1999). European brain death codes: A comparison of national guidelines. *Journal of Neurology*, *246*, 432–437.
Korein, J. (1978). The problem of brain death: Development and history. *Annals of the New York Academy Sciences*, *315*, 19–38.
Kosteljanetz, M., Ohrstrom, J. K., Skjodt, S., & Teglbjaerg, P. S. (1988). Clinical brain death with preserved cerebral arterial circulation. *Acta Neurologica Scandinavica*, *78*, 418–421.
Lizza, J. (2005). Potentiality, irreversibility, and death. *Journal of Medicine and Philosophy*, *30*, 45–64.
Loeb, J. (1916). *The organism as a whole*. New York: G. P. Putnam's Sons.
Lynn, J., & Cranford, R. E. (1999). The persisting perplexities in the determination of death. In S. J. Youngner, R. M. Arnold, & R. Schapiro (Eds.), *The definition of death: Contemporary controversies* (pp. 101–114). Baltimore, MD: Johns Hopkins University Press.
Mahner, M., & Bunge, M. (1997). *Foundations of biophilosophy* (pp. 29–30). Berlin: Springer-Verlag.
McMahan, J. (1995). The metaphysics of brain death. *Bioethics*, *9*, 91–126.
Miles, S. (1999). Death in a technological and pluralistic culture. In S. J. Youngner, R. M. Arnold, & R. Schapiro (Eds.), *The definition of death: Contemporary controversies* (pp. 311–318). Baltimore, MD: Johns Hopkins University Press.
Mollaret, P., & Goulon, M. (1959). Le coma dépassé (mémoire préliminaire). *Revue Neurologique*, *101*, 3–15.
Pallis, C. (1995). *ABC of brainstem death* (2nd ed.). London: British Medical Journal Publishers.
President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. (1981). *Defining death: Medical, legal and ethical issues in the determination of death* (pp. 31–43). Washington, DC: U.S. Government Printing Office.
President's Council on Bioethics. (2009). *Controversies in the determination of death: A White Paper by the President's Council on Bioethics*. Washington, DC. http://

www.bioethics.gov/reports/death/index.html (accessed January 17, 2009).

Repertinger, S., Fitzgibbons, W. P., Omojola, M. F., & Brumback, R. A. (2006). Long survival following bacterial meningitis-associated brain destruction. *Journal of Child Neurology*, *21*, 591–595.

Robertson, J. A. (1999). The dead donor rule. *Hastings Center Report*, *29*(6), 6–14.

Rosner, F. (1999). The definition of death in Jewish law. In S. J. Youngner, R. M. Arnold, & R. Schapiro (Eds.), *The definition of death: Contemporary controversies* (pp. 210–221). Baltimore, MD: John Hopkins University Press.

Seifert, J. (1993). Is brain death actually death? A critique of redefinition of man's death in terms of 'brain death'. *The Monist*, *76*, 175–202.

Shewmon, D. A. (1997). Recovery from 'brain death': A neurologist's apologia. *Linacre Quarterly*, *64*(1), 30–96.

Shewmon, D. A. (1998). Chronic ''brain death:'' Meta-analysis and conceptual consequences. *Neurology*, *51*, 1538–1545.

Shewmon, D. A. (2001). The brain and somatic integration: Insights into the standard biological rationale for equating ''brain death'' with death. *Journal of Medicine and Philosophy*, *26*, 457–478.

Shewmon, D. A. (2004). The ''critical organ'' for the organism as a whole: Lessons from the lowly spinal cord. *Advances in Experimental Medicine and Biology*, *550*, 23–42.

Shewmon, D. A. (2009). Brain death: Can it be resuscitated? *Hastings Center Report*, *39*(2), 18–24.

Shewmon, D. A., & Shewmon, E. S. (2004). The semiotics of death and its medical implications. *Advances in Experimental Medicine and Biology*, *550*, 89–114.

Steinbrook, R. (2007). Organ donation after cardiac death. *The New England Journal of Medicine*, *357*, 209–213.

Veatch, R. M. (1975). The whole brain-oriented concept of death: An outmoded philosophical formulation. *Journal of Thanatology*, *3*, 13–30.

Veatch, R. M. (1993). The impending collapse of the whole-brain definition of death. *Hastings Center Report*, *23*(4), 18–24.

Veatch, R. M. (1999). The conscience clause: How much individual choice in defining death can our society tolerate? In S. J. Youngner, R. M. Arnold, & R. Schapiro (Eds.), *The definition of death: Contemporary controversies* (pp. 137–160). Baltimore, MD: Johns Hopkins University Press.

Veith, F. J., Fein, J. M., Tendler, M. D., Veatch, R. M., Kleiman, M. A., & Kalkines, G. (1977). Brain death: A status report of medical and ethical considerations. *Journal of the American Medical Association*, *238*, 1651–1655.

Wijdicks, E. F. M. (Ed.). (2001). *Brain death*. Philadelphia, PA: Lippincott Williams & Wilkins.

Wijdicks, E. F. M. (2002). Brain death worldwide: Accepted fact but no global consensus in diagnostic criteria. *Neurology*, *58*, 20–25.

Youngner, S. J.,, Arnold, R. M., & Schapiro, R. (Eds.). (1999). *The definition of death: Contemporary controversies*. Baltimore, MD: Johns Hopkins University Press.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 4

Behavioral assessment in patients with disorders of consciousness: gold standard or fool's gold? ☆

Joseph T. Giacino[1,2,*], Caroline Schnakers[3], Diana Rodriguez-Moreno[4], Kathy Kalmar[1], Nicholas Schiff[5] and Joy Hirsch[4]

[1]*JFK Johnson Rehabilitation Institute, Edison, NJ, USA*
[2]*New Jersey Neuroscience Institute, Edison, NJ, USA*
[3]*Coma Science Group, Cyclotron Research Centre, University of Liege, Liège, Belgium*
[4]*fMRI Research Center, Columbia University, New York, USA*
[5]*Weill Medical College of Cornell University, New York, USA*

Abstract: In the absence of "hard" neurophysiologic markers, the burden of proof for establishing conscious awareness in individuals who sustain severe brain injury lies in behavioral assessment. Because behavior represents indirect evidence of consciousness, reliance on behavioral markers presents significant challenges and may lead to misdiagnosis. Detection of conscious awareness is confounded by numerous factors including fluctuations in arousal level, difficulty differentiating reflexive or involuntary movement from intentional behavior, underlying sensory and motor impairments, and medication side effects. When an ambiguous behavior is observed, the onus falls to the clinician to determine where along the continuum of unconsciousness to consciousness, it lies. This paper (1) summarizes the current diagnostic criteria for coma, the vegetative state, and the minimally conscious state, (2) describes current behavioral assessment methods, (3) discusses the limitations of behavioral assessment techniques, (4) reviews recent applications of functional neuroimaging in the assessment of patients with disorders of consciousness, and (5) concludes with a case study that illustrates the disparity between behavioral and functional neuroimaging findings that may be encountered in this population.

Keywords: disorders of consciousness; vegetative state; minimally conscious state; assessment scales; brain injury; rehabilitation

Progress in intensive care has increased the number of patients who survive severe acute brain injury. Most recover from coma within the first 2 weeks after the insult, others require more time and pass through different stages before fully or partially recovering consciousness. One of the most challenging problems facing clinicians is understanding the natural history of recovery from severe brain injury. In clinical practice, it is often difficult to detect unambiguous signs of consciousness in patients with limited behavioral repertoires. This complication is reflected in frequent misdiagnoses (Andrews et al., 1996; Childs et al., 1993). Assessment of residual brain

☆Both Joseph T. Giacino and Caroline Schnakers have contributed equally to this study.

*Corresponding author.
Tel.: 732-205-1461; Fax: 732-632-1584;
E-mail: jgiacino@solarishs.org

DOI: 10.1016/S0079-6123(09)17704-X

function in severely brain-injured patients is difficult because motor responses may be impaired, inconsistent, or easily exhausted. For these reasons, diagnostic criteria and standardized behavioral scales have been developed to facilitate the assessment of consciousness in patients recovering from coma. Other techniques such as functional neuroimaging can provide additional information to gauge cognitive processing and aid in diagnostic assessment. This paper (1) summarizes the current diagnostic criteria for coma, the vegetative state (VS), and the minimally conscious state (MCS), (2) describes current behavioral assessment methods, (3) discusses the limitations of behavioral assessment techniques, (4) reviews recent applications of functional neuroimaging in the assessment of patients with disorders of consciousness (DOC), and (5) concludes with a case study that illustrates the disparity between behavioral and functional neuroimaging findings that may be encountered in this population.

Diagnostic criteria

It is essential to distinguish DOC's such as coma, VS, and MCS (see Table 1) as there are important differences in recovery course and outcome. These disorders must also be distinguished from the locked-in syndrome (LIS) and brain death as these conditions have overlapping features, although neither represents a DOC.

Coma

Plum and Posner (1966) defined coma as a pathological state marked by severe and prolonged dysfunction of vigilance and consciousness. This state results from global brain dysfunction (most often due to diffuse axonal injury following traumatic brain injury), or from a lesion limited to brainstem structures involving the reticular activating system. The distinguishing feature of coma is the continuous absence of eye-opening (spontaneously or following stimulation). There is no evidence of visual fixation or pursuit, even after manual eye-opening. No voluntary motor behavior is observed and behavioral responses are limited to reflex activity only. Brain electrical activity is observed, albeit characterized by slow frequency bands (i.e., mostly delta and theta activity). This state must last at least 1 h to be differentiated from a transient DOC such as syncope, acute confusion, or delirium. Prolonged coma is rare as this condition usually resolves within 2–4 weeks, most often evolving into VS or MCS.

Vegetative state

The term "vegetative state" denotes reactivation of autonomic functions (e.g., cardio-vascular, respiratory, and thermoregulation functions) with concomitant reemergence of the sleep–wake cycle (i.e., periods of spontaneous eyes opening). VS often results from trauma-induced bi-hemispheric injury involving the white matter or from bilateral lesions in the thalamus with sparing of the brainstem, hypothalamus, and basal ganglia (Plum and Posner, 1983). Behaviorally, there is no response to verbal order and, although moaning may occur, there is no intelligible speech (The Multi-Society Task Force on PVS, 1994). Infrequently, behaviors such as inappropriate smiling, crying, or grimacing, and even randomly produced single words have been reported in patients diagnosed with VS (Schiff et al., 1999; Working Party of the Royal College of Physicians, 2003). With serial multimodal assessment, the probability that these behaviors are not voluntary or goal directed can be further investigated, although not proven. When this state lasts 1 month or more, the term "persistent VS" has been applied (The Multi-Society Task Force on PVS, 1994). In view of the high rate of recovery of consciousness after 1 month (Choi et al., 1994; Giacino and Kalmar, 1997), and well-documented cases of late recovery (Childs and Mercer, 1996), the American Congress of Rehabilitation Medicine has recommended that the term "persistent VS" be abandoned in favor of documenting the cause of the VS (trauma, anoxia) and the length of time post-onset, as both carry prognostic information (American Congress of Rehabilitation Medicine, 1995). When VS lasts more than 3 months after non-traumatic brain injury, and 1 year following

Table 1. Diagnostic criteria for brain death, coma, vegetative and minimally conscious states, and locked-in syndrome

Consciousness level	Diagnostic criteria	Reference(s)
Brain death	No arousal/eye-opening	Medical Consultants on the Diagnosis of Death (1981)
	No behavioral signs of awareness	
	Apnea	
	Loss of brain functions (brainstem reflexes)	
Coma	No arousal/eye-opening	Plum and Posner (1966)
	No behavioral signs of awareness	
	Impaired spontaneous breathing	
	Impaired brainstem reflexes	
	No vocalizations	
	>1 h	
Vegetative state	Arousal/spontaneous or stimulus-induced eye opening	The Multi-Society Task Force on PVS (1994)
	No behavioral signs of awareness	
	Preserved spontaneous breathing	
	Preserved brainstem reflexes	
	No purposeful behaviors	
	No language production or comprehension	
	>1 month: persistent vegetative	
	Compatible	Working Party of the Royal College of Physicians (2003)
	Grimaces to pain	
	Localization to sounds	
	Atypical but compatible	
	Visual fixation	
	Response to threat	
	Inappropriate single words	
Minimally conscious state	Arousal/spontaneous eye-opening	Giacino et al. (2002)
	Fluctuating but reproducible behavioral signs of awareness	
	Response to command	
	Environmentally contingent emotional/motor responses	
	Object localization and manipulation	
	Sustained visual fixation and pursuit	
	Intelligible verbalization	
	Intentional but unreliable communication	
	Emergence from MCS	
	Functional communication	
	Functional object use	
Locked-in syndrome	Arousal/spontaneous eye-opening	American Congress of Rehabilitation Medicine (1995)
	Preserved cognitive functions	
	Communication via eye gaze	
	Anarthria	
	Tetraplegia	

traumatic etiologies, VS can be considered ''permanent'' (The Multi-Society Task Force on PVS, 1994).

Minimally conscious state

MCS is characterized by the presence of inconsistent but clearly discernible behavioral signs of consciousness (Giacino et al., 2002). Command-following, recognizable yes–no responses, and intelligible verbalizations represent the clearest evidence of conscious awareness. In contrast to patients in VS who may display random episodes of crying or smiling, in MCS, these behaviors occur in contingent relation to appropriate environmental triggers. Reemergence of visual pursuit appears to be an early behavioral marker of the transition from VS to MCS (Giacino

and Whyte, 2005). Although behavior may fluctuate across examinations, at least one of these signs must be replicated within a given examination to meet the diagnostic criteria for MCS.

Regarding prognosis, the probability of functional recovery at 1 year following traumatic brain injury is significantly more favorable relative to VS (50% vs. 3% attaining moderate disability). Some patients in MCS progress slowly while others remain in this condition permanently (Fins et al., 2007). It is also important to recognize that, unlike VS, clearly defined temporal parameters for recovery do not yet exist (Lammi et al., 2005), and there is wide heterogeneity in the degree of functional recovery ultimately attained. Emergence from MCS occurs when the patient is able to reliably communicate through verbal or gestural yes–no responses, or is able to demonstrate use of two or more objects (e.g., hairbrush, cup) in a functional manner (Giacino et al., 2002).

Differential diagnosis

Two additional conditions characterized by behavioral unresponsiveness must be differentiated from VS and MCS. In the first, consciousness is retained, while in the second, it is permanently lost.

Locked-in syndrome

LIS is marked by tetraplegia and anarthria in the setting of near-normal to normal cognitive function (American Congress of Rehabilitation Medicine, 1995). This state is caused by a lesion involving the ventral pons and, in 60% of cases, is due to basilar thrombosis. Because patients with LIS have spontaneous eyes opening, but are unable to speak or move the extremities, this state can be confused with VS because of the confluence of behavioral signs. On average, the diagnosis of LIS is not established until 2.5 months post-onset. There is evidence that family members tend to detect signs of consciousness (55% of cases) prior to medical staff (23% of cases) (Laureys et al., 2005a). Classic LIS consists of complete paralysis of the orobuccal musculature and all four extremities, however, vertical eyes movements are spared, allowing nonverbal communication through directional gaze. Perceptual functions are also usually spared as ascending corticospinal axons remain intact (American Congress of Rehabilitation Medicine, 1995). Bauer et al. (1979) have described multiple varieties of LIS, including the incomplete form in which there is residual motor activity (frequently, finger or head movement), and total LIS, in which there is complete immobility including both horizontal and vertical eye movements. Data on life expectancy suggest that some patients with LIS live 12 or more years post-onset. Surprisingly, chronic LIS patients rate their quality of life similarly to the healthy population (Laureys et al., 2005a). In the absence of other structural or functional brain abnormalities, patients with LIS are generally able to make independent decisions and communicate their preferences (Schnakers et al., 2008b; Smart et al., 2008).

Brain death

Brain death is a condition in which there is ''irreversible unconsciousness with complete loss of brain function.'' It is marked by the presence of apnea and the lack of any behavioral response to the environment (Medical Consultants on the Diagnosis of Death, 1981). Generally, an electroencephalogram is completed to demonstrate an iso-electrical signal reflecting the absence of electrical brain activity. Transcranial Doppler studies reveal the absence of cerebral blood flow. Finally, functional imaging, using cerebral perfusion tracers and single photon emission tomography (SPECT), illustrate the ''empty skull'' sign in which the ''whole brain'' is inactive (Facco et al., 1998). After excluding brain dysfunction due to drug toxicity or hyperthermia, a final diagnosis can be established after 6–24 h.

Behavioral assessment methods

Twenty-five years ago, Plum and Posner (1983) noted that, ''the limits of consciousness are hard to define satisfactorily and we can only infer the

self-awareness of others by their appearance and their acts''. As noted, behavioral observation remains the ''gold standard'' for detecting signs of consciousness in severely brain-injured patients. Preservation of arousal is a necessary but insufficient condition for consciousness (see Fig. 1). The search for consciousness rests on the demonstration of behavioral qualities that are distinct from simple reflexes. Behavioral assessment may not, however, definitively distinguish between behaviors associated with the state of arousal and those linked to conscious awareness. This dilemma is illustrated in the difficulty clinicians often have in differentiating reflexive eye blinks from eye-closure to command. Additionally, consciousness may not be a static phenomenon and may be better conceptualized as a continuum. It is possible, for example, for a patient in coma to rapidly evolve into VS, gradually transition to MCS, and subsequently lapse back into VS (Giacino and Trott, 2004; Majerus et al., 2005).

Behavioral scales

Numerous behavioral rating scales have been developed and validated to assess level of consciousness and establish diagnosis (Majerus et al., 2005). In this section, we briefly review instruments commonly used in the acute and rehabilitation settings.

Acute setting

The *Glasgow Coma Scale* (GCS) remains the most widely used scale in trauma and acute care settings. The GCS was the first validated rating scale developed to monitor level of consciousness in the intensive care unit (Teasdale and Jennett, 1974). This scale is relatively brief and can easily be incorporated into routine clinical care. It includes three subscales that address arousal level, motor function, and verbal abilities. Subscales scores are added and yield a total score ranging from 3 to 15. Despite its widespread use, the GCS has been criticized for variable inter-rater agreement and problems deriving scores in patients with ocular trauma, tracheostomy, or ventilatory support (McNett, 2007).

The *Full Outline of UnResponsiveness* (FOUR) scale was recently developed to replace the GCS to assess severely brain-injured patients in intensive care (Wijdicks, 2006; Wijdicks et al., 2005).

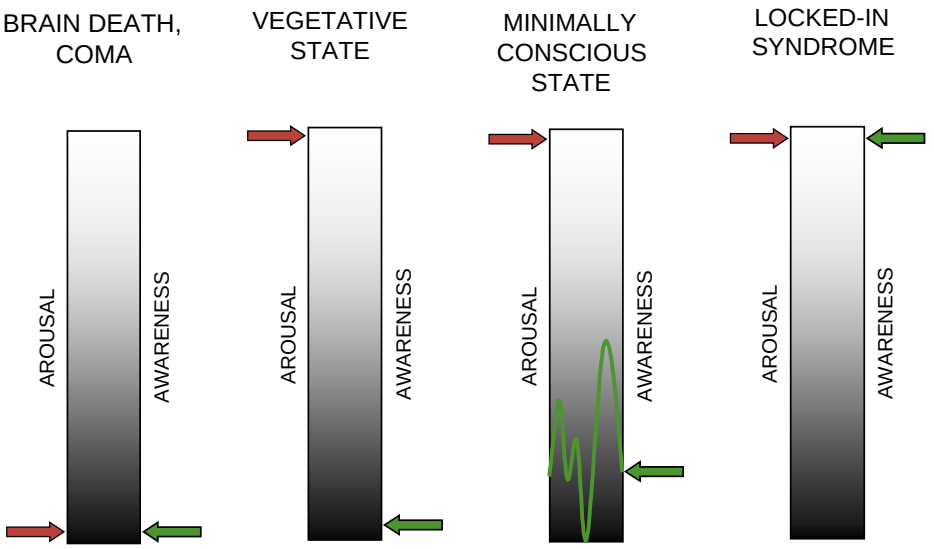


Fig. 1. Behavioral observation assesses two dimensions of consciousness: arousal and awareness. In brain death and coma, both dimensions are absent. In the vegetative state, arousal level is relatively preserved in the absence of signs of awareness. In the minimally conscious state, both dimensions are present although behavioral signs of awareness often fluctuate. In the locked-in syndrome, both dimensions are fully preserved despite complete loss of speech and motor functions.

The scale is comprised of four subscales assessing motor and ocular responses, brainstem reflexes, and breathing. The total score ranges from 0 to 16. Unlike the GCS, the FOUR does not assess verbal functions to accommodate the high number of intubated patients in intensive care. A score of 0 on the FOUR assumes the absence of brainstem reflexes and breathing and, therefore, helps to diagnose brain death. The scale also monitors recovery of autonomic functions and tracks emergence from VS. The FOUR is specifically designed to detect patients with LIS as it uses oculomotor commands that exploit vertical eye movements and eye blinks, both of which are preserved in LIS.

The *Wessex Head Injury Matrix* (WHIM) (Shiel et al., 2000) was developed to capture changes in patients in VS through emergence from post-traumatic amnesia. This tool is particularly sensitive to detecting changes in patients in MCS not captured by traditional scales such as the GCS (Majerus and Van der Linden, 2000). Shiel and collaborators longitudinally followed 97 severely brain-injured patients recovering from coma to create the WHIM. WHIM items were ordered according to the sequence of recovery observed in these patients. The 62-item WHIM's six sections assess arousal level and concentration, visual consciousness (i.e., visual pursuit), communication, cognition (i.e., memory and spatiotemporal orientation), and social behaviors. The WHIM score represents the rank of the most complex behavior observed.

The *Sensory Modality Assessment and Rehabilitation Technique* (SMART) (Gill-Thwaites, 1997) was developed to identify signs of consciousness observed during "sensory stimulations programs" intended to support cerebral plasticity and improve level of consciousness (Wood, 1991). The SMART assesses eight modalities including visual, auditory, tactile, olfactory and gustatory sensation, motor functions, communication, and arousal level. The SMART is a hierarchical scale consisting of five response levels ("absence of response" — Level 1; "reflex response" — Level 2; "withdrawal response" — Level 3; "localization response" — Level 4; "discriminative response" — Level 5). The SMART has previously been shown to have very good validity and reliability in a population of 60 patients diagnosed as being in a VS or in a MCS (Gill-Thwaites and Munday, 2004).

The JFK *Coma Recovery Scale* (CRS) was originally developed by investigators from the JFK Johnson Rehabilitation Institute in 1991 (Giacino et al., 1991). The scale was revised and republished in 2004 as the JFK Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004). The purpose of the CRS-R is to assist with differential diagnosis, prognostic assessment, and treatment planning in patients with DOC. The scale consists of 23 items that comprise 6 subscales addressing auditory, visual, motor, oromotor, communication, and arousal functions (see Table 2). CRS-R subscales are comprised of hierarchically arranged items associated with brain stem, subcortical, and cortical processes. The lowest item on each subscale represents reflexive activity while the highest items represent cognitively mediated behaviors. Scoring is standardized and based on the presence or absence of operationally defined behavioral responses to specific sensory stimuli. Psychometric studies indicate that the CRS-R meets minimal standards for measurement and evaluation tools designed for use in interdisciplinary medical rehabilitation. Adequate inter-rater and test–retest reliability have been established indicating that the CRS-R can be administered reliably by trained examiners and produces reasonably stable scores over repeated assessments. Validity analyses support use of the scale as an index of neurobehavioral function and have shown that the CRS-R is capable of discriminating patients in MCS from those in VS which is of critical importance in establishing prognosis and formulating treatment interventions (Schnakers et al., 2006, 2008a; Vanhaudenhuyse et al., 2008). Spanish, Portuguese, Italian, German, French, Dutch, Norwegian, and Danish translations of the CRS-R are available.

Limitations of behavioral assessment

Differentiating between MCS and VS can be challenging as voluntary and reflexive behaviors can be difficult to distinguish and subtle signs of consciousness may be missed (Majerus et al.,

Table 2. Coma Recovery Scale-Revised record sheet

Auditory Function Scale	
4 — Consistent movement to command[a]	
3 — Reproducible movement to command[a]	
2 — Localization to sound	
1 — Auditory startle	
0 — None	
Visual Function Scale	
5 — Object recognition[a]	
4 — Object localization: Reaching[a]	
3 — Pursuit eye movements[a]	
2 — Fixation[a]	
1 — Visual startle	
0 — None	
Motor Function Scale	
6 — Functional object use[b]	
5 — Automatic motor response[a]	
4 — Object manipulation[a]	
3 — Localization to noxious stimulation[a]	
2 — Flexion withdrawal	
1 — Abnormal posturing	
0 — None/flaccid	
Oromotor/Verbal Function Scale	
3 — Intelligible verbalization[a]	
2 — Vocalization/oral movement	
1 — Oral reflexive movement	
0 — None	
Communication Scale	
2 — Functional: Accurate[b]	
1 — Non-functional: Intentional[a]	
0 — None	
Arousal Scale	
3 — Attention[a]	
2 — Eye opening w/o stimulation	
1 — Eye opening with stimulation	
0 — Unarousable	

[a]Denotes MCS.
[b]Denotes emergence from MCS.

2005). Prior studies have shown that 37–43% of patients with DOC are erroneously diagnosed with VS (Andrews et al., 1996; Childs et al., 1993). The recent development of diagnostic criteria for MCS (Giacino et al., 2002) would reasonably be expected to reduce the incidence of misdiagnosis relative to the rates reported before these criteria were established (Jennett, 2005). However, a recent study found that 41% of patients believed to be in VS were misdiagnosed. This study also found that the majority of cases with an uncertain diagnosis were in MCS (89%), not in VS. Another 10% diagnosed with MCS had actually emerged from this condition (Schnakers et al., 2009).

The high rate of misdiagnosis reported by Schnakers and collaborators likely reflects different sources of variance. Variance in diagnostic accuracy may result from biases contributed by the examiner, patient, and environment. Examiner error may arise when the range of behaviors sampled is too narrow, response-time windows are over or under-inclusive, criteria for judging purposeful responses are poorly defined or not adhered to, and examinations are conducted too infrequently to capture the full range of behavioral fluctuation. The use of standardized rating scales offers some protection from these errors, although failure to adhere to specific administration and scoring guidelines may jeopardize diagnostic accuracy (Schnakers et al., 2009). The second source of variance concerns the patient. Fluctuations in arousal level, fatigue, subclinical seizure activity, occult illness, pain, cortical sensory deficits (e.g., cortical blindness/deafness), motor impairment (e.g., generalized hypotonus, spasticity, or paralysis), or cognitive (e.g., aphasia, apraxia, agnosia) disturbance can conspire to confound accurate diagnostic assessment, constitute a bias to the behavioral assessment, and therefore decrease the probability to observe signs of consciousness. Finally, the environment in which the patient is evaluated may bias assessment findings. Paralytic and sedating medications, restricted range of movement stemming from restraints and immobilization techniques, poor positioning and excessive ambient noise, heat or light can decrease or distort voluntary behavioral responses.

Some sources of error can be avoided, but this is not always possible or within the examiner's control. This is particularly troubling as clinical management, from treatment of pain to end-of-life decision-making, often depends on behavioral observations. To address this problem, neuroimaging procedures have begun to assume an adjunctive role in the diagnostic assessment of patients with DOC.

Functional neuroimaging

Functional neuroimaging techniques such as positron emission tomography (PET) and

functional magnetic resonance imaging (fMRI) can provide an objective index of brain activity at rest and during active cognitive processing. Thus, these techniques are well equipped to identify covert cognitive processes in patients who are otherwise incapable of intelligible or sustained behavioral expression, and offer complementary information to bedside examination findings.

In vegetative patients, brain hypometabolism appears similar to individuals in coma, with a 50–60% decreased global metabolic rate relative to healthy individuals. Hypometabolic activity is further reduced to 60–70% in patients in ''permanent vegetative state'' (Tommasino et al., 1995). In VS, the frontoparietal network, including the parietal, mesio-frontal, prefrontal, parieto-temporal, precuneus, and posterior cingular cortex are disproportionately disturbed (Laureys, 2004; Laureys et al., 2004a). In MCS, these regions remain relatively well preserved and their functional connectivity is generally retained (Laureys et al., 2000). Prior investigations have demonstrated that, in VS, auditory or nociceptive stimuli activate primary cortices only, suggesting failure to integrate this information and consequently, absence of conscious perception (Laureys, 2005).

The metabolic pattern differs significantly for patients in MCS. In spite of a global hypometabolism measured at 20–40% of normal (Schiff et al., 2005), the activity in precuneus and posterior cingular cortex (the most activated regions during wakefulness and the least activated under general anesthesia or during deep slow sleep) was greater as compared to rates noted in patients diagnosed with VS (Laureys et al., 2005b). Similar findings have been noted in functional imaging studies employing auditory or noxious stimulation (Bekinschtein et al., 2004; Boly et al., 2004, 2008; Laureys et al., 2004b; Schiff et al., 2005). Perhaps most importantly, there is evidence that patients in MCS retain higher functional connectivity between the secondary auditory cortex and prefronto-temporal associative cortices (Boly et al., 2005), corroborating the expectation that information processing is more highly integrated in MCS relative to VS.

Case report (AZ)

A 20-year-old right-handed college student (referred to here as AZ) was admitted for a course of acute neurorehabilitation approximately 3 months after sustaining a severe hypoxic-ischemic brain injury related to cardio-respiratory arrest caused by a drug overdose. He was found pulseless by at the scene by the emergency medical team and required cardiopulmonary resuscitation for 10 min before cardioversion was achieved. The initial CT scan was normal but a follow-up scan on day two showed global white matter ischemic changes. The acute medical course was complicated by central fevers and recurrent infections. Medical records from the acute care setting noted that the patient remained unresponsive across the 3-month course, however, family members reported observing episodes of simple command-following and occasional periods of appropriate laughter.

On admission to the rehabilitation unit, flexion contractures were noted in all four extremities (upper greater than lower) and there was no spontaneous purposeful movement. Arousal was well maintained and the auditory startle reflex was intact but there was no evidence of auditory localization. On formal command-following trials using the CRS-R, there was questionable movement of the right toes, however, these responses could not be clearly differentiated from random movement, and there was no other indication of proximal or axial movement to command. To further investigate verbal comprehension in the setting of severe contractures, vocalization commands were administered (i.e., ''say ah''). Vocalizations were noted in association with increased oral movement, despite the absence of any spontaneous vocalizations prior to presentation of the commands. No evidence of verbal or gestural communication was observed in response to simple yes/no questions. Assessment of visuoperceptual functions failed to reveal any evidence of object recognition (via eye gaze) and there was a single documented episode of visual pursuit in response to horizontal and vertical movement of a mirror. Noxious stimulation applied to the upper extremities produced facial

grimace and slight flexion of both lower extremities only.

Over the course of the next 10 months, AZ was evaluated weekly using the JFK CRS-R. Arousal (i.e., eye-opening) was generally well maintained and, despite anecdotal reports of occasional visual fixation, there were no documented episodes of either fixation or pursuit on formal examination. Active and passive range of movement remained severely compromised due to increased tone and spasticity involving all four extremities. The severity of the neuromuscular impairment placed significant constraints on the assessment of command-following. There were, however, infrequent reports of command-following by family members and treating staff, although these behaviors could not be replicated on standardized assessments performed during the 10-month observational period. Incomprehensible vocalizations and crying episodes were frequently noted, but there were no intelligible verbalizations or discernible gestural communication signs at any time. Examination findings were most compatible with VS, although diagnostic certainty was low in view of the occasional manifestation of behaviors associated with conscious awareness. Table 3 shows AZ's CRS-R subscale scores on admission and on follow-up at 3, 6, and 11 months post-onset.

In light of the characteristically infrequent, inconsistent, and qualitatively ambiguous signs of consciousness noted in this case, AZ was enrolled in an IRB-approved fMRI study designed to investigate neurophysiologic changes induced by exposure to meaningful sensory stimuli in patients with DOC. Specialized ''passive-stimulation'' paradigms were administered to monitor changes in cortical networks associated with language and visual processing (Hirsch et al., 2001). In the passive language paradigm, AZ listened to familiar personal stories recounted by a family member (e.g., vacation, wedding). Familiar voices and events were employed to facilitate sustained attention. Thereafter, he was exposed to a second condition in which the narratives were time-reversed rendering them unintelligible. Results revealed robust language-specific activation during both the forward and reversed conditions, mirroring previously reported findings in healthy volunteers (Schiff et al., 2005). Extensive clusters of activity were observed extending bilaterally over the transverse temporal gyrus, the middle and superior temporal gyrus, and portions of the precentral and postcentral gyrus bilaterally. More importantly, there were several clusters of activity unique to the forward speech condition observed following subtraction of the reversed from the forward condition. Specific areas of activity tied to high-level language processing included the left superior temporal gyrus (i.e., Wernicke's area), the left supramarginal and superior frontal gyri, and the right medial frontal gyrus. Unexpectedly, both conditions also elicited activity in the occipital cortex (cuneus and lingual gyrus), raising the possibility of language comprehension accompanied by visual imagery (see Fig. 2).

A second ''passive viewing'' paradigm was presented to engage the visual processing network. A series of back-projected visual images were presented under three conditions. Condition 1 consisted of a combination of familiar (i.e., family members and close friends) and unfamiliar faces, condition 2 was comprised of landscape scenes, and condition 3 utilized flashing checkerboards. AZ was exposed to these three forms of visual stimuli to gauge the selectivity of the activation as well as the degree of preservation of the central nodes comprising this system. Prior studies with healthy volunteers have demonstrated that while each of these stimuli produces visual network activity, faces and landscapes activate mutually exclusive structures (i.e., fusiform face area and parahippocampal place area, respectively) (Epstein et al., 1999; Kanwisher et al., 1997). Findings showed strong activation of the primary visual cortex bilaterally across all three conditions. Of more importance, facial stimuli engaged the fusiform face area of the right inferior temporal gyrus as well as the lingual gyrus bilaterally and right precuneus, consistent with high-level processing of faces. The landscapes elicited activity in the parahippocampal gyrus, lingual gyrus bilaterally, and bilateral precuneus, approximating the response observed in healthy volunteers exposed to landscape scenes (see Fig. 3).

Table 3. CRS-R response profile on admission to rehabilitation and 3, 6, and 11 months post-injury in patient "AZ," a 20-year-old male with severe anoxic encephalopathy

JFK Coma Recovery Scale – Revised (record form)				
Patient: BB	Date			
	ADM	3 months	6 months	11 months
Auditory Function Scale				
4 — Consistent movement to command[a]				
3 — Reproducible movement to command[a]				
2 — Localization to sound		+	+	+
1 — Auditory startle	+			
0 — None				
Visual Function Scale				
5 — Object recognition[a]				
4 — Object localization: Reaching[a]				
3 — Pursuit eye movements[a]			+	
2 — Fixation[a]				+
1 — Visual startle				
0 — None	+	+		
Motor Function Scale				
6 — Functional object use[b]				
5 — Automatic motor response[a]				
4 — Object manipulation[a]				
3 — Localization to noxious stimulation[a]				
2 — Flexion withdrawal	+	+	+	+
1 — Abnormal posturing				
0 — None/flaccid				
Oromotor/Verbal Function Scale				
3 — Intelligible verbalization[a]				
2 — Vocalization/oral movement	+	+	+	+
1 — Oral reflexive movement				
0 — None				
Communication Scale				
2 — Functional: Accurate[b]				
1 — Non-functional: Intentional[a]				
0 — None	+	+	+	+
Arousal Scale				
3 — Attention[a]				
2 — Eye opening w/o stimulation	+	+		+
1 — Eye opening with stimulation			+	
0 — Unarousable				
Total score	7	8	10	10

[a]Denotes MCS.
[b]Denotes emergence from MCS.

What do these findings mean?

The results of these studies suggest that some commonly held notions about brain–behavior relationships should be revisited in this patient population. Perhaps most importantly, they clearly illustrate the wide discrepancy that may exist between observable behavior and the underlying neurophysiologic processes believed to support cognitive processing. Such findings also force us to consider the unsettling possibility that cognitive function may be at least partially

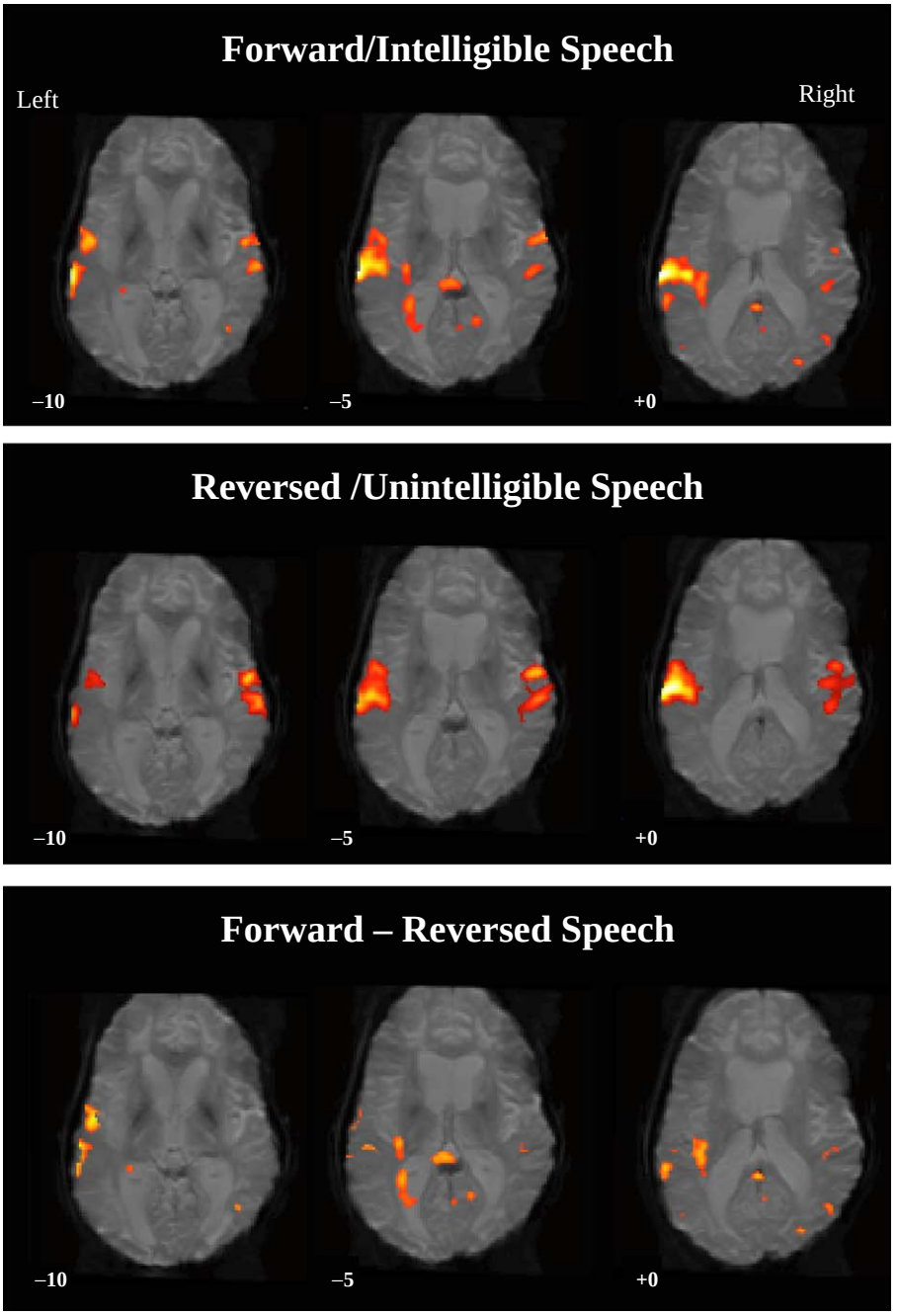


Fig. 2. Regions of activation noted in patient AZ when exposed to spoken narratives. The top panel shows robust activation in left temporal association cortex observed during presentation of comprehensible speech. In the middle panel, regions of activation are well maintained during exposure to unintelligible speech. In the bottom panel, several clusters of activity unique to the forward condition are retained following subtraction of the reversed from forward condition, suggesting preservation of high-level language processing.

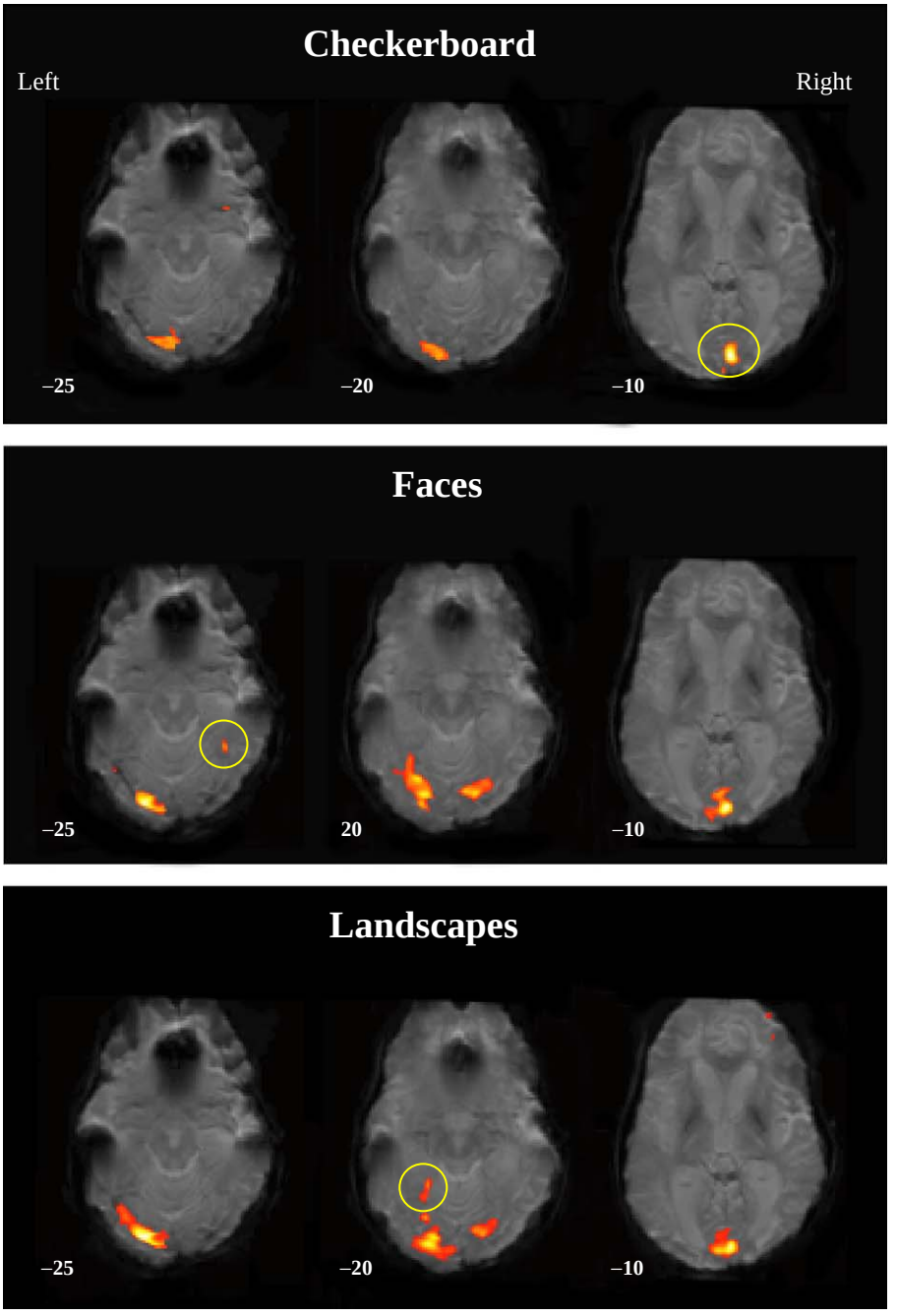


Fig. 3. Regions of activation noted in patient AZ in response to visual stimuli. The top panel shows bilateral activation in the primary cortex observed during exposure to flashing checkerboards. In the middle panel, activation of the fusiform face area is noted during exposure to familiar and unfamiliar faces. The bottom panel shows activation of the parahippocampal place area during presentation of landscape scenes.

preserved in this case, but lack a mode of expression as the consequence of severely dysfunctional sensory and motor systems. In a sense, these findings may reflect a ''functional'' LIS. Alternatively, the selective activation of key nodes in the language and visual networks may stem from a more extensively hard-wired neural network than has traditionally been assumed. This premise is supported by recent evidence from electrophysiological and other fMRI activation studies. Employing an event-related cognitive evoked potential paradigm, Perrin et al. (2006) detected a P300 response in three of five patients diagnosed with VS who listened to their own first name versus an unfamiliar name. Similarly, Coleman et al. (2007) found evidence of extensive activation in temporal association cortices in three vegetative patients presented with meaningful speech (i.e., high and low semantically ambiguous sentences) versus unintelligible noise. The contrast between intelligible speech and unintelligible speech sounds provided an opportunity to parse brain regions involved in processing acoustic as well as semantic components of speech from those responsible for processing elementary speech components only. These studies suggest that automatic speech recognition processes mediated by surviving cortical association areas may be preserved in the absence of conscious awareness.

In an effort to circumvent the ''automatic versus effortful'' processing problem, investigators have relinquished their reliance on passive-stimulation paradigms in favor of adopting those that require active processing. Unlike their passive counterparts, active stimulation paradigms direct the subject to perform a cognitive activity on cue. Owen et al. (2006) devised a hierarchical fMRI scanning paradigm in which subjects were directed to imagine either playing tennis or walking around the rooms of their home. Results in normal controls indicated distinct network activation tied to each instructional set. When subjects were instructed to imagine playing tennis, robust activity was observed in the supplementary motor area. In contrast, when subjects were verbally prompted to navigate the rooms of the house, activity shifted to the posterior parietal, parahippocampal gyrus, and lateral premotor regions. Surprisingly, the same findings were observed in a patient whose behavioral profile was reportedly indicative of VS. The authors suggested that, despite the behaviorally unresponsive presentation on bedside examination, the shift in activation patterns coupled to the verbal instructions, constituted evidence that the patient was capable of comprehending language and executing goal-directed behavior. In a similar vein, Schnakers et al. (2008c) recorded event-related potentials while subjects either passively listened to their own first name or received instructions to count the number of times they heard their name. The authors reported that healthy controls and patients in MCS, but not those in VS, demonstrated a larger P300 in response to their own name in both the active and passive conditions. The P300 differential was viewed as evidence of intentional compliance with task instructions. As active paradigms such as these continue to be refined, clinicians will be able to convincingly discern whether the capacity for cognitive processing is intact without relying on overt behavior analysis.

Although the standard of the field is now moving toward active paradigms to infer conscious processing, it is unlikely that all patients with DOC will benefit from these paradigms. Those least likely to benefit occupy opposite ends of the severity spectrum. Patients with very little residual brain activity who fail to show activation on passive paradigms (consistent with VS), as well as cases like AZ who demonstrate robust activity (consistent with MCS) but, for unclear reasons are unable to perform effortful tasks, will not be able to engage in active paradigms. Therefore, we believe that both passive and active paradigms will continue to play a role in capturing the full range of cognitive processing capacity characterizing patients with DOC.

Conclusion

Recovery of consciousness is usually gradual, sometimes marked by emergence of clear behavioral signs, but more often by subtle improvements. Additionally, bedside assessment of

residual cognitive function is often difficult because of poor arousal, motor impairment, sedating medications, and other confounding factors. Nonetheless, every effort should be made to recognize subtle signs of consciousness as early as possible in the recovery course to avoid misdiagnosis. An accurate diagnosis is crucial not only for daily management (particularly, pain treatment) and end-of-life decisions, but also for prognosis as outcome from MCS is significantly more favorable on average, relative to VS. Knowledge of accepted diagnostic criteria and reliance on validated behavioral assessment scales enhance diagnostic and prognostic accuracy, and facilitate clinical management decisions. Continued development of electrophysiological and functional neuroimaging paradigms designed to detect voluntary brain activity in patients with minimal behavioral output is expected to reduce diagnostic error, increase prognostic specificity, and foster the development of novel interventions to promote recovery.

Acknowledgments

This study is supported in part by the National Institute on Disability and Rehabilitation Research (Award# H133A070030), the Belgian National Funds for Scientific Research (FNRS), European Commission, James McDonnell Foundation, Mind Science Foundation, French Speaking Community Concerted Research Action, International Rotary Foundation, Fondation Médicale Reine Elisabeth, and University of Liège.

References

American Congress of Rehabilitation Medicine. (1995). Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. *Archives of Physical Medicine and Rehabilitation*, *76*, 205–209.

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*(7048), 13–16.

Bauer, G., Gerstenbrand, F., & Rumpl, E. (1979). Varieties of the locked-in syndrome. *Journal of Neurology*, *221*(2), 77–91.

Bekinschtein, T., Niklison, J., Sigman, L., Manes, F., Leiguarda, R., Armony, J., et al. (2004). Emotion processing in the minimally conscious state. *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*(5), 788.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, P., Del Fiore, G., et al. (2004). Auditory processing in severely brain injured patients: Differences between the minimally conscious state and the persistent vegetative state. *Archives of Neurology*, *61*(2), 233–238.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, F., Luxen, A., et al. (2005). Cerebral processing of auditory and noxious stimuli in severely brain injured patients: Differences between VS and MCS. *Neuropsychological Rehabilitation*, *15*(3–4), 283–289.

Boly, M., Faymonville, M. E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., et al. (2008). Perception of pain in the minimally conscious state with PET activation: An observational study. *Lancet Neurology*, *7*(11), 1013–1020.

Childs, N. L., & Mercer, W. N. (1996). Late improvement in consciousness after post-traumatic vegetative state. *The New England Journal of Medicine*, *334*(1), 24–25.

Childs, N. L., Mercer, W. N., & Childs, H. W. (1993). Accuracy of diagnosis of persistent vegetative state. *Neurology*, *43*(8), 1465–1467.

Choi, S. C., Barnes, T. Y., Bullock, R., Germanson, T. A., Marmarou, A., & Young, H. F. (1994). Temporal profile of outcomes in severe head injury. *Journal of Neurosurgery*, *81*(2), 169–173.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, *130*(Pt. 10), 2494–2507.

Epstein, R., Harris, A., Stanley, D., & Kanwisher, N. (1999). The parahippocampal place area: Recognition, navigation, or encoding? *Neuron*, *23*(1), 115–125.

Facco, E., Zucchetta, P., Munari, M., Baratto, F., Behr, A. U., Gregianin, M., et al. (1998). 99mTc-HMPAO SPECT in the dia-
gnosis of brain death. *Intensive Care Medicine*, *24*(9), 911–917.

Fins, J. J., Schiff, N. D., & Foley, K. M. (2007). Late recovery from the minimally conscious state: Ethical and policy implications. *Neurology*, *68*(4), 304–307.

Giacino, J., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*(3), 349–353.

Giacino, J., & Kalmar, K. (1997). The vegetative and minimally conscious states: A comparison of clinical features and functional outcome. *The Journal of Head Trauma Rehabilitation*, *12*(4), 36–51.

Giacino, J., Kalmar, K., & Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation*, *85*(12), 2020–2029.

Giacino, J. T., Kezmarsky, M. A., DeLuca, J., & Cicerone, K. D. (1991). Monitoring rate of recovery to predict outcome in minimally responsive patients. *Archives of Physical Medicine and Rehabilitation*, *72*(11), 897–901.

Giacino, J. T., & Trott, C. T. (2004). Rehabilitative management of patients with disorders of consciousness: Grand rounds. *The Journal of Head Trauma Rehabilitation*, *19*(3), 254–265.

Giacino, J., & Whyte, J. (2005). The vegetative and minimally conscious states: Current knowledge and remaining questions. *The Journal of Head Trauma Rehabilitation*, *20*(1), 30–50.

Gill-Thwaites, H. (1997). The Sensory Modality Assessment Rehabilitation Technique — A tool for assessment and treatment of patients with severe brain injury in a vegetative state. *Brain Injury*, *11*(10), 723–734.

Gill-Thwaites, H., & Munday, R. (2004). The sensory modality assessment and rehabilitation technique (SMART): A valid and reliable assessment for vegetative state and minimally conscious state patients. *Brain Injury*, *18*(12), 1255–1269.

Hirsch, J., Kamal, A., Moreno, D., Petrovich, N., Giacino, J., Plum, F., et al. (2001). fMRI reveals intact cognitive systems for two minimally conscious patients. *Society for Neuroscience, Abstracts*, *271*, 1397.

Jennett, B. (2005). Thirty years of the vegetative state: Clinical, ethical and legal problems. *Progress in Brain Research*, *150*, 537–543.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience*, *17*(11), 4302–4311.

Lammi, M. H., Smith, V. H., Tate, R. L., & Taylor, C. M. (2005). The minimally conscious state and recovery potential: A follow-up study 2 to 5 years after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *86*(4), 746–754.

Laureys, S. (2004). Functional neuroimaging in the vegetative state. *NeuroRehabilitation*, *19*(4), 335–341.

Laureys, S. (2005). The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences*, *9*(12), 556–559.

Laureys, S., Faymonville, M. E., Luxen, A., Lamy, M., Franck, G., & Maquet, P. (2000). Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet*, *355*(9217), 1790–1791.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004a). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*(9), 537–546.

Laureys, S., Pellas, F., Van Eeckhout, P., Ghorbel, S., Schnakers, C., Perrin, F., et al. (2005a). The locked-in syndrome: What is it like to be conscious but paralyzed and voiceless? *Progress in Brain Research*, *150*, 495–511.

Laureys, S., Perrin, F., Faymonville, M. E., Schnakers, C., Boly, M., Bartsch, V., et al. (2004b). Cerebral processing in the minimally conscious state. *Neurology*, *63*(5), 916–918.

Laureys, S., Perrin, F., Schnakers, C., Boly, M., & Majerus, S. (2005b). Residual cognitive function in comatose, vegetative and minimally conscious states. *Current Opinion in Neurology*, *18*(6), 726–733.

Majerus, S., Gill-Thwaites, H., Andrews, K., & Laureys, S. (2005). Behavioral evaluation of consciousness in severe brain damage. In S. Laureys (Ed.), *The boundaries of consciousness: Neurobiology and neuropathology* (Vol. 150, pp. 397–413). Amsterdam: Elsevier.

Majerus, S., & Van der Linden, M. (2000). Wessex Head Injury Matrix and Glasgow/Glasgow-Liège Coma Scale: A validation and comparison study. *Neuropsychological Rehabilitation*, *10*(2), 167–184.

McNett, M. (2007). A review of the predictive ability of Glasgow Coma Scale scores in head-injured patients. *The Journal of Neuroscience Nursing*, *39*(2), 68–75.

Medical Consultants on the Diagnosis of Death. (1981). Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Journal of the American Medical Association*, *246*(19), 2184–2186.

Owen, A., Coleman, M., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. (2006). Detecting awareness in the vegetative state. *Science*, *313*(5792), 1402.

Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Bredart, S., et al. (2006). Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Archives of Neurology*, *63*(4), 562–569.

Plum, F., & Posner, J. B. (1966). *The diagnosis of stupor and coma* (1st ed.). Philadelphia: F.A. Davis.

Plum, F., & Posner, J. B. (1983). *The diagnosis of stupor and coma* (3rd ed.). Philadelphia: F.A. Davis.

Schiff, N., Ribary, U., Plum, F., & Llinás, R. (1999). Words without mind. *Journal of Cognitive Neuroscience*, *11*(6), 650–656.

Schiff, N. D., Rodriguez-Moreno, D., Kamal, A., Kim, K. H., Giacino, J. T., Plum, F., et al. (2005). fMRI reveals large-scale network activation in minimally conscious patients. *Neurology*, *64*(3), 514–523.

Schnakers, C., Giacino, J., Kalmar, K., Piret, S., Lopez, E., Boly, M., et al. (2006). Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Annals of Neurology*, *60*(6), 744–745. author reply 745.

Schnakers, C., Majerus, S., Giacino, J., Vanhaudenhuyse, A., Bruno, M. A., Boly, M., et al. (2008a). A French validation study of the Coma Recovery Scale-Revised (CRS-R). *Brain Injury*, *22*(10), 786–792.

Schnakers, C., Majerus, S., Goldman, S., Boly, M., Van Eeckhout, P., Gay, S., et al. (2008b). Cognitive function in the locked-in syndrome. *Journal of Neurology*, *255*(3), 323–330.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., et al. (2008c). Voluntary brain processing in disorders of consciousness. *Neurology*, *71*(20), 1614–1620.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., et al. (2009). Diagnostic accuracy of

the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, *9*, 35.

Shiel, A., Horn, S. A., Wilson, B. A., Watson, M. J., Campbell, M. J., & McLellan, D. L. (2000). The Wessex Head Injury Matrix (WHIM) main scale: A preliminary report on a scale to assess and monitor patient recovery after severe head injury. *Clinical Rehabilitation*, *14*(4), 408–416.

Smart, C. M., Giacino, J. T., Cullen, T., Moreno, D. R., Hirsch, J., Schiff, N. D., et al. (2008). A case of locked-in syndrome complicated by central deafness. *Nature Clinical Practice. Neurology*, *4*(8), 448–453.

Teasdale, G., & Jennett, B. (1974). Assessment of coma and impaired consciousness. A practical scale. *Lancet*, *2*(7872), 81–84.

The Multi-Society Task Force on PVS. (1994). Medical aspects of the persistent vegetative state (1). *The New England Journal of Medicine*, *330*(21), 1499–1508.

Tommasino, C., Grana, C., Lucignani, G., Torri, G., & Fazio, F. (1995). Regional cerebral metabolism of glucose in comatose and vegetative state patients. *Journal of Neurosurgical Anesthesiology*, *7*(2), 109–116.

Vanhaudenhuyse, A., Schnakers, C., Bredart, S., & Laureys, S. (2008). Assessment of visual pursuit in post-comatose states: Use a mirror. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*(2), 223.

Wijdicks, E. F. (2006). Clinical scales for comatose patients: The Glasgow Coma Scale in historical context and the new FOUR Score. *Reviews in Neurological Disease*, *3*(3), 109–117.

Wijdicks, E. F., Bamlet, W. R., Maramattom, B. V., Manno, E. M., & McClelland, R. L. (2005). Validation of a new coma scale: The FOUR score. *Annals of Neurology*, *58*(4), 585–593.

Wood, R. L. (1991). Critical analysis of the concept of sensory stimulation for patients in vegetative states. *Brain Injury*, *5*(4), 401–409.

Working Party of the Royal College of Physicians. (2003). The vegetative state: Guidance on diagnosis and management. *Clinical Medicine*, *3*(3), 249–254.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 5

The problem of aphasia in the assessment of consciousness in brain-damaged patients ☆

Steve Majerus[1,3], Marie-Aurélie Bruno[2,3], Caroline Schnakers[2], Joseph T. Giacino[4] and Steven Laureys[2,3,*]

[1]*Center for Cognitive and Behavioral Neuroscience and Coma Science Group, University of Liège, Belgium*
[2]*Cyclotron Research Center and Coma Science Group, University of Liège, Belgium*
[3]*Fund for Scientific Research – FNRS, Belgium*
[4]*JFK Medical Center, Edison, NJ, USA*

Abstract: The assessment of the level and content of consciousness in brain-damaged patients relies to a large extent on behavioral assessment techniques. The limited behavioral repertoire displayed by vegetative and minimally conscious states requires the use of highly sensitive and reliable behavioral assessment methods, allowing the detection of subtle changes in behavior and associated level of consciousness. This situation is further complicated when patients with such disorders of consciousness have underlying deficits in the domain of communication functions, such as aphasia. The present paper examines the consequences of receptive and/or productive aphasia on the already limited behavioral repertoire presented in these patients and discusses a number of behavioral and neuroimaging assessment procedures designed to: (1) detect the presence of aphasia in patients with disorders of consciousness, and (2) reliably assess the level of consciousness of brain-damaged patients while taking into account the existence of receptive and/or expressive language deficits. The combined use of behavioral and neuroimaging assessment techniques appears to be particularly promising for disentangling impaired consciousness and aphasia.

Keywords: minimally conscious state; vegetative state; aphasia; dysphasia; communication; consciousness; responsiveness; behavioral assessment; neuroimaging

Introduction

The assessment of level of cognition in patients with altered states of consciousness such as vegetative state (VS) and minimally conscious state (MCS) is primarily based on the observation of spontaneous behaviors and those that occur in response to verbal, visual, or tactile stimulation. A number of consensus-based criteria have been proposed to distinguish MCS from VS. These criteria entail the observation of a number of behaviors considered to be inconsistent with VS and indicating the presence of minimal signs of consciousness, such as (1) visual fixation and pursuit, (2) response to verbal commands,

☆ Steve Majerus and Marie-Aurélie Bruno, both authors contributed equally to this study.

*Corresponding author.
Tel.: +3243662316; Fax: +3243662946;
E-mail: steven.laureys@ulg.ac.be

DOI: 10.1016/S0079-6123(09)17705-1

(3) intelligible verbalization, (4) localization to noxious stimuli (Giacino, 2004; Giacino and Whyte, 2005; Majerus et al., 2005; Working Party of the Royal College of Physicians, 2003). Many of these behaviors require language comprehension or a response to verbal stimulation. The possible existence of unrecognized language disorders might, in some patients, prevent consistent behavioral responses to these verbal items, leading to an underestimation of the patient's level of consciousness. The present chapter examines the likelihood of the co-occurrence of language disturbance and alteration in consciousness, presents specific assessment procedures for detecting language impairment in patients with disorders of consciousness and discusses a number of precautionary measures when determining level of consciousness in patients likely to have associated language disorders.

A brief overview of the cognitive architecture of language processing and underlying neuroanatomical correlates

Before considering the likelihood of language disorders in patients with impaired consciousness, we will provide here a brief overview of the cognitive architecture of language processing and underlying neuroanatomical correlates, since this knowledge will be determinant when trying to delineate the nature of possible language disorders in patients with alterations in consciousness.

At the receptive level, different levels have to be distinguished, starting with sound-based analysis processes, involving acoustic and phonetic analysis. Acoustic processing, common to verbal and nonverbal sounds, involves the bilateral primary auditory cortex and surrounding lateral superior temporal cortex, with a dominance of left superior temporal cortex for temporal analysis, and right superior temporal cortex for spectral analysis (Formisano et al., 2003; Wessinger et al., 2001; Zatorre and Belin, 2001). Phonetic processing, that is, the extraction of temporal and spectral acoustic features necessary for identifying the basic verbal units (phonemes), involves the same neural substrates in the superior temporal lobes (Binder et al., 2000; Joanisse and Gati, 2003; Scott et al., 2000; Shestakova et al., 2004; Zatorre and Belin, 2001). The next level, phonological processing, involves the mapping of phonetic information to abstract representations of the speech sounds defining the phonology of a language (the vowels and consonants of a given language); this type of processing is subtended by the bilateral posterior superior temporal gyri and the superior temporal sulci (Binder et al., 2000; Scott et al., 2000). Finally, at the lexico-semantic stage, sounds are mapped to existing word forms and their associated semantic features, resulting in speech comprehension. The neural substrate involved in lexico-semantic stages are much more distributed, involving anterior temporal, middle and inferior temporal, medial temporal, inferior parietal as well as anterior inferior prefrontal regions (Binder et al., 2000; Longoni et al., 2005; Majerus et al., 2002; Martin et al., 1996). The precise role of these different areas involved in lexico-semantic processes has been proposed to vary as a function of semantic content, more abstract representations activating preferably the inferior prefrontal regions, animal categories activating the inferior temporo-occipital cortex and the tool category activating premotor regions (Martin et al., 1996; Noppeney and Price, 2004).

At the level of speech production, the starting point will be the lexico-semantic network, followed by the activation of phonological codes in the superior temporal lobe which, via the arcuate fasciculus, will activate corresponding articulatory patterns for speech motor production (Hickok and Poeppel, 2007). Speech motor production is subtended by a network involving the left frontal operculum (Broca's area), the left insula and adjacent sensori-motor cortex, subcortical nuclei (thalamus, putamen, pallidum) as well as the cerebellum (Hickok and Poeppel, 2007; Riecker et al., 2005). Finally, the precise neural substrate of sentence-level processing is less clearly understood. However, many studies have shown that Broca's area and adjacent inferior prefrontal cortex is critical for syntactic processing while the anterior temporal pole has also been frequently

shown to be involved in sentence comprehension processes (e.g., Longoni et al., 2005; Vigneau et al., 2006).

Language disorders as a result of brain lesion (i.e., aphasia) can concern any combination of these different language processes, depending on the type and extent of brain lesions. However, for the issue of interest here, it is important to note that, except for very large lesions involving approximately two-thirds of the left hemisphere, aphasic patients rarely present global aphasia for a prolonged time (Kirshner, 1995; Laska et al., 2001). Global aphasia refers to the situation where both expressive and receptive language processing are severely impaired, leading to near complete loss of language comprehension and production. Global aphasia is frequent at the acute stage (25%) but its incidence rapidly decreases to a few percent after 18 months (Laska et al., 2001). The more typical and lasting situation is characterized by selective difficulties involving speech perception, lexical retrieval (word form access — anomia), semantic access (word meaning access), speech production (articulation — dysarthria, apraxia of speech), sentence comprehension and sentence production (agrammatism), patients presenting difficulties in one or several of these domains, but often retaining the capacity to understand high frequency and highly familiar words, to perceive words that are phonetically quite distinctive (e.g., car — bike, as opposed to bike — pike), to understand simple sentences and to utter single words.

The likelihood of aphasia in altered states of consciousness

The type of brain lesion causing an alteration of consciousness levels provides a first indication of the likelihood of associated language problems. Overall, in the light of the results presented above, any brain lesion involving the left superior, middle and/or inferior temporal lobes is likely to be associated with receptive aphasia, as well as word finding difficulties during language production; any brain lesion involving Broca's area and surrounding cortical and subcortical areas is indicative of possible speech output difficulties. More specifically, lesions in these regions are most frequent in patients presenting a left-hemisphere ischemic or hemorrhagic pathology, most frequently due to thrombosis or aneurysms in the territory of the left-middle cerebral artery (Kirshner, 1995). Cerebral vascular pathologies are among the most frequent etiologies of aphasia; the prevalence of aphasia after an ischemic stroke ranges between 15 and 30% (Inatomi et al., 2008; Laska et al., 2001). Traumatic brain injury less often leads to focal brain injury that could result in aphasic type language disorders (15% of all patients presenting traumatic brain injury; Chapman et al., 1995; Eisenberg et al., 1990). At the same time, it should be noted that for focal lesions in severe traumatic brain injury, they tend to be most widely distributed in the fronto-temporal area (Chapman et al., 1995; Levin et al., 1988; Newton et al., 1992). Severe aphasia is however very rarely reported as a result of traumatic brain injury. The most frequent language impairment at acute stages of closed traumatic brain injury is anomia (Heilman et al., 1971). Receptive language difficulties are most often related to sentence complexity, comprehension of simple sentence structures being in general preserved. However, discourse level deficits are a very common consequence of traumatic brain injury (Chapman et al., 1995). Given the limited and simplified verbal instructions used during assessment of levels of consciousness, this type of language disturbance should however be of little consequence in the accurate assessment of consciousness in these patients. Finally, carbon monoxide intoxications and herpes simplex encephalitis are other causes leading to altered states of consciousness (e.g., Schnakers et al., 2008a, b). Given that these pathologies preferentially lead to brain lesions in medial temporal and hippocampal areas, they very rarely lead to severe aphasic syndromes, but semantic impairments can nevertheless be a frequent consequence of these pathologies.

With respect to functional brain imaging findings in patients with altered states of consciousness such as MCS and VS, Laureys et al. (2000a, b, 2004a, b) showed that the regions that are most hypometabolic in patients presenting a VS or a

MCS involve posterior parietal areas, including the precuneus and posterior cingulate cortex, and that recovery of activation in these areas is what best differentiates patients in a VS and those in a MCS. At the same time, this does not necessarily imply that language-processing regions show preserved brain metabolism in MCS patients. In order to investigate this question, we explored the level of glucose metabolism in 36 MCS patients (minimum inclusion criterion: patients had to show visual fixation; Giacino, 2004) and 40 age-matched healthy controls using [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography (PET FDG) brain imaging. These patients either had suffered from anoxia, traumatic brain injury, hemorrhagic, stroke, or other lesions (see Table 1). The images were spatially normalized into standard stereotactic space, smoothed using a smoothing kernel width at a half maximum of 14 mm owing to the severely damaged brains of the patients in minimally conscious state (MCS) (Friston, 1997). The images were then analyzed using an ANOVA design (SPM8b, www.fil.ion.ucl.ac.uk/spm), with participant group as group factor. Global scaling by proportional scaling was used. We focused the analyses specifically on main language-processing regions. This was achieved by applying an inclusive mask covering major language-processing regions in the left superior, middle and inferior temporal gyri, and the left inferior frontal gyrus, as well as the right inferior temporal gyri, based on the coordinates published in the functional neuroimaging studies of language processing reported earlier (Binder et al., 2000; Joanisse and Gati, 2003; Longoni et al., 2005; Majerus et al., 2002; Martin et al., 1996; Noppeney and Price, 2004; Scott et al., 2000; Shestakova et al., 2004; Vigneau et al., 2006; Zatorre and Belin, 2001). As shown in Fig. 1, the estimated metabolism of regions included in this mask volume was significantly lower in all MCS patients relative to the control group, and this irrespective of type of insult. Furthermore, as shown by the individual metabolic values in Fig. 1, there was a remarkably comparable level of hypometabolism in language-processing regions, despite the fact that the patients within each group varied greatly in terms of lesion site and lesion extent (see Table 1). This means that reduced levels of metabolism in language-processing areas might be a common characteristic of patients in a MCS.

In sum, the possibility of co-occurrence of severe aphasia and an alteration of consciousness should be considered especially in the context of left hemisphere cerebro-vascular pathologies or any other pathology leading to direct focal lesions in the left perisylvian area (e.g., focal traumatic brain injury). However, resting metabolic levels in language-processing areas cannot be used to directly infer the existence of possible language impairment given that hypometabolism in these regions appears to be a wide-ranging characteristic of minimally conscious patients.

Detection of aphasia in altered states of consciousness

Given the data presented in the previous section, the first important information to gather is structural information about the existence of focal brain lesions, and the extent and localization of these lesions, using CT or structural MRI scans. However, although structural brain imaging will

Table 1. Characteristics of 36 minimally conscious patients under going PET-FDG resting state brain imaging for determining metabolism levels in language processing areas

Brain injury type	Focal lesion in left hemisphere language processing areas	Other focal lesions	Diffuse or non-specified lesions	Age range (years)	Time post-onset
Anoxia	0	1	11	26–64	1 month-7 years
Traumatic brain injury	2	3	12	16–43	2 months-22 years
Hemorrhagic lesions, stroke, other	3	4	0	45–88	1 month-5 years

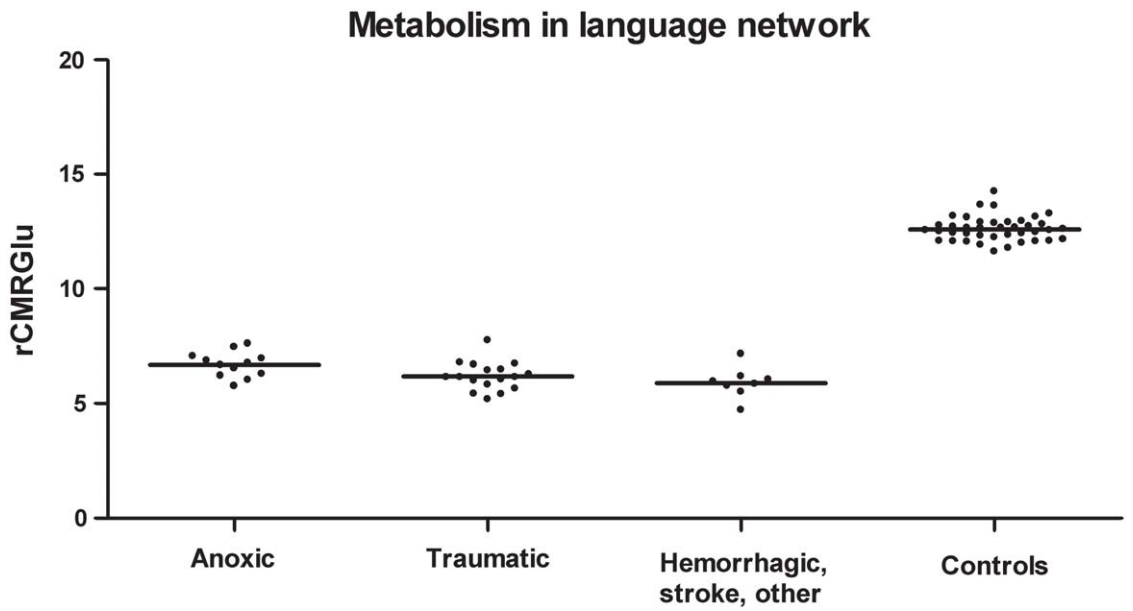


Fig. 1. Resting state metabolism (PET-FDG) in main fronto-temporal language-processing areas, in minimally conscious state patients as a result of anoxia, traumatic brain injury, or hemorrhagic, stroke, and other lesion types, and in age-matched healthy controls (first eigenvariate of main group effect for the volume of interest as defined by an inclusive mask covering major language-processing areas; see text for further details).

reveal potential lesions in temporal and inferior prefrontal language-processing areas, they give no information about the functionality of lesional and peri-lesional areas and their residual ability to support processing of language stimuli. As we have seen, looking at basic resting state metabolism in language processing will not be very informative given the general hypometabolism observed in these areas in MCS patients. The implementation and adaptation of specific event-related functional neuroimaging and event-related potential paradigms could however be of particular interest. Based on single case and group studies, it has been shown that language-processing areas in the superior, middle, and inferior temporal lobes can be reliably activated in patients in a MCS. Using functional MRI or $H_2{}^{15}O$-PET, Laureys et al. (2000a, 2004b; Boly et al., 2004) presented to their patients auditory-verbal information such as the patient's own name, as opposed to noise, and observed extensive activation in the superior and middle temporal lobes specifically for the meaningful linguistic stimulus. Similar results have been observed by a different research team when presenting meaningful linguistic stimuli to a lower bound MCS patient (e.g., Owen et al., 2006). Even for patients in a VS, it has been shown that language stimuli activate language-processing areas in the temporal lobe, although this activation is restricted to the superior temporal lobe surrounding the primary auditory cortex and is disconnected from other temporal lobe regions (Laureys et al., 1999, 2000a, b). Other investigators have shed further light on the integrity of the underlying language network in patients with disorders of consciousness by contrasting fMRI responses to intelligible and unintelligible speech. Schiff et al. (2005) presented fully-comprehensible spoken narratives to a group of healthy volunteers and two patients who fulfilled the diagnostic criteria for MCS. In a second condition, the narratives were digitally reversed resulting in loss of speech content and prosody. Both the volunteers and patients showed robust activity in the superior and middle temporal gyri during

exposure to the comprehensible narratives. However, unlike the volunteers, the MCS patients demonstrated marked reductions in activity during presentation of the reversed narratives. The investigators suggested that the MCS patients' inactivity in the reversed condition reflected an inability to drive language structures when exposed to effortful processing demands. This hypothesis was supported by post-scan interviews in which volunteers reported that they recognized the stimuli as potential speech stimuli and initially increased their attempts to understand it. Given these results, the possibility of receptive language processing deficits in MCS patients should be considered if a patient fails to show consistent activation in superior middle and inferior temporal lobes in response to the presentation of meaningful verbal stimuli in an fMRI paradigm, relative to other MCS patients and healthy controls.

It should be noted that although fMRI studies allow us to compare activation patterns in patients and control subjects, the existence of a similar activation profile in patients and control subjects does not automatically imply similar and accurate language processing in both populations, and hence language comprehension. For example, functional neuroimaging studies in healthy controls have shown that similar activation profiles are observed in superior, middle, and inferior temporal gyri when word (e.g., trailer) and non-word stimuli (e.g., traimer) are presented (Binder et al., 2000; Price et al., 1996), suggesting that even when verbal stimuli have no defined lexical and semantic content, and hence cannot be understood, lexical and semantic-processing areas in the temporal lobes are activated. This also means that a patient showing activation in these temporal areas following the presentation of a meaningful verbal stimulus might still be unable to comprehend the stimulus. More generally, fMRI activation provides information about the type of regions involved in a specific cognitive process, but does not necessarily provide information about the result and accuracy of the ongoing cognitive process. At the same time, negative findings in response to activation paradigms do not rule out the possibility that the capacity for language processing is retained. Many other factors may mask or suppress cortical activity associated with fMRI-based language tasks including disturbances in the blood-brain barrier, cerebrovascular and structural anomalies, impairments in subjects' level of arousal, attention and motivation, motion artifact and the field strength of the magnet (Brown, 2007).

Neurophysiological paradigms, using event-related potentials (ERP) measuring the electrical correlate of neural activity in response to specific stimuli, could provide further helpful information. Although this technology has a much lower spatial resolution, the temporal resolution is at the millisecond level, and, relative to fMRI which has a temporal resolution of 1000 ms at best, is much more suited to study the temporal succession of the different cognitive processes involved in online speech perception processes. In standard listening conditions, a spoken word is identified (i.e., its meaning is accessed) in less than 400 ms (Kotz et al., 2005; Marslen-Wilson and Welsh, 1978). In the speech perception literature, different paradigms have been developed allowing to capture the functioning of perceptual, lexical, and semantic processes. A very interesting ERP component is the negative amplitude occurring 100–200 ms after stimulus onset (mismatch negativity, MMN), and this particularly when a new stimulus occurs within a sequence of repetitive stimuli (e.g., da — da — da — ba). This component has been used very extensively to study acoustic and phonological processes (e.g., Hisagi et al., 2006; Näätänen, 1990; Ylinen et al., 2006). A further quality of the MMN is that it can be obtained in very passive conditions, where conscious awareness of the target stimulus is not necessary. In this paradigm, the participants are often exposed to a secondary task such as viewing a film, and the auditory stimuli of interest are presented via headphones to the participant, without the participant having to pay attention to the stimuli (Näätänen, 1990). The MMN is also used to reliably study speech perception processes in pre-conscious neonates and infants (e.g., Dehaene-Lambertz and Baillet, 1998). This renders the paradigm particularly interesting to identify speech perception problems in MCS, and

possibly, also VS patients. This paradigm can be used to explore sensitivity to all phonetic contrasts existing in a given language at the consonant and vowel level (e.g., ba — ba — ba — pa or bi — bi — bi — bi — bu). If the patient fails to present an MMN response to deviant stimuli differing at the acoustic, phonetic or phonological level, this may suggest that linguistic information is not accurately processed at this level. Later potentials, such as the positive peak at 300 ms and the negative peak at 400 ms post-stimulus, have been used to study lexical and semantic processes. For example, in a lexical decision task, where word (e.g., house) and nonword stimuli (e.g., houme) are successively presented, an earlier P300 and an earlier N400 are observed if the target word stimulus is primed (preceded for a brief time period) by a semantically related word, indicating that the word and its semantic relationships have been identified (e.g., Hill et al., 2005). In a lexical decision task, the P300 to words shows a larger amplitude and a shorter latency when the words have been acquired early or are more frequent, indicating that the P300 indexes lexical recognition processes (Tainturier et al., 2005; Polich and Donchin, 1988). The P300 response is also larger for words as compared to nonwords (Pulvermüller et al., 2004). The later negativity at 400 ms (N400) has been extensively used to study higher level semantic processes, such as the detection of semantic plausibility of sentences, an N400 component being observed when a sentence ends with a semantically implausible word (e.g., the cat chased the door; Kutas and Hillyard, 1980). Hence, the observation of unexpected P300 and N400 patterns in response to word and sentence stimuli is likely to indicate abnormal lexical and/or semantic processes, consistent with findings of abnormal P300 and N400 in aphasic patients with lexico-semantic impairment (e.g., Hagoort et al., 1996; Pulvermüller et al., 2004).

Although the paradigms used for eliciting P300 and N400 components are attentionally more demanding paradigms (listening to words, pseudowords, or sentences) than the paradigms used to elicit MMN components, previous research in MCS patients has shown that reliable P300 components can be observed in MCS patients when hearing their own name as compared to an unfamiliar name (e.g., Laureys et al., 2004b; Perrin et al., 2006; Schnakers et al., 2008b). Even in some vegetative state (VS) patients, a P300 has been observed when comparing the patients' own names to unfamiliar names, however, these responses are less consistent for this patient group (Glass et al., 1998; Perrin et al., 2006). N400 components can also be reliably observed in MCS patients: Schoenle and Witzke (2004) showed that 67 MCS patients (from a total of 74 patients) showed N400 waves for semantically incongruent sentences, while this was only the case in 5 out of 46 VS patients (see also Kotchoubey et al., 2005, for related findings). On the other hand, early negative amplitudes involved in perceptual and phonological processes appear to be identifiable in the vast majority of VS patients (Perrin et al., 2006; Schnakers et al., 2008b).

Finally, at the behavioral level, and for patients in a MCS, the detection of possible signs for aphasia could also be attempted by using customized bedside aphasia screening batteries, varying the linguistic complexity (such as word frequency, age of acquisition, word length) of single word instructions and alternating the use of auditory-verbal, visual-verbal, and visual-nonverbal instructions. If a patient responds to simple instructions using short, high frequency words (''Raise your arm''; ''Close your eyes'') but not to more complex instructions using longer and less frequent words (''Elevate your arm and lower your eyelids''), then this could be a possible indication of language-related, attentional or short-term memory difficulties. Evidence to support this contention is provided by a recent study by Nakase-Richardson et al. (2008). These authors found that patients who had emerged from MCS and were able to respond reliably to yes/no questions concerning situational orientation (e.g., ''Am I pointing to the ceiling?''), showed a high rate of inconsistency (34% correct) when responding to questions of greater semantic complexity (e.g., ''Will a stone sink in water?'').

The presentation modality of verbal information should also be varied and possible preserved capacities for processing written language should

not be underestimated. If a patient responds consistently better to a written command than to the same command presented auditorily, then this is likely to indicate specific difficulties at the level of auditory-verbal input processing (assuming that audiometric testing, using auditory evoked potentials, has ruled out the existence of peripheral or central hearing disorders). It must be noted here that the processing of written and spoken language share the same semantic levels of representation, but that access to these semantic representations from written visual input uses a specific network involving the left posterior inferior temporal gyrus (fusiform gyrus) and the left supramarginal gyrus (e.g., Fiez and Petersen, 1998; McCandliss et al., 2003). Hence, in case of severe speech perception problems due to bilateral lesions at the level of the primary auditory cortex and superior temporal gyri, a patient might still be able to (partially) comprehend speech using the written input modality (Kirshner, 1995). Dissociations between written and auditory language processing have been very frequently reported in the aphasia literature (e.g., Caramazza and Hillis, 1990; Coppens et al., 1998; Majerus et al., 2001, 2004; Puel et al., 1982). Finally, visual-nonverbal communication capacities should also be assessed by providing the patient a visual or gestural description of the command he/she is requested to perform. If the patient is able to raise his/her hand after the examiner has performed the requested movement in front of the patient and the examiner has pointed to the patient to invite him/her to do the same, but if the patient does not perform the same movement upon auditory and written verbal request, then the existence of language-related disorders should be considered. This sort of dissociation in response accuracy to auditory and written verbal requests is illustrated in a case reported by one of the current authors (Smart et al., 2008). A 53-year-old male who developed locked-in syndrome following a pontine hemorrhage showed significantly poorer response consistency and accuracy when answering semantically complex questions presented verbally, but had little difficulty when the same questions were presented in written form. Although this pattern of findings was not indicative of language disturbance, auditory processing impairment was strongly suspected. Presentation of a passive fMRI speech paradigm failed to elicit the expected activity in primary and secondary auditory cortices. In contrast, exposure to passive visual stimuli revealed activation of the primary visual cortex with selective activation of the fusiform face and hippocampal place areas in response to faces and landscape scenes, respectively. Taken together with the bedside findings, these results were strongly suggestive of central deafness. Information gathered via this type of multimodal aphasia assessment will likely yield more clues regarding the probability of unrecognized language and auditory processing impairments in nonverbal and behaviorally unresponsive patients.

Implications for behavioral assessment of level of consciousness

Despite the different techniques discussed here, the detection of language disorders in the context of altered states of consciousness remains a very difficult enterprise. With respect to the assessment of levels of consciousness, the difficulty resides in the detection of behaviors consistent with minimal voluntary and conscious control, while ruling out the possibility that the non-observation of these behaviors is due to language difficulties preventing the patient from comprehending the task instruction and/or producing the required response. The aim of behavioral assessment should thus be to use the most appropriate presentation formats for items containing a verbal request and to avoid the situation where a response is entirely dependent upon the production of a verbal response. Although this general recommendation might conflict with the very precisely defined and standardized administration procedures guaranteeing the reliability of modern behavioral assessment scales such as the CRS-R (Giacino et al., 2004), the WHIM (Shiel et al., 2000), or the SMART (Gill-Thwaites and Munday, 2004), the sensitivity and validity of assessment might depend upon the possibility of adapting the administration modes of individual

items to the patient's best receptive and productive abilities. In case of probable aphasic disorders, or simply in case of doubt, the following recommendations for behavioral assessment are proposed:

1. An item containing an auditory or a written verbal instruction should be presented repeatedly, and the best possible response should be scored.
2. If an item is designed to be administered through the auditory mode, and the patient fails to respond, a written prompt should be presented. Similarly, if there is no response to written presentation, an auditory prompt should be provided.
3. In any case, any failed verbal item should be readministered using a gestural or graphical presentation mode; for example, the experimenter performs the command in front of the participant, and the participant is asked (or requested via a gesture) to imitate the command. Aphasic patients should be able to imitate the gestural commands. However, examiners should be cautious in interpreting this type of performance as responses similar to the expected ones may be noted in patients who present with non-intentional imitation or utilization behavior arising from mesiobasal frontal lesions (Lhermitte et al., 1986).
4. Although the verbal instructions of most items are standardized, slight deviations should be allowed in order to allow for shorter formulations, to allow for reformulations using more frequent or familiar words.
5. When there is no explicit formulation associated with the item (such as ''patient obeys to a verbal command,'' Item 15, WHIM), the shortest possible formulation should be used avoiding any unnecessary verbal additions (e.g., say ''Raise your arm'' or ''Raise your arm, please'', but do not say ''May I ask you to raise your arm?'' nor ''Can you raise your arm?'').

These recommendations are based upon the findings that aphasic symptoms are rarely global in the case of circumscribed cerebral lesions in the perisylvian area, and that elementary speech comprehension and production processes, as needed during the administration of behavioral assessment tools for altered states of consciousness, are still possible in the vast majority of aphasic patients. Cases of global aphasia leading to near complete loss of language comprehension and production abilities are possible, but they are typically associated with very extensive left-hemisphere lesions that can be easily identified based on structural CT or MRI scans.

Discussion

In this work, we proposed that a multimodal assessment protocol, combining specific fMRI, ERP and behavioral assessment protocols could allow to detect possible language impairment in patients with disorders of consciousness. However, the reader should keep in mind that results indicating possible language impairment obtained via these techniques will need to be considered with great care, and that some techniques and paradigms might be more informative than others.

First, with respect to functional neuroimaging results, the observation of resting state hypometabolism in language-processing areas is probably the most difficult-to-interpret situation. As we have shown, most MCS patients, irrespective of lesion location, will show hypometabolism in language-processing areas, relative to controls. However, this does not automatically imply that all MCS patients have language impairment. Hypometabolism in language-processing areas informs us about a decrease of the spontaneous level of activity in language-processing areas; this spontaneous decrease of activity could reflect the MCS patients' reduction of spontaneous verbal behavior and inner verbal thought rather than impaired language processing. In other words, language processing is reduced but not necessarily impaired. A number of studies have shown that resting state brain activity in healthy controls involves the active recruitment of language-processing areas and is related to the participants' engagement in ''conceptual'' processing (e.g.,

Binder et al., 1999). Hence the observation of hypometabolism in language-processing areas in MCS patients during passive, resting state conditions is probably not highly informative with respect to the detection of potential language impairment. On the other hand, fMRI paradigms trying to activate language-processing areas as a function of the controlled presentation of language stimuli may be a more powerful paradigm: if a patient activates semantic-processing areas following the presentation of word stimuli, then this indicates more clearly that language-processing areas can indeed be reliably activated. However, this does not yet inform us about the accuracy of language processes subserved by these regions. Furthermore, an absence of stimulus-related activation in language-processing areas could signal language impairment, but could also be due to sensory, anatomical, statistical, and technical factors described earlier. ERP techniques will probably present the highest informative value, as they measure online brain responses signaling the actual, successful identification of linguistic contrasts by the language system, and allow the exploration of a patient's speech perception abilities in a highly refined manner. Furthermore, as we have seen at least for perceptual and phonological factors, reliable ERP signals can be obtained even in patients with severely compromised consciousness levels such as VS patients. Finally, the power of structural imaging to highlight structural damage to language-processing areas should not be underestimated. In sum, ERP paradigms and structural imaging, in combination with adapted behavioral assessment protocols, might represent the fastest and most powerful techniques to explore the brain's potential to process language information in VS and MCS patients.

Conclusion and perspectives

Future research will be necessary to improve and refine multimodal assessment techniques for language impairment in VS and MCS patients. In order to reliably determine that a specific brain response or its absence signal potential language impairment, be it for fMRI or ERP paradigms, brain responses obtained in VS and MCS patients for stimulations contrasting phonological, lexical, and/or semantic information need to be directly compared with those of aphasic but conscious patients, and this as a function of phonological, lexical, and/or semantic language impairments that have been identified in these patients. A major challenge for conducting these across-patient group studies will be to select the appropriate baseline or control tasks (see also Crosson et al., 2007, for a review of additional methodological concerns for language-related fMRI in patient groups). For example, when identifying semantic processes, brain activation is often compared to a non-semantic linguistic condition such as distorted, meaningless speech stimuli. As we have seen, patients in MCS, whether language impaired or not, will present altered activation in language-processing areas during these baseline conditions or even rest; when contrasting the condition-of-interest to this type of baseline condition, abnormal brain activation patterns might in fact arise due to abnormal activation in the baseline condition, and not necessarily in the experimental condition. A possible solution is to use a nonlinguistic control condition, such as listening to simple environmental sounds and tone stimuli, for which we know that MCS patients present normal activation levels in at least a subset of language-processing areas (Laureys et al., 2000a), and to contrast activity of the language processing condition-of-interest with this nonlinguistic control condition.

With respect to the bedside aphasia assessment protocols we have proposed, their feasibility and sensitivity need to be validated via their administration to representative groups of MCS and aphasic patient groups in order to determine what type of language complexity (phonological, semantic, syntactic) affects verbal communication modes in MCS patients and whether language complexity affects communication in MCS and aphasic patients to the same extent. Similarly, with respect to the adaptations we have proposed for the administration of consciousness assessment scales, existing scales such as the WHIM, the

CRS-R, or the SMART should be screened for linguistic complexity of item formulations, as well as for the possibility to allow for repeated presentation and the use of alternative item presentation modalities (e.g., auditory vs. written item presentation). These scales should also be administered, following standard administration procedures, to fully conscious aphasic patients, in order to determine: (1) the extent to which the scoring of existing behavioral assessment scales is affected by concomitant language impairment, (2) what type of aphasic symptom is most detrimental for the assessment of levels of consciousness, and (3) what behavioral assessment scale is most affected by the patient's language impairment.

Acknowledgments

Steve Majerus, Steven Laureys, and Marie-Aurélie Bruno are, respectively, Research Associate, Senior Research Associate, and Research Fellow, at the Fund for Scientific Research-FNRS, Belgium. This study was also supported by the James S. McDonnell Foundation, Mind Science Foundation, European Commission and Concerted Research Action.

References

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Rao, S. M., & Cox, R. W. (1999). Conceptual processing during the conscious resting state: A functional MRI study. *Journal of Cognitive Neuroscience*, *11*, 80–93.

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Springer, J. A., Kaufman, J. N., et al. (2000). Human temporal lobe activation by speech and nonspeech sounds. *Cerebral Cortex*, *10*, 512–528.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, P., Del Fiore, G., et al. (2004). Auditory processing in severely brain injured patients: Differences between the minimally conscious state and the persistent vegetative state. *Archives of Neurology*, *61*, 233–238.

Brown, G. G. (2007). Functional magnetic resonance imaging in clinical practice: Look before you leap. *Neuropsychological Review*, *17*, 103–106.

Caramazza, A., & Hillis, A. E. (1990). Spatial representation of words in the brain implied by studies of a unilateral neglect patient. *Nature*, *346*, 267–269.

Chapman, S. B., Levin, H. S., & Culhane, K. A. (1995). Language impairment in closed head injury. In H. S. Kirshner (Ed.), *Handbook of neurological speech and language disorders* (pp. 387–414). New York: Informa Health Care.

Coppens, P., Lebrun, Y., & Basso, A. (1998). *Aphasia in atypical populations*. New York: Lawrence Erlbaum Associates.

Crosson, B., McGregor, K. K., Gopinath, K. S., Conway, T. W., Benjamin, M., Chang, Y. L., et al. (2007). Functional MRI of language and aphasia: A review of the literature and the methodological challenges. *Neuropsychological Review*, *17*, 157–177.

Dehaene-Lambertz, G., & Baillet, S. (1998). A phonological representation in the infant brain. *NeuroReport*, *9*, 1885–1888.

Eisenberg, H. M., Gary, H. E. J., Aldrich, E. F., Saydjari, C., Turner, B., Foulkes, M. A., et al. (1990). Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. *Journal of Neurosurgery*, *73*, 688–698.

Fiez, J. A., & Petersen, S. E. (1998). Neuroimaging studies of word reading. *Proceedings of the National Academy of Sciences*, *95*, 914–921.

Formisano, E., Kim, D. S., Di Salle, F., van de Moortele, P. F., Ugurbil, K., & Goebel, R. (2003). Mirror-symmetric tonotopic maps in human primary auditory cortex. *Neuron*, *40*, 859–869.

Friston, K. J. (1997). Testing for anatomically specified regional effects. *Human Brain Mapping*, *5*, 133–136.

Giacino, J. T. (2004). The vegetative state and minimally conscious states: Consensus-based criteria for establishing diagnosis and prognosis. *NeuroRehabilitation*, *19*, 293–298.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation*, *85*, 2020–2029.

Giacino, J. T., & Whyte, J. (2005). The vegetative and minimally conscious states: Current knowledge and remaining questions. *Journal of Head Trauma and Rehabilitation*, *20*, 30–50.

Gill-Thwaites, H., & Munday, R. (2004). The Sensory Modality Assessment and Rehabilitation Technique (SMART): A valid and reliable assessment for vegetative state and minimally conscious state patients. *Brain Injury*, *18*, 1255–1269.

Glass, I., Sazbon, L., & Grosswasser, Z. (1998). Mapping ''cognitive'' event-related potentials in prolonged postcoma unawareness state. *Clinical Electroencephalography*, *29*, 19–30.

Hagoort, P., Brown, C. M., & Swaab, T. Y. (1996). Lexical-semantic event-related potential effects in patients with left hemiphere lesions and aphasia, and patients with right hemisphere lesions without aphasia. *Brain*, *119*, 627–649.

Heilman, K. M., Safran, A., & Geschwind, N. (1971). Closed head trauma and aphasia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *34*, 265–269.

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience*, *8*, 393–402.

Hill, H., Ott, F., & Weisbrod, M. (2005). SOA-dependent N400 and P300 semantic priming effects using pseudoword primes and a delayed lexical decision. *International Journal of Psychophysiology*, *56*, 209–221.

Hisagi, M., Shafer, V., & Sussman, E. (2006). Neurophysiological basis of temporally cued phonetic contrasts in Japanese and American English listeners (A). *Journal of the Acoustical Society of America*, *120*, 3172.

Inatomi, Y., Yonehara, T., Omiya, S., Hashimoto, Y., Hirano, T., & Uchino, M. (2008). Aphasia during the acute phase in ischemic stroke. *Cerebrovascular Disorders*, *25*, 316–323.

Joanisse, M. F., & Gati, J. S. (2003). Overlapping neural regions for processing rapid temporal cues in speech and nonspeech signals. *NeuroImage*, *19*, 64–79.

Kirshner, H. S. (1995). *The handbook of neurological speech and language disorders*. New York: Informa Health Care.

Kotchoubey, B., Lang, S., Mezger, G., Schmalohr, D., Schneck, M., Semmler, A., et al. (2005). Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. *Clinical Neurophysiology*, *116*, 2441–2453.

Kotz, S. A., Von Cramon, D., & Friederici, A. D. (2005). On the role of phonological short-term memory in sentence processing: ERP single case evidence on modality-specific effects. *Cognitive Neuropsychology*, *22*, 931–958.

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science*, *207*, 203–205.

Laska, A. C., Hellblom, A., Murray, V., Kahan, T., & Von Arbin, M. (2001). Aphasia in acute stroke and relation to outcome. *Journal of Internal Medicine*, *249*, 413–422.

Laureys, S., Faymonville, M. E., Degueldre, C., Del Fiore, G., Damas, P., Lambermont, B., et al. (2000a). Auditory processing in the vegetative state. *Brain*, *123*, 1589–1601.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., et al. (2000b). Impaired effective cortical connectivity in vegetative state: Preliminary investigation using PET. *NeuroImage*, *9*, 377–382.

Laureys, S., Lemaire, C., Maquet, P., Phillips, C., & Franck, G. (1999). Cerebral metabolism during vegetative state and after recovery to consciousness. *Journal of Neurology, Neurosurgery, and Psychiatry*, *67*, 121.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004a). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*, 537–546.

Laureys, S., Perrin, F., Faymonville, M. E., Schnakers, C., Boly, M., Bartsch, V., et al. (2004b). Cerebral processing in the minimally conscious state. *Neurology*, *63*, 916–918.

Levin, H. S., Williams, D., Crofford, M. J., High, W. M. J., Eisenberg, H. M., Amparo, E. G., et al. (1988). Relationship of depth of brain lesions to consciousness and outcome after closed head injury. *Journal of Neurosurgery*, *69*, 861–866.

Lhermitte, F., Pillon, B., & Serdaru, M. (1986). Human autonomy and the frontal lobes. Part I: Imitation and utilization behavior: A neuropsychological study of 75 patients. *Annals of Neurology*, *19*, 326–334.

Longoni, F., Grande, M., Hendrich, V., Kastrau, F., & Huber, W. (2005). An fMRI study on conceptual, grammatical, and morpho-phonological processing. *Brain and Cognition*, *57*, 131–134.

Majerus, S., Collette, F., Van der Linden, M., Peigneux, P., Laureys, S., Delfiore, G., et al. (2002). A PET investigation of lexicality and phonotactic frequency in oral language processing. *Cognitive Neuropsychology*, *19*, 343–360.

Majerus, S., Gill-Thwaites, H., Andrews, K., & Laureys, S. (2005). Behavioral evaluation of consciousness in severe brain damage. *Progress in Brain Research*, *50*, 401–418.

Majerus, S., Lekeu, F., Van der Linden, M., & Salmon, E. (2001). Deep dysphasia: Further evidence on the relationship between phonological short-term memory and language processing impairments. *Cognitive Neuropsychology*, *18*, 385–410.

Majerus, S., Van der Linden, M., Poncelet, M., & Metz-Lutz, M. N. (2004). Can phonological and semantic short-term memory be dissociated? Further evidence Landau-Kleffner Syndrome. *Cognitive Neuropsychology*, *21*, 491–512.

Marslen-Wilson, W., & Welsh, A. (1978). Processing interactions and lexical access during word recognition in continuous speech. *Cognitive Psychology*, *10*, 29–63.

Martin, A., Wiggs, C. L., Ungerleider, L. G., et al. (1996). Neural correlates of category-specific knowledge. *Nature*, *379*, 649–652.

McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: Expertise for reading in the fusiform gyrus. *Trends in Cognitive Sciences*, *7*, 293–299.

Näätänen, R. (1990). The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behavioral and Brain Sciences*, *13*, 201–288.

Nakase-Richardson, R., Yablon, S. A., Sherer, M., Evans, C. C., & Nick, T. G. (2008). Serial yes/no reliability after traumatic brain injury: Implications regarding the operational criteria for emergence from the minimally conscious state. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*, 216–218.

Newton, M. R., Greenwood, R. J., Britton, K. E., Charlesworth, M., Nimmon, C. C., Carroll, M. J., et al. (1992). A study comparing SPECT with CT and MRI after closed head injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*, 92–94.

Noppeney, U., & Price, C. (2004). Retrieval of abstract semantics. *NeuroImage*, *22*, 164–170.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Brédart, S., et al. (2006). Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Archives of Neurology*, *63*, 562–569.

Polich, J., & Donchin, E. (1988). P300 and the word frequency effect. *Electroencephalography and Clinical Neurophysiology*, *70*, 33–45.

Price, C. J., Wise, R. J. S., & Frackowiak, R. S. J. (1996). Demonstrating the implicit processing of visually presented words and pseudowords. *Journal of Cognitive Neuroscience*, *6*, 62–70.

Puel, M., Joanette, Y., Levrat, M., Nespoulous, J. L., Viala, M. F., Lecours, A. R., et al. (1982). Crossed aphasia in right-handed patients. II. Neuropsychological and neurolinguistic study of a case. Evolution over a 2 year period. *Revue Neurologique*, *138*, 587–600.

Pulvermüller, F., Mohr, B., & Lutzenberger, W. (2004). Neurophysiological correlates of word and pseudo-word processing in well-recovered aphasics and patients with right-hemispheric stroke. *Psychophysiology*, *41*, 584–591.

Riecker, A., Mathiak, K., Wildgruber, D., Erb, M., Hertrich, I., Grodd, W., et al. (2005). fMRI reveals two distinct cerebral networks subserving speech motor control. *Neurology*, *64*, 700–706.

Schiff, N. D., Rodriguez-Moreno, D., Kamal, A., Kim, K. H., Giacino, J. T., Plum, F., et al. (2005). fMRI reveals large-scale network activation in minimally conscious patients. *Neurology*, *64*, 514–523.

Schnakers, C., Ledoux, D., Majerus, S., Damas, P., Damas, F., Lambermont, B., et al. (2008a). Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders. *Brain Injury*, *22*, 926–931.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., et al. (2008b). Voluntary brain processing in disorders of consciousness. *Neurology*, *71*, 1614–1620.

Schoenle, P. W., & Witzke, W. (2004). How vegetative is the vegetative state? Preserved semantic processing in VS patients — Evidence from N400 event-related potentials. *NeuroRehabilitation*, *19*, 329–334.

Scott, S. K., Catrin Blank, C., Rosen, S., & Wise, R. J. S. (2000). Identification of a pathway for intelligible speech in the left temporal lobe. *Brain*, *123*, 2400–2406.

Shestakova, A., Brattico, E., Soloviev, A., Klucharev, V., & Huotilainen, M. (2004). Orderly cortical representation of vowel categories presented by multiple exemplars. *Cognitive Brain Research*, *21*, 342–350.

Shiel, A., Horn, S., Wilson, B. A., McLellan, D. L., Watson, M., & Campbell, M. (2000). The Wessex Head Injury Matrix main scale: A preliminary report on a scale to assess and monitor patients recovery after severe head injury. *Clinical Rehabilitation*, *14*, 408–416.

Smart, C. M., Giacino, J. T., Cullen, T., Moreno, D. R., Hirsch, J., Schiff, N. D., et al. (2008). A case of locked-in syndrome complicated by central deafness. *Nature Clinical Practice. Neurology*, *4*, 448–453.

Tainturier, M. J., Tamminen, J., & Thierry, G. (2005). Age of acquisition modulates the amplitude of the P300 component in spoken word recognition. *Neuroscience Letters*, *379*, 17–22.

Vigneau, M., Beaucousin, V., Hervé, P. Y., Duffau, H., Crivello, F., Houdé, O., et al. (2006). Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing. *NeuroImage*, *30*, 1414–1432.

Wessinger, C. M., VanMeter, J., Tian, B., Van Laren, J., Pekar, J., & Rauschecker, J. P. (2001). Hierarchical organization of the human auditory cortex revealed by functional magnetic resonance imaging. *Journal of Cognitive Neuroscience*, *13*, 1–7.

Working Party of the Royal College of Physicians. (2003). The vegetative state: Guidance on diagnosis and management. *Clinical Medicine*, *3*, 249–254.

Ylinen, S., Shestakova, A., Huotilainen, M., Alku, P., & Näätänen, R. (2006). Mismatch negativity (MMN) elicited by changes in phoneme length: A cross-linguistic study. *Brain Research*, *1072*, 175–185.

Zatorre, R. J., & Belin, P. (2001). Spectral and temporal processing in human auditory cortex. *Cerebral Cortex*, *11*, 946–953.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 6

Predictors of short-term outcome in brain-injured patients with disorders of consciousness ☆

J. Whyte[1,*], O. Gosseries[2], I. Chervoneva[3], M.C. DiPasquale[1], J. Giacino[4], K. Kalmar[4], D.I. Katz[5], P. Novak[6], D. Long[7], N. Childs[8], W. Mercer[8], P. Maurer[9] and B. Eifert[9]

[1]*Moss Rehabilitation Research Institute/Albert Einstein Healthcare Network, Philadelphia, PA, USA*
[2]*Coma Science Group, Cyclotron Research Center, University of Liege, Liege, Belgium*
[3]*Division of Biostatistics, Department of Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA, USA*
[4]*JFK Johnson Rehabilitation Institute, Edison, NJ, USA*
[5]*Brain Injury Program, Braintree Rehabilitation Hospital, Braintree, MA; Department of Neurology, Boston University School of Medicine, Boston, MA, USA*
[6]*Sunnyview Hospital and Rehabilitation Center, Schenectady, NY, USA*
[7]*Bryn Mawr Rehab Hospital, Malvern, PA, USA*
[8]*Texas NeuroRehab Center, Austin, TX, USA*
[9]*Fachkrankenhaus Neresheim Hospital, Neresheim, Germany*

Abstract:
Objectives: To investigate predictors of recovery from the vegetative state (VS) and minimally conscious state (MCS) after brain injury as measured by the widely used Disability Rating Scale (DRS) and to explore differences in rate of recovery and predictors of recovery during inpatient rehabilitation in patients with non-traumatic (NTBI) and traumatic brain injury (TBI).

Design: Longitudinal observational cohort design and retrospective comparison study, in which an initial DRS score was collected at the time of study enrollment. Weekly DRS scores were recorded until discharge from the rehabilitation center for both NTBI and TBI patients.

Setting: Seven acute inpatient rehabilitation facilities in the United States and Europe with specialized programs for VS and MCS patients (the Consciousness Consortium).

Participants: One hundred sixty-nine patients with a non-traumatic (N = ~~50~~) and a traumatic (N = ~~41~~19) brain injury who were in the VS or MCS states.

Interventions: Not applicable.

Main Outcome Measures: DRS score at 13 weeks after injury; change in DRS score over 6 weeks post-admission; and time until commands were first followed (for patients who did not show command-following at or within 2 weeks of admission).

☆Both J. Whyte and O. Gosseries have contributed equally to this study.

*Corresponding author.
Tel.: 00 1 215 663-6872; Fax: 00 1 215 663-6113;
E-mail: JWHYTE@einstein.edu

DOI: 10.1016/S0079-6123(09)17706-3

Results: Both time between injury and enrollment and DRS score at enrollment were significant predictors of DRS score at week 13 post-injury but the main effect of etiology only approached significance. Etiology was however a significant predictor of the amount of recovery observed over the 6 weeks following enrollment. Time between injury and enrollment was also a good predictor of this outcome, but not DRS score at enrollment. For the time until commands were first followed, patients with better DRS scores at enrollment, and those with faster early rates of change recovered command following sooner than those with worse DRS scores or slower initial rates of change. The etiology was not a significant predictor for this last outcome. None of these predictive models explained sufficient variance to allow their use in individual clinical decision making.

Conclusions: Time post-injury and DRS score at enrollment are predictors of early recovery among patients with disorders of consciousness, depending on the outcome measure chosen. Etiology was also a significant predictor in some analyses, with traumatically injured patients recovering more than those with non-traumatic injuries. However, the hypothesized interaction between etiology and time post-injury did not reach significance in any of the analyses suggesting that, within the time frame studied, the decline in prognosis with the passage of time was similar in the two groups.

Keywords: brain injuries; minimally conscious state; vegetative state; Disability Rating Scale; following command; prognosis; consciousness

Introduction

Outcome prediction is a frequent topic in the literature on neurologic recovery and rehabilitation. However, one may have several different purposes in mind in outcome prediction and each of these purposes places different performance requirements on the predictive model. Relatively gross aggregate prediction of rates of recovery may suffice for the purpose of planning healthcare services, estimating costs, or generating payment schemes. Similar gross aggregate models may highlight predictor variables that may have theoretical interest as possible causal factors in recovery. A much more demanding use of outcome prediction is to assist in the healthcare decision making for individual patients. Here one might wish to avoid ''wasting'' resources on someone who will not show substantial recovery, and to ensure that someone with good recovery potential receives services that will optimize that recovery. In this context, even a relatively accurate aggregate model may make inaccurate predictions about substantial numbers of individual cases. Outcome prediction may also differ in the time frame of interest. In many cases, the ''final outcome'' is of greatest interest to predict, but when the model is being used to allocate clinical services, one may be interested primarily in the outcome within the time frame that those services will be provided.

Prediction of outcome among patients with disorders of consciousness (DOC) is still difficult to establish individually. Moreover, most prognostic studies have begun on the day of injury when the diagnoses of vegetative (VS) and minimally conscious states (MCS) are not yet defined, and have studied the full range of injury severity. This provides little guidance to clinicians who see patients who have evolved from coma into the VS or MCS, and who wish to assess the likelihood of further progress, to determine the appropriate level of treatment intensity, and to provide guidance to caregivers in their decision making.

It is known that among patients with DOC one month after injury, those who show some minimal signs of consciousness have a better chance of recovery than patients who are still in a VS at that time, and the earlier the return of consciousness is detected, the better is the outcome (Giacino and Zasler, 1997; Giacino and Whyte, 2005; Whyte et al., 2005; Giacino and Kalmar, 1997). The etiology is also a relevant predictor of recovery.

Traumatic brain injury (TBI) tends to have a better outcome than non-traumatic etiology (NTBI) (especially anoxia) (The Multi-Society Task Force on PVS, 1994b). Moreover, the recovery phase lasts longer for a traumatic etiology: it has been suggested that the term *permanent vegetative state* should not be applied until 1 year after traumatic injury whereas for a non-traumatic injury, this diagnosis may be applied after only 3 months (The Multi-Society Task Force on PVS, 1994a, b). Note that the term *permanent* implies zero probability of recovery and can therefore give rise to serious decisions about the cessation of medication and nutrition.

Potential recovery is also linked to the location, extent, and nature of the brain damage as well as to the condition of the brain before the injury. Young age of the patient and the absence of medical history (such as alcoholism, drug use, or mental illness) lead to a better outcome (The Multi-Society Task Force on PVS, 1994b; Laureys et al., 2001). For patients with DOC of traumatic origin, the Disability Rating Scale (DRS) at 16 weeks post-injury, and the time at which commands were first followed, during the acute rehabilitation hospitalization, were related to the DRS score at rehabilitation admission, the time between injury and admission, and rate of DRS change during the first 2 weeks of rehabilitation (Whyte et al., 2005). New assessment methods, such as event-related potential (ERP) techniques, and evaluation with functional imaging modalities such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) scanning, offer promise in improving the precision of prognostic prediction, since they may help distinguish among patients with different neurophysiologic profiles (which confer different prognoses) at a time when behavioral assessments are at floor for all of them (Di et al., 2008; Owen et al., 2006; Schnakers et al., 2008; Kotchoubey, 2007). However, although these techniques appear to be able to identify a subgroup of VS patients with greater recovery potential or to identify subtle signs of consciousness not apparent on behavioral examination, they have not yet been used in systematic prediction at defined time points post-injury along with already known predictors.

Research on prediction of recovery from DOC is particularly challenging to conduct, at least in the United States, because intensive academically oriented healthcare services are severely restricted for this patient population after the first few weeks post-onset. This is based on a general pessimism that meaningful recovery is unlikely, the belief that the process of rehabilitation requires a level of voluntary participation that such patients cannot meet, and the sense that there is little evidence that intensive rehabilitation services can alter the outcome. Thus, such patients are generally dispersed to family homes or non-specialized nursing care facilities soon after injury, and, accordingly, lost to involvement in longitudinal research.

Because many of the available outcome studies follow a sample from the time of injury, so that a large proportion of the sample (those with milder injury) regain consciousness quickly, predictors of outcome in this rapidly recovering population may not apply to the sample with prolonged DOC. Other studies have followed patients with DOC for longer intervals, but typically restrict their prediction to the return of consciousness as a dichotomous variable (e.g., Multi-Society Task Force), shedding little light on the overall level of functional recovery. In this context, therefore, it is important to examine whether those patients with DOC who are available for study show sufficient recovery during the subacute period to suggest greater rehabilitation potential than is currently appreciated. In addition, if predictors of their short-term outcome are sufficiently accurate to guide individual service decisions, then these could be used to help tune rehabilitation admission criteria to accept the individuals with the greatest potential to benefit, and to avoid admitting individuals who will fail to make progress, and may present difficult placement problems. In this context, then, a number of important outcome questions need to be addressed. (1) As a group, how much recovery do patients admitted with DOC make in the subacute period? (2) Are there variables, available at the time that admission decisions are being made, that can help predict the amount of functional recovery that will occur in the time span over which rehabilitation services

might be delivered? (3) Are there differences in the factors that predict recovery for patients with traumatic versus non-traumatic injuries during this interval?

We hypothesized that substantial recovery would be seen in a large proportion of patients who present with DOC in the first few weeks after brain injury. We also hypothesized, based on prior studies and our own previous work with a pure sample of individuals with traumatic brain injuries, that the etiology of injury (in particular traumatic vs. non-traumatic), the time post-event at which the patient was admitted to rehabilitation, and the functional level at which they were admitted, would all predict differences in the short-term recovery seen over the ensuing weeks.

Methods

Participants in this research were enrolled from the Consciousness Consortium (CC), which consists of a set of facilities in the United States and Europe that have specialized programs for the care and rehabilitation of patients with DOC, and an interest in conducting research in this area. The CC began a longitudinal descriptive study in 1996, and reported the results of the traumatic sample ($n = 424$) in 2005 (Whyte et al., 2005) which laid the groundwork for a randomized controlled treatment study currently underway (Giacino and Whyte, 2003; Whyte, 2007). Here we report the data for the non-traumatic sample also enrolled by CC facilities, and also analyze comparative results for the two subsamples.

Participants

Participants were enrolled in the study between December 1996 and June 2001 when they were admitted to one of the seven CC-member rehabilitation centers. Admission criteria were a severe acquired brain injury of traumatic or non-traumatic etiology and a DRS score on admission greater than 15, with no more than inconsistent command-following. These score criteria were chosen because all patients in VS or MCS should have DRS scores of at least 16, but lack of consistent command following helps ensure that those who have emerged from MCS are excluded. One hundred forty-eight (148) traumatic and 77 non-traumatic patients diagnosed as vegetative or minimally conscious on admission were entered into the longitudinal database. However, because specific variables required for the analyses were missing from some participants, the number of participants included in this report is smaller (see Table 1 for details).

Note that there is a bias of selective admission in rehabilitation centers. Indeed, acute inpatient rehabilitation facilities tend to select, to varying degrees, candidates who are believed to have a

Table 1. Outcome variables

	Traumatic brain injury (TBI)			Non-traumatic brain injury (NTBI)			Definition
	No. of subjects	Mean/median/SD	Min./max.	No. of subjects	Mean/median/SD	Min./max.	
DRS_{13}	99	18.14/20/5.65	5/28	36	19.72/20.5/4.3	9/26	DRS score at week 13 post-injury
$Change_{DRS6}$	99	4.96/4/4.23	−2/11	36	2.86/2.5/2.93	−1/16	[DRS score at enrollment]–[DRS score 6 weeks later]
T_{Follow}	71	62.04/30/79.72	0/473	37	42.27/27/44.73	0/196	[Date of command following or date of discharge if not following commands]−[date of 2 weeks post-admission]

chance of recovery and who will benefit from intensive therapy. Admission is therefore based, at least informally, on various prognostic factors that are perceived to be positive indicators of functional improvement (e.g., recent injury, possible signs of consciousness, etc.). Thus, this is not a population-based study, although it is relevant to decision making in the types of facilities in which the study was conducted.

The study was determined by the relevant Institutional Review Boards to be exempt from the need for individual informed consent because it involved only anonymous recording of observational data but no changes in clinical care.

The Disability Rating Scale (DRS)

The DRS is a measure of impairment, disability (now referred to as ''activity''), and handicap (now referred to as ''participation'') across the span of recovery to track an individual from coma to community (Rappaport et al., 1982). The first three items of the DRS (''Eye Opening,'' ''Communication Ability,'' and ''Motor Response'') reflect impairment ratings whereas cognitive ability for ''Feeding,'' ''Toileting,'' and ''Grooming'' reflect the level of disability and, finally, the ''Level of Functioning'' item reflects handicap, as does the last item, ''Employability''. The DRS is scored from 0 (no disability) to 29 (extreme VS). Note that this scale does not disentangle VS from MCS because it was constructed before the development of the MCS criteria (Giacino et al., 2002).

Data collection

For those patients who met the enrollment criteria for this study, demographic information, injury history and early complications, and admission DRS score were recorded. DRS scoring was repeated weekly as long as the patient remained at the facility. Data were recorded on paper forms and then faxed or mailed to the data center at the Moss Rehabilitation Research Institute, where they were entered into a computer database. For these analyses, the database was queried for demographic information (age, gender, ethnicity), the cause of injury (traumatic or non-traumatic brain injury), the time between the injury and the admission to the rehabilitation facility, the DRS score on admission, the weekly DRS score until discharge, and the time between the admission and the first command following (if not present at admission).

Three outcomes were addressed in the analyses: the DRS score at 13 weeks after injury (DRS_{13}), the change in DRS score over 6 weeks post-admission ($Change_{DRS6}$), and the time until commands were first followed for patients who did not show command following at or within 2 weeks of admission (T_{Follow}). Patients that did not follow commands during admission were censored at the discharge time. The operational definition of each outcome is reported in Table 1. DRS score at 13 weeks post-injury was chosen because the largest sample was available at that time and DRS score over 6 weeks post-enrollment was selected because it is the average length of stay in the rehabilitation facilities. For practical relevance, T_{Follow} would ideally be calculated from the time of admission since a clinician admitting a patient wants to know whether and when he/she will begin to follow commands thereafter. Moreover, calculating this index from the time of injury would be problematic in this sample, since many injured individuals would have recovered command following much earlier, but would not be included in the sample. However, because the rate of functional improvement in the first 2 weeks after admission was used as one of the predictor variables (see below for details), in fact we attempted to predict recovery of command following from that point forward.

Of the participants meeting the enrollment criteria, only those who had complete data for the outcome and predictor variables were used in each analysis (see Tables 1 and 2). This resulted in an effective sample of 135 (99TBI, 36NTBI) for the DRS_{13} and $Change_{DRS6}$ analyses and 108 (71TBI, 37NTBI) for the T_{Follow} analysis. Out of these 108 patients, 48 were censored at the time of discharge. Seventy-four (74) participants (50TBI, 24NTBI) were included in all of the analyses.

Table 2. Predictor variables

	DRS_{13} and 6-week change		T_{Follow}	
	TBI ($N = 99$)	NTBI ($N = 36$)	TBI ($N = 71$)	NTBI ($N = 37$)
Continuous variables	Mean/median/SD	Mean/median/SD	Mean/median/SD	Mean/median/SD
Age	31.58/28/14.09	40.78/39.5/16.33	28.79/26/12.54	36.89/35/14.85
$\text{Log}T_{enroll}$	5.55/5.39/0.55	5.44/5.51/0.49	5.59/5.39/0.59	6.05/5.73/1.29
(T_{enroll})	(50.4/42/20.15)	(45.75/45.5/14.18)	(52.37/42/23.07)	(115.49/53/186.19)
DRS_{enroll}	22.85/23/2.23	23.06/23/2.57	23.84/24/2.14	23.84/24/1.72
Nominal variables	No. of subjects (%)	No. of subjects (%)	No. of subjects (%)	No. of subjects (%)
Gender				
Male	67 (67)	15 (41.7)	54 (76.06)	13 (64.86)
Female	32 (32.3)	21 (58.3)	17 (23.94)	24 (35.14)
Ethnicity				
White	77 (77.8)	29 (80.5)	61 (85.91)	28 (75.68)
Non-white	22 (22.2)	7 (19.4)	10 (14.09)	9 (24.32)

Abbreviations: $\text{Log}T_{enroll}$: $\log_2$ transformation of T_{enroll}; T_{enroll}: date of command following−date of enrollment; DRS_{enroll}: DRS score at enrollment.

The characteristics of the patients in both analyses sets are shown in Table 2.

Data analysis

The independent variable *time to enrollment* (T_{enroll}) was log transformed ($\text{Log}T_{enroll}$), since the assumption of linear association with the outcome was more appropriate on the log scale. NTBI and TBI were analyzed jointly to allow evaluation of the difference in outcomes by etiology. Different statistical models were used for the different outcomes. DRS at week 13 and the change in DRS scores 6 weeks post-admission were analyzed on a total of 135 observations using the robust MM regression (Yohai, 1987), since distributions of residuals from the standard multiple regression models exhibited heavy tails compromising the normality assumption. Etiology, admission DRS, and time to enroll (log base 2 transformed) as well as gender, age, and ethnicity were considered as predictors of DRS at week 13 and change in DRS scores 6 weeks post-admission. The interactions between etiology and admission DRS, etiology and time to enroll, and admission DRS and time to enroll were also considered in the models. The final models included the etiology, admission DRS, and time to enroll and controlled for potentially important age difference. Other demographic variables, which were not significantly associated with outcome, were excluded from the models.

For the last outcome, the time until commands were first followed, the analyses were performed on a partially overlapping sample because some patients in the previous analyses had already followed commands before admission and because some patients were admitted after 13 weeks post-injury. A Cox proportional hazards model was initially fitted to the time from admission to follow commands. Etiology, admission DRS, and time to enroll (log base 2 transformed) as well as gender, age, and ethnicity were considered as predictors. The interactions between etiology and admission DRS, etiology and time to enroll, and admission DRS and time to enroll were also considered in the model. Data from 169 patients were available for these analyses. Because the proportional hazards assumptions were not satisfied, the 2-week rate of change in DRS was also introduced into Cox model, which improved the overall model fit. In the earlier work (Whyte et al., 2005), the 2-week rate of change in DRS was found to be a strong predictor of the time to follow commands in TBI patients. Time from 2 weeks post-admission until commands were followed was then modeled. The final Cox model was based on 108 patients who also had 2-week rate of change in DRS available and did not follow commands within the first 2

weeks of admission. Etiology, admission DRS, and time to enroll (log base 2 transformed) as well as gender, age, and ethnicity were considered as predictors. The interactions between etiology and admission DRS, etiology and time to enroll, and admission DRS and time to enroll were also considered in the model.

Results

DRS score at week 13

None of the demographic variables was significantly associated with DRS score at week 13, but age was retained in the model because of prior research suggesting that age may influence the pace of neurologic recovery (Millis et al., 2001; Ritchie et al., 2000). Both time between injury and enrollment ($\text{Log}T_{\text{enroll}}$) and DRS score at enrollment ($\text{DRS}_{\text{enroll}}$) were highly significant predictors of DRS score at week 13 post-injury. The main effect of etiology approached significance (difference = 1.4, 95% CI: −0.2, 3.0; $p = 0.083$). However, the interactions between etiology and DRS at enrollment and time to enrollment were not significant. Table 3 reports the slopes for the different predictors from the final model. The model implies that an increase of 1 point in DRS at enrollment translates on average into a 1.2 point increase in DRS at week 13 (note that higher DRS scores indicate worse outcomes). Meanwhile doubling of the time to enrollment (1 unit increase of the $\text{Log}T_{\text{enroll}}$) implies a 3.7 point increase in DRS at week 13. Thus, this analysis did not provide strong evidence for a difference in the recovery pattern between TBI and NTBI patients during this time frame. Finally, the R^2 is 0.355 for this robust regression model.

DRS score improvement over the 6 weeks post-enrollment

Etiology was a significant predictor of the amount of recovery observed over the 6 weeks following enrollment. On average TBI patients had 2.0 points (95% CI: 0.4, 3.5; $p = 0.011$) greater improvement in DRS scores over the 6-week interval than NTBI patients. In this analysis, time until enrollment, but not DRS score at enrollment was a significant predictor of recovery. Table 4 reports the slopes for the different predictors in the final model. The model implies that doubling of the time to enrollment (1 unit increase of the log base 2 transformed time to enroll) implies ~1.9 point reduction in the DRS change over this interval. Once again, the interaction between etiology and $\text{DRS}_{\text{enroll}}$ and $\text{Log}T_{\text{enroll}}$ was not significant. Thus, although NTBI patients showed less recovery, during this interval, this lesser degree of recovery was not accounted for by a more prominent decline in prognosis with the passage of time. Note that the R^2 for this robust regression model is only 0.094.

Time to follow commands

The final model was reduced to two significant predictors plus etiology, because models incorporating additional non-significant covariates did not yield adequate goodness-of-fit test results. As noted in Table 5, with inclusion of the 2-week rate variable, etiology was not a significant predictor of the time until commands were followed.

Table 3. Results for the robust regression model for DRS at week 13

	Slope or difference[a]	95% confidence limits		*p*-value
		Lower	Upper	
Etiology[a]	1.4	−0.2	3.0	0.083
$\text{Log}T_{\text{enroll}}$	5.4	3.6	7.2	<0.0001
$\text{DRS}_{\text{enroll}}$	1.12	0.9	1.5	<0.0001
Age	0.0	−0.1	0.0	0.565

[a]Difference between TBI and NTBI groups.

Table 4. Results from the robust regression model for the change in DRS scores 6 weeks post-admission

	Slope or difference[a]	95% confidence limits		*p*-value
		Lower	Upper	
Etiology[a]	2	0.4	3.5	0.011
$\text{Log}T_{\text{enroll}}$	−1.87	−3.12	−0.62	<0.003
$\text{DRS}_{\text{enroll}}$	−0.14	−0.42	0.15	0.358
Age	0.03	−0.01	0.08	0.184

[a]Difference between TBI and NTBI groups.

Table 5. Results from the Cox model for time to follow commands from 2-week admission

	Hazard ratio	95% hazard ratio confidence limits		*p*-value
		Lower	Upper	
Etiology	1.14	0.66	1.98	0.637
$\text{DRS}_{\text{enroll}}$	0.87	0.77	0.99	0.033
2-week rate	11.26	1.65	76.67	0.013

However, both $\text{DRS}_{\text{enroll}}$ and the 2-week rate of change were significant predictors. Patients with lower (better) DRS scores at enrollment, and those with faster early rates of change recovered command following sooner than those with higher DRS scores or slower initial rates of change.

Discussion

These results demonstrate that considerable recovery is possible during the typical time frame of acute rehabilitation care, for both TBI and NTBI patients. Overall 83.7% of patients improved their DRS score by at least 1 point over the 6 weeks of observation (84.8% of TBI and 80.5% of NTBI), and 61.1% of those who were not following commands at admission began to follow them prior to discharge (67.6% TBI and 48.6% NTBI). How much rehabilitation services enhance this recovery is unknown, but these findings suggest that the majority of patients who are admitted to acute rehabilitation will demonstrate meaningful recovery.

These results also confirm, in a sample of TBI and NTBI patients followed in a comparable manner, that time between injury and enrollment is a key predictor of recovery, with the passage of time reducing the chances of recovery. This was true for DRS_{13} and for 6-week change, but not for the time until commands were followed. However, in the latter analysis, direct measurement of the rate of recovery, captured by the 2-week change variable, may have reduced the significance of the more indirectly predictive T_{enroll} variable. The DRS score at enrollment was predictive of the DRS score at 13 weeks post-injury, but not of the amount of recovery that would be seen over a defined interval, suggesting that the admission DRS score is primarily a predictor of functional *status* rather than functional *change*, whereas the time until enrollment is particularly relevant to the probability of *change*. DRS at enrollment was also predictive of the time at which commands would be followed. This may indicate that, at equivalent rates of change, patients who start at a better functional level need less improvement (and hence less time) to reach the criterion of command following.

The effects of etiology on outcome in this study were more complex. NTBI patients had significantly or marginally worse outcomes in terms of 6-week change and DRS_{13}, respectively, but etiology was not a significant predictor of time until commands were followed. As mentioned above, the inclusion of the 2-week rate of change

in the latter model, necessitated for statistical reasons, may have reduced the significance of less direct predictors such as time post-injury or etiology. Even though NTBI patients had somewhat poorer outcomes than TBI patients, depending on the outcome measure chosen, the specific prediction that the prognosis of NTBI patients would decline more precipitously over time (i.e., an interaction between etiology and $\mathrm{Log}T_{\mathrm{enroll}}$) was not supported. This is in contrast to prior studies suggesting that the ''window of recovery'' is shorter for NTBI than for TBI patients (The Multi-Society Task Force on PVS, 1994b). However, the differential impact of time may be more dramatic in the 3–12 month range, whereas these data were collected primarily in the early weeks post-injury.

In the aggregate, these results confirm the importance of etiology, initial functional status, and time since injury in determining outcome in individuals with DOC. However, the majority of the variance in individual outcome remains unaccounted for. The final models described here account for approximately 35.5% of the variance in DRS_{13}, and about 9% of the variance in 6-week change. Thus, these predictors cannot be used with confidence to predict the outcomes of individual patients or to make admission decisions, without a high risk of error in both directions.

This study has a number of important limitations. Most importantly, it was conducted on a select referral sample, not a population-based sample. Thus, the large proportion of patients who recover in hours or days after injury are not included in the analysis. But even if one focuses on those patients who might be considered for rehabilitation care because they are still suffering from DOC several weeks post-injury, this remains a biased sample, since it involved only those patients who were admitted to rehabilitation services but not those who were not referred or were referred but not admitted. The specific clinical factors used in making those admission decisions are unknown, but surely may have included some subtle prognostic factors. In particular, since clinicians are generally aware of the more negative prognosis of NTBI patients reported in the literature, they may have had more stringent admission screening of non-traumatic referrals than of traumatic referrals. This, in turn, may have led to smaller differences in outcome based on etiology than might be seen in a less selected sample. This implicitly assumes, however, that some of the variance in recovery not accounted for by the predictors used in this study, was accounted for by unmeasured variables available to clinical decision makers, rather than simply being altogether unexplained. There is no direct evidence for a more stringent admission screening of NTBI patients since, for example, their DRS scores at enrollment were actually slightly worse than those of the TBI patients. Finally, the relatively short-term nature of this study, constrained by the current realities of acute inpatient rehabilitation stays in the United States, meant that a substantial number of patients were not following commands by the time of discharge and were censored in the Cox analysis. Longer intervals of follow up and larger samples, particularly of those with non-traumatic injuries might have more clearly informed the pattern of recovery.

Conclusion

In this selected sample of patients with DOC, referred and approved for inpatient rehabilitation admission, significant recovery was seen over the hospital stay, with the majority of patients with both traumatic and non-traumatic injuries demonstrating improvements in DRS scores and, among vegetative patients, the development of command following. The time between injury and rehabilitation admission and the DRS score at admission were each predictive of two of the three outcomes. Etiology was predictive of amount of functional improvement seen over 6 weeks of hospitalization, but less so of the DRS score at 13 weeks post-injury or the time until commands were followed. In the one model in which early rate of change was included, it was strongly predictive of outcome while etiology was not, suggesting that the clinical trajectory, itself, is highly predictive. None of the predictive outcome models accounted for sufficient variance to be used in individual clinical decision making.

Abbreviations

CC	Consciousness Consortium
$\text{Change}_{\text{DRS6}}$	change in DRS score over 6 weeks post-admission
DOC	disorders of consciousness
DRS	Disability Rating Scale
DRS_{13}	Disability Rating Scale score at 13 weeks after injury
$\text{DRS}_{\text{enroll}}$	Disability Rating Scale score at enrollment
ERP	event-related potential
fMRI	functional magnetic resonance imaging
$\text{Log}T_{\text{enroll}}$	log transformation of the time between injury and enrollment
MCS	minimally conscious state
NTBI	non-traumatic brain injury
PET	positron emission tomography
PVS	persistent vegetative state
TBI	traumatic brain injury
T_{enroll}	time between injury and enrollment
T_{Follow}	time until commands were first followed for patients who did not show command following at or within 2 weeks of admission
VS	vegetative state

Acknowledgments

We would like to thank Gemma Baldon and David Kennedy for database management. This study was supported in part by the Albert Einstein Society, and the Irving I. and Felicia F. Rubin Family Foundation. OG was funded by the Fonds de la Recherche Scientifique (Research Fellow), European Commission, and the James S. McDonnell Foundation.

References

Di, H., Boly, M., Weng, X., Ledoux, D., & Laureys, S. (2008). Neuroimaging activation studies in the vegetative state: Predictors of recovery? *Clinical Medicine*, *8*, 502–507.

Giacino, J., & Kalmar, K. (1997). The vegetative and minimally conscious states: A comparison of clinical features and functional outcome. *The Journal of Head Trauma Rehabilitation*, *12*(4), 36–51.

Giacino, J., & Whyte, J. (2005). The vegetative and minimally conscious states: Current knowledge and remaining questions. *The Journal of Head Trauma Rehabilitation*, *20*(1), 30–50.

Giacino, J., & Zasler, N. (1997). Outcome after severe traumatic brain injury: Coma, the vegetative state, and the minimally responsive state. *The Journal of Head Trauma Rehabilitation*, *10*(1), 40–56.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*(3), 349–353.

Giacino, J. T., & Whyte, J. (2003). Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: A pilot double-blind randomized trial. *The Journal of Head Trauma Rehabilitation*, *18*(1), 4–5. author reply 5–6.

Kotchoubey, B. (2007). Event-related potentials predict the outcome of the vegetative state. *Clinical Neurophysiology*, *118*(3), 477–479.

Laureys, S., Berré, J., & Goldman, S. (2001). Cerebral function in coma, vegetative state, minimally conscious state, locked-in syndrome and brain death. In J. L. Vincent (Ed.), *2001 yearbook of intensive care and emergency medicine* (pp. 386–396). Berlin: Springer-Verlag.

Millis, S. R., Rosenthal, M., Novack, T. A., Sherer, M., Nick, T. G., Kreutzer, J. S., Jr., et al. (2001). Long-term neuropsychological outcome after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *16*(4), 343–355.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*(5792), 1402.

Rappaport, M., Hall, K. M., Hopkins, K., Belleza, T., & Cope, D. N. (1982). Disability rating scale for severe head trauma: Coma to community. *Archives of Physical Medicine and Rehabilitation*, *63*(3), 118–123.

Ritchie, P. D., Cameron, P. A., Ugoni, A. M., & Kaye, A. H. (2000). A study of the functional outcome and mortality in elderly patients with head injuries. *Journal of Clinical Neuroscience*, *7*(4), 301–304.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., et al. (2008). Voluntary brain processing in disorders of consciousness. *Neurology*, *71*(20), 1614–1620.

The Multi-Society Task Force on PVS. (1994a). Medical aspects of the persistent vegetative state (1). *The New England Journal of Medicine*, *330*(21), 1499–1508.

The Multi-Society Task Force on PVS. (1994b). Medical aspects of the persistent vegetative state (2). *The New England Journal of Medicine*, *330*(22), 1572–1579.

Whyte, J. (2007). Treatments to enhance recovery from the vegetative and minimally conscious states: Ethical issues surrounding efficacy studies. *American Journal of Physical Medicine and Rehabilitation*, *86*(2), 86–92.

Whyte, J., Katz, D., Long, D., DiPasquale, M. C., Polansky, M., Kalmar, K., et al. (2005). Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. *Archives of Physical Medicine and Rehabilitation*, *86*(3), 453–462.

Yohai, V. J. (1987). High breakdown point and high efficiency robust estimates for regression. *Annals of Statistics*, *15*, 642–656.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 7

Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1–4 year follow-up

Douglas I. Katz[1,2,*], Meg Polyak[2], Daniel Coughlan[2,3], Meliné Nichols[2] and Alexis Roche[2]

[1]*Department of Neurology, Boston University School of Medicine, Boston, MA, USA*
[2]*Brain Injury Program, Braintree Rehabilitation Hospital, Braintree, MA, USA*
[3]*Sargent College of Health and Rehabilitation Sciences, Boston University, Boston, MA, USA*

Abstract: The natural history of recovery from brain injury typically consists of a period of impaired consciousness, a subsequent period of confusion and amnesia, followed by a period of post-confusional recovery of function. Patients with more severe injuries may have more prolonged episodes of unconsciousness or minimal consciousness and may not fully evolve through this continuum of recovery. There is limited information on the course of recovery and long-term outcome of patients with prolonged unconsciousness, particularly those with extended periods in the minimally conscious state. Further, patients with impaired consciousness are frequently denied access to hospital-based rehabilitation services because of uncertain prognosis and a perceived lack of benefit from rehabilitative interventions.

Methods: A consecutive series of 36 patients with traumatic (TBI) and non-traumatic brain injury (nonTBI) in a vegetative state (VS) or minimally conscious state (MCS) on admission to a specialized, slow-to-recover brain injury program in an acute rehabilitation hospital was retrospectively reviewed to evaluate course of recovery during rehabilitation hospitalization and in follow-up, 1–4 years post-injury. Independent variables included: time to resolution of VS, MCS and confusional state/posttraumatic amnesia (CS/PTA), based on Aspen criteria, Coma Recovery Scale-Revised (CRS-R) and Galveston Orientation and Amnesia Test (GOAT) scores. Outcome measures (calculated separately for TBI, nonTBI, VS, or MCS on admission subgroups) included: proportion of patients who recover and recovery time to MCS, CS/PTA stages, household independence, and return to school or work, as well as Disability Rating Scale (DRS) scores at 1, 2, 3, and 4 years post-injury.

Results: The majority emerged from MCS (72%) and CS/PTA (58%) by latest follow-up. It took significantly longer for patients admitted in VS (means: MCS, 16.43 weeks; CS/PTA, 30.1 weeks) than

*Corresponding author.
Tel.: 781-848-5353; Fax: 781-380-4809;
E-mail: dkatz@bu.edu

DOI: 10.1016/S0079-6123(09)17707-5

MCS (means: MCS, 7.36 weeks; CS/PTA, 11.5 weeks) to reach both milestones. Almost all who failed to clear CS/PTA by latest follow-up were patients with nonTBI or TBI with VS lasting over 8 weeks. Duration of MCS was a strong predictor of duration CS/PTA after emergence from MCS, accounting for 57% of the variance. Nearly half the patients followed at least 1 year achieved recovery to, at least, daytime independence at home and 22% returned to work or school, 17% at or near pre-injury levels. Discharge FIM score or duration of MCS, along with age, were best predictors of DRS in outcome models. DRS scores continued to improve after 2 and 3 years post-injury.

Conclusions: Patients in VS whose transition to MCS occurred within 8 weeks of onset are likely to continue recovering to higher levels of functioning, a substantial proportion to household independence, and productive pursuits. Patients with TBI are more likely to progress than patients with nonTBI, though significant improvement in the nonTBI group is still possible. Active, higher intensity, rehabilitation should be strongly considered for patients with severely impaired consciousness after brain injury, especially for patients with TBI who have signs of progression to the MCS.

Keywords: vegetative state; minimally conscious state; traumatic brain injury; brain injuries; disorder of consciousness; posttraumatic amnesia; confusional state; outcome; rehabilitation; natural history; coma

Introduction

Patients with traumatic brain injury (TBI) typically progress in recovery from a period of impaired consciousness to a posttraumatic confusional state with amnesia, to a period of post-confusional improvement of attention, memory, and executive capacities (Povlishock and Katz, 2005). This pattern is observed across a broad range of TBI severity. Patients with non-traumatic brain injury (nonTBI) may have a similar pattern of recovery, though prognosis is usually worse within the same range of severity (Multi-Society Task Force on PVS, 1994). The natural history of recovery of TBI has been further characterized by a series of clinically defined conditions or stages of recovery that have been labeled according to various schemas, including, the one most commonly used for TBI, the Rancho Los Amigos (RLA) Scale of cognitive recovery (Table 1) (Hagen et al., 1972). The first three levels on the RLA Scale describe unconsciousness and emerging consciousness. The terms coma, vegetative state (VS), and minimally conscious state (MCS) largely correspond to these first three levels on the RLA Scale. The posttraumatic confusional state and posttraumatic amnesia (CS/PTA) are included in the next three levels, Rancho 4–6, and the post-confusional period corresponds to levels 7 and 8. Another schema describes these stages using some of the more familiar neurologic nomenclature (Table 2) (Alexander, 1982; Katz, 1992; Povlishock and Katz, 2005). The transition from *coma* to *VS*, which occurs within 2–3 weeks in the vast majority of survivors, is marked by spontaneous eye opening. The transition from *VS* to *MCS*, is defined by the first signs of minimal, inconsistent, but reproducible behavioral evidence of self or environmental awareness, as defined by the Aspen workgroup criteria (Giacino et al., 2002). The transition from the *MCS* to the next stage, labeled *CS/PTA* is marked by the Aspen workgroup criteria of accurate yes/no communication or object use. Sometimes object use and functional communication return simultaneously, and sometimes one or the other criterion returns first (Giacino and Kalmar, 2005; Taylor

Table 1. Rancho Los Amigos levels of cognitive functioning

1. No response
2. Generalized responses
3. Localized responses
4. Confused — agitated
5. Confused — inappropriate
6. Confused — appropriate
7. Automatic — appropriate
8. Purposeful and appropriate

Table 2. Braintree Scale of neurologic stages of recovery from brain injury

1. *Coma:* No purposeful responses, eyes closed, no sign of wakefulness [Rancho 1]
2. *Vegetative state* (*VS*): {spontaneous eye opening} no cognitive awareness; gross wakefulness, sleep-wake cycles begin [Rancho 2]
3. *Minimally conscious state* (*MCS*): {CRS-R criteria for MCS (Kalmar and Giacino, 2005)} inconsistent, simple purposeful behavior, inconsistent response to commands begin; often mute [Rancho 3]
4. *Confusional state/post-traumatic amnesia* (*CS/PTA*): {CRS-R criteria for emergence from MCS (Kalmar and Giacino, 2005)} interactive communication and appropriate object use begin; amnesic, severe basic attentional deficits, hypokinetic or agitated, labile behavior; later more appropriate goal-directed behavior with continuing anterograde amnesia [Rancho 4, 5, and partly 6]
5. *Post-confusional/emerging independence* (*PC/EI*): {GOAT scores $\geq$75 (Levin, 1979)} marked by resolution of PTA; cognitive impairments in higher level attention, memory retrieval, and executive functioning; deficits in self-awareness, social awareness, behavioral and emotional regulation; achieving functional independence in daily self-care, improving social interaction; developing independence at home [Rancho 6 and partly 7]
6. *Social competence/community reentry* (*SC/CR*): {household independence $>$8 h} developing independence in community, household management skills, and later returning to academic or vocational pursuits; recovering higher level cognitive abilities (divided attention, cognitive speed, executive functioning), self-awareness, social skills; developing effective adaptations and compensations for residual problems [Rancho 7 and 8]

Notes: {criteria for transition to stage}; [corresponding Rancho Los Amigos Scale levels] are in brackets.

et al., 2007). Transition to the next stage, *post-confusional/emerging independence* is marked by clearing of PTA that can be designated using standardized measures such as the Galveston Orientation and Amnesia Test (GOAT) (Levin, 1979). The transition to the last stage, *community reentry/social competence* is defined in this schema by achievement of daytime independence at home, the ability to be left alone for an 8-h period.

Patients with TBI may progress through these stages of recovery at different rates, largely depending on injury severity; not all stages will be clinically recognized in every patient. Patients with more severe injuries may have more prolonged episodes of coma, VS, MCS or CS/PTA and may not fully evolve through this continuum of recovery. There is some information about the probability of recovery beyond the VS if it lasts a month or more; but there is more limited information on the probability of recovery beyond a MCS that extends a month or more.

For patients in a prolonged VS, the evolution and probability of recovery for survivors has been described in a meta-analysis of *persistent vegetative state* (defined by the Multi-Society Task Force on PVS as those fully unconscious for a month or more) (Multi-Society Task Force on PVS, 1994). Prognosis for recovery was substantially better for victims of TBI than those with nonTBI. The report described functional outcome using the Glasgow Outcome Scale (Jennett and Bond, 1975). Of adults with TBI who were unconscious at least 1 month, 33% recovered consciousness by 3 months post-injury, 46% by 6 month, and 52% by 1 year. If patients with TBI were still unconsciousness at 3 months, 35% regained consciousness by 1 year; if still unconscious for 6 months, 16% regained consciousness by 1 year. Of those adults with nonTBI who were unconscious for 1 month, only 11% recovered consciousness by 3 months, and 15% by 6 months. No person with nonTBI regained consciousness after 6 months post-injury. Functional outcomes at 12 months for patients with TBI who regained consciousness were as follows: more than 1/2 were *severely disabled*, nearly 1/3 were *moderately disabled*, and about 13% reached a *good recovery* level. Functional outcome was worse after non-TBI. Nearly 3/4 of those who regained consciousness were severely disabled at 12 months, though 1/5 were moderately disabled, and 1/15 achieved good recovery (Multi-Society Task Force on PVS, 1994).

There is less information available for patients in a prolonged MCS. One study (Giacino and Kalmar, 1997) compared outcomes of patients in VS versus MCS admitted to a rehabilitation facility. In this study 55 patients in a VS were compared to 49 patients in a MCS when initially evaluated a mean of 9.6 weeks post-injury. Causes of injury were TBI (n = ~~70~~) and nonTBI (n = ~~34~~)

(mostly anoxic brain injury and stroke). Using the Disability Rating Scale (DRS) (Rappaport et al., 1982) as the outcome measure at 1, 3, 6, and 12 months post-injury, they reported that the probability for the most favorable outcomes (moderate or no disability) by 1 year was much greater for the MCS group (38%) than the VS group (2%) and only occurred in those patients with TBI. Of the MCS group, 43% remained severely disabled or worse (1/10 of the nonTBI, MCS group was vegetative and 2/10 died) at 12 months.

Another study of 18 patients with TBI admitted to rehabilitation in a MCS of at least 27 days duration (median 56 days), followed them for 2–5 years (Lammi et al., 2005). Two patients persisted in a MCS at follow-up, 4 or more years after injury. On the DRS, 1 was mildly disabled (DRS = ~~4~~), 2 partially disabled (DRS = ~~2~~), 11 moderate to moderate/severe (DRS 4–11), and 4 extremely severe or vegetative (DRS 25–30). There was no significant correlation between the duration of MCS and outcome on the DRS or the FIM but there was a correlation with level of cognitive impairment on the Dementia Rating Scale (Schmidt et al., 2005). Of 14 working full-time prior to injury, four returned to part-time work at latest follow-up. Overall, the authors concluded that outcome after prolonged MCS following TBI was heterogeneous and difficult to predict.

Although the previous study fell short of developing a prognostic model, a study of 124 patients admitted among several rehabilitation facilities in either VS or MCS, at least 4 weeks post-injury, did demonstrate significant outcome prediction models for outcome over a shorter interval (Whyte et al., 2005). Level of initial disability (on the DRS), rate of early DRS change and time from injury to initial assessment were the best predictors of the level of disability at 4 months post-injury and time to begin following commands, for those who were not following commands at the initial assessment.

Most of these outcome studies were performed with patients admitted to hospital-level rehabilitation facilities with specialized programs for patients with prolonged impairments of consciousness. It remains unclear what proportion of surviving patients with extended periods of impaired consciousness are treated in such specialized facilities, as opposed to long-term care nursing facilities, home care or rehabilitation facilities without specific expertise in treating this population. In the United States, public and private payers for health services have traditionally considered persons with prolonged impairments of consciousness inappropriate candidates for active rehabilitation assessment and treatment and they are often denied admission to hospital-level rehabilitation facilities. This is in part because traditional admission criteria require active engagement of the individual for a minimum of 3 h/day. Some consider it costly and wasteful to admit patients, who cannot actively interact with therapists, to hospital-level rehabilitation programs. Further, when considering patients who are unconscious or minimally conscious for several weeks after injury, decisions for care are often based on the conclusion that prognosis is uncertain and that the prospect for meaningful recovery is highly unlikely. As a result, once medical problems are stabilized in acute or chronic hospital-level treatment, many patients in VS or MCS remain in long-term nursing facilities, without specialized assessment and rehabilitative care. More cost-effective, intermediate levels of rehabilitative care facilities (subacute rehabilitation, transitional medical rehabilitation) have been proposed (Walker et al., 1996) but few such facilities exist for this population. Once admitted to skilled nursing facilities, patients are unlikely to be transferred to hospital-level rehabilitation facilities. In a large sample of patients with very severe TBI at a low level of functioning, only 3% of those admitted to hospital-level rehabilitation were in a long-term care facility between the acute hospital and hospital-level rehabilitation (Whitlock and Hamilton, 1995). There is very little information on what proportion of patients with severe disorders of consciousness are admitted to hospital-level rehabilitation facility versus a skilled nursing facility after discharge from the acute hospital. There are a variety of clinical and non-clinical factors that influence these admission decisions (Buntin, 2007; Ottenbacher and

Graham, 2007). Health insurance was a factor in one study that found that patients with moderate-to-severe TBI were more likely to be admitted to skilled nursing facilities if they had Medicaid or an HMO, as opposed to a fee-for-service plan (Chan et al., 2001).

It remains uncertain what effect treatment at different levels of care or in dedicated programs for patient with impaired consciousness may have on outcome in this population of patients. Although they did not separately evaluate patients with severe impairments of consciousness, a survey of 1059 patients with TBI in Colorado, tracked for their pathway of rehabilitative treatment (inpatient rehabilitation vs. long-term care vs. community-based care) and outcome, found that those who were treated in long-term care facilities had worse outcome at 1 year post-injury at any severity of injury (Mellick et al., 2003). Nevertheless, it is difficult to draw conclusions from such studies with regard to whether placement in a particular level of care is the cause or effect of the level of disability. It is still a realistic concern that a lack of rehabilitation services or inability of less experienced clinicians to recognize subtle or inconsistent manifestations of emerging consciousness may significantly and permanently reduce the potential for recovery of patients with severely impaired consciousness. Indeed, the chance of misdiagnosing patients who are in a MCS as being in a VS is as high as 40% in non-specialized centers (Andrews et al., 1996; Childs et al., 1993). If small signs of emerging consciousness are missed, patients are much less likely to receive active rehabilitation services aimed at promoting further recovery by engaging patients with limited capacities. As more time passes, the chance that payers would approve active rehabilitation services in specialized programs becomes more remote.

Included in this report is an observational study of a cohort of patients who were evaluated in a specialized, inpatient brain injury rehabilitation program, for patients with prolonged disorders of consciousness. Almost all continued to receive some rehabilitation services in other institutions, at home or in outpatient facilities after discharge from the program. The purpose of this study is to better characterize the natural history of recovery and outcome from prolonged disorders of consciousness after brain injury by examining the path of recovery through the stages described above and assessing predictors of long-term functional outcome. Patients with TBI or nonTBI were either in a VS or MCS at the time of admission to this inpatient rehabilitation program. Although this study is not designed to assess the individual contributions of such specialized rehabilitation programs to recovery, it aims to further enlighten awareness of the range of possible outcomes for patients with prolonged disorders of consciousness who are provided active rehabilitation services.

Materials and methods

Participants

We retrospectively reviewed records and program data of patients who were consecutively admitted to an inpatient rehabilitation TBI unit and enrolled in a program for patients with impaired consciousness, fitting diagnostic criteria for VS or MCS, over a 4 year period between September, 2003 and November, 2007. As an observational investigation of deidentified, existing clinical data, the study was exempt from institutional review board monitoring but was approved by the hospital ethics committee.

There were 36 patients included. Inclusion criterion was admission to inpatient rehabilitation at a VS or MCS level. All but one patient was in a VS or MCS for at least 4 weeks. See Table 3 for patient characteristics.

All patients received a program of physical, occupational and speech therapies totaling at least 3 h/day. The treatment program included management of tone problems, autonomic disturbances, and other problems that are common in this population. Additionally, a specialized protocol assisted in the evaluation and treatment of those with impairments of consciousness, utilizing recognized tools such as the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004;

Table 3. Patient characteristics ($n = 36$)

Characteristics	All patients	nonTBI	TBI	*P*-value (nonTBI vs. TBI)
Total	36	14	22	
Male	22 (61%)	6	16	
Female	14 (39%)	8	6	
Admitted in VS	11 (31%)	3	8	
Admitted in MCS	25 (69%)	11	14	
Mean age (±SD)	38 (±21)	50 (±18)	29 (±18)	$P = .002$
Mean lag — days from onset to rehab. admission	35 (±25.9)	33 (±19.0)	37 (±29.9)	ns
Mean admission FIM score	18 (±0)	18 (±0)	18 (±0)	ns
Mean discharge FIM score	55 (±31)	43 (±32)	63 (±28)	$P = .06$
Mean inpatient rehab. length of stay (days)	162 (±165)	143 (±175)	173 (±157)	ns
Discharge destination				
Skilled nursing facility	17 (8 VS, 9 MCS)	10	7	
Home	18 (2 VS, 16 MCS)	4	14	$P = .03$
Acute hospital	1 (1 VS, 0 MCS)	0	1	
NonTBI diagnoses		Anoxia 5 Vascular 6 Other 3		

Kalmar and Giacino, 2005) and a quantitative assessment protocol, similar to that described by Whyte et al. (1999) to identify and track visual discrimination, command following or yes/no communication in patients with infrequent and ambiguous responsiveness. Once identified, the rehabilitation team developed treatments aimed at promoting more consistent purposeful interactions and functional communication. All patients were treated with dopamine agonist or stimulant medications during some portion of their inpatient admission. Almost all patients were treated with amantadine for some part of their inpatient admission and nine patients were enrolled in an ongoing multicenter, randomized, placebo-controlled, 6-week trial of amantadine during their rehabilitation admission that will be reported separately in the future. Most of those in the trial received open label treatment with amantadine after completing the 6 week placebo-controlled trial. A few patients were also treated with methylphenidate, bromocriptine, carbidopa/l-dopa, modafanil, or other CNS active medications aimed at improving alertness and responsiveness. The specific types, dosages or durations of treatment with these medications were not calculated for the purposes of this analysis.

Measures

Patients were divided into TBI ($N = 22$) and nonTBI ($n = 14$) categories of injury. The nonTBI group was significantly older than the TBI group (means: nonTBI 50; TBI 29; $P = .002$). NonTBI diagnoses included anoxic brain injury, vascular diagnoses (ischemic and hemorrhagic stroke, aneurysm rupture) and other category (viral encephalitis and acute disseminated encephalomyelitis). Admission level of consciousness was either VS ($N = 11$) or MCS ($N = 25$). Patients were tracked through their course of recovery by time to transition through stages of the Braintree Scale (Table 2), from VS to MCS to CS/PTA, to the two higher, post-confusional, stages. Patients in VS or MCS were followed with the CRS-R, at least 1–2 times/week and patients in CS/PTA were tracked with an attention and memory screening battery that included the GOAT (Levin, 1979). Emergence from VS was marked by first clinical observations of cognitive awareness according to Aspen Consensus criteria and confirmed by achieving subscale scores on the CRS-R that indicate behavioral responses consistent with MCS. Emergence from MCS was marked by functional communication or proper

object use on two separate occasions, as described in the Aspen criteria (Giacino et al., 2002) and based on CRS-R subscale scores confirming these capacities. Duration of CS/PTA was marked by first of consecutive GOAT scores ≥ 75.

Outcome measures included FIM score at discharge from inpatient rehabilitation and yearly DRS scores at 1 through 4 years post-injury, if available. The FIM is an 18-item, 7 level ordinal scale that is widely used to measure physical (13 items) and cognitive (5 items) functioning and dependency (Keith et al., 1987). The DRS was scored by 2 of 3 clinicians (neurologist, speech therapist, physical therapist) based on structured interviews during half-yearly follow-up examinations; disagreements were resolved by consensus. Other outcome measures included transition from *post-confusional/emerging independence* to the *community reentry/social competence* stage (independence at home ≥ 8 h), and return to work or school at a full, partial, or supported level at latest follow-up.

Data analysis

Descriptive statistics were used to characterize proportions of patients who achieved various milestones, transitioning to subsequent stages of recovery and achieving particular outcomes of interest (return to work or school; household independence). Fisher's Exact Test was used to test differences in proportions achieving milestones, between subgroups, such as patients with TBI versus nonTBI, or patients who were in VS versus MCS at admission. T-tests and analysis of variance (ANOVA) were used to evaluate differences in means of durations to emerge from different stages of recovery and to test for differences in selected independent variables among patients, such as age and discharge FIM scores, between selected subgroups (brain injury type, level of consciousness at admission, extent of follow-up). Simple regression was used to test predictive relationships in duration of recovery stages, such as duration of MCS to predict duration of CS/PTA after emergence from MCS. Bivariate correlation was used to assess relationships between variables, especially significant predictors of DRS outcome scores. Finally, stepwise multiple regression analysis was used to determine the best models to predict outcome on the DRS for all patients and for patients with TBI.

Results

Patients progressed through the stages of recovery at varying rates, a minority stalling a one or another stage. Figure 1 illustrates the proportion of patients at each stage of recovery, at monthly time intervals over the first year post-injury, and at 2, 3, and 4 years post-injury, for those with available follow-up information.

Emergence from VS to MCS

Of the 36 patients, 11 were admitted in VS and 8 of the 11 transitioned to MCS during rehabilitation admission. Seven of eight with TBI emerged from VS and one of three with nonTBI emerged from VS. For those who emerged from VS, the mean duration of VS was 8.07 weeks (SD 2.65), 8.41 weeks (SD 2.68) for patients with TBI, and 5.71 weeks for the patient with nonTBI. Late emergence from VS could not be ruled out for the three patients who did not emerge from VS by rehabilitation discharge. However they were followed for an extended period of time, beyond the 3-month duration (20.9 and 22.4 weeks) deemed "permanent" for patients with nonTBI (Multi-Society Task Force on PVS, 1994). The patient with TBI was followed 43.3 weeks, 2 months short of the 12-month period beyond which recovery from VS is considered very unlikely for TBI (Multi-Society Task Force on PVS, 1994).

All patients admitted in MCS were observed to transition from VS to MCS prior to rehabilitation admission. Although estimates were available for most of these patients based on family and clinician observations, these estimates could not be accurately confirmed and were not used for any of these analyses.

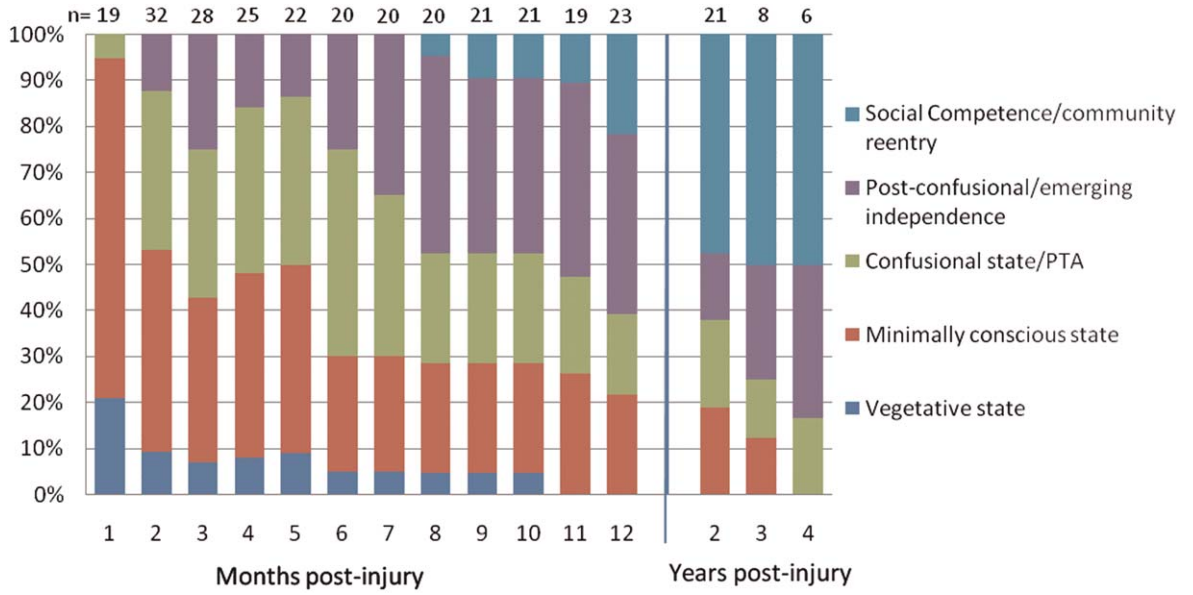


Fig. 1. Proportion of patients evolving to each of the Braintree Scale stages of recovery at various intervals post-injury. (Number of patient observations at each time interval varies depending on availability of evaluation information.)

Emergence from MCS to CS/PTA

Of the 36 patients admitted at the VS or MCS level of recovery, 25 patients (69%) emerged from MCS to the CS/PTA level of recovery during rehabilitation admission. One additional patient (TBI, MCS at admission) emerged from MCS after rehabilitation hospitalization, between 5½ and 10 months post-injury (72%) (see Table 4 and Fig. 1). Of 23 patients with long-term follow-up, at least 1 year, 5 failed to emerge from MCS. All were patients with either nonTBI or TBI, with a VS of over 8 weeks. All patients with TBI, admitted in a MCS, or with a VS of less than 8 weeks, eventually emerged from MCS.

Although a greater percentage of those with TBI (77%) than those with nonTBI (57%) emerged from MCS, the difference was not significant (Fisher's Exact Test, $P = .273$), perhaps due to small sample sizes. The mean time from injury to emergence from MCS was 9.18 weeks (SD 5.47). There was no significant difference in the time to emerge from MCS between those with TBI (mean 9.62 weeks, SD 6.09) and those with nonTBI (mean 8.23 weeks, SD 4.04) (Table 4).

Patients admitted in VS were less likely to emerge from MCS than patients admitted in MCS (45% admitted in VS and 80% admitted in MCS emerged from MCS). The difference was nearly significant (Fisher's Exact Test, $P = .056$). Of the patients admitted in a VS, the ones who emerged from MCS all had emerged from VS in less than 8 weeks. The time to emerge from MCS was significantly longer for those admitted in VS (16.43 weeks, SD 5.39) that those admitted in MCS (7.36 weeks, SD 3.79) ($P < .05$).

Emergence from CS/PTA to post-confusional levels

Of all patients admitted, 58% emerged from CS/PTA by latest follow-up; of those followed up at least 1 year, 65% emerged from CS/PTA (see Table 4).

Confining the analysis to the 25 patients who emerged from MCS, at least, 84% cleared CS/PTA by 1-year follow-up. Of those who emerged from MCS after 2 months post-injury ($n = 40$), 70% cleared CS/PTA by 1-year post-injury and of those who took longer than 3 months to emerge

Table 4. Emergence from minimally conscious state (MCS), confusional state/PTA (CS/PTA), and post-confusional/emerging independence (PC/EI) stages of recovery

	All patients ($n = 36$)			nonTBI ($n = 14$)			TBI ($n = 22$)				VS on admission ($n = 11$)			MCS on adm. ($n = 25$)			
	% emerged	Time to emerge (wks)	SD	% emerged	Time to emerge (wks)	SD	% emerged	Time to emerge (wks)	SD	P^*	% emerged	Time to emerge (wks)	SD	% emerged	Time to emerge (wks)	SD	P^{**}
MCS	72	9.18	5.47	57	8.23	4.04	77	9.62	6.09	ns	45	16.43	5.39	80	7.36	3.79	$<.05$
CS/PTA	58	15.80	9.28	29	11.50	7.69	77	17.71	9.68	ns	36	30.1	3.83	68	11.5	4.80	$<.0001$
PC/EI	28	32-88	NA	7	32	NA	41	36–88	NA	NA	9	88	NA	36	32–88	NA	NA

*Significance between nonTBI and TBI groups — time to emerge.
**Significance between VS and MCS on admission groups — time to emerge.

from MCS ($n = 8$), 62.5% cleared CS/PTA by 1-year post-injury.

Of 23 patients followed between 1 and 4 years post-injury, 8 (34.8%) failed to clear CS/PTA by GOAT criteria; 7 of 8 patients who failed to clear CS/PTA were patients with nonTBI or patients admitted in a VS that lasted more than 8 weeks.

Mean time from injury to emergence from CS/PTA was 15.8 weeks (SD 9.3). The duration of CS/PTA was significantly longer for those admitted in VS (30.1 weeks; SD 3.83) than those admitted in MCS (11.5 weeks; SD 4.80), even when patients with TBI were considered separately ($P < .0001$) (Table 4).

Relationship of duration VS, duration MCS, and duration CS/PTA

The duration of VS did not predict the duration of MCS in the small number of patients for whom the relationship could be tested ($n = 8$). However, the duration of MCS did have a significant relationship with the duration of CS/PTA after emergence from MCS ($r = .754$; $P < .005$, $n = 13$) as represented by the following linear regression model: duration of CS/PTA following resolution MCS (weeks) = .44 (duration MCS [weeks]) + 1.74.

Discharge setting

Half of the 36 patients were discharged directly to home and 47% were discharged to a skilled nursing facility after inpatient rehabilitation hospital admission (see Table 3). One patient was discharged to an acute hospital. There was a significant difference in discharge destination depending on injury type ($P = .03$). The majority of those with TBI (64%) were discharged home and most of those with nonTBI (71%) were discharged to a skilled nursing facility.

Outcome 1–4 years post-injury (DRS scores)

DRS scores were available for 61% of patients overall and 77% of patients with TBI at 1 year post-injury. Comparing the groups with and without long-term follow-up data, there was no significant difference in discharge FIM scores between the group that had long-term follow-up (mean discharge FIM: 58/126) and those that did not have long-term follow-up (mean discharge FIM: 51/126), suggesting that they were comparable in severity and level of functioning at inpatient rehabilitation discharge.

Mean DRS score was 9.8 (SD 6.79) for the 22 patients with 1 year DRS scores (see Fig. 2). Mean DRS score was greater (12.0, SD 6.41, $n = 5$) for those with nonTBI (*severe level of disability*), compared to those with TBI (7.9, SD 6.30, $n = 17$) (*moderately severe level of disability*) but the difference was not significant ($P = .3$). Although the level of disability on the DRS at 1 year was greater for patients admitted in VS (mean 12.1, SD 6.6, $n = 7$) than those admitted in MCS (mean 7.3, SD 6.4, $n = 15$), the difference was also not significant ($P = .15$). The sample sizes of some of the groups were small which may account for the lack of statistical significance.

Of 22 patients with follow-up between 1 and 4 years post-injury, 6 patients (27%) improved to a DRS score of 3 or less (*partial*, *mild*, or *no disability*) by latest follow-up and 7 patients (32%) had a score between 12 and 21 (*severe* or *extremely severe disability*) at latest follow-up. The rest (41%) were at a *moderate* to *moderately severe* level of disability at latest follow-up (Table 5).

Of 16 patients who had 2 or more years follow-up, DRS scores continued to improve between year 1 and 2 in 56% (9/16) of the patients, and in 38% (3/8) between years 2 and 4.

Return to household independence

Of 23 patients followed 1–4 years, 10 (43%) patients achieved household independence (ability to be left alone for 8 h — consistent with transition from *post-confusional/emerging independence* to a *community reentry/social competence* level of recovery) (see Fig. 1). Return to independence at home was more likely for patients with TBI (53%, $n = 17$) than patients with nonTBI (16.7%, $n = 6$), although the difference did not reach significance, likely because of small sample size ($P = .13$).

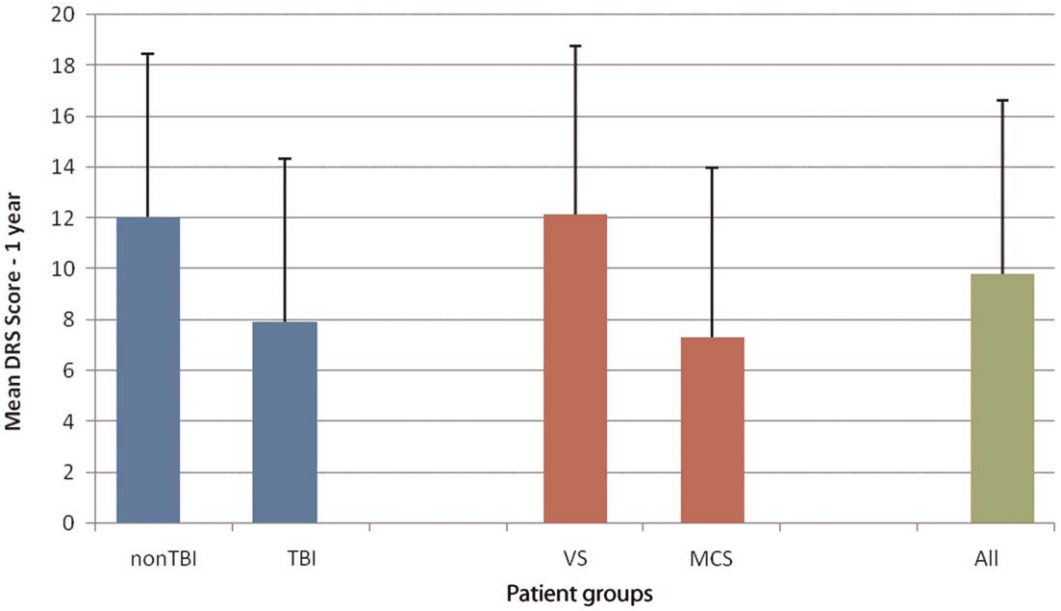


Fig. 2. Mean DRS scores at 1 year post-injury for all patients with DRS at follow-up ($n = 22$) with comparisons of patients subgroups: nonTBI ($n = 5$) versus TBI ($n = 17$); VS level at admission ($n = 7$) versus MCS level at admission ($n = 15$) (Error bars = SD).

Table 5. DRS scores 1–4 years post onset

	1 year ($n = 22$) (%)	2 years ($n = 16$) (%)	3–4 years ($n = 8$) (%)	Latest follow-up ($n = 22$) (%)
DRS score range				
12–21 (severe to extremely severe disability)	32	25	12	27
4–11 (moderate to moderately severe disability)	41	44	38	41
0–3 (partial to no disability)	27	31	38	32

Return to work and school

Of 23 patients followed at least 1 year, 5 (22%) were able to return to work or school, 4 (17%) at a full level, or close to their premorbid level of functioning (DRS score 0 or 1). Three of the four were students who successfully returned to full-time college matriculation, between 1 and 2 years post-TBI. None of them required major program modification, although they all reported that they used some personal compensatory strategies, including taking greater time and effort to maintain successful academic achievement. All were able to maintain grades above a B average. The fourth patient, age 57, had a nonTBI (complications of aneurysm rupture), and returned to full-time employment at a previous level of responsibility in a middle level managerial position, within 1–2 years post-onset; although she also noted greater effort and the need to use personal compensatory strategies to maintain expected level of performance, she has

maintained employment at the same job for over 3 years since returning.

Best outcome prediction variables and models

According to the bivariate correlation analysis, the predictor variables with the strongest bivariate correlation with DRS scores at 1 year were: *lag time* from brain injury onset to rehabilitation admission ($r = .630$, $n = 22$, $P = .002$); *FIM at discharge* from inpatient rehabilitation ($r = -.895$, $n = 22$, $P < .0001$); *time from onset to clear CS/PTA* ($r = .785$, $n = 7$, $P < .05$). Age, type of brain injury, admission level of consciousness, duration of VS, duration of MCS were not significantly correlated with 1 year outcome on the bivariate correlation analysis.

When the outcome variable was DRS score 3 or less versus over 3, to distinguish patients with *partial* to *no disability* from those with greater disability, the significant predictor variables were *FIM at discharge* ($r = .596$, $n = 22$, $P = .003$) and *lag from onset to rehabilitation admission* ($r = -.467$, $n = 21$, $P = .029$). There were variables at a nearly significant level: *duration of CS/PTA* ($r = .681$, $n = 7$, $P = .092$) and *admission level of consciousness* ($r = .455$, $n = 16$, $P = .077$).

When the outcome was DRS score of 12 or more versus less than 12, to distinguish those with *severe* and *extremely severe* disability from those with less disability, the significant predictor variables were also *FIM at discharge* ($r = -.730$, $n = 22$, $P = .000$), and *lag from onset to rehabilitation admission* ($r = .464$, $n = 22$, $P = .030$).

The stepwise regression model predicting DRS outcome at 1 year and the model to predict DRS at latest follow-up between 1 and 4 years both included 2 predictor variables: *FIM at discharge* from inpatient rehabilitation and *age*. Better FIM discharge score and younger age predicted lower disability on the DRS in long-term follow-up (DRS 1year: $R^2 = .742$, $F(2,13) = 18.667$, $P = .000$; DRS latest score: $R^2 = .707$, $F(2,13) = 19.125$, $P = .000$). When just the patients with TBI were included in a stepwise analysis, the model included the predictor variables *time to emerge from MCS* and *age* (DRS 1 year: $R^2 = .720$, $F(2,10) = 12.875$, $P = .002$).

Discussion

The majority in this consecutive series of patients with prolonged disorders of consciousness, admitted to inpatient rehabilitation at a VS or MCS level of recovery, emerged from MCS, cleared the post-injury confusional state and PTA, and progressed to post-confusional levels of recovery. Even the majority of those patients with MCS of 3 months or longer recovered beyond the CS/PTA stage of recovery. In fact, if patients emerged from MCS, it was highly probable (84%) they would eventually recover to post-confusional levels of recovery. The few who remained in MCS were patients with nonTBI or those remaining in a VS over 8 weeks. Likewise, 7 out of 8 of those who did not clear CS/PTA by latest follow-up were either patients with nonTBI or admitted in a VS that lasted over 8 weeks. Nearly half of the patients with long-term follow-up achieved recovery to safe, daytime independence at home and 22% returned to work or school within 2 years after injury. A noteworthy proportion (17%) returned to productive pursuits at or near their previous level of functioning. Overall, there was a favorable prognosis for continued evolution of recovery to post-confusional levels for patients with prolonged, severe disorders of consciousness. The data in this series support that once patients recover to the MCS level of recovery, especially if they make the transition within 8 weeks of onset, they have good prospects to continue recovering to a level of, at least, partially independent functioning.

Other studies have reported significant improvement in patients with extended periods of impaired consciousness, especially for those with TBI who make it to the MCS level of recovery. A study of 104 patients admitted to rehabilitation in a VS or MCS similarly reported that 50% of patient with TBI, who were admitted in MCS, recovered to an independent range of functioning (*moderate level* of disability or better on the DRS) (Giacino and Kalmar, 1997). As in the present study, they found that outcome was better for those with TBI than nonTBI and for those admitted in a MCS than those admitted in a VS (Giacino and Kalmar, 1997). The level of disability on the DRS at 1 year

in that study was similar, though slightly worse, than outcomes in this report. The average outcome at 1 year for those with TBI admitted in a MCS was a *moderate* level of disability in the series reported here, compared to a *moderately severe* level in the Giacino and Kalmar report. Average 1-year outcome for those with TBI admitted in a VS was at a *severe* level in this report, compared to an *extremely severe* level in the Giacino and Kalmar series. Both studies found that patients with nonTBI, admitted in a MCS averaged a *severe* level of disability at 1 year. Those with nonTBI admitted in a VS averaged an *extremely severe* to *VS* range of outcome in the Giacino and Kalmar study; the only patient in the present study in this category with long-term follow-up was also at the *extremely severe* disability level at 1 year and was deceased by year 2 post-injury.

Another small series of 23 patients with TBI, admitted to rehabilitation at a ''low level'' with an average Glasgow Coma Score of 8.7, demonstrated substantial functional improvement in all but 3 patients and improvement in 35% to a moderate disability or good recovery level on the Glasgow Outcome Scale by 6 months post-injury (Whitlock, 1992). A larger series of 328 patients admitted to rehabilitation with very severe TBI, reported by the same investigator, also demonstrated substantial functional recovery in a majority of patients (Whitlock and Hamilton, 1995). Although the study did not specify admission level of consciousness, the inclusion criteria included those with the lowest FIM score of 18/126, suggesting that the vast majority had a disorder of consciousness, since they had no functional communicative or physical capacity. Seventy-five percent improved functional status to an average FIM score of 53 at discharge and 79 at follow-up (mean of 99 days post discharge). The discharge FIM in the series in this report was in a comparable range at 55 for all patients and 63 for patients with TBI, though average length of rehabilitation admission was 49 days longer (173 days). The evidence from all of these studies support prospects for substantial functional recovery for the larger proportion of patients who present to rehabilitation with severe disorders of consciousness, especially those in a MCS.

Although this study reports a relatively small sample of patients, the data provided some other prognostic information. The duration of time to emerge from MCS was a strong predictor of the duration of the CS/PTA stage of recovery, accounting for nearly 60% of the variance. A relationship was similarly reported for predicting PTA using the duration of unconsciousness (time to follow commands) in a larger series of 243 patients across a broad range of severity after TBI (Katz and Alexander, 1994). The ability to prognosticate clearing of confusion and PTA can be useful for rehabilitation and other treatment planning in patients with severe brain injury, such as managing agitation, setting goals, and planning discharge.

Important correlates for long-term outcome according to the DRS at 1 year or at latest follow-up included the lag time from brain injury onset to rehabilitation admission, FIM at discharge and duration of CS/PTA. Lag time to admission was a key variable in predicting outcome in prolonged posttraumatic disorders of consciousness in other studies (Pape et al., 2006; Whyte et al., 2005). FIM scores and PTA duration are well known as predictors of outcome after TBI over a wider range of severity (Asikainen et al., 1999; Cifu et al., 1997; Haslam et al., 1994; Katz and Alexander, 1994; Keyser-Marcus et al., 2002; Sherer et al., 2002). The best predictors of disability level on the DRS in the regression models were the FIM at inpatient rehabilitation hospital discharge, with a significant influence of age on this relationship. These predictors accounted for over 70% of the variance in these models. If only patients with TBI were considered, the duration of time to emerge from MCS, along with age, were the predictor variables in the model, accounting for 72% of the variance. Although another study of patients with prolonged disorders of consciousness after TBI had a similar range of outcomes on the DRS, it did not show a relationship between MCS duration or FIM and outcome on the DRS (Lammi et al., 2005). This study included an even smaller sample of patients ($n = 18$) and statistical relationships may have been lost because of small sample size.

Neither this study nor the other studies that demonstrate substantial recovery of patients with prolonged disorders of consciousness can make any definitive claims regarding the effects of rehabilitation or specialized programming on recovery. Nevertheless, the implication is that rehabilitation played some role in recovery and that the same level of improvement would not have occurred entirely passively and spontaneously. Some qualities, particular to this population, suggest that the role of proper, expert assessment and effective rehabilitation is even more critical than in less severe injuries. The difficulties recognizing emerging consciousness that may be exploited to develop early rehabilitative interactions and the vulnerability of this population to secondary neurologic, medical, and chronic maladaptive complications are just some of these critical issues.

There is some evidence to support the role of more intensive, early rehabilitation in this population. A number of reports have supported the benefit of rehabilitation, even later interventions, in promoting functional improvement in slow-to-recover patients with brain injury (Gray, 2000). Several studies with comparison groups have demonstrated beneficial effects of specialized, coordinated, multidisciplinary rehabilitation programs, and programs of greater intensity in comparison to less specialized and less intense programs for patients with moderate-to-severe TBI (Semlyen et al., 1998; Shiel et al., 2001; Turner-Stokes et al., 2005; Zhu et al., 2001, 2007). There is less information on rehabilitative treatment for nonTBI populations but one study comparing patients with TBI and nonTBI admitted to a hospital-level brain injury rehabilitation program claimed equivalent functional gains for both populations (Shah et al., 2004). Data on low level patients treated in less intense rehabilitation facilities are lacking. One study described benefits of a long-term rehabilitation program in Canada for patients with TBI and nonTBI who were low functioning and not considered candidates for a short-term, comprehensive rehabilitation program (Gray and Burnham, 2000). However, services and medical treatment intensity were more consistent with chronic hospital-level care than skilled nursing facility care in the United States. More research is needed on several important treatment questions including: the relative benefits of different levels of care and varying expertise of rehabilitative care for this population; how benefits of more intensive rehabilitation vary at different stages in the natural history of recovery; the injury and non-injury predictors that will suggest the best candidates for active rehabilitation; and specific intervention techniques that are effective for particular subpopulations.

This study has several limitations including a small sample size and incomplete long-term follow-up. Nevertheless, there were some clear patterns of recovery and prognostic trends that should be confirmed with larger cohorts of patients studied longitudinally, over several years time. One important, unanswered question is what the prognosis for recovery is after even longer durations of MCS than are reported here. The role of type of rehabilitation facility, treatment intensity, program specialization, and expertise in promoting recovery will require larger observational studies or experimental studies of specific treatments in defined populations, aimed at determining who will best benefit from more intensive treatment and what are the beneficial elements of rehabilitation for this population.

Acknowledgement

The study has been supported in part by the National Institute on Disability and Rehabilitation Research (grant no. H133A031713, PIs: Joseph T. Giacino, PhD, John Whyte, MD, PhD) and the Braintree Rehabilitation Hospital Edward Wilkinson Memorial Fund. The authors gratefully acknowledge Hiram Brownell, PhD (Boston College) for statistical assistance, as well as Julianne McCormick, MSOT, and Laura D'Angelo, MSPT for assistance in data acquisition.

References

Alexander, M. P. (1982). Traumatic brain injury. In D. F. Benson & D. Blumer (Eds.), *Psychiatric aspects of neurologic disease* (pp. 251–278). New York: McGraw-Hill.

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*, 13–16.

Asikainen, I., Kaste, M., & Sarna, S. (1999). Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: Brain injury factors causing late seizures and influence of seizures on long-term outcome. *Epilepsia*, *40*, 584–589.

Buntin, M. B. (2007). Access to postacute rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *88*, 1488–1493.

Chan, L., Doctor, J., Temkin, N., MacLehose, R. F., Esselman, P., Bell, K., et al. (2001). Discharge disposition from acute care after traumatic brain injury: The effect of insurance type. *Archives of Physical Medicine and Rehabilitation*, *82*, 1151–1154.

Childs, N. L., Mercer, W. N., & Childs, H. W. (1993). Accuracy of diagnosis of persistent vegetative state. *Neurology*, *43*, 1465–1467.

Cifu, D. X., Keyser-Marcus, L., Lopez, E., Wehman, P., Kreutzer, J. S., Englander, J., et al. (1997). Acute predictors of successful return to work 1 year after traumatic brain injury: A multicenter analysis. *Archives of Physical Medicine and Rehabilitation*, *78*, 125–131.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*, 349–353.

Giacino, J. T., & Kalmar, K. (1997). The vegetative and minimally conscious states (a comparison of clinical features and functional outcome). *The Journal of Head Trauma Rehabilitation*, *12*, 36–51.

Giacino, J. T., & Kalmar, K. (2005). Diagnostic and prognostic guidelines for the vegetative and minimally conscious states. *Neuropsychological Rehabilitation*, *15*, 166–174.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation*, *85*, 2020–2029.

Gray, D. S. (2000). Slow-to-recover severe traumatic brain injury: A review of outcomes and rehabilitation effectiveness. *Brain Injury*, *14*, 1003–1014.

Gray, D. S., & Burnham, R. S. (2000). Preliminary outcome analysis of a long-term rehabilitation program for severe acquired brain injury. *Archives of Physical Medicine and Rehabilitation*, *81*, 1447–1456.

Hagen, C., Malkmus, D., & Durham, P. (1972). *Levels of cognitive functioning*. Downey, CA: Ranchos Los Amigos Hospital.

Haslam, C., Batchelor, J., Fearnside, M. R., Haslam, S. A., Hawkins, S., & Kenway, E. (1994). Post-coma disturbance and post-traumatic amnesia as nonlinear predictors of cognitive outcome following severe closed head injury: Findings from the Westmead Head Injury Project. *Brain Injury*, *8*, 519–528.

Jennett, B., & Bond, M. (1975). Assessment of outcome after severe brain damage. *Lancet*, *1*, 480–484.

Kalmar, K., & Giacino, J. T. (2005). The JFK Coma Recovery Scale-Revised. *Neuropsychological Rehabilitation*, *15*, 454–460.

Katz, D. I. (1992). Neuropathology and neurobehavioral recovery from closed head injury. *The Journal of Head Trauma Rehabilitation*, *7*, 1–15.

Katz, D. I., & Alexander, M. P. (1994). Traumatic brain injury. Predicting course of recovery and outcome for patients admitted to rehabilitation. *Archives of Neurology*, *51*, 661–670.

Keith, R. A., Granger, C. V., Hamilton, B. B., & Sherwin, F. S. (1987). The functional independence measure: A new tool for rehabilitation. *Advances in Clinical Rehabilitation*, *1*, 6–18.

Keyser-Marcus, L. A., Bricout, J. C., Wehman, P., Campbell, L. R., Cifu, D. X., Englander, J., et al. (2002). Acute predictors of return to employment after traumatic brain injury: A longitudinal follow-up. *Archives of Physical Medicine and Rehabilitation*, *83*, 635–641.

Lammi, M. H., Smith, V. H., Tate, R. L., & Taylor, C. M. (2005). The minimally conscious state and recovery potential: A follow-up study 2 to 5 years after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *86*, 746–754.

Levin, H. S. (1979). The Galveston orientation and amnesia test: A practical scale to assess cognition after head injury. *The Journal of Nervous and Mental Disease*, *167*, 675–684.

Mellick, D., Gerhart, K. A., & Whiteneck, G. G. (2003). Understanding outcomes based on the post-acute hospitalization pathways followed by persons with traumatic brain injury. *Brain Injury*, *17*, 55–71.

Multi-Society Task Force on PVS. (1994). Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. *The New England Journal of Medicine*, *330*, 1499–1508.

Ottenbacher, K. J., & Graham, J. E. (2007). The state-of-the-science: Access to postacute care rehabilitation services. A review. *Archives of Physical Medicine and Rehabilitation*, *88*, 1513–1521.

Pape, T. L., Lundgren, S., Heinemann, A. W., Guernon, A., Giobbie-Hurder, A., Wang, J., et al. (2006). Establishing a prognosis for functional outcome during coma recovery. *Brain Injury*, *20*, 743–758.

Povlishock, J. T., & Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *20*, 76–94.

Rappaport, M., Hall, K. M., Hopkins, K., Belleza, T., & Cope, D. N. (1982). Disability rating scale for severe head trauma: Coma to community. *Archives of Physical Medicine and Rehabilitation*, *63*, 118–123.

Schmidt, K. S., Mattis, P. J., Adams, J., & Nestor, P. (2005). Alternate-form reliability of the Dementia Rating Scale-2. *Archives of Clinical Neuropsychology*, *20*, 435–441.

Semlyen, J. K., Summers, S. J., & Barnes, M. P. (1998). Traumatic brain injury: Efficacy of multidisciplinary rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *79*, 678–683.

Shah, M. K., Al-Adawi, S., Dorvlo, A. S., & Burke, D. T. (2004). Functional outcomes following anoxic brain injury: A comparison with traumatic brain injury. *Brain Injury*, *18*, 111–117.

Sherer, M., Sander, A. M., Nick, T. G., High, W. M., Jr., Malec, J. F., & Rosenthal, M. (2002). Early cognitive status and productivity outcome after traumatic brain injury: findings from the TBI model systems. *Archives of Physical Medicine and Rehabilitation*, *83*, 183–192.

Shiel, A., Burn, J. P., Henry, D., Clark, J., Wilson, B. A., Burnett, M. E., et al. (2001). The effects of increased rehabilitation therapy after brain injury: Results of a prospective controlled trial. *Clinical Rehabilitation*, *15*, 501–514.

Taylor, C. M., Aird, V. H., Tate, R. L., & Lammi, M. H. (2007). Sequence of recovery during the course of emergence from the minimally conscious state. *Archives of Physical Medicine and Rehabilitation*, *88*, 521–525.

Turner-Stokes, L., Disler, P. B., Nair, A., & Wade, D. T. (2005). Multi-disciplinary rehabilitation for acquired brain injury in adults of working age. *Cochrane Database of Systematic Reviews*, CD004170.

Walker, W. C., Kreutzer, J. S., & Witol, A. D. (1996). Level of care options for the low-functioning brain injury survivor. *Brain Injury*, *10*, 65–75.

Whitlock,, J. A., Jr. (1992). Functional outcome of low-level traumatically brain-injured admitted to an acute rehabilitation programme. *Brain Injury*, *6*, 447–459.

Whitlock,, J. A., Jr., & Hamilton, B. B. (1995). Functional outcome after rehabilitation for severe traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *76*, 1103–1112.

Whyte, J., DiPasquale, M. C., & Vaccaro, M. (1999). Assessment of command-following in minimally conscious brain injured patients. *Archives of Physical Medicine and Rehabilitation*, *80*, 653–660.

Whyte, J., Katz, D., Long, D., DiPasquale, M. C., Polansky, M., Kalmar, K., et al. (2005). Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. *Archives of Physical Medicine and Rehabilitation*, *86*, 453–462.

Zhu, X. L., Poon, W. S., Chan, C. C., & Chan, S. S. (2007). Does intensive rehabilitation improve the functional outcome of patients with traumatic brain injury (TBI)? A randomized controlled trial. *Brain Injury*, *21*, 681–690.

Zhu, X. L., Poon, W. S., Chan, C. H., & Chan, S. H. (2001). Does intensive rehabilitation improve the functional outcome of patients with traumatic brain injury? Interim result of a randomized controlled trial. *British Journal of Neurosurgery*, *15*, 464–473.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 8

Cognitive deficits after traumatic coma

Philippe Azouvi[1,2,4,*], Claire Vallat-Azouvi[3,4] and Angelique Belmont[1,4]

[1]*AP-HP, Department of Physical Medicine and Rehabilitation, Raymond Poincare Hospital, Garches, France*
[2]*University of Versailles-Saint Quentin, France*
[3]*UGECAM-antenne UEROS, Raymond Poincare Hospital, Garches, France*
[4]*Er 6, UPMC, Paris, France*

Abstract: Survivors from a coma due to severe traumatic brain injury (TBI) frequently suffer from long-lasting disability, which is mainly related to cognitive deficits. Such deficits include slowed information processing, deficits of learning and memory, of attention, of working memory, and of executive functions, associated with behavioral and personality modifications.

This review presents a survey of the main neuropsychological studies of patients with remote severe TBI, with special emphasis on recent studies on working memory, divided attention (dual-task processing), and mental fatigue. These studies found that patients have difficulties in dealing with two simultaneous tasks, or with tasks requiring both storage and processing of information, at least if these tasks require some degree of controlled processing (i.e., if they cannot be carried out automatically). However, strategic aspects of attention (such as allocation of attentional resources, task switching) seem to be relatively well preserved. These data suggest that severe TBI is associated with a reduction of resources within the central executive of working memory. Working memory limitations are probably related to impaired (i.e., disorganized and augmented) activation of brain executive networks, due to diffuse axonal injury. These deficits have disabling consequences in everyday life.

Keywords: traumatic brain injury; cognition; memory; attention; working memory; executive functions

Introduction

Survivors from a traumatic coma frequently suffer from lifelong disability. For example, in a population-based study, Masson et al. (1996) found that, five years post-injury, 44.4% of survivors had a moderate disability, and 14.4% a severe disability, according to the Glasgow Outcome Scale (GCS). Cognitive deficits are the main cause of long-lasting disability in survivors from a severe traumatic brain injury (TBI). These deficits are a complex combination of slowed information processing, of deficits of long-term memory, of working memory and attention, of executive functions, and of personality and behavioral changes. They are mainly the consequences of diffuse axonal injury. They have a profound impact on family interactions (Brooks, 1984), social and recreational life (Oddy et al., 1985; Tate et al., 1989), vocational reintegration (Dikmen et al., 1994; Ponsford et al., 1995b), and quality of life (Mailhan et al., 2005; Webb et al., 1995). This review addresses the main cognitive deficits experienced by patients who survive from a

*Corresponding author.
Tel.: +33 1 47 10 70 74; Fax: +33 1 47 10 70 73;
E-mail: philippe.azouvi@rpc.aphp.fr

DOI: 10.1016/S0079-6123(09)17708-7

coma due to a severe TBI, with special emphasis on recent findings of limitations of central executive functions after TBI. Severe TBI is usually defined by a score of 8 or less on the GCS, and/or by a post-traumatic amnesia (PTA) duration of seven days or more. However, a few studies covered in the present review also included patients with moderate TBI, as defined by a GCS score 9–12, and a PTA of 1–7 days. Mild TBI (GCS 13–15, PTA $<$ 24 h) will not be addressed in this review, as it is usually associated with a very brief loss of consciousness and raises quite different methodological and scientific issues. An Appendix Table A1 at the end of the paper summarizes the main results of cognitive testing after TBI that are presented in this review

Long-term memory

After emerging from coma and vegetative state, TBI patients usually pass through a phase of global cognitive disturbance, generally termed post-traumatic amnesia (Russel and Smith, 1961). Patients with PTA have regained consciousness, but remain confused, disoriented for time and place, unable to store and retrieve new information; some degree of retrograde amnesia is usually present as well. Recovery is usually gradual, beginning with orientation for the person (name, age), followed in 70% of cases by orientation for place, then ultimately for time (High et al., 1990). The consistent return to continuous memory indicates clearing of PTA.

However, memory problems frequently persist after the period of PTA. Memory impairment is one of the most frequent complaints from patients and their relatives after a severe TBI (Brooks et al., 1986; Oddy et al., 1985; Van Zomeren and Van den Burg, 1985). Brooks et al. (1987) reported that memory deficit was significantly correlated with the inability to return to work seven years post-injury. However, memory is not a unitary system. Long-term memory is usually considered as composed of different cognitive subsystems, which will be addressed in the following sections. Short-term memory will be considered separately, as it is closely related to executive and attention functions.

Anterograde episodic memory

Anterograde long-term episodic memory has been one of the most extensively studied domain (for a recent review see Vakil, 2005). This term refers to the ability to acquire new information. Patients with severe TBI perform poorer than controls on all types of memory tasks, such as paired-associates (learning of pairs of words), free recall (either immediate or delayed), cued recall (recall after providing a cue, such as the semantic category), and recognition (Baddeley et al., 1987; Bennett-Levy, 1984; Brooks, 1975, 1976). Although visual memory has been less investigated, it seems to be impaired to a comparable extent with verbal memory (Brooks, 1974, 1976; Hannay et al., 1979). Zec et al. (2001) investigated the very long term effect of severe TBI (at an average of 10 years post-injury) with standardized index scores from the Wechsler memory scale-revised (WMS-R) that allows a comparison with well-established norms. The mean scores after very severe TBI were below 1 SD of the norms for all long-term memory indexes (verbal memory, visual memory, general memory, and delayed recall). Patients also tend to produce more intrusions (words not belonging to the list they had learned) than controls (Crosson et al., 1993).

There are at least three stages of information processing in episodic memory: encoding (acquisition of new information), consolidation (maintaining a memory trace), and retrieval (recovery of stored information either through recall or recognition processes). Whether these different processes could be selectively impaired after TBI is a matter of debate (Vakil, 2005).

Learning rate can be assessed with multiple repeated trials of information presentation. Most studies found that the learning rate (i.e., increase in the number of items correctly recalled across successive trials) of patients with severe TBI was slower compared to that of controls (Crosson et al., 1988; DeLuca et al., 2000; Haut and Shutty, 1992; Levin et al., 1979; Novack et al., 1995; Shum et al., 2000; Zec et al., 2001), although a few studies reported opposite results (Shum et al., 2000; Vanderploeg et al., 2001). Patients with severe TBI required more learning trials than

controls in order to reach the same level of performance (DeLuca et al., 2000). TBI patients also showed inconsistent and disorganized learning with a greater turnover of words from one trial to the other, as compared to controls (Levin et al., 1979; Paniak et al., 1989).

Semantic encoding can be assessed by different methods. Vakil et al. (1992) found that the recall of a short story after a long delay (until one day) was not significantly influenced in patients with TBI, by the relative importance of the information in the story: contrary to controls, patients did not show a better retention of the most important items. When lists of words belonging to different semantic categories were presented in a random, nonclustered order, patients exhibited less semantic clustering than controls (Crosson et al., 1988; Levin and Goldstein, 1986). In contrast, if the words were presented in a clustered order (i.e., grouped according to their semantic category), their performance improved like that of controls. Patients were able to benefit from semantic encoding, but to a lesser extent than controls (Goldstein et al., 1990). These results suggest that patients with TBI have a reduced ability to spontaneously use active or effortful semantic encoding to improve learning efficiency, but that they are able to benefit from externally provided semantic organization (Levin, 1989; Perri et al., 2000; Vakil, 2005).

Patients with TBI are able to benefit from memory aids such as cued recall or recognition. Under the cued recall condition, patients are given a cue (usually the semantic category) that is assumed to facilitate memory retrieval. Recall of patients with severe TBI has been found to be significantly improved by semantic cues (Crosson et al., 1988; Vakil and Oded, 2003). Vanderploeg et al. (2001) found that TBI patients demonstrated comparable benefit from semantic and recognition retrieval cues as compared to controls (Vanderploeg et al., 2001).

The generation of mental images is an efficient method to improve learning. Richardson and colleagues (Richardson and Barry, 1985; Richardson, 1979) found that patients with minor head injury were impaired as compared to controls in the recall of concrete but not abstract words. This difference disappeared when subjects were instructed to use mental imagery for improving encoding efficiency, a finding also reported by others (Twum and Parente, 1994). This finding was interpreted as a failure to construct spontaneously interactive images for improving encoding efficiency.

TBI has been found associated with an accelerated forgetting rate, and with a most profound deficit for delayed as compared to early memory indexes, suggesting a consolidation deficit (Carlesimo et al., 1997; Crosson et al., 1988; Hart, 1994; Haut and Shutty, 1992; Haut et al., 1990; Vanderploeg et al., 2001; Zec et al., 2001). This seems to be true even after equating baseline initial acquisition of information (Hart, 1994; Vanderploeg et al., 2001).

A few studies assessed sensitivity to interference after TBI. The basic principle is to present successively two lists of words (A and B), and to assess whether the first list interferes with learning of the second (proactive interference) or whether the second list interferes with later recall of the first list (retroactive interference). Patients with TBI were found to be more vulnerable than controls to retroactive interference but not to proactive interference (Crosson et al., 1988; Goldstein et al., 1989; Shum et al., 2000).

The degree of impairment may vary quantitatively from one patient to the other (Haut and Shutty, 1992). A minority of patients suffer from a dense amnesic syndrome, comparable to that observed after diencephalic amnesia (Levin, 1989; Levin et al., 1988a). The majority of patients present less severe impairments. But qualitative differences may also exist. Subgroups of patients characterized by different learning strategies have been identified by means of cluster analysis with subscores from the California Verbal Learning Test (CVLT) (Deshpande et al., 1996; Millis and Ricker, 1994): active (impaired unassisted retrieval but with active encoding strategies and preserved ability to store novel information), passive (over-reliance on serial position of words in the list), disorganized (inconsistent, haphazard learning style), and deficient (the most impaired, with a slow acquisition rate, passive learning style, and rapid forgetting). Cluster analysis with CVLT

has also been used to determine whether memory disorder subtypes within TBI correspond to deficits in underlying conceptualizations of memory constructs (Curtiss et al., 2001). Three subgroups were identified, corresponding to specific disorders in consolidation, retention, and retrieval processes. No cluster was identified corresponding to encoding problems (Curtiss et al., 2001).

Retrograde memory

Retrograde amnesia is the loss of memory of events experienced prior to injury, involving the individual's experiences (autobiographical memory), memory for public events, and semantic knowledge. Although such disorders may affect social adjustment and the resumption to normal life, they have received little attention. Individual case reports of disproportionate impairment of retrograde memory has been reported (Markowitsch et al., 1993; Mattioli et al., 1996). A high prevalence of retrograde memory deficits has been reported after TBI, encompassing both the domains of autobiographical and public events memories, and also early acquired basic and cultural knowledge (Carlesimo et al., 1998). Levin et al. (1985) found evidence of partial retrograde amnesia for episodic memories of no personal salience (titles of television programmes) during and shortly after the resolution of PTA, without any temporal gradient (i.e., earliest memories were not selectively preserved). In a recent study, chronic (>1 year) TBI patients were found significantly impaired in recalling autobiographical episodes and spatio-temporal details, without any temporal gradient (Piolino et al., 2007). Interestingly, deficits involved not only the ability to recall memories, but also the ability to mentally travel back through subjective time and to re-experience or relive the past (autonoetic consciousness). In addition, patients also had impaired ability to use a mentally generated image with a subjective point of view similar to that of the original episode (self-perspective). These disorders were significantly correlated with tests of executive functions, suggesting that they might be related to frontal dysfunction (Piolino et al., 2007).

Prospective memory

Prospective memory involves remembering to perform a previously planned action at a given time (time-based), or after a predetermined event has occurred (event-based prospective memory). Although little research has been carried out in this field, all studies found evidence of deficits of both time-based and event-based prospective memory after TBI (Groot et al., 2002; Kinsella et al., 1996; Shum et al., 1999). The mechanisms of prospective memory deficits after TBI remain to be elucidated. A relationship with episodic memory has been reported (Kinsella et al., 1996), while another study found that poor performance was related to impaired executive functions (Kliegel et al., 2004).

Other aspects of memory

Implicit memory refers to the unconscious expression of memories. Implicit memory is inferred from changes in the efficiency or the accuracy with which an item is processed when it is repeated, independently of conscious (explicit) memory of this item (Moscovitch et al., 1994). It is operationally assessed by priming effects. Procedural memory refers to acquisition of a general cognitive or sensorimotor skill. Data on implicit memory and procedural learning after TBI are contradictory (for a review, see Vakil, 2005). Implicit memory could be relatively preserved after TBI, but only for tasks that can be processed relatively automatically.

Additional difficulties have been reported after TBI in recalling the temporal sequence of the information (Vakil et al., 1994) and the frequency of occurrence of items in a series (Levin et al., 1988b) and in attributing proper source to a familiar event (source memory) (Dywan et al., 1993).

In summary, although it is clear that survivors from a traumatic coma suffer from long-lasting deficits of long-term episodic memory, the mechanisms underlying such deficit remain

debated. Also, it is not clear whether other aspects of memory (implicit memory, procedural learning) are impaired. In many aspects, memory impairments after TBI seem closely related to attentional and executive impairments, and resemble the kind of memory disorders found after frontal lobe lesion. For example, difficulty in applying active or effortful strategy in learning, the deficient use of semantic encoding, susceptibility to interference, and poor temporal and contextual memory have been reported both after TBI and with other focal prefrontal lesions (Shimamura et al., 1991).

Working memory

Theoretical aspects

The concept of working memory has replaced the older concept of ''short-term memory'' (Baddeley, 1986). Working memory is as a system used for both storage and manipulation of information, hence playing a central role in complex cognitive abilities such as problem solving, planning, language, and more globally in nonroutine tasks (Baddeley, 1986). According to the Baddeley and Hitch model, working memory is assumed to be divided into three subsystems (Baddeley and Hitch, 1974; Baddeley, 1986). The central executive is an attentional control system, while the phonological loop and the visuo-spatial sketchpad are two modality-specific slave systems responsible for storage and rehearsal of verbal and visuo-spatial information, respectively. The central executive functions to coordinate and schedule mental operations. It has a limited capacity and also serves as an interface between the two slave systems. The central executive is assumed to be a control system, very close conceptually from executive functions.

Case studies

A few individual case reports of TBI patients suffering from a selective impairment of the central executive have been reported. Van der Linden et al. (1992) reported the case of a 29-year old man examined one year after a severe TBI with left prefrontal contusion. This patient complained of difficulties in his work, particularly for reading and understanding complex technical texts. Neuropsychological assessment showed preserved long-term memory and executive functions. He was found however to suffer from a selective deficit of the central executive of working memory, as indicated by low verbal and nonverbal spans, and an impairment of short-term memory tasks with interference. In these latter tasks, known as the Brown–Peterson paradigm (Brown, 1958; Peterson and Peterson, 1959), patients are required to recall trigrams of items (usually consonants, but visual stimuli can also be used) after short delays (ranging from 3 to 20 s). During the delay, different interfering tasks can be used to prevent subvocal rehearsal of information (either simple articulatory suppression by repeating aloud phonemes such as ''ba-ba,'' or more complex tasks such as backward counting and mental calculation). This patient was profoundly impaired in Brown–Peterson tasks, particularly when complex interfering tasks were used. Two case studies of patients with remote (more than 30 months post-injury) severe TBI and relatively isolated deficit of the central executive of working memory have also been reported recently (Vallat-Azouvi et al., 2009).

Experimental studies

There have been only few studies that systematically addressed the different subcomponents of working memory in survivors of a severe TBI. Brooks (1975) used the digit span task. Subjects were required to recall a series of digits, either forwards or backwards. He found that severe TBI patients did not differ from controls on forward digit span, but performed significantly poorer on backward digit span. Stuss et al. (1985) assessed a group of 20 patients with various degrees of injury severity, which had an apparent good recovery but yet continued to have persistent complaints more than two years after the injury. Patients received a comprehensive battery of neuropsychological tests. On multivariate analysis, the test that best discriminated patients from controls was

the Brown–Peterson paradigm of short-term memory with interference, described earlier (Stuss et al., 1985).

The Paced Auditory Serial Addition Test (PASAT) has been widely used to assess speed of information processing and working memory after TBI (Gronwall and Wrightson, 1981; Gronwall, 1977). This task requires the subject to add pairs of digits presented at a predetermined rate. After each digit, the subject has to give the sum of that and the immediately preceding digit. This task is assumed to tap different cognitive functions, such as sustained attention and working memory, but also to be strongly related to speed of processing. Information processing speed, as assessed with the PASAT, was significantly reduced one year after a severe TBI (Levin et al., 1990). However, patients' performance did not decrease significantly more than that of controls when increasing stimuli presentation rate (Ponsford and Kinsella, 1992; Spikman et al., 1996). This suggests that performance in the PASAT may be more dependent on processing speed than on working memory.

In the n-back task, subjects are presented at a regular rate string of stimuli (letters, digits, figures etc.), either visually or auditory, and are required to decide whether each stimulus matches a predetermined target (Asloun et al., 2008). The 0-back (control) condition has a minimal working memory load: individuals are asked to decide whether the current stimulus matches a single predetermined target, which is always the same throughout the task. During the 1-back condition, individuals are asked to decide whether the current stimulus matches the previous one. The 2-back condition requires a comparison of the current stimulus with the one that had been presented 2-back in the sequence. The n-back task allows the opportunity to assess the effect of parametrically increasing working memory load without any other modification in task structure. Perlstein et al. (2004) used a visually presented letter n-back task. They found that patients with moderate and severe TBI were impaired, in terms of performance accuracy, but not in terms of speed of responding only in the more demanding 2- and 3- back conditions. We also used a letter n-back task in patients with remote severe TBI. We found a load-dependent deficit, with a decrement of accuracy (percentage hits) under the 2-back condition (Fig. 1) (Asloun et al., 2008). Similar findings were reported in children with severe TBI (Levin et al., 2004; Newsome et al., 2007).

Random item generation requires individuals to spell out a sequence of items (letters or numbers) as close as possible as a random series (i.e., like drawing numbers or letters from a hat, one at a time, calling them out, then replacing them, so that on any draw any of the stimuli was equally likely to be selected). It has been shown (Baddeley, 1966, 1986) that the ability to generate pseudo-random series depends on a limited-capacity response selection mechanism, similar to the central executive system. Random generation requires the constant inhibition of routine procedures, the ability to generate new retrieval plans, and the rapid shifting from one strategy to another. We used random generation in a series of studies (Azouvi et al., 1996, 2004; Leclercq et al., 2000). In a first study (Azouvi et al., 1996), patients had to generate 100 letters at an externally paced rate (every 1, 2, or 4 s). As compared to controls, patients' randomness indexes were poorer and deteriorated more with increasing generation rate (Fig. 2). In two subsequent studies on patients, at a

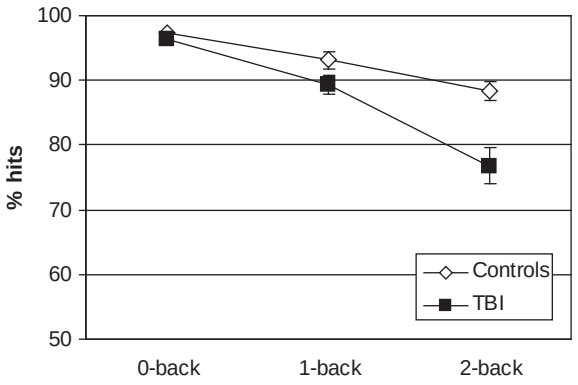


Fig. 1. n-back task. Data are the percentage of hits (targets successfully identified) under 0-, 1-, and 2-back condition. TBI patients' performance decreased disproportionately under the higher-load condition. Adapted with permission from Asloun et al. (2008).

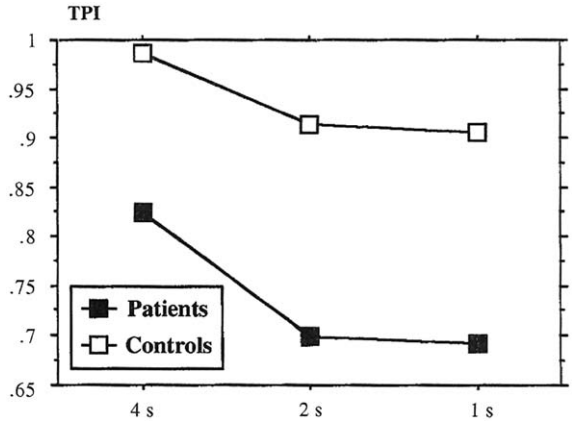


Fig. 2. Random letter generation. The figure presents an index of randomness (the Turning Point Index (TPI) which measures the ability to alternate ascending and descending order in random generation) according to the generation rate (one letter every 1, 2, or 4 s). Patients with severe TBI obtained a significantly lower TPI than controls. Adapted with permission from Azouvi et al. (1996).

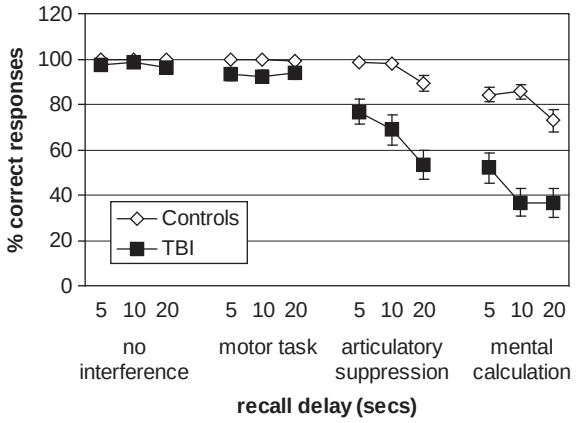


Fig. 3. Short-term memory with interference: Brown–Peterson task, verbal modality. Subjects were asked to recall three letters after 5, 10, or 20 s, with or without an interfering task of increasing complexity. Data are mean ($\pm$1 SE) percentage correct responses for the three recall delays and for each experimental condition. The figure shows the greater proportional decrease of performance of patients with severe TBI, as compared to controls, when faced with a complex interfering task. Adapted with permission from Vallat-Azouvi et al. (2007).

subacute/chronic stage after a severe TBI, we used random number (1–10) generation, at a self-paced rate to avoid any effect due to slowed processing (Azouvi et al., 2004; Leclercq et al., 2000). Compared to controls, patients used a slower generation rate and obtained a lower score on a composite index of randomness (Azouvi et al., 2004; Leclercq et al., 2000).

More recently, we conducted a systematic study of the three components of working memory. Thirty patients with severe chronic TBI and 28 controls were assessed (Vallat-Azouvi et al., 2007). The tasks were designed in order to tap, as selectively as possible, the main functions of working memory, according to the Baddeley model (Baddeley, 1986). Regarding the two slave systems, a marginally significant impairment was found in the patient group for digit span (both forward and backward), while there was no significant deficit of visual spans. The main group differences were found with central executive tasks. The Brown–Peterson paradigm of short-term memory with interference, described earlier in this section, was used to assess the ability to simultaneously store and process information, both in verbal and visual modalities. Results showed a dramatic decrease of performance of patients with TBI under interference. In the verbal Brown–Peterson task, three interfering tasks of increasing complexity were used. A significant triple group by interfering task by recall delay interaction was found, due to a poorer performance of TBI patients under the more demanding interfering task, and for longer recall delays (Fig. 3). Other central executive tasks, requiring either simultaneous storage and processing of information, or the ability to update and monitor information in short-term memory, were also performed significantly poorer by patients as compared to controls.

In summary, the results of the different studies reviewed above suggest that the slave systems of working memory, responsible for passive storage of verbal or visual information, are relatively well preserved after a severe TBI. However, central executive aspects of working memory (particularly the ability to simultaneously store and process complex information, or to monitor and update information) seem to be impaired. This could be due to impaired activation of executive

networks, as suggested by recent functional neuroimaging studies (Cazalis et al., 2006; Christodoulou et al., 2001; Fontaine et al., 1999; McAllister et al., 1999, 2001; Perlstein et al., 2004). Another important aspect of working memory functioning, dual-task processing, will be addressed in the section on divided attention.

Speed of processing and attention

Theoretical aspects

Van Zomeren and Brouwer (1994) proposed a clinically-oriented model of attention, based on the assumption that attention can be divided into four cognitive modules under two broad dimensions, intensity and selectivity, both under the supervision of an attentional executive supervisory system. Intensity refers to the quantitative variations in the amount of mental activity required on a given task. Phasic alertness is the sudden increase of mental activity, resulting for example from a warning signal. Sustained attention refers to slower and longer tonic changes of mental activity, corresponding to the ability to maintain attention continuously over long periods of time during which the subject has to detect and respond to small and/or infrequent changes. Selectivity refers to the limited amount of information that can be dealt with, and is in turn divided into two components: focused and divided attention. Focused attention refers to the ability to attend to one particular stimulus, and to discard irrelevant stimuli (or distractors). Divided attention refers to the ability to share attentional resources between two simultaneous stimuli.

Behavioral aspects

Attentional disorders are among the most frequent complaints of survivors of a TBI, and of their close relatives. In a group of 57 severe TBI patients two years after the injury, 33% complained of mental slowness, 33% of poor concentration, and 21% of inability in doing two things simultaneously (Van Zomeren and Van den Burg, 1985). Brooks et al. (1986) found that 67% of relatives reported mental slowness five years post-injury. Difficulty in concentrating was reported by 50% of the relatives seven years after the injury (Oddy et al., 1985). Therapists using the Rating Scale of Attentional Behaviour reported that the most severe problems (out of 14) of severe TBI patients were: ''performed slowly on mental tasks,'' ''been unable to pay attention to more than one thing at once,'' ''made mistakes because he/she wasn't paying attention properly,'' and ''missed important details in what he/she is doing'' (Ponsford and Kinsella, 1991).

Mental slowness

Slowed information processing has been one of the most robust findings across all neuropsychological studies after TBI (Miller, 1970; Ponsford and Kinsella, 1992; Van Zomeren, 1981). However, although TBI patients perform slower, they do not make more errors than controls, at least in self-paced tasks where they are able to sacrifice speed to achieve greater accuracy (Ponsford and Kinsella, 1992). This has been called the speed–accuracy tradeoff.

Speed of processing was found significantly inversely correlated with severity of injury (Van Zomeren and Deelman, 1976), and was one of the best neuropsychological predictors of the ability to return to work, seven years after the injury (Brooks et al., 1987).

Mental slowness is dependent on task complexity and is related to prolonged decision times rather than to prolonged movement times (Norrman and Svahn, 1961; Ponsford and Kinsella, 1992; Van Zomeren, 1981; Van Zomeren and Deelman, 1976). Van Zomeren and Brouwer (1994) carried out a meta-analysis of seven RT studies in subacute TBI patients. They found a remarkably constant ratio (about 1.4) between the RTs of patients and controls. The ratio appeared slightly larger in more complex tasks, producing RTs of 700 ms or more in control subjects.

Phasic alertness

Most neuropsychological studies agree on the fact that phasic alertness, as assessed by the shortening

of RT when the targets are preceded by a warning signal, is preserved after TBI (Ponsford and Kinsella, 1992; Whyte et al., 1997; Zoccolotti et al., 2000).

Sustained attention

Sustained attention is addressed by measuring the stability of task performance over relatively long periods of time. Although the level of vigilance is reduced in patients with TBI, the existence of a deficit of sustained attention remains debated. Most studies found that patients' performance did not decrease more than controls' with time (Ponsford and Kinsella, 1992; Spikman et al., 1996; Stuss et al., 1989; Van Zomeren and Brouwer, 1994; Whyte et al., 2006; Zoccolotti et al., 2000). But greater variability of performance has been evident in other studies using continuous tasks requiring an active processing of a rapid flow of information or the inhibition of highly automatized responses (Dockree et al., 2006; McAvinue et al., 2005; Stuss et al., 1989; Whyte et al., 1995).

Focused attention

Distractibility and difficulty in concentrating are frequent complaints after TBI, suggesting a decrease of response selectivity. However, contrary to expectations, a behavioral study in a naturalistic setting showed that the number and duration of off-task behaviors of TBI patients were not particularly influenced by the presence of distractors (Whyte et al., 1996, 2000). Accordingly, most experimental studies failed to demonstrate disproportionate distraction and sensitivity to interference. In the Stroop paradigm (Stroop, 1935), subjects are asked to name the ink color of color names in incongruent conditions, for example, the word ''green'' written with red ink. Color naming requires the inhibition of the strong automatic reading tendency. TBI patients performed the task slower than controls, but without being more distracted by the interference condition (Chadwick et al., 1981; Ponsford and Kinsella, 1992; Stuss et al., 1989). Similar negative findings were found with experimental paradigms based on response interference, in which distractors strongly elicit response tendencies competing with those of the target stimuli (Spikman et al., 1996; Stablum et al., 1994; Van Zomeren and Brouwer, 1994; Veltman et al., 1996).

However, one study found that distractors irrelevant to the task (a brightly colored moving stimulus appearing above the target location), occurring simultaneously or shortly after the target, produced slowing of RT that was significantly greater for TBI patients than controls (Whyte et al., 1998). These data were interpreted as reflecting a greater distractibility. Also, TBI participants were found to have more difficulty than controls to ignore irrelevant information only in a condition with high target-distractor similarity (Schmitter-Edgecombe and Kibby, 1998). This suggests that the presence of a deficit of focused attention may depend on the manner in which relevant information is made distinct from irrelevant information.

Divided attention

Clinicians frequently report difficulties in doing two things simultaneously after TBI. Such difficulties may interfere with daily-life demands, and with return to work. Divided attention is determined by at least two factors (Van Zomeren and Brouwer, 1994). The first one is the speed of processing, and the second corresponds to control mechanisms involved in sharing resources and switching between tasks. Divided attention is closely related to the concept of working memory, since the ability to carry out two tasks at the same time is considered as one of the key functions of the central executive (Baddeley, 1986). However, the relationships between divided attention and working memory are complex and debated (Asloun et al., 2008; Miyake et al., 2000).

Brouwer et al. (1989) and Veltman et al. (1996) used a dual task combining a visual choice RT and a driving simulator task in which the difficulty of each single task was adjusted to the individuals' performance level. Such adjustment permitted to control for differences in speed. TBI patients did not show any disproportionate dual-task decrement as compared with controls (Brouwer et al.,

1989; Veltman et al., 1996). However, a significant correlation was found within the patient group between injury severity and divided attention cost (Brouwer et al., 1989; Veltman et al., 1996). Indeed, the performance of patients with a PTA of more than two weeks was poorer, compared with less severely injured participants. Veltman et al. (1996) suggested that less severely injured patients use a compensatory strategy characterized by cautiousness and increased mental effort, while such strategies would not be available to more severely injured patients.

Several other studies tended to confirm this hypothesis and suggested the existence of deficits of dual-task processing after severe TBI at least in complex tasks performed under time pressure (McDowell et al., 1997; Park et al., 1999; Stablum et al., 1994; Vilkki et al., 1996). McDowell et al. (1997) used a simple visual RT performed concurrently with articulation or digit span tasks. To control for the effect of slowed processing, an analysis was performed by pairing a subsample of TBI patients with control subjects matched for single-task reaction time. The dual-task decrement assessed in this way was significantly higher for TBI patients than controls. Park et al. (1999) reported a meta-analysis on divided attention after TBI. They found that the effect size of the divided attention deficit varied considerably from one study to another (range: 0.03–1.28). TBI patients did not differ from controls when the divided attention tasks could be performed relatively automatically, while they were impaired relative to controls on tasks including substantial working memory load (Park et al., 1999).

In our department, we conducted a series of studies on divided attention that also lead to the conclusion that deficits were strongly determined by tasks characteristics. In a first study, severe subacute TBI patients were given two different dual tasks (Azouvi et al., 1996). The first task was performed without time pressure and associated a modified Stroop paradigm and a random generation task. No disproportionate dual-task impairment was found in the TBI group. The second task included a higher time pressure. Patients were asked to perform a card sorting task of variable difficulty level combined with random generation of letters at an imposed rate (Baddeley, 1966). A disproportionate decrease in performance occurred under dual-task condition in the TBI group, even after statistical control for slowed information processing. These results again suggest that the presence of divided attention deficits in TBI depends on the attentional demands of the task, and that in complex resource-demanding conditions, slowness is not sufficient to explain such deficit. In two subsequent studies, we used a dual task combining self-paced random number generation with a choice visual RT (Azouvi et al., 2004; Leclercq et al., 2000). Comparatively to controls, severe TBI patients showed a disproportionate dual-task decrement of performance. In the second study (Azouvi et al., 2004), two additional conditions were given, in which subjects were instructed to emphasize alternatively one of each task. We found that TBI patients were able to allocate their resources according to task instructions as efficiently as controls, while they had difficulties in managing the two tasks simultaneously (Fig. 4). This suggests that the divided attention deficit could be related to a

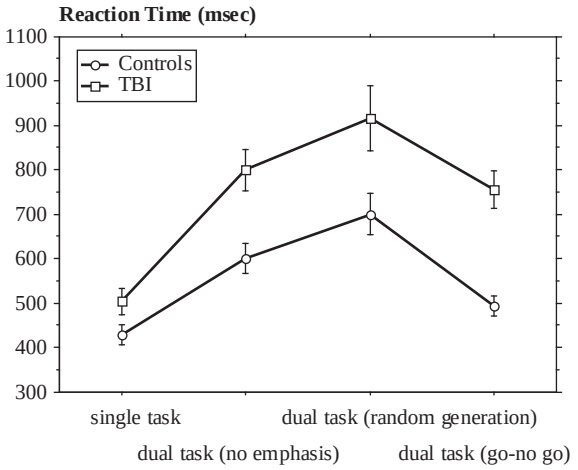


Fig. 4. Dual-task performance. The figure shows the mean (±1 SE) RT of patients and controls in a selective attention task (go–no go) performed under four conditions: single task, dual task without any instruction regarding the task to emphasize, dual task with emphasis on random generation, and dual task with emphasis on go–no go. Adapted with permission from Azouvi et al. (2004).

reduction of available central executive resources rather than to a deficient strategic control (Leclercq and Azouvi, 2002).

In summary, mental slowness is one of the most robust findings after severe TBI. Whether attentional functions are additionally impaired remains debated. The presence of specific impairments of attentional functions (particularly of divided attention) may depend on the nature and complexity of the task.

Mental fatigue

Mental fatigue is a highly frequent complaint after TBI, reported by 30–70% of patients (Brooks et al., 1986; Dijkers and Bushnik, 2008; Ponsford et al., 1995a; Ziino and Ponsford, 2005). Olver et al. (1996) compared patients with predominantly severe TBI at two and five years post-injury and found a high prevalence of fatigue at both time points (respectively 68% and 73%). Bushnik et al. (2008a, b) found that self-reported fatigue improved during the first year, and then did not change significantly up to two years after TBI. Several studies found no significant relationships between fatigue and injury severity (Borgaro et al., 2004; Cantor et al., 2008; Ziino and Ponsford, 2005). In a population-based study, five years post-injury, fatigue was reported more frequently by individuals with severe TBI (58%), as compared to minor or moderate TBI (35% and 32%), but the difference was not statistically significant (Masson et al., 1996).

The mechanisms of fatigue after TBI remain debated. It has been found associated with depression, pain, disturbed sleep, or neuroendocrine abnormalities (Bushnik et al., 2007; Chaumet et al., 2008; Clinchot et al., 1998; Kreutzer et al., 2001). Van Zomeren et al. (1984) argued that fatigue after TBI could be due to the constant compensatory effort required to reach an adequate level of performance in everyday life, despite cognitive deficits and slowed processing. This is known as the ''coping hypothesis.''

The coping hypothesis has received support from experimental studies. Riese et al. (1999) assessed the performance of eight very severe TBI patients in a continuous dual task lasting 50 min. They found that, although sustained task performance did not significantly differ between TBI and control subjects, TBI patients showed more subjective and physiological distress than controls. They reported higher levels of task load and more visual complaints. Moreover, while controls' systolic blood pressure decreased from pre- to post-test, it showed the reverse pattern in the TBI group, suggesting higher psychophysiological costs to sustain task performance. Azouvi et al. (2004) found that TBI patients, as compared to controls, reported higher levels of subjective mental effort during completion of a complex divided attention task. Ziino and Ponsford (2006a, b) studied in two parallel studies the relationships between self-reported fatigue and cognitive deficits (vigilance and selective attention). In a group of patients with TBI of various severities, fatigue was significantly correlated with performance on the vigilance task and on the complex selective attention test, but not with more simple attentional tasks.

We assessed the relationships between subjective mental fatigue, mental effort, attention deficits, and mood in 27 patients with subacute/chronic severe TBI (Belmont et al., in press). Subjects first rated their baseline subjective fatigue on the Fatigue Severity Scale (FSS) and on the Visual Analog Scale for Fatigue (VAS-F). Then, they performed a long-duration selective attention task, separated in two parts. Fatigue on the VAS-F was assessed again between the two parts, and at the end of the attention task. Subjects were also asked to rate on a visual analog scale the level of subjective mental effort devoted to the task. Patients reported a higher baseline fatigue than controls. They performed significantly poorer on the selective attention task. Significant correlations were found in the group with TBI between attention performance, mental effort, and subjective fatigue. In contrast, fatigue did not significantly correlate with mood (depression and anxiety). These findings suggest that patients with more severe attention deficits have to produce higher levels of mental effort to manage a complex task, which may increase subjective fatigue, in line with the coping hypothesis.

Executive functions

Theoretical aspects

Executive functions are the cognitive abilities involved in programming, regulation, and verification of goal-directed behavior. The model proposed by Shallice (1988) is one of the most widely used in clinical neuropsychology. This model proposes two different control levels. Automatic overlearned motor programs (or schemata) can be executed without conscious control. Because some of these schemata may conflict with each other, the model proposes the intervention of a semiautomatic processor, or ''contention scheduler,'' that gives precedence to one of the conflicting schemata on the basis of internal or external contingencies. In certain situations, a subject might need to override automatic actions and consciously focus its attention elsewhere. The model proposes a supervisory system to serve this function. This system is assumed to have limited capacity. Its main function is to coordinate and control information processing, particularly in novel or complex situations. It is generally agreed that the functions of the supervisory system depend on multiple separable control processes located within the frontal lobes (Shallice and Burgess, 1996).

Behavioral aspects

Survivors from a traumatic coma frequently show dramatic personality and behavioral changes. These changes may be related to lack of control (disinhibition, impulsivity, irritability, hyperactivity, aggressiveness) or lack of drive (apathy, reduced initiative, poor motivation).These modifications are frequently associated with lack of awareness (anosognosia). The prevalence of such disorders after a severe TBI is high. For example, Brooks et al. (1986) asked the relatives of 55 severe TBI patients to state whether the brain injured was ''the same person as before the accident.'' Three months after the accident, 49% of relatives answered that the patient was ''not the same as before,'' but this proportion increased to 60% at one year and 74% at five years. Five years post-injury, the most frequent behavioral changes reported by the relatives were irritability (64%); bad temper (64%); tiredness (62%); depression (57%); rapid mood changes (57%); tension and anxiety (57%); and threats of violence (54%). Personality change was associated with a high subjective burden on the relative. In another study conducted two years after a severe TBI, irritability was also one of the most frequent problem, but lack of initiative was reported in 44% of cases, and socially inappropriate behavior in 26% of cases (Ponsford et al., 1995a).

TBI patients also demonstrate a loss of communication skills, even when basic language abilities are preserved (McDonald and Flanagan, 2004). Their conversational discourse is disorganized. Some patients are overtalkative but inefficient, often drifting from topic to topic, and making tangential and irrelevant comments. Other patients have impoverished communication, with slow and incomplete responses and numerous pauses. Patients often fail to follow social conversational rules.

Objective assessment of behavioral modifications is difficult. The Dysexecutive Questionnaire (DEX) includes 20 items addressing a range of problems commonly associated with the dysexecutive syndrome (Burgess et al., 1998; Wilson et al., 1998). It has been found nearly as sensitive to brain injury as more formal neuropsychological tests (Bennett et al., 2005). Wilson et al. (1998) documented with the DEX the five items that obtained the highest rankings in a group of 16 severely brain-injured patients in a rehabilitation department: poor planning, poor self-appraisal, trouble in decision-making, distractibility, and apathy. The same five items also obtained the highest ranking (mean score higher than 2/4) in a study conducted in our department with the same scale (Cazalis et al., 2001).

Conceptualization and set-shifting

Sorting tasks require subjects to classify items (cards, tokens) according to varying sorting criteria (such as color, shape, number of stimuli,

etc.) to adapt their responses to cues given by the examiner, and to shift criteria when required to. The Wisconsin Card Sorting Test (WCST) is the most widely sorting test used in clinical neuropsychology. It may show a reduction in number of sorting criteria found by the subject and, more importantly, shifting difficulties, defined by perseverative errors. The sensitivity of this test in TBI subjects has been questioned, and seems to depend on the version of the test used. A number of studies found a higher number of perseverative errors after TBI, at least when using the original, longer, and more difficult version (Ferland et al., 1998; Stuss et al., 1985), while a modified, easier version (Nelson, 1976) seems to be less sensitive, except at the early stage post-injury (Levin et al., 1990; Spikman et al., 2000). Interestingly, Stuss et al. (1985) found that the WCST (original version) was one of the two neuropsychological tests that best discriminated from controls a group of brain-injured subjects with apparent good recovery, but with persisting complaints. Vilkki (1992) designed a categorization and sorting test with tokens of different color, size, and shape. TBI patients performed poorer on that task as compared to healthy controls or to patients with lesions of the posterior part of brain of different nature.

Planning

The ''Tower of London'' task addresses the planning component of the supervisory system (Shallice, 1982). The test apparatus consists of three beads of different colors, on three sticks of different length in a row. Subjects are presented with two possible arrangements of the beads, the starting position and the goal position. They are asked to reach the goal position with as few moves as possible, but they are not allowed to move more than one bead at a time, to leave a bead out, or to put more beads on a stick than possible. TBI patients performed the Tower of London as accurately as controls but more slowly (Cockburn, 1995; Ponsford and Kinsella, 1992; Spikman et al., 2000; Veltman et al., 1996). However, it seems that at least some patients, with more severe injuries, may perform poorly on the Tower of London (Cicerone and Wood, 1987; Levin et al., 1994; Veltman et al., 1996). Accordingly, we found a high interindividual variability in a study with a modified computerized version of the task (Cazalis et al., 2006). Four severe TBI patients out of ten obtained a good performance, within the upper range of healthy controls, in terms of both speed and accuracy, while six patients (60%) demonstrated a very poor performance, far below the range of controls. This variability in performance was accompanied by variability in brain activation patterns in fMRI, with good performers showing a brain activation comparable to that of controls, while poor performers had a reduced activation of prefrontal and cingulate areas (Cazalis et al., 2006). Vilkki (1992) designed another mental planning task, requiring to learn a spatial configuration by self-set goals. Patients with TBI performed poorer than controls or than patients with posterior surgical lesions of the brain (Vilkki, 1992). However, opposite results were found by Spikman et al. (2000) in patients at a later post-injury stage.

Mental flexibility

The Trail Making Test (Reitan, 1958) requires patients to alternate between two sets of responses (letters and numbers). Subjects must first draw lines to connect consecutively numbered circles on one work sheet (part A) and then connect the same number of consecutively numbered and lettered circles on another work sheet by alternating between the two sequences (part B). Patients with TBI performed the task slower than controls (Dikmen et al., 1990; Levin et al., 1990). However, it seems that speed of processing was not significantly more affected by the more difficult (B) condition as compared to the easiest (A) condition, suggesting that patients had no deficit of mental flexibility, in addition to slowed processing (Spikman et al., 2000).

Generation of new information

Tasks of verbal or design fluency are of common use in clinical practice. These tasks require the

ability to generate in a limited time the maximal number of items pertaining to a given category (e.g., animals, words beginning with an F, designs). Impaired performance in TBI patients is usually characterized by a low number of items generated per minute, and in some cases, by a tendency to use repetitive or stereotyped response patterns (Levin et al., 1990, 1991). As previously mentioned, TBI patients also have an impaired ability to generate random series (Azouvi et al., 1996, 2004).

Inhibition of dominant responses

The Stroop test is usually used to assess inhibition. Data obtained with this test have been presented in the section 'Focused attention'.

Executive functions in a naturalistic setting

Executive functions are by nature mainly involved in novel, open-ended, and unstructured situations that are different from most structured neuropsychological tasks or from routine life in a rehabilitation setting. Patients who seem to behave appropriately while in a stable, quiet, nondemanding environment may show important difficulties in adapting to more complex situations (Eslinger and Damasio, 1985; Shallice and Burgess, 1991). Shallice and Burgess (1991) reported three cases of frontally-injured patients who had a nearly normal performance on standard tests, but were dramatically impaired in two open-ended tests. The six-element test required patients to carry out six simple open-ended tasks in 15 min. They had to judge how much time to devote to each task so as to optimize their performance given some simple rules. The second task, the multiple errands test, involves scheduling a set of simple shopping activities in real time in a street.

Script generation is another way to assess everyday life disorders. Cazalis et al. (2001) asked severe TBI patients to generate scripts, that is, to spell out in the proper order the successive actions that were necessary to reach a given goal. Three scripts of increasing difficulty were given: a routine (preparing to go to work in the morning), a nonroutine (taking a trip to Mexico), and a novel script (opening a beauty salon). The results showed that TBI patients, in opposition with patients with focal prefrontal lesions, were able to generate proper actions, in the correct order, and to state which actions were the more important to reach the goal, just as efficiently as controls. However, when asked to reorganize actions belonging to different scripts that were presented in a mixed array, they were less able than controls to discriminate actions, and tended to make sorting errors. This was attributed to a difficulty in dealing with multiple sources of information, rather than to a deficient access to script knowledge (Cazalis et al., 2001).

Chevignard et al. (2000, 2008) also used a script generation task in patients with prefrontal lesions. Patients were required to generate the actions necessary to prepare two simple meals. Then, in a second time, they were asked to perform the task in a real kitchen. In comparison to controls, patients produced a disproportionate number of errors in the execution compared to the generation condition.

In the route finding task, patients are required to reach a previously unknown location in the hospital (Boyd and Sautter, 1993). Using this task in a sample of patients with severe TBI, we found that patients performed poorer than controls (Cazalis et al., 2001). While they were able to understand task instructions like controls, they were less able than controls to set an appropriate search strategy, to detect and correct errors, and to memorize information. They also showed more inappropriate on-task behavior and needed more prompting from the examiner than controls. Spikman et al. (2000) found that the route finding test significantly discriminated patients with chronic TBI from healthy controls, while all the other executive tests in this study did not.

Heterogeneity of executive disorders after TBI

Executive functions are not a unitary construct. Inter-test correlations of measures of executive functions within a group of 90 patients with TBI have been found to be weak, and not stronger

than correlations with nonexecutive tests (Duncan et al., 1997). A factorial analysis has been conducted on a battery of tests of executive functions in a sample of 104 TBI patients (Busch et al., 2005). The results revealed three weakly intercorrelated factors: higher-level executive functions (self-generated behavior and flexibility/shifting); mental control on information in working memory; and intrusions or perseverations in long-term memory.

Anosognosia and Lack of Insight

Severe TBI patients have repeatedly been found to underestimate their difficulties in comparison to relatives' and/or therapists' reports (Prigatano and Altman, 1990). This lack of awareness mainly concerns cognitive and behavioral problems, whereas physical or sensory impairments are usually acknowledged. Oddy et al. (1985) found that 40% of TBI patients did not admit memory difficulties that were reported by family members seven years post-injury. Sunderland et al. (1983) found that self-assessment of memory was poorly correlated with actual memory tests by TBI patients, in contrast with relatives' judgment. It was also found that 33% of severe TBI patients reported that memory was not a problem at all in their everyday life, an amount that was similar to that of patients with mild TBI. Patients with TBI also underestimate their behavioral modifications, and overestimate their social skills and emotional control, in comparison with their relatives' reports (Fordyce and Roueche, 1986; Prigatano and Altman, 1990; Prigatano et al., 1990). Lack of insight is a complex phenomenon and may reflect (organic) anosognosia and/or psychological adjustment to neurological impairments (i.e., denial). The relationship between lack of awareness and injury severity is debated. Prigatano & Altman (1990) did not find any significant correlation with injury severity, while Leathem et al. (1998) found that only severe TBI patients overestimated their skills, in contrast with individuals with mild and moderate TBI whose judgment did not differ from that of relatives.

Conclusion

Cognitive deficits after a traumatic coma are complex, and often difficult to detect and to measure. Some patients may perform well on standardized cognitive tests, while showing significant difficulties in everyday life. Moreover, patients frequently have poor awareness of their difficulties. For these reasons, assessment of cognitive deficits should rely on careful examination, including specific psychometric tests, but also questionnaires for family members, and ecological measures, in situations close to real life. A comprehensive assessment and understanding of cognitive difficulties is important, as there is now a large agreement on the fact that cognitive rehabilitation is effective, particularly for deficits of executive functions, attention and working memory (Cicerone et al., 2000; Kennedy et al., 2008).

Acknowledgments

Studies reported in this review were supported by grants from the French Ministry of Health (PHRC national 2001, P011204), by AP-HP, by the Institut Garches and by the Fondation de l'Avenir pour la Recherche Médicale.

Appendix

Table A1. Summary of studies of cognitive testing after TBI

Cognitive domain/functions	Testing procedure	Performance (vs. controls)
Long-term memory		
Anterograde episodic memory	Verbal/visual learning of new information	Impaired (below 1 SD/norms)
Learning rate	Multiple repeated trials of information presentation	Slower, inconsistent, and disorganized learning
Semantic encoding	Influence of the relative importance of the information; spontaneous use of semantic clustering	Impaired
Benefit from semantic memory aids	Comparison of free recall vs. cued recall	Preserved
Ability to use mental imagery to improve encoding efficiency	Comparison of concrete vs. abstract words; benefit from imagery instructions	Impaired
Forgetting rate	Comparison of delayed vs. early recall	Accelerated forgetting rate
Sensitivity to interference	Presentation of two successive lists of words (A and B)	Impaired retroactive interference (effect of list B on list A) but preserved proactive interference
Retrograde memory: autobiographical memory, public events, semantic knowledge	Questionnaires on different personal life periods; general knowledge	Impaired without temporal gradient
Prospective memory	Remembering to perform a previously planned action, either time-based (performance of action at a given time point) or event-based (after a predetermined event has occurred)	Impaired
Implicit and procedural memory	Priming effect; skill learning	Debated (seems preserved only for automatic tasks)
Working memory		
Short-term storage	Digit or visual spans	Mildly impaired
Storage and processing of information in short-term memory	PASAT; n-back; updating and monitoring; Brown–Peterson (interference in short-term memory)	Load-dependant impairment
Attention		
Speed of processing	Timed tasks (reaction times, PASAT, etc.)	Reduced
Phasic alertness	Benefit from a warning signal	Preserved
Sustained attention	Stability of performance over a long period of time	Debated seems relatively preserved
Focused attention	Ability to discard irrelevant stimuli or distractors (e.g., Stroop test)	Preserved
Divided attention	Dual tasks	Load-dependant impairment
Executive functions		
Conceptualization and set shifting	Sorting tasks	Impaired (at least with more difficult versions of the task)
Planning	Tower of London or other planning tasks	Debated, seems relatively preserved
Mental flexibility	Trail Making Test	Preserved (but slowed)
Generation of new information	Verbal or design fluency; Random generation	Impaired
Inhibition of dominant responses	Stroop test	Preserved
Executive functions in naturalistic settings	Open-ended tasks (multiple errands; six-element; route finding; kitchen task)	Impaired

Note: For clarity of presentation, references for tasks and studies are not included in the table, but they are indicated in the text.

References

Asloun, S., Soury, S., Couillet, J., Giroire, J. M., Joseph, P. A., Mazaux, J. M., et al. (2008). Interactions between divided attention and working-memory load in patients with severe traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, *30*, 481–490.

Azouvi, P., Couillet, J., Leclercq, M., Martin, M., Asloun, S., & Rousseaux, M. (2004). Divided attention and mental effort after severe traumatic brain injury. *Neuropsychologia*, *42*, 1260–1268.

Azouvi, P., Jokic, C., Van der Linden, M., Marlier, N., & Bussel, B. (1996). Working memory and supervisory control after severe closed head injury. A study of dual task performance and random generation. *Journal of Clinical and Experimental Neuropsychology*, *18*, 317–337.

Baddeley, A., Harris, J., Sunderland, A., Watts, K. P., & Wilson, B. (1987). Closed head injury and memory. In H. S. Levin, J. Grafman, & H. M. Eisenberg (Eds.), *Neurobehavioral recovery from head injury* (pp. 295–317). New York: Oxford University Press.

Baddeley, A., & Hitch, G. (1974). Working memory. In G. A. Bower (Ed.), *Recent advances in learning and motivation* (Vol. 8, pp. 47–90). New York: Academic Press.

Baddeley, A. D. (1966). The capacity for generating information by randomization. *Quarterly Journal of Experimental Psychology*, *18*, 119–129.

Baddeley, A. D. (1986). *Working Memory*. New York: Oxford University Press.

Belmont, A., Agar, N., & Azouvi, P. (in press). Subjective fatigue, mental effort and attention deficits after severe traumatic brain injury. *Neurorehabilitation and Neural Repair*.

Bennett, P. C., Ong, B., & Ponsford, J. (2005). Measuring executive dysfunction in an acute rehabilitation setting: Using the dysexecutive questionnaire (DEX). *Journal of the International Neuropsychological Society*, *11*, 376–385.

Bennett-Levy, J. M. (1984). Long-term effects of severe closed head injury on memory: Evidence from a consecutive series of young adults. *Acta Neurologica Scandinavica*, *70*, 285–298.

Borgaro, S. R., Gierok, S., Caples, H., & Kwasnica, C. (2004). Fatigue after brain injury: Initial reliability study of the BNI Fatigue Scale. *Brain Injury*, *18*, 685–690.

Boyd, T. M., & Sautter, S. W. (1993). Route finding: A measure of everyday executive functioning in the head-injured adult. *Applied Cognitive Psychology*, *7*, 171–181.

Brooks, D. N. (1974). Recognition memory after head injury: A signal detection analysis. *Cortex*, *11*, 224–230.

Brooks, D. N. (1975). Long and short term memory in head injured patients. *Cortex*, *11*, 329–340.

Brooks, D. N. (1976). Wechsler Memory Scale performance and its relationship to brain damage after severe closed head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *39*, 593–601.

Brooks, D. N., Campsie, L., Symington, C., Beattie, A., & MacKinlay, W. (1986). The five year outcome of severe blunt head injury: A relative's view. *Journal of Neurology, Neurosurgery and Psychiatry*, *49*, 764–770.

Brooks, N. (1984). Head injury and the family. In N. Brooks (Ed.), *Closed head injury: Psychological, social and family consequences* (pp. 123–147). Oxford: Oxford University Press.

Brooks, N., Mc Kinlay, W., Symington, C., Beattie, A., & Campsie, L. (1987). Return to work within the first seven years of severe head injury. *Brain Injury*, *1*, 5–19.

Brouwer, W. H., Ponds, R. W. H. M., Van Wolffelaar, P. C., & Van Zomeren, A. H. (1989). Divided attention 5 to 10 years after severe closed head injury. *Cortex*, *25*, 219–230.

Brown, J. (1958). Some tests of the decay theory of immediate memory. *Quarterly Journal of Experimental Psychology*, *10*, 12–21.

Burgess, P. W., Alderman, N., Evans, J., Emslie, H., & Wilson, B. (1998). The ecological validity of tests of executive function. *Journal of the International Neuropsychological Society*, *4*, 547–558.

Busch, R. M., McBride, A., Curtiss, G., & Vanderploeg, R. D. (2005). The components of executive functioning in traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, *27*, 1022–1032.

Bushnik, T., Englander, J., & Katznelson, L. (2007). Fatigue after TBI: Association with neuroendocrine abnormalities. *Brain Injury*, *21*, 559–566.

Bushnik, T., Englander, J., & Wright, J. (2008a). The experience of fatigue in the first 2 years after moderate-to-severe traumatic brain injury: A preliminary report. *Journal of Head Trauma Rehabilitation*, *23*, 17–24.

Bushnik, T., Englander, J., & Wright, J. (2008b). Patterns of fatigue and its correlates over the first 2 years after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *23*, 25–32.

Cantor, J. B., Ashman, T., Gordon, W., Ginsberg, A., Engmann, C., Egan, M., et al. (2008). Fatigue after traumatic brain injury and its impact on participation and quality of life. *Journal of Head Trauma Rehabilitation*, *23*, 41–51.

Carlesimo, G. A., Sabbadini, M., Bombardi, P., Di Porto, E., Loasses, A., & Caltagirone, C. (1998). Retrograde memory deficits in severe closed-head injury patients. *Cortex*, *34*, 1–23.

Carlesimo, G. A., Sabbadini, M., Loasses, A., & Caltagirone, C. (1997). Forgetting from long-term memory in severe closed-head injury patients: Effect of retrieval conditions and semantic organization. *Cortex*, *33*, 131–142.

Cazalis, F., Azouvi, P., Sirigu, A., Agar, N., & Burnod, Y. (2001). Script knowledge after severe traumatic brain injury. *Journal of the International Neuropsychological Society*, *7*, 795–804.

Cazalis, F., Feydy, A., Valabregue, R., Pelegrini-Issac, M., Pierot, L., & Azouvi, P. (2006). fMRI study of problem solving after severe traumatic brain injury. *Brain Injury*, *20*, 1019–1028.

Chadwick, O., Rutter, M., Brown, G., Shaffer, D., & Traub, M. (1981). A prospective study of children with head injuries: II. Cognitive sequelae. *Psychological Medicine*, *11*, 49–61.

Chaumet, G., Quera-Salva, M. A., Macleod, A., Hartley, S., Taillard, J., Sagaspe, P., et al. (2008). Is there a link between

alertness and fatigue in patients with traumatic brain injury? *Neurology*, *71*, 1609–1613.

Chevignard, M., Pillon, B., Pradat-Diehl, P., Taillefer, C., Rousseau, S., Le Bras, C., et al. (2000). An ecological approach to planning dysfunction: Script execution. *Cortex*, *36*, 649–669.

Chevignard, M. P., Taillefer, C., Picq, C., Poncet, F., Noulhiane, M., & Pradat-Diehl, P. (2008). Ecological assessment of the dysexecutive syndrome using execution of a cooking task. *Neuropsychological Rehabilitation*, *18*, 461–485.

Christodoulou, C., DeLuca, J., Ricker, J. H., Madigan, N. K., Bly, B. M., Lange, G., et al. (2001). Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. *Journal of Neurology Neurosurgery and Psychiatry*, *71*, 161–168.

Cicerone, K. D., Dahlberg, C., Kalmar, K., Langenbahn, D. M., Malec, J. F., Bergquist, T. F., et al. (2000). Evidence-based cognitive rehabilitation: Recommendations for clinical practice. *Archives of Physical Medicine and Rehabilitation*, *81*, 1596–1615.

Cicerone, K. D., & Wood, J. C. (1987). Planning disorder after closed head injury: A case study. *Archives of Physical Medicine and Rehabilitation*, *68*, 111–115.

Clinchot, D. M., Bogner, J., Mysiw, W. J., Fugate, L., & Corrigan, J. (1998). Defining sleep disturbance after brain injury. *American Journal of Physical Medicine and Rehabilitation*, *77*, 291–295.

Cockburn, J. (1995). Performance on the Tower of London test after severe head injury. *Journal of the International Neuropsychological Society*, *1*, 537–544.

Crosson, B., Novack, T. A., Trenerry, M. R., & Craig, P. L. (1988). California Verbal Learning Test (CVLT) performance in severely head-injured and neurologically normal adult males. *Journal of Clinical and Experimental Neuropsychology*, *10*, 754–768.

Crosson, B., Sartor, K., Jenny, A., Nabors, N., & Moberg, P. (1993). Increased intrusions during verbal recall in traumatic and nontraumatic lesions of the temporal lobe. *Neuropsychology*, *7*, 193–208.

Curtiss, G., Vanderploeg, R. D., Spencer, J., & Salazar, A. M. (2001). Patterns of verbal learning and memory in traumatic brain injury. *Journal of the International Neuropsychological Society*, *7*, 574–585.

DeLuca, J., Schultheis, M. T., Madigan, N. K., Christodoulou, C., & Averill, A. (2000). Acquisition versus retrieval deficits in traumatic brain injury: Implications for memory rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *81*, 1327–1333.

Deshpande, S. A., Millis, S. R., Reeder, K. P., Fuerst, D., & Ricker, J. H. (1996). Verbal learning subtypes in traumatic brain injury: A replication. *Journal of Clinical and Experimental Neuropsychology*, *18*, 836–842.

Dijkers, M. P., & Bushnik, T. (2008). Assessing fatigue after traumatic brain injury: An evaluation of the Barroso Fatigue Scale. *Journal of Head Trauma Rehabilitation*, *23*, 3–16.

Dikmen, S., Machamer, J., Temkin, N., & McLean, A. (1990). Neuropsychological recovery in patients with moderate to severe head injury: 2 year follow-up. *Journal of Clinical and Experimental Neuropsychology*, *12*, 507–519.

Dikmen, S. S., Temkin, N. R., Machamer, J. E., Holubkov, A. L., Fraser, R. T., & Winn, H. R. (1994). Employment following traumatic head injuries. *Archives of Neurology*, *51*, 177–186.

Dockree, P. M., Bellgrove, M. A., O'Keeffe, F. M., Moloney, P., Aimola, L., Carton, S., et al. (2006). Sustained attention in traumatic brain injury (TBI) and healthy controls: Enhanced sensitivity with dual-task load. *Experimental Brain Research*, *168*, 218–229.

Duncan, J., Johnson, R., Swales, M., & Freer, C. (1997). Frontal lobe deficits after head injury: Unity and diversity of function. *Cognitive Neuropsychology*, *14*, 713–741.

Dywan, J., Segalowitz, S. J., Henderson, D., & Jacoby, L. (1993). Memory for source after traumatic brain injury. *Brain and Cognition*, *21*, 20–43.

Eslinger, P. J., & Damasio, A. R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: Patient EVR. *Neurology*, *35*, 1731–1741.

Ferland, M. B., Ramsay, J., Engeland, C., & O'Hara, P. (1998). Comparison of the performance of normal individuals and survivors of traumatic brain injury on repeat administrations of the Wisconsin Card Sorting Test. *Journal of Clinical and Experimental Neuropsychology*, *20*, 473–482.

Fontaine, A., Azouvi, P., Remy, P., Bussel, B., & Samson, Y. (1999). Functional anatomy of neuropsychological deficits after severe traumatic brain injury. *Neurology*, *53*, 1963–1968.

Fordyce, D., & Roueche, J. (1986). Changes in perspective of disability among patients, staff, and relatives during rehabilitation of brain injury. *Rehabilitation Psychology*, *31*, 217–229.

Goldstein, F. C., Levin, H. S., & Boake, C. (1989). Conceptual encoding following severe closed head injury. *Cortex*, *25*, 541–554.

Goldstein, F. C., Levin, H. S., Boake, C., & Lohrey, J. H. (1990). Facilitation of memory performance through induced semantic processing in survivors of severe closed-head injury. *Journal of Clinical and Experimental Neuropsychology*, *12*, 286–300.

Gronwall, D., & Wrightson, P. (1981). Memory and information processing capacity after closed head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *44*, 889–895.

Gronwall, D. M. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills*, *44*, 367–373.

Groot, Y. C., Wilson, B. A., Evans, J., & Watson, P. (2002). Prospective memory functioning in people with and without brain injury. *Journal of the International Neuropsychological Society*, *8*, 645–654.

Hannay, H. J., Levin, H. S., & Grossman, R. G. (1979). Impaired recognition memory after head injury. *Cortex*, *15*, 269–283.

Hart, R. (1994). Forgetting in traumatic brain-injured patients with persistent memory impairment. *Neuropsychology*, *8*, 325–332.

Haut, M., & Shutty, M. (1992). Patterns of verbal learning after closed head injury. *Neuropsychology*, *6*, 51–58.

Haut, M. W., Petros, T. V., & Frank, R. G. (1990). The recall of prose as a function of importance following closed head injury. *Brain Injury*, *4*, 281–288.

High, W. M., Jr., Levin, H. S., & Gary, H. E., Jr. (1990). Recovery of orientation following closed-head injury. *Journal of Clinical and Experimental Neuropsychology*, *12*, 703–714.

Kennedy, M. R., Coelho, C., Turkstra, L., Ylvisaker, M., Moore Sohlberg, M., Yorkston, K., et al. (2008). Intervention for executive functions after traumatic brain injury: A systematic review, meta-analysis and clinical recommendations. *Neuropsychological Rehabilitation*, *18*, 257–299.

Kinsella, G., Murtagh, D., Landry, A., Homfray, K., Hammond, M., O'Beirne, L., et al. (1996). Everyday memory following traumatic brain injury. *Brain Injury*, *10*, 499–507.

Kliegel, M., Eschen, A., & Thone-Otto, A. I. (2004). Planning and realization of complex intentions in traumatic brain injury and normal aging. *Brain and Cognition*, *56*, 43–54.

Kreutzer, J. S., Seel, R. T., & Gourley, E. (2001). The prevalence and symptom rates of depression after traumatic brain injury: A comprehensive examination. *Brain Injury*, *15*, 563–576.

Leathem, J. M., Murphy, L. J., & Flett, R. A. (1998). Self- and informant-ratings on the Patient Competency Rating Scale in patients with traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, *20*, 694–705.

Leclercq, M., & Azouvi, P. (2002). Attention after traumatic brain injury. In M. Leclercq & P. Zimmermann (Eds.), *Applied neuropsychology of attention* (pp. 251–273). Hove, UK: Psychology Press.

Leclercq, M., Couillet, J., Azouvi, P., Marlier, N., Martin, Y., Strypstein, E., et al. (2000). Dual task performance after severe diffuse traumatic brain injury or vascular prefrontal damage. *Journal of Clinical and Experimental Neuropsychology*, *22*, 339–350.

Levin, H. S. (1989). Memory deficit after closed head injury. *Journal of Clinical and Experimental Neuropsychology*, *12*, 129–153.

Levin, H. S., Gary, H. E., Jr., Eisenberg, H. M., Ruff, R. M., Barth, J. T., Kreutzer, J., et al. (1990). Neurobehavioral outcome 1 year after severe head injury: Experience of the Traumatic Coma Data Bank. *Journal of Neurosurgery*, *73*, 699–709.

Levin, H. S., & Goldstein, F. C. (1986). Organization of verbal memory after severe closed head injury. *Journal of Clinical and Experimental Neuropsychology*, *8*, 643–656.

Levin, H. S., Goldstein, F. C., High, W. M., & Eisenberg, H. M. (1988a). Disproportionately severe memory deficit in relation to normal intellectual functioning after closed head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *51*, 1294–1301.

Levin, H. S., Goldstein, F. C., High, W. M., Jr., & Williams, D. (1988b). Automatic and effortful processing after severe closed head injury. *Brain and Cognition*, *7*, 283–297.

Levin, H. S., Goldstein, F. C., Willliams, D. H., & Eisenberg, H. M. (1991). The contribution of frontal lobe lesions to the neurobehavioral outcome of closed head injury. In H. S. Levin, H. M. Eisenberg, & A. L. Benton (Eds.), *Frontal lobe function and dysfunction* (pp. 318–338). New York: Oxford University Press.

Levin, H. S., Grossman, R. G., Rose, J. E., & Teasdale, G. (1979). Long-term neuropsychological outcome of closed head injury. *Journal of Neurosurgery*, *50*, 412–422.

Levin, H. S., Hanten, G., Zhang, L., Swank, P. R., Ewing-Cobbs, L., Dennis, M., et al. (2004). Changes in working memory after traumatic brain injury in children. *Neuropsychology*, *18*, 240–247.

Levin, H. S., High, W. M., Meyers, C. A., Von Laufen, A., Hayden, M. E., & Eisenberg, H. M. (1985). Impairment of remote memory after closed head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *48*, 556–563.

Levin, H. S., Mendelsohn, D., Lily, M. A., Fletcher, J. M., Culhane, K. A., Chapman, S. B., et al. (1994). Tower of London performance in relation to magnetic resonance imaging following closed head injury in children. *Neuropsychology*, *8*, 171–179.

Mailhan, L., Azouvi, P., & Dazord, A. (2005). Life satisfaction and disability after severe traumatic brain injury. *Brain Injury*, 227–238.

Markowitsch, H. J., Calabrese, P., Liess, J., Haupts, M., Durwen, H. F., & Gehlen, W. (1993). Retrograde amnesia after traumatic injury of the fronto-temporal cortex. *Journal of Neurology, Neurosurgery and Psychiatry*, *56*, 988–992.

Masson, F., Maurette, P., Salmi, L. R., Dartigues, J. F., Vecsey, J., Destaillats, J. M., et al. (1996). Prevalence of impairments 5 years after a head injury, and relationship with disabilities and outcome. *Brain Injury*, *10*, 487–497.

Mattioli, F., Grassi, F., Perani, D., Cappa, S. F., Miozzo, A., & Fazio, F. (1996). Persistent post-traumatic retrograde amnesia: A neuropsychological and (18F)FDG PET study. *Cortex*, *32*, 121–129.

McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., et al. (1999). Brain activation during working memory 1 month after mild traumatic brain injury: A functional MRI study. *Neurology*, *53*, 1300–1308.

McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. *Neuroimage*, *14*, 1004–1012.

McAvinue, L., O'Keeffe, F., McMackin, D., & Robertson, I. H. (2005). Impaired sustained attention and error awareness in traumatic brain injury: Implications for insight. *Neuropsychological Rehabilitation*, *15*, 569–587.

McDonald, S., & Flanagan, S. (2004). Social perception deficits after traumatic brain injury: Interaction between emotion recognition, mentalizing ability, and social communication. *Neuropsychology*, *18*, 572–579.

McDowell, S., Whyte, J., & D'Esposito, M. (1997). Working memory impairments in traumatic brain injury: Evidence from a dual-task paradigm. *Neuropsychologia*, *35*, 1341–1353.

Miller, E. (1970). Simple and choice reaction time following severe head injury. *Cortex*, *6*, 121–127.

Millis, S. R., & Ricker, J. H. (1994). Verbal learning patterns in moderate and severe traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology*, *16*, 498–507.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology*, *41*, 49–100.

Moscovitch, M., Goshen-Gottstein, Y., & Vierzen, E. (1994). Memory without conscious recollection: A tutorial review from a neuropsychological perspective. In C. Umila & M. Moscovitch (Eds.), *Attention and performance* (Vol. 15, pp. 619–660). Cambridge MA: MIT Press.

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex*, *12*, 313–324.

Newsome, M. R., Scheibel, R. S., Steinberg, J. L., Troyanskaya, M., Sharma, R. G., Rauch, R. A., et al. (2007). Working memory brain activation following severe traumatic brain injury. *Cortex*, *43*, 95–111.

Norrman, B., & Svahn, K. (1961). A follow-up study of severe brain injuries. *Acta Psychiatrica Scandinavica*, *37*, 236–264.

Novack, T., Kofoed, B., & Crosson, B. (1995). Sequential performance on the California Verbal Learning test following traumatic brain injury. *Clinical Neuropsychologist*, *9*, 38–43.

Oddy, M., Coughlan, T., Tyerman, A., & Jenkins, D. (1985). Social adjustment after closed head injury: A further follow-up seven years after injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *48*, 564–568.

Olver, J. H., Ponsford, J. L., & Curran, C. A. (1996). Outcome following traumatic brain injury: A comparison between 2 and 5 years after injury. *Brain Injury*, *10*, 841–848.

Paniak, C. E., Shore, D. L., & Rourke, B. P. (1989). Recovery of memory after severe closed head injury: Dissociations in recovery of memory parameters and predictors of outcome. *Journal of Clinical and Experimental Neuropsychology*, *11*, 631–644.

Park, N. W., Moscovitch, M., & Robertson, I. H. (1999). Divided attention impairments after traumatic brain injury. *Neuropsychologia*, *37*, 1119–1133.

Perlstein, W. M., Cole, M. A., Demery, J. A., Seignourel, P. J., Dixit, N. K., Larson, M. J., et al. (2004). Parametric manipulation of working memory load in traumatic brain injury: Behavioral and neural correlates. *Journal of the International Neuropsychological Society*, *10*, 724–741.

Perri, R., Carlesimo, G. A., Loasses, A., & Caltagirone, C. (2000). Deficient intentional access to semantic knowledge in patients with severe closed-head injury. *Cortex*, *36*, 213–225.

Peterson, L. R., & Peterson, M. J. (1959). Short term retention of individual verbal items. *Journal of Experimental Psychology*, *58*, 193–198.

Piolino, P., Desgranges, B., Manning, L., North, P., Jokic, C., & Eustache, F. (2007). Autobiographical memory, the sense of recollection and executive functions after severe traumatic brain injury. *Cortex*, *43*, 176–195.

Ponsford, J., & Kinsella, G. (1991). The use of a rating scale of attentional behaviour. *Neuropsychological Rehabilitation*, *1*, 241–257.

Ponsford, J., & Kinsella, G. (1992). Attentional deficits following severe closed head injury. *Journal of Clinical and Experimental Neuropsychology*, *14*, 822–838.

Ponsford, J. L., Olver, J. H., & Curran, C. (1995a). A profile of outcome: 2 years after traumatic brain injury. *Brain Injury*, *9*, 1–10.

Ponsford, J. L., Olver, J. H., Curran, C., & Ng, K. (1995b). Prediction of employment status 2 years after traumatic brain injury. *Brain Injury*, *9*, 11–20.

Prigatano, G. P., & Altman, I. M. (1990). Impaired awareness of behavioral limitations after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *71*, 1058–1064.

Prigatano, G. P., Altman, I. M., & O'Brien, K. P. (1990). Behavioral limitations that traumatic-brain-injured patients tend to underestimate. *Clinical Neuropsychologist*, *4*, 163–176.

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, *8*, 271–276.

Richardson, J., & Barry, C. (1985). The effect of minor closed head injury upon human memory: Further evidence on the role of mental imagery. *Cognitive Neuropsychology*, *2*, 149–168.

Richardson, J. T. (1979). Mental imagery, human memory, and the effects of closed head injury. *British Journal of Social and Clinical Psychology*, *18*, 319–327.

Riese, H., Hoedemaeker, M., Brouwer, W. H., Mulder, L. J. M., Cremer, R., & Veldman, J. (1999). Mental fatigue after very severe closed head injury: Sustained performance, mental effort and distress at two levels of workload in a driving simulator. *Neuropsychological Rehabilitation*, *9*, 189–205.

Russel, W. R., & Smith, A. (1961). Post traumatic amnesia in closed head injury. *Archives of Neurology*, *5*, 16–29.

Schmitter-Edgecombe, M., & Kibby, M. K. (1998). Visual selective attention after severe closed head injury. *Journal of the International Neuropsychological Society*, *4*, 144–159.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London B*, *298*, 199–209.

Shallice, T. (1988). *From neuropsychology to mental structure*. Cambridge: Cambridge University Press.

Shallice, T., & Burgess, P. (1991). Deficits in strategy application following frontal lobe damage in man. *Brain*, *114*, 727–741.

Shallice, T., & Burgess, P. (1996). The domain of supervisory processes and temporal organization of behaviour. *Philosophical Transactions of the Royal Society of London, B*, *351*, 1405–1412.

Shimamura, A. P., Janowsky, J. S., & Squire, L. R. (1991). What is the role of frontal lobe damage in memory disorders? In H. S. Levin, H. M. Eisenberg, & A. L. Benton (Eds.), *Frontal lobe function and dysfunction* (pp. 173–195). New York: Oxford University Press.

Shum, D., Valentine, M., & Cutmore, T. (1999). Performance of individuals with severe long-term traumatic brain injury on time-, event-, and activity-based prospective memory tasks. *Journal of Clinical and Experimental Neuropsychology*, *21*, 49–58.

Shum, D. H., Harris, D., & O'Gorman, J. G. (2000). Effects of severe traumatic brain injury on visual memory. *Journal of Clinical and Experimental Neuropsychology*, *22*, 25–39.

Spikman, J., van Zomeren, A. H., & Deelman, B. G. (1996). Deficits of attention after closed-head injury: Slowness only? *Journal of Clinical and Experimental Neuropsychology*, *18*, 755–767.

Spikman, J. M., Deelman, B. G., & van Zomeren, A. H. (2000). Executive functioning, attention and frontal lesions in patients with chronic CHI. *Journal of Clinical and Experimental Neuropsychology*, *22*, 325–338.

Stablum, F., Leonardi, G., Mazzoldi, M., Ulmita, C., & Morra, S. (1994). Attention and control deficits following closed head injury. *Cortex*, *30*, 603–618.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*, 643–662.

Stuss, D. T., Ely, P., Hugenholtz, H., Richard, M. T., Larochelle, S., Poirier, C. A., et al. (1985). Subtle neuropsychological deficits in patients with good recovery after closed head injury. *Neurosurgery*, *17*, 41–47.

Stuss, D. T., Stethem, L. L., Hugenholtz, H., Picton, T., Pivik, J., & Richard, M. T. (1989). Reaction time after head injury: Fatigue, divided and focused attention, and consistency of performance. *Journal of Neurology, Neurosurgery and Psychiatry*, *52*, 742–748.

Sunderland, A., Harris, J., & Baddeley, A. (1983). Do laboratory tests predict everyday memory? A neuropsychological study. *Journal of Verbal Learning and Verbal Behavior*, *22*, 341–357.

Tate, R. L., Lulham, J. M., Broe, G. A., Strettles, B., & Pfaff, A. (1989). Psychosocial outcome for the survivors of severe blunt head injury: The results from a consecutive series of 100 patients. *Journal of Neurology, Neurosurgery and Psychiatry*, *52*, 1128–1134.

Twum, M., & Parente, R. (1994). Role of imagery and verbal labeling in the performance of paired associates tasks by persons with closed head injury. *Journal of Clinical and Experimental Neuropsychology*, *16*, 630–639.

Vakil, E. (2005). The effect of moderate to severe traumatic brain injury (TBI) on different aspects of memory: A selective review. *Journal of Clinical and Experimental Neuropsychology*, *27*, 977–1021.

Vakil, E., Arbell, N., Gozlan, M., Hoofien, D., & Blachstein, H. (1992). Relative importance of informational units and their role in long-term recall by closed-head-injured patients and control groups. *Journal of Consulting and Clinical Psychology*, *60*, 802–803.

Vakil, E., Biederman, Y., Liran, G., Groswasser, Z., & Aberbuch, S. (1994). Head-injured patients and control group: Implicit versus explicit measures of frequency of occurrence. *Journal of Clinical and Experimental Neuropsychology*, *16*, 539–546.

Vakil, E., & Oded, Y. (2003). Comparison between three memory tests: Cued recall, priming and saving closed-head injured patients and controls. *Journal of Clinical and Experimental Neuropsychology*, *25*, 274–282.

Vallat-Azouvi, C., Pradat-Diehl, P., & Azouvi, P. (2009). Rehabilitation of the central executive of working memory after severe traumatic brain injury: Two single-case studies. *Brain Injury*, *23*, 585–594.

Vallat-Azouvi, C., Weber, T., Legrand, L., & Azouvi, P. (2007). Working memory after severe traumatic brain injury. *Journal of the International Neuropsychological Society*, *13*, 770–780.

Van der Linden, M., Coyette, F., & Seron, X. (1992). Selective impairment of the "central executive" component of working memory: A single case study. *Cognitive Neuropsychology*, *9*, 301–326.

Van Zomeren, A. H. (1981). *Reaction time and attention after closed head injury*. Lisse: Swets & Zeitlinger.

Van Zomeren, A. H., & Brouwer, W. H. (1994). *Clinical neuropsychology of attention*. New York: Oxford University Press.

Van Zomeren, A. H., Brouwer, W. H., & Deelman, B. G. (1984). Attentional deficits: The riddles of selectivity, speed, and alertness. In D. Brooks (Ed.), *Closed head injury: Psychological, social and family consequences* (pp. 74–107). Oxford: Oxford University Press.

Van Zomeren, A. H., & Deelman, B. G. (1976). Differential effects of simple and choice reaction after closed head injury. *Clinical Neurology and Neurosurgery*, *79*, 81–90.

Van Zomeren, A. H., & Van den Burg, W. (1985). Residual complaints of patients two years after severe head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, *48*, 21–28.

Vanderploeg, R. D., Crowell, T. A., & Curtiss, G. (2001). Verbal learning and memory deficits in traumatic brain injury: Encoding, consolidation, and retrieval. *Journal of Clinical and Experimental Neuropsychology*, *23*, 185–195.

Veltman, J. C., Brouwer, W. H., van Zomeren, A. H., & van Wolffelaar, P. C. (1996). Central executive aspects of attention in subacute severe and very severe closed head injury patients: Planning, inhibition, flexibility and divided attention. *Neuropsychology*, *10*, 357–367.

Vilkki, J. (1992). Cognitive flexibility and mental programming after closed head injuries and anterior or posterior cerebral excisions. *Neuropsychologia*, *30*, 807–814.

Vilkki, J., Virtanen, S., Surma-Aho, O., & Servo, A. (1996). Dual task performance after focal cerebral lesions and closed head injuries. *Neuropsychologia*, *34*, 1051–1056.

Webb, C. R., Wrigley, M., Yoels, W., & Fine, P. R. (1995). Explaining quality of life for persons with traumatic brain injuries 2 years after injury. *Archives of Physical Medicine and Rehabilitation*, *76*, 1113–1119.

Whyte, J., Fleming, M., Polansky, M., Cavallucci, C., & Coslett, H. B. (1997). Phasic arousal in response to auditory warnings after traumatic brain injury. *Neuropsychologia*, *35*, 313–324.

Whyte, J., Fleming, M., Polansky, M., Cavalucci, C., & Coslett, H. B. (1998). The effect of visual distraction following traumatic brain injury. *Journal of the International Neuropsychological Society*, *4*, 127–136.

Whyte, J., Grieb-Neff, P., Gantz, C., & Polansky, M. (2006). Measuring sustained attention after traumatic brain injury: Differences in key findings from the sustained attention to response task (SART). *Neuropsychologia*, *44*, 2007–2014.

Whyte, J., Polansky, M., Cavalucci, C., Fleming, M., Lhulier, J., & Coslett, H. B. (1996). Inattentive behavior after traumatic brain injury. *Journal of the International Neuropsychological Society*, *2*, 274–281.

Whyte, J., Polansky, M., Fleming, M., Coslett, H. B., & Cavalucci, C. (1995). Sustained arousal and attention after traumatic brain injury. *Neuropsychologia*, *33*, 797–813.

Whyte, J., Schuster, K., Polansky, M., Adams, J., & Coslett, H. B. (2000). Frequency and duration of inattentive behavior after traumatic brain injury: Effects of distraction, task, and practice. *Journal of the International Neuropsychological Society*, *6*, 1–11.

Wilson, B. A., Evans, J. J., Emslie, H., Alderman, N., & Burgess, P. (1998). The development of an ecologically valid test for assessing patients with a dysexecutive syndrome. *Neuropsychological Rehabilitation*, *8*, 213–228.

Zec, R. F., Zellers, D., Belman, J., Miller, J., Matthews, J., Femeau-Belman, D., et al. (2001). Long-term consequences of severe closed head injury on episodic memory. *Journal of Clinical and Experimental Neuropsychology*, *23*, 671–691.

Ziino, C., & Ponsford, J. (2005). Measurement and prediction of subjective fatigue following traumatic brain injury. *Journal of the International Neuropsychological Society*, *11*, 416–425.

Ziino, C., & Ponsford, J. (2006a). Selective attention deficits and subjective fatigue following traumatic brain injury. *Neuropsychology*, *20*, 383–390.

Ziino, C., & Ponsford, J. (2006b). Vigilance and fatigue following traumatic brain injury. *Journal of the International Neuropsychological Society*, *12*, 100–110.

Zoccolotti, P., Matano, A., Deloche, G., Cantagallo, A., Passadori, A., Leclercq, M., et al. (2000). Patterns of attentional impairment following closed head injury: A collaborative European study. *Cortex*, *36*, 93–107.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 9

Long-term survival after severe TBI: clinical and forensic aspects

Nathan D. Zasler*

Concussion Care Centre of Virginia, Ltd.; Tree of Life Services, Inc., Richmond, VA;
Department of Physical Medicine and Rehabilitation, Virginia Commonwealth University, Richmond, VA;
Department of Physical Medicine and Rehabilitation, University of Virginia,
Charlottesville, VA, USA

Abstract: This article will review current knowledge germane to understanding estimations of survival time of persons following severe traumatic brain injury (STBI). Nomenclature issues relevant to biostatistics and the neuroscientific investigation of survival after STBI will also be explored. Biostatistical methods used for determining survival time will be reviewed. The latest evidence-based data on morbidity and mortality risk factors after STBI as related to the nature of neurologic and functional impairments will be explored. Clinical as well as forensic issues pertinent to prognosticating survival time will also be enumerated.

Current literature (i.e., within the last 5 years) examining life expectancy issues after STBI will be reviewed. Concluding remarks will identify directions for future research in the area of survival time following STBI.

keywords: life expectancy; median survival time; morbidity; mortality; disorders of consciousness; traumatic brain injury

Introduction

Prognoses regarding survival time are often considered to be one of the most debated and challenging questions that specialist physicians working with persons with severe traumatic brain injury (STBI) must respond to, whether in a clinical or forensic context. It is important to realize that the determination of survival time following STBI is important for several reasons. In the context of planning future care it is clinically relevant, since families will often desire physician estimates on such issues. It is also important in terms of assessing cost allocation for either clinical or medicolegal reasons, the latter often in the context of translating a life care plan's proposed care to an economic equivalent based on expected survival time.

Physicians, the professionals typically asked to opine on issues of survival time following catastrophic TBI, often are unfamiliar with biostatistics and/or the historical and, more importantly, current literature on this topic. From both a clinical and forensic standpoint, there is little utility in individual clinician experience with patients in predicting either life expectancy or median survival time following severe TBI, regardless of the level

*Corresponding author.
Tel.: +(804) 346 1803; Fax: +(804) 346 1956;
E-mail: nzasler@cccv-ltd.com

DOI: 10.1016/S0079-6123(09)17709-9

of consciousness of the individual in question. Adequate knowledge of both biostatistics and the evidence-based medicine on life expectancy related issues after TBI can greatly facilitate the abilities of physicians to provide more accurate and data-driven opinions about anticipated survival time in persons after TBI and in particular, given the greater mortality risk, in persons with severe residual impairments, including those associated with disorders of consciousness (DOC).

This review article will examine issues germane to survival time analysis and in particular survival time assessment in persons after severe brain injury with resultant severe neurological impairment and functional disability. The topics that will be covered include terminology, life tables, biostatistics and life expectancy determination, methods for survival data analysis, caveats on interpreting survival studies, clinical experience and life expectancy determination, life expectancy literature in STBI, as well as recent literature on life expectancy in STBI.

Terminology

There is often confusion regarding some of the terminology that is critical to understanding survival issues in persons after STBI and, in particular, in persons with DOC. *Survival time*, by definition, is the time period that a given patient or member of a study population lives. A person who is alive at the end of the study period is said to have a *censored* survival time as of the date the study was completed. *Life expectancy*, on the other hand, is a population-based statistic referring to the mean time that persons within a defined group will survive. Life expectancy is not a prediction of a specific individual's time to death. It is important to understand that within a given population such as those with STBI, there will be a broad range of survival times and that the life expectancy is simply the mean of all those survival times. *Median survival time*, on the other hand, refers to that time at which one can state that 50% of a large defined population will still be alive (as opposed to dead). The median refers to the middle value of a set of values, in this case survival times.

In TBI survivors with significant morbidity risk factors, the mean survival time or life expectancy is often some 50% larger than the median survival time (Strauss and Shavelle, 1998b). The risk of dying, particularly after events such as STBI, is often much higher at the start, that is early after the traumatic injury, than in later years (the first 2 years seem to hold the highest risk of mortality). Clinicians and lawyers should be cognizant of this fact as the biostatistics can be manipulated to the advantage of a given party in a legal matter by simply choosing to use the number that provides either the basis for the larger financial settlement (typically the life expectancy) or the smaller one (typically the median survival time).

Other terminology that clinicians involved with providing information about prediction of survival times after STBI including DOC should be aware of include the following:

(1) *Censored survival time*: The survival time arising from observations where the dependent variable of interest represents the time to a terminal event and the duration of the study is limited in time. Censored survival times arise most commonly when a study participant remains alive beyond the study period or they are lost to follow-up. Observations result either in knowing the exact value that applies or in knowing that the value lies either above or below a given threshold (for upper and lower censoring, respectively). The problem of censored data, in which the observed value of some variable is partially known, is related to the problem of missing.
(2) *Confidence interval (CI)*: The CI is an interval estimate of a population parameter. CIs are used to indicate the reliability of an estimate. How likely the interval is to contain the parameter is determined by the confidence level or confidence coefficient. A CI is always qualified by a particular confidence level, usually expressed as a percentage; thus, one speaks of a "95% CI." The end points of the CI are referred to as confidence limits.
(3) *Excess death rate (EDR)*: The difference between the death rate in the study population and the reference population.
(4) *Exposure time*: The number of person-years lived by all the members of a given study population during the duration of the study.
(5) *Life expectancy*: The mean or average survival time in a large group of similar individuals.

(6) *Life tables*: A standard table summarizing mortality information about a group. Life tables are constructed in two different ways: for an entire population or for a suitably large subgroup. Life tables provide specific mortality rate information, that is, they provide life expectancy data at every age.
(7) *Median survival time*: The time at which 50% of a large group of similar persons are still alive.
(8) *Mortality rate*: The number of deaths in the study population divided by the number of person-years and exposure time. The MR will generally be larger than the mortality probability over the same time period except in very high-risk populations where the mortality rate could be greater than 1.
(9) *Mortality probability*: The chance of dying in a given period and expressed numerically as between 0 and 1, inclusively.
(10) *Parity age*: The age at which the mortality rate among the group in question and the general population become equal for the life table.
(11) *Predicted age at death*: The remaining life expectancy plus present age.
(12) *Relative risk (RR)*: The ratio of the mortality rate in the study population to the mortality rate in the reference population. In actuarial literature, the RR is often referred to as the mortality ratio (MR).
(13) *Standardized mortality ratio (SMR)*: The ratio of the observed number of deaths in the study population to the expected number.
(14) *Survival time*: The actual number of years lived by an individual.

Knowledge of the aforementioned terminology is not only helpful in understanding and interpreting studies on survival time after TBI but also essential if one is going to be involved in forensic testimony (Anderson, 2002; Shavelle et al., 2007).

Life tables

Due to the fact that there is inadequate data spanning survival times for a large group of patients from injury through to death, one needs to determine the expected number of years remaining for a typical member of that population. These types of calculations are the basis for what has been referred to as *life tables* or *mortality tables*. The life table allows an estimation of a patient's mortality risk over the entire life span. The life table allows some assumptions to be made based on the absence of reliable information about what actually happens to large groups of persons with STBI as related to survival time given that most studies rarely track patients for long periods of time.

Therefore, to be reliable in either a clinical or medicolegal setting, one must calculate life expectancy using actuarially sound data. That is, one needs to know what the likelihood is of living into "old age" not just surviving to the point in time where 50% of people like the individual in question have already died (i.e. - median survival time). Normal life expectancy changes with each year of life and this fact must be consider if opinions are given early, whether clinical or medicolegal, and then provided again at some later date.

One might think that calculating the mean survival time utilizing a CI would be a logical way to determine a given individual's likely period of life after an STBI resulting in a DOC. This approach, though, is rarely useful. One problem is that one cannot calculate the mean survival time until one knows the survival time of each individual within the population in question, which means that one cannot analyze the data until the last person in the population has died. Another problem, both practically and theoretically, is that survival times are unlikely to follow a Gaussian distribution. For the aforementioned reasons, as well as others, special biostatistical techniques must be utilized to analyze survival data. The simplest of these techniques is to construct a survival curve which plots survival as a function of time. Time 0 is not a specified calendar date but, rather, the time at which each patient entered the study. For this latter reason, there may be a span of several years during the "enrollment period." Each group member's death should be clearly visible as a downward shift in the curve. If, for example, a population had 100 persons and 1 died, then the percent survival should drop from 100% to 99%, that is, 99/100. When the next group member died, the percent survival rate would drop to 98%. If, at 12 months, an additional eighth patient died, then the downward step created by the additional 8% loss would be more significant (Motulsky, 1995; Strauss, 1999).

Life expectancy tables take into account the likelihood of demise from any etiology. Clearly, however, there are some individuals with severe TBI who had a lifestyle, genetic predisposition or existing disease that carried with it an increased chance of morbidity and potentially mortality. Some of the risk factors for such early demise include a history of smoking, alcohol use and/or substance abuse. Other risk factors for early demise include sexually transmitted disease (in particular HIV), lack of physical activity/fitness (leading to increased risk for hypertension, diabetes, osteoporosis, cancer of the colon and breast, affective disorders coronary artery disease), socioeconomic and geographic risk factors, and genetically linked disease vulnerabilities (Carroll and Barnes, 2002).

Biostatistics and life expectancy determination

One area that is often confusing for clinicians unfamiliar with biostatistics is that of censored versus non-censored survival data (see above). In most survival studies, some surviving subjects are not followed for the entire span of the study and, therefore, the investigator ends up knowing that the person survived up to a certain time but has no useful information about what happened during the period in which the person was not followed. Information about such patients is said to be censored. Before the censored time, one knows that the person was alive and potentially following an experimental protocol and/or being tracked for specific mortality risk factors and during this time, was therefore, contributing useful data to the study. After they are ''censored'', one cannot use any information on the subject as one either does not have the information beyond the censoring day because the data was not available or could not be collected, or the information is available but cannot be used because the individual was no longer following the interventional protocol for being formally monitored for mortality risk factors (Motulsky, 1995).

As per the science of survival time determination, it is important to acknowledge that it is impossible to predict an individual's actual survival time with certainty, that is, with 100% accuracy. The best that we can do is to estimate the life expectancy, realizing that this is a population-based statistic or alternatively, determine the median survival time, as previously defined. Neither prediction, again, examines the survival time of that specific individual per se. Clearly, although no expert can take into consideration every factor that might influence an individual person's survival time that does not mean that scientifically valid opinions cannot be provided about survival time. One needs to therefore work with the data that one has and consider other factors for which data are not available. Based on the summation of the information available, one should then be able to logically argue for either an increase or decrease in the predicted survival time relative to either actuarial norms or other predictions.

Methods for survival data analysis

The Kaplan–Meier method is the usual technique used to analyze survival time data and requires recalculating every time a patient in the cohort dies. This latter method is preferred unless the number of patients is very large. The Kaplan–Meier or ''product-limit'' method is logically simple but tedious. Most of the time, these calculations are done using computer software programs. This method automatically accounts for censored patients as both a numerator and denominator are reduced on the day a patient is censored. In this context, day one is the first day of the study for each subject, not a particular day of the calendar year (Chan, 2004).

Among the methods for analyzing multiple risk factors on cohort data, the most widely utilized model is known as the Cox Proportional Hazard Model. When survival analysis is performed, utilizing this methodology, one estimates the survival curve and, thereby, provides the subjects probability of surviving many specific time periods. One should note, however, that this model is not without problems, as it does not immediately handle cases where subjects may enter the study several years after injury date or first diagnosis, and it is cumbersome when the subjects characteristics change over time. This method is awkward at separating the intertwined effects of age, current calendar year, and time since onset for diagnosis (Anderson, 2002).

There is also a model known as the person-year method which has been used in the Framingham Study on heart disease. This methodology has not gained use in the context of assessing longitudinal mortality in TBI including severe TBI. This analytical method involves utilizing logistical regression analysis which is a form of discreet survival analysis. A simple cross-sectional methodology such as this is facilitated by the use of standard computer packages that come with a variety of options and diagnostics (Strauss et al., 2000).

Caveats on interpreting survival data studies

In order to extrapolate the cohort data samples to the overall population, the survival curve should have a 95% CI, thereby, implying that one can be 95% sure that the true population survival curve lies within the 95% CI shown in the sample population of that particular study. Unfortunately, when looking at survival data on persons with TBI, many of the published studies do not include CIs which limit their generalizability and utility in the context of both clinical and forensic applications.

The interpretation of a survival curve depends on several assumptions (Motulsky, 1995):

- independent observations … that is, choosing any one subject in the population should not affect the chance of choosing any of other particular subject;
- random sampling methodology;
- consistent entry criteria;
- consideration criteria for defining survival;
- time of censoring should be unrelated to survival; and
- average survival time does not change during the course of the study.

There are some inherent problems with survival studies, the most significant being when the study should start. Typically, this is done at the time when an objective occurrence such as the TBI itself occurs. Another confounding variable is how investigators handle death that may have nothing to do with the TBI itself and/or related morbidity such as someone purposely ending the individual's life by withdrawal or withholding of care or, for example, having a significant pre-existing condition that subsequent to the injury takes a person's life. Some investigators would count these as deaths; others would count them as censored subjects. Both approaches are sensible but the approach should be decided before the study is started and then used consistently throughout the study and clearly defined in the methodology.

Most studies looking at survival time following brain injury utilize survival curves to provide information on the percentage of individuals within the experimental cohort who survive to a given age. Such data will provide only a median survival time if there is a high enough mortality rate such that 50% of the subjects die within the study period; however, if 50% of the subjects do not die within the study period, then the median survival time can only be estimated. Similarly, and more commonly, it is unusual that such studies will allow the biostatistical calculation of life expectancy for the entire cohort, given the inability of such studies to attract individuals for their remaining survival time.

Clinical experience and prediction of survival time

From both a clinical and forensic standpoint, there is little utility in individual clinician experience with patients in predicting either life expectancy or median survival time following severe TBI, regardless of the level of consciousness of the individual in question and/or their functional status. Clinicians will often refer to their personal experience with patients as a basis for stating that a given person will live a particular period of time. This is, at best, anecdotal data and not collected in a manner that would make any opinions provided consistent with the methodologies that should be used in evidence-based medicine. Regardless of how many cases of STBI one has seen, including cases of individuals with DOC, it is highly unlikely that the sample size followed was either large in number or were followed for more than a few years. So, unless the clinician has worked in a setting for 20, 30 or more years and followed large numbers of patients that have either stayed in the facility and/or been tracked in a formal manner, the opinions generated by that clinician based on ''clinical experience'' are irrelevant and non-scientific in a medicolegal context. Such testimony would certainly be generally criticized on numerous levels in a forensic setting relative to both the Daubert and Frye

standards in the United States and likely other legal standards for scientific testimony in other countries (Strauss and Shavelle, 1998a).

Predictors of morbidity and mortality in STBI and DOC

Based on fairly extensive literature examining risk factors for mortality in persons with ABI and significant functional disability, certain factors clearly increase the risk for early demise. These factors seem to be applicable to persons with severe impairments secondary to traumatic brain injury including those with DOC. Clearly, the strongest predictor of shorter survival in this patient population is severe impairment of mobility. Compromised self-feeding ability is also strongly associated with shorter life span with persons receiving gastrostomy tube feedings being the most at risk of shortened survival time. Other risk factors that have been correlated with survival time following TBI include age (with rate of male mortality being appreciably higher than that of females, however, this discrepancy disappears at the more severe end of the impairment spectrum), time since injury (mortality risk is highest during the first 2 years after injury and then stabilizes), need for ventilator support and/or suctioning, more severe cognitive and communication impairments (mainly due to their correlation with more severe motor impairments), respiratory problems including pneumonia, diseases of the circulatory system including pulmonary embolism and post-traumatic epilepsy (Gaiyayzis et al., 2004; Day et al., 2005; Shavelle et al., 2007; Englander et al, 2009). The role that decubitus ulcers, deep vein thrombosis, renal disease/impairment, contractures, dysphagia, constipation and incontinence play in increasing long-term mortality is still somewhat unclear based on the relative lack of studies addressing these issues and/or the absence of data indicating that these morbidities ultimately lead to earlier demise (Shavelle et al., 2007). One must establish that an individual's level of neurological impairment is stable and that no further functional changes of significance are expected prior to opining on survival time. If someone is continuing to show evidence of neurological recovery and/or functional improvement or, alternatively, if they are demonstrating evidence of decline, there will likely be some impact on survival time estimations.

Quality of care and impact on survival time

The issue of quality of care relative to life expectancy has profound clinical, as well as forensic, implications. One of the problems in studying this phenomenon is the issue of what defines good quality care versus suboptimal care and the context in which quality of care is discussed, that is, whether the quality of care is only being defined in medical terms or whether psychosocial aspects of care are also included. As Strauss and Shavelle point out, quality of care issues also rely at least in part on factoring in the knowledge base and expertise of caregivers, the access to regular health monitoring/surveillance, preventative health care and emergency services, as well as the quantity/intensity of care provided. These various factors, to a great extent, are driven by the financial resources of the injured person and the health care system in which they are taken care of which will vary from country to country. Interestingly, in work previously published by Strauss and his colleagues, the authors found that mortality rates in state facilities were generally lower than those in private group homes or in family homes. The reasons for these differences were posited to include quality of care advantages of the long-term state run facilities including around-the-clock staffing, continuity of care of centralized record keeping, and immediate access to medical attention when needed. Although it seems clear that quality of care is a factor that impacts survival time, there is not enough data available yet to know to what extent it ultimately makes a difference to the relative longevity of severely disabled persons after TBI, but clearly, as far as rank order, it appears to be less important than other factors such as degree of immobility (Shavelle et al., 2007).

Life expectancy literature in STBI: Historical perspectives and criticisms

Probably, one of the most well known and controversial articles published dealing with the

issue of life expectancy in persons with severe brain injury was the two part ''Medical Aspects of the Persistent Vegetative State'' published in the New England Journal of Medicine in 1994. Based on this publication, which was written by the Multisociety Task Force (MSTF) on Persistent Vegetative State (PVS) (composed of clinicians from neurology and neurosurgery but not neurorehabilitation), the authors noted that the mortality rate for adults in PVS after an acute brain injury, albeit not just traumatic, was 82% in 3 years and 95% in 5 years. Based on a summation of data from four larger series with a total of 251 patients, these authors noted that the reported causes of death, based on data from 143 cases, included infection (i.e., pulmonary or urinary tract), generalized systemic failure, sudden death of unknown causes, respiratory failure, and other disease related causes such as recurrent stroke. Age also factored in significantly. The authors concluded that those in a vegetative state, either child or adult, had an average life expectancy of 2–5 years with survival beyond 10 years being unusual, although they did note that a very small number of well-described patients in a PVS had survived more than 15 years including three patients that survived for more than 17, 37, and 41 years. They went on to note the following statement: ''considering the small total number of patients in a persistent vegetative state, the probability that an individual patient will have such a prolonged survival (i.e., over 15 years) is exceedingly low, probably less than 1 in 15,000 to 75,000'' (MSTF, 1994). The fact that there had been no formal studies on the effect of level of care on the survival time of persons in PVS was duly noted.

A. A. Howsepian provided an extensive and constructive critique of the MSTF consensus statement on the PVS in a 1996 article published in ''Issues in Law and Medicine'' but interestingly issued no direct criticisms at the author's conclusions regarding life expectancy (Howsepian, 1996).

Up until around 1998, and even beyond that, many physicians in the neurosciences continued to follow the 2–5 years guidelines set forth by the MSTF for life expectancy of persons in a ''permanent'' vegetative state. Unfortunately, it seemed that these impressions also permeated opinions about life expectancy in those with severe disability following TBI, in general, including individuals with DOC. If clinicians were unaware of the MSTF document, they often referred to literature by Eyman and Grossman that had been collected in severely disabled institutionalized patients, not necessarily with TBI/DOC. That work has been greatly criticized for numerous methodological flaws and is generally not considered ''good science'' based on more recent analyses of said data (Plioplys, 2004).

There have been some limited published criticisms of the literature utilized in life expectancy determination in TBI that are worth briefly reviewing, some of these made by ''neurolitigators'' include the following:

- The professionals typically testifying on survival time have not been involved in the actual studies and/or data collection.
- The studies typically quoted lacked quality control in terms of whether the data can be considered reliable and truly representative of the cohort sample.
- The researchers publishing these studies had not reviewed the actual medical charts of the individuals in their studies or examined the patients.

Another more significant criticism levied at the life expectancy research in TBI is the relatively small numbers of patients included in any of the databases that have more profound impairments including the small number of persons with DOC. There is also very little data tracking patients with STBI and/or DOC beyond one year post-injury relative to answering the question of long-term survival patterns. There are also certainly questions on whether diagnostic labels used in various studies were even accurate as related to whether specific patients were in fact truly unconscious. One also has to look at what percentage of the initial patient population that entered the study was later potentially excluded due to lack of adequate data or follow-up, both of which could potentially create a bias to the results collected. Another relevant factor is the issue of whether the cause of death was directly attributable to the TBI or an indirect consequence of same, and how the cause of death may have been related to adequate versus inadequate medical surveillance and care.

Michael Kessler, Esq., made note of several criticisms of an article by Strauss entitled "Long-Term Survival of Children and Adolescents After Traumatic Brain Injury" (Kessler, 2004) specifically:

- Subjects were included with a diagnostic code of either skull fracture or intracranial injury without skull fracture, although the two categories might in fact yield very different types of patients, the study lumped them together.
- More than one-third of the subjects were injured before 1987, some as early as the 1960s. Since the standard of medical and rehabilitative care over that period of time has certainly changed, there was the concern that it would impact how one could compare data across patients over such a long time period.
- The date of entry into the study was based on the date of the first evaluation after the TBI even when the survival period was known to be longer. As was noted, 12.6% of cases were more than 10 years out from their injury at the time of the first TBI evaluation.
- Sample size was small and subgroup size was even smaller with only 38 deaths actually being documented and the deaths not being stipulated by subgroup.
- The data were only presented for life expectancy at age 50 which could markedly impact the life expectancy calculation more generally.
- No adjustments were made for decreased mortality rate over time and, yet, life tables and insurance data were argued to certainly support the position that from the 1960s through the end of the study in 1995, mortality rates changed (*author's note*: that is, they decreased) in the general population.
- The short time span of the study limited the conclusions that can be drawn from it.
- The mortality comparison was to the general male population instead of a basic mortality table broken down by gender, which may cause an overstatement of increased mortality due to the tendency for men to not survive as long as women.

There have also been medicolegal criticisms germane to the current scientific evidentiary rules in the United States regarding testimony on life expectancy after TBI relative to:

- the untested nature of a specific model to calculate life expectancy of a particular individual;
- the lack of peer reviewed publications related to specific models to calculate the life expectancy of a particular individual;
- the lack of any expert having a published article that actually provides methodologies or formulas for calculating/predicting the life expectancy of a particular individual;
- the lack of consensus regarding the chosen/best methodology to calculate life expectancy of a particular individual with TBI; and
- the mixed population of patients in the life expectancy databases for TBI relative to type of brain injury, quality of care and impact of intensity, and level of care on ultimate survival time of a given individual.

It is this author's opinion that these criticisms deserve attention in future discussions of the topic and consideration in the context of future studies on survival time in persons with acquired brain injury.

Recent literature on survival time and STBI

Shavelle and Strauss at the Life Expectancy Project (www.lifeexpectancy.com) have refined earlier published work and take into account issues of age, sex, and functional status, as related to predictors of survival time following TBI (Shavelle et al., 2007). They note that the average life expectancy is, at most, 12 years for individuals in a vegetative state and that no significant sex differences were noted. The data beyond age 50 were not provided. When an individual is non-ambulatory but can self-feed, then life expectancy can range anywhere from 46 years for a 10-year old to 19 years for a 50-year old. When fed by others and non-ambulatory, life expectancy significantly diminishes to 27 years for a 10-year old to a low of 11 years for a 50-year old. Once independent walking ability is achieved, then life expectancy significantly improves and approaches

that of the general population. The same authors have taken the position that persons in minimally conscious state (MCS) may have only slightly better life expectancies than persons with PVS, although the data specifics and clinical criteria for diagnosing MCS were not specifically stipulated.

What is unclear from the description of their data is how long each member of the cohort was actually followed either from the date of their injury and/or from the date of entry into the study. It is, therefore, unclear exactly how much data was derived from cohort participants beyond 12 months post-injury. This fact, in part, is made more significant by the lack of data on what happens to patients many years post-injury relative to some demonstrating continued progress and neurorecovery, which may lead to decreasing morbidity/mortality risk factors and others, actually getting worse over time and potentially increasing their morbidity/mortality risk factors. Both of the aforementioned phenomena have clear ramifications on the likely survival time of these individuals.

Based on the literature in the last 5 years, the following studies should be mentioned in the context of their analysis of survival time in patients with TBI and as relevant to STBI:

- ←Brown et al. (2004). This was a retrospective cohort study of 1448 patients between 1985 and 2000. Of the sample, 11% had moderate to severe TBI. Comparison of observed mortality over the full period of follow-up with that expected revealed a risk ratio (95% CI) of 5.29 (4.11–6.71) for moderate to severe cases. Interestingly, these researchers found that the case fatality rate for persons with moderate to severe TBI, although very high early on, approached that of mild TBI for individuals surviving 6 months or longer. Based on review of this study, it is apparent that the functional status of the patients were not delineated, leaving one to wonder what proportion of the moderate to severe TBI group had good functional outcomes relative to mortality risk factors such as mobility status and self-feeding capability.
- ←Harrison-Felix et al. (2004). This study involved a cohort of 2178 individuals with TBI completing inpatient rehabilitation at one of fifteen federally funded TBI research centers. A total of 8793 person-years of life data were accumulated for the analysis with lengths of follow-up ranging from 17 days to 12.8 years post-injury. Of this group studied, 37% had severe TBI. These researchers estimated an average reduction in life expectancy of 7 years. The SMR was 2.00 (95% CI) (1.69–2.31) indicating that individuals with TBI were two times more likely to die than individuals of comparative age, gender and race from the general population. The SMR for individuals with TBI who survived past their one year post-injury anniversary was 1.95 (also with a 95% CI) indicating a slightly higher risk for those who died between inpatient rehabilitation discharge and 1-year post-injury; however, these SMRs were not significantly different. Based on the analysis used, specifically a multivariate Cox regression analysis, older age, unemployment at the time of injury, and greater functional disability at rehabilitation discharge remained the most significant risk factors for shorter life expectancy. The results also indicated that there was a 5% increased risk of death for each additional year of age at injury and a 12% increased risk of death for every one point increase in the Disability Rating Scale (DRS) score. Also of interest was the fact that the Glasgow Coma Scale (GCS) score at the time of admission, commonly accepted as predictive of early mortality, was not found to be predictive of mortality after 1-year post-injury.
- ←Strauss et al. (2004). Along with Harrison-Felix and coworkers submitted a letter to the editors of ''Neurorehabilitation'' reviewing a methodology relating mortalities to severity of disability at inpatient rehabilitation discharge, as measured by the DRS. The authors then calculated, using a standard Cox proportional hazard modeling of the data assembled, a simple model with linear terms for age and DRS. The estimated risk ratio for DRS was 1.126 indicating that the mortality risk increased by 12.6% for each additional DRS point scored on this 30 point

scale (where 0 is no disability and 30 is dead). Based on available data, they constructed a life table from which the life expectancy and other estimates of interest were immediately available. They noted that the methodology would be further defined and improved as more data became available.

- ←Pentland et al. (2005). These investigators utilized a computerized database with details of 1919 admissions who were compared with deaths registered by the NHS Central Register in Scotland for the years 1981 to mid-2002. Death certificate information for matches was also analyzed. Of the 1919 admissions, which refer to 1871 individuals, there were 93 severe, 205 moderate, and 1573 mild TBIs based on GCS criteria. There were 57 deaths during the initial admission and 340 in the subsequent years. Substance abuse, principally alcohol, was a factor in 37 deaths, suicide accounted for 20, and accidents for 25. The great majority of the latter deaths were in people under the age of 70. When the researchers examined the deaths post-discharge, as related to injury severity, they noted that 51 of the 93 patients categorized as severe survived to be discharged from the unit, 6 of whom subsequently died in the ensuing 20 to 21 years. Causes of death were variable. Importantly no data regarding functional status or type of care rendered was provided for these individuals. No CIs were provided for the data generated.
- ←Ratcliff et al. (2005). This study was a retrospective cohort design to examine long-term mortality rates and predictors of mortality for persons after moderate to severe TBI and included 642 eligible individuals who were discharged from a large rehabilitation hospital between 1974 and 1984, in 1988 and in 1989. The reasons for the non-continuity with regards to the years of retrospective assessment were not stipulated. The patients were followed as long as 24 years post-injury. Of those individuals, 128 were found to be deceased. A Poisson regression analysis revealed at least a twofold increased risk of mortality compared to the general population. Pre-injury characteristics such as alcohol abuse and risk taking behavior were among the strongest predictors of shorter life expectancy along with the level of functional disability. There were multiple limitations adequately acknowledged by the authors of this study in the context of the quality of their data, although the results seem to parallel findings of other studies in this area.
- ←Selassie et al. (2005). Examined mortality among a representative sample of 3679 persons within one year of being discharged from 62 acute care hospitals in the State of South Carolina following TBI and identifying factors associated with early death using a multivariable Cox proportional hazard model. The mortality experience of the cohort was also paired with that of the general population by using SMRs for selected causes of death by age adjusted for race and sex. Of the eligible pool of patients, 91.6% within 15 months of hospital discharge. Twenty-three percent of deaths were injury related (not necessarily secondary to the TBI). Of the TBI related deaths, 63% occurred within the first three months of discharg compared with 47% of non-injury related deaths. Estimated survival curves of the study cohort varied significantly depending on the severity of the TBI. Decedents were more likely to be older females insured by Medicare with more comorbidities and have sustained a severe TBI than were survivors. In contrast, patients who were alive at the end of the follow-up period were more likely to be white, from a rural area, to have associated injuries, and to have been treated at a level 1 trauma center. The presence of comorbid conditions significantly influenced the likelihood of death as, for example, patients with three or more comorbidities were four times more likely to die within the first year after injury compared with patients with no comorbidities (95% CI, 2.7–5.9). The severity of TBI, type of insurance and level of trauma center within the hospital that provided the acute medical care were also significant determinants of death within 15 months of hospital discharge. Patients with severe TBI were 1.8 times more likely to die post-discharge compared with those experiencing mild TBI, and those insured by

Medicare were 1.6 times (95% CI, 1.1–2.5) more likely to die than a patient covered by commercial insurance. The study cohort when compared with the general US population experienced a sevenfold excess risk of death overall (SMR = 7.1; 95% CI, 6.3–7.9) within 15 months of hospital discharge.

- Harrison-Felix et al. (2006). This study was a retrospective cohort study investigating causes of death in individuals with TBI and utilized data from a federally funded TBI national database, supplemented with vital status data from the Social Security Death Index, death certificates, and the US population age- race- gender-cause-specific mortality rates for 1994. Those 2140 individuals with TBI who completed inpatient rehabilitation at one of the 15 federally funded TBI Model Systems of Care between 1988 and 2001 and who survived at least one year post-injury were included in the study. Persons with TBI were about 37 times more likely to die of seizures; 12 times more likely to die of septicemia; 4 times more likely to die of pneumonia; and approximately 3 times more likely to die of other respiratory conditions excluding pneumonia, digestive conditions, and all external causes of injury including poisoning than were individuals that were age, gender and race matched in the general population. Although there were 6648 person-years of follow-up data, the average range of follow-up was only 3.1 years from the one year post-injury anniversary. In this study, the severity of injury and nature of the patient's functional degree of impairment were not otherwise analyzed aside from notation that the average age was 37 years with 76% being male, 50% Caucasian, and 42% severe TBI, the latter based on an emergency department GCS score between 3 and 8.
- McMillan and Teasdale (2007). This study's goal was to determine the rate of death in the first and six subsequent years after severe TBI in a prospective cohort design which compared a structured sample of 767 patients, age 14 years and over, and compared their outcome/mortality rate with the general death rates in the Scottish population. The patients were prospectively identified as they were admitted to a hospital and followed up to seven years later. Of the 2995 people hospitalized over the period of February 1995 to February 1996, some of 769 were selected for follow-up at 1 year. The process of selection did not appear to be otherwise stipulated (e.g., random vs. non-random). Of them, 101 had severe injury, 133 had moderate injuries, and 507 had mild injury as defined by the GCS with 28 being unclassified. Risk of death was noted to be 23 times higher in months 1–2, three times higher in months 3–12, and two times higher in months 13–84. Risk of demise within the first two months post-injury was most significant in persons older than 54 years of age. Individuals younger than 54 years of age had a risk of mortality seven times as high as the general population between 13–84 months post-injury. Mortality was only associated with greater severity of head injury during the first year, pre-injury medical history was associated both with earlier and later deaths, but risk of death remained higher in those with no injury. Later deaths were often associated with suboptimal post-injury lifestyles. Primary causes of death after TBI were parallel to those seen in the general population. Compared with the general population death rate after admission to the hospital with TBI remained high for at least seven years and was particularly high for those under age 55.
- Shavelle et al. (2008). Reported a re-analysis of data originally published by others dealing with life expectancy and locked-in syndrome. They noted that there were methodological issues with the manner in which the investigators in two serial studies calculated survival time, noting that survival time was counted from the first anniversary of the onset of LIS, yet follow-up began many years later and that subjects were guaranteed to survive until the beginning of follow-up, but those who died never entered the study. Using the investigators' original data, they corrected the survival probability by counting each person's survival time only from the time at which they were ''exposed to death'' and then performed a Kaplan–Meier analysis which gave survival probabilities of 84% at 5 years and 56% at

10 years. They also noted that although the 20-year survival could be computed directly from the observed data, that with use of standard actuarial assumptions, it led to an estimate of a 20-year survival rate of 32%. They also interestingly noted that the population being studied all consisted of elective admissions admitted to a ''world-class facility'' and that this fact may have led to overestimating survival … specifically, the implications here are that Shavelle and his coauthors believed that the better care rendered at such an institution would result in longer survival time. They also noted that any advances in medical care since the study period would potentially under-estimate survival. It should be noted that the original numbers calculated for five, seven and twenty year survival, based on the original investigators analysis, was 83%, 83% and 40%.

- Baguley et al. (2008). Investigated mortality trends in functionally dependent adults following TBI by analyzing data from 966 consecutive admissions to a specialized TBI rehabilitation service. Details for 69 of those subjects who were functionally dependent at rehabilitation discharge were cross- referenced against the state government death register. The observed mortality rate was compared to an equivalent population sample derived from Australian life tables. Twenty-five subjects or 36% were deceased at an average of 10.5 years post-injury (standard deviation 5 years; range 1.7–18.8 years). The observed numbers of deaths far exceeded the expected population figure for the same period (1989–2007), yielding a standardized mortality rate (SMR) of 13.2. Mortality trends suggested a bimodal distribution with more deaths in the first five years post-injury following by no further deaths until nine years post-injury. The authors noted that the bimodal distribution of mortality data suggested different contributory mechanisms too early versus late mortality in this group of patients.
- Cameron et al. (2008). This group of investigators performed a ten year health service study examining mortality outcomes for people with traumatic brain injury utilizing a population-based matched cohort study using linked administrative data from Manitoba, Canada (Manitoba Injury Outcome Study). An inception cohort running from 1988 through 1991 of hospitalized cases with TBI age 18–64 years, consisting of a sample size of 1290 individuals, was identified and matched to a non-injured comparison group of 1290 individuals. Survival analysis, negative binomial and Poisson regression were used to quantify associations between injury and health service use (HSU)/mortality outcomes for 10 years following the TBI. Investigators found that the majority of the deaths (47.2%) occurred in the first 60 days following injury. Excluding the first 60 days, the adjusted 10-year mortality remained elevated (mortality rate ratio equal 1.4, 95% CI = 1.02–2.15). After adjusting for demographic characteristics and pre-existing health status, the TBI cohort had more post-injury hospitalizations, greater cumulative length of stay, and a greater post-injury physician claims rate, than the non-injured cohort HSU. Based on the injury severity score (ISS), 314 individuals sustained severe, 81 moderate, and 786 minor TBI. There was also clearly an association between severity of injury and increased mortality. Unfortunately, the functional status of those included in the samples was not explored relative to being a risk factor for earlier demise. The study also found no significantly increased risk in long-term mortality for people who sustained mild, moderate, or moderately severe brain injuries. Persons with severe TBI were 9.9 times more likely to die than their non-injured counterparts, and for those who survived the first 60 days following the injury continued to have a significant risk of mortality during the remaining years of follow-up (adjusted MRR = 4.16, 95% CI = 1.96–8.84). Due to the nature of the data collection, concerns can be levied relative to study limitations in that the quality of rehabilitation service has certainly changed over the more than 16 years time period of this study, thereby, bringing into question the ability to generalize of the data presented by these investigators.

- ←Colantonio et al (2008) investigated the rate and predictors of post-acute mortality after severe TBI of a group of patients one to nine years post injury over an approximate two year window (April 1993–March 1995) using a retrospective cohort design. The sample size was 2721 with a control group of 557 patients with lower extremity injuries. Post-acute death was defined as death one year or more post discharge. Poisson regression modeling demonstrated that having a TBI predicted a premature death when there were controls for age and injury severity (SMR was 2.90 for the TBI group vs. 2.26 for the control group with $p = 0.046$). Age, number of co-morbidities, injury severity, mechanism of injury, and discharge destination were significant predictors of SMR in the multivariate analyses utilizing a parametric model and not the Cox proportional hazard model for the TBI population. Parallel to studies by Ratcliff (2005) as well as Shavelle et al (2007), the investigators found that SMR decreased with age due to the fact that the ratio of raw death rate to the expected death rate actually decreased with older age.
- ←Brooks (personal communication, 2009). This researcher, who is part of Dr. Strauss and Shavelle's group, has preliminary unpublished data on approximately 4000 persons over age 10 who suffered TBI and received services from the California Department of Developmental Services between the years 1988 and 2002. Survival was monitored until December 31, 2006 using state vital records. Of the study group, 10% died before the end of follow-up. They used logistic regression analyses on person-months to test for secular trends in mortality. The analyses was adjusted for age, time since injury, and functional disability (i.e., mobility and feeding), however, it did not provide any statistical evidence for secular trends in mortality rates in the TBI population. These findings are similar to those for SCI, but contrast with those from cerebral palsy. For example, in cerebral palsy, the most severely disabled individuals experienced significantly increased survival over the years 1983–2002. The investigators, however, were unable to identify any subgroups in the TBI population for which this was true. Harrison-Felix et al. (2009) utilized a retrospective cohort design to examine mortality rates, life expectancy death risk factors and causes of death in 1678 persons with TBI who survived the first anniversary of their injury and admitted to acute rehabilitation within one year of injury between 1961 and 2002. They found that persons with TBI were 1.5 times more likely to die than persons in the general population of similar age, sex and race with an average life expectancy reduction of four years. The strongest independent risk factors for death beyond one year post-injury were older age, being male, less education, longer hospital stays post injury, being injured earlier than later and being vegetative on discharge from rehabilitation. Risk of death due to aspiration pneumonia was 49 times higher than the general population with risk of dying from seizures, pneumonia, suicide and digestive conditions being 22, 4, 3 and 2.5 times higher, respectively.

Conclusions

Clinicians must be familiar with the current literature on survival time in TBI and understand how it applies to survival time determination in persons after STBI including those with DOC. In the context of both clinical care and provision of medicolegal testimony, it is of utmost importance for physicians to also understand what is known about the risk factors for mortality in this special patient population, the application of biostatistics to survival time determination, and the relevant terminology applicable to discussing biostatistics and survival time. There are still many unanswered questions germane to issues surrounding survival time after STBI with questions pertaining to quality of care probably generating the most debate and controversy. Further, long-term studies looking at more homogeneous populations of patients with severe TBI including persons with DOC (coma, VS, and MCS) should be performed. Additionally, studies adequately tracking not only factors associated with post-injury morbidity and mortality but also pre-injury factors negatively impacting long-term survival should be

performed prospectively utilizing multisite longitudinal participation to accumulate as large a cohort as possible. Qualitative and quantitative aspects of care as related to neuromedical as well as psychological morbidity and mortality should be studied, as should the influence of said care on functional outcome over time and consequential potential effect on survival time.

References

Anderson, T. W. (2002). *Life expectancy in court: A textbook for doctors and lawyers*. Vancouver, BC: Granville Island Publishing.

Baguley, I. J., Nott, M. T., & Slewa-Younan, S. (2008). Long-term mortality trends in functionally-dependent adults following severe traumatic-brain injury. *Brain Injury*, *22*(12), 919–925.

Brooks. (2009). Personal communication.

Brown, A. W., Leibson, C. L., Malec, J. F., Perkins, P. K., Diehl, N. N., & Larson, D. R. (2004). Long-term survival after traumatic brain injury: A population-based analysis. *NeuroRehabilitation*, *19*, 37–43.

Cameron, C. M., Purdie, D. M., Kliewer, E. V., & McClure, R. J. (2008). Ten-year outcomes following traumatic brain injury: A population-based cohort. *Brain Injury*, *22*(6), 437–449.

Carroll, A., & Barnes, M. (2002). Life expectancy determination. *Physical Medicine and Rehabilitation Clinics of North America*, *13*, 309–332. Elsevier Science, USA.

Chan, Y. H. (2004). Biostatistics 203. Survival analysis. *Singapore Medical Journal*, *45*(6), 249.

Colantonio, A., Escobar, M. D., Chipman, M., McLeilan, B., Austin, P. C., Mirabella, G., et al. (2008). Predictors of post-acute mortality following traumatic brain injury in a seriously injured population. *Journal of Trauma*, *64*(4), 876–882.

Day, S. M., Wu, Y. W., Strauss, D. J., Shavelle, R. M., & Reynolds, R. J. (2005). Causes of death in remote symptomatic epilepsy. In Life Expectancy Project. AAN Enterprises, Inc., San Francisco, CA.

Englander, J., Bushnik, T., Wright, J. M., Jamison, L., & Duong, T. T. (2009). Mortality in late post-traumatic seizures. *Journal of Neurotrauma*, June 9 (Epub ahead of print).

Gaiyayzis, A., Johnson, A. L., Chadwick, D. W., Shorvon, S. D., & Sander, J. W. (2004). Life expectancy in people with newly diagnosed epilepsy. *Brain*, *127*(11), 2427–2434.

Harrison-Felix, C., Whiteneck, G. G., DeVivo, M. J., Hammond, F. M., & Jha, A. (2004). Mortality following rehabilitation in the traumatic brain injury model systems of care. *NeuroRehabilitation*, *19*, 45–54.

Harrison-Felix, C., Whiteneck, G., DeVivo, M. J., Hammond, F. M., & Jha, A. (2006). Causes of death following 1 year postinjury among individuals with traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *21*(1), 22–23.

Harrison-Felix, C., Whiteneck, G. G., Jha, A., DeVivo, M. J., Hammond, F. M., Hart, D. M. (2009). Mortality over four decades after traumatic brain injury rehabilitation: A retrospective cohort study. *Archives of Physical Medicine and Rehabilitation*, *90*(9), 1506–1513.

Howsepian, A. A. (1996). The 1994 Multi-Society Task Force consensus statement on the persistent vegetative state: A critical analysis. *Issues in Law and Medicine*, *12*(1), 3–29.

Kessler, M. W. (2004). Critical analysis of the life expectancy research from an attorney's perspective. In S. Riddick-Grisham (Ed.), *Pediatric life care planning and case management*. Boca Raton, FL: CRC Press.

McMillan, T. M., & Teasdale, G. M. (2007). Death rate is increased for at least 7 years after head injury: A prospective study. *Brain*, *130*(Pt 10), 2520–2527.

Motulsky, H. (1995). *Intuitive biostatistics*. New York: GraphPad Software Publisher: Oxford University Press.

Multi-Society Task Force. (1994). Medical aspects of the persistent vegetative state—second of two parts. *The New England Journal of Medicine*, *330*(22), 1572–1579.

Pentland, B., Hutton, L. S., & Jones, P. A. (2005). Late mortality after head injury. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*, 395–400.

Plioplys, A. V. (2004). Life expectancy of severely disabled children: A brief review. In *Pediatric life care planning and case management*. CRC Press, Boca Raton, FL.

Ratcliff, G., Colantonio, A., Escobar, M., Chase, S., & Vernich, L. (2005). Long-term survival following traumatic brain injury. *Disability and Rehabilitation*, *27*(6), 305–314.

Selassie, A. W., McCarthy, M. L., Ferguson, P. L., Tian, J., & Langlois, J. A. (2005). Risk of post-hospitalization mortality among persons with traumatic brain injury, South Carolina 1999–2001. *The Journal of Head Trauma Rehabilitation*, *20*(3), 257–269.

Shavelle, R. M., Strauss, D. J., Day, S. M., & Ojdana, K. A. (2007). Life expectancy. In N. D. Zasler, D. Katz, & R. Zafonte (Eds.), *Brain injury medicine: Principles and practice*. New York: Demos Publishers.

Shavelle, R. M., Strauss, D. J., & Katz, R. T. (2008). Survival of persons with locked-in syndrome: A correction. *Archives of Physical Medicine and Rehabilitation*, *89*, 1005.

Strauss, D. J. (1999). Life tables for people with traumatic brain injury. *Journal of Insurance Medicine*, *31*, 104–105.

Strauss, D. J., & Shavelle, R. M. (1998a). Doctors are not experts on life expectancy. *The Expert Witness*, *3*(2), 1–4.

Strauss, D. J., & Shavelle, R. M. (1998b). Life expectancy: What lawyers need to know. *AVMA Medical and Legal Journal*, *5*, 25–26.

Strauss, D. J., Shavelle, R. M., DeVivo, M. J., & Day, S. M. (2000). An analytic method for longitudinal mortality studies. *Journal of Insurance Medicine*, *32*, 225–328.

Strauss, D. J., Shavelle, R. M., DeVivo, M. J., Harrison-Felix, C., & Whiteneck, G. G. (Eds.). (2004). Letter to the editor: Life expectancy after traumatic brain injury. *NeuroRehabilitation*, *19*, 257–258.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 10

Waking up the brain: a case study of stimulation-induced wakeful unawareness during anaesthesia

Christian K.E. Moll[1,*], Andrew Sharott[1], Wolfgang Hamel[2], Alexander Münchau[3], Carsten Buhmann[3], Ute Hidding[3], Simone Zittel[3], Manfred Westphal[2], Dieter Müller[2] and Andreas K. Engel[1]

[1]*Department of Neurophysiology and Pathophysiology, Center of Experimental Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[2]*Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[3]*Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*

Abstract: Hitherto, little is known about the specific functional contributions of extrathalamic arousal systems to the regulation of wakefulness in humans. Here, we describe a 42-year-old woman with treatment resistant tremulous cervical dystonia who underwent microelectrode-guided stereotactic implantation of deep brain stimulation (DBS) electrodes in the internal segment of the globus pallidus internus (GPi) under general anaesthesia. Acute unilateral DBS of circumscribed sites within the subpallidal fibre-field with 130 Hz caused a transient state of wakefulness with an increased responsiveness to external stimuli but without detectable signs of conscious awareness. The extent of behavioural arousal could be titrated as a function of stimulus intensity. At lower stimulation intensities, bilateral eye opening occurred in response to verbal commands or tactile stimulation. At suprathreshold intensities, the patient's eyes remained open and conjugated throughout the stimulation period. The arousal effect ceased abruptly when DBS was discontinued. Behavioural arousal was accompanied by global cortical EEG activation in the gamma-frequency range (40–120 Hz) and by autonomic activation as evidenced by increased heart rate. The observed effect was reproducible in both hemispheres and topographically restricted to 6 out of 15 tested sites in the fibre-field between the GPi and the posterior aspect of the basal nucleus of Meynert. We conclude that the stimulated neural substrate in the subpallidal basal forebrain is involved in the premotor control of lid and eye position and the control of the activation state of the human neocortex. It may thus be important for the induction and maintenance of anaesthesia-induced unconsciousness in humans. It is suggested that subpallidal DBS released a downstream arousal circuit from anaesthesia-related inhibitory modulation either by direct excitation of an arousal nucleus or by inhibition of a sleep-promoting centre in the basal forebrain.

Keywords: arousal; general anaesthesia; deep brain stimulation; nucleus basalis of Meynert; dystonia

*Corresponding author.
Tel.: +49 40 7410 57044; Fax: +49 40 7410 57752;
E-mail: c.moll@uke.de

DOI: 10.1016/S0079-6123(09)17710-5

Introduction

Both sleep and anaesthesia are reversible states of eyes-closed unresponsiveness to environmental stimuli in which the individual lacks both wakefulness and awareness. In contrast to sleep, where sufficient stimulation will return the individual to wakefulness, even the most vigorous exogenous stimulation cannot produce awakening in a generally anaesthetized patient. In clinical practice as well as everyday life, awakening from sleep or anaesthesia is commonly defined as opening of the eyes in response to verbal commands (Dutton et al., 1995). The palpebral fissures widen, the eyes are fixed in the primary position, the striated muscle tone is enhanced throughout the body and large cardio-respiratory changes occur (Horner et al., 1997). These physiological concomitants of wakefulness are brought into action more or less simultaneously by a global state change within the central nervous system (Pfaff et al., 2008). In the mammalian neocortex, this state change is reflected in a characteristic transformation of the spectral content of electroencephalographic recordings (EEG) known as 'activation' or 'desynchronization': During the transition from sleep or anaesthesia to waking, low-frequency activity with high amplitudes (the EEG signature of sleep and anaesthesia) is replaced by low amplitude EEG fluctuations at relatively high frequencies (>15 Hz), which are indicative of the awake and aroused state (Steriade et al., 2001).

Moruzzi and Magoun (1949) demonstrated that electrical stimulation of brainstem-thalamic projections switches the neocortex of anaesthetized animals into an arousal state. Their pioneering work laid the foundations for our current understanding of the midbrain reticular formation and midline thalamic structures as important nodal points of an ascending neural network which exerts a tight control over the activation state of the cortex and the level of wakefulness (Steriade, 1996). Later work with implanted electrodes in unrestrained animals showed that behavioural arousal is accompanied by similar EEG changes irrespective of whether alerting occurs naturally or is mimicked by electrical stimulation (Steriade and McCarley, 2005). Some of the classical electrocortical and behavioural arousal responses seen in laboratory animals have been replicated during electrical test stimulation in humans undergoing stereotactic surgery in the thalamus for different pathological conditions, including movement disorders (Hassler et al., 1960; Housepian and Purpura, 1963), neuropsychiatric disorders (Velasco et al., 2006) or epilepsy (Velasco et al., 1997). Although only rarely observed (Schaltenbrand et al., 1973; Umbach, 1961), these artificial conditions mimicking natural arousal raised the particular interest of clinicians and resulted in clinical applications of thalamic deep brain stimulation (DBS) for otherwise untreatable patients with serious abnormalities of arousal or behavioural responsiveness resulting from severe brain injury (Hassler et al., 1969; Katayama et al., 1991; Schiff and Plum, 2000; Yamamoto et al., 2002). Progressive arousal and improved neurological function following thalamic DBS has recently been demonstrated in a minimally conscious patient (Schiff et al., 2007), further highlighting the outstanding role of the midline thalamus as an arousal-regulating relay and appropriate site for neuromodulatory interventions in disorders of consciousness. Moreover, the midline thalamus also plays an important role in the regulation of anaesthetic-induced unconsciousness (Alkire et al., 2000; Fiset et al., 1999; Franks, 2008; Keifer, 2003; Stienen et al., 2008).

The anatomy of subcortical arousal systems producing wakefulness is, however, more complex than initially thought. The view has emerged that, rather than operated by a single transthalamic arousal system, arousal-control is regulated by an orchestration of different subcortical arousal- and sleep-promoting systems that act in parallel and involve different neurotransmitters (Franks, 2008; Jones, 2008). The dynamics of thalamo-cortical activity depends not only on ascending influences from the mesencephalon (Francesconi et al., 1988; Munk et al., 1996), but is also modulated by inputs from the hypothalamus and basal forebrain (Buzsaki and Gage, 1989; Franks, 2008; Pinault and Deschenes, 1992; Semba, 1991; Steriade and Buzsaki, 1990; Steriade and McCarley, 2005). Several lines of evidence stress the importance of arousal-related neuronal populations located in

the basal forebrain area extending between the globus pallidus internus (GPi) and the nucleus basalis Meynert (NBM) in the regulation of cortical arousal and wakefulness (Buzsaki and Gage, 1989; Semba, 1991). First, recent electrophysiological studies have revealed strong correlations between the firing of individual cholinergic and GABAergic basal forebrain cells and cortical activity across the sleep–wake cycle (Lee et al., 2004, 2005; Lin et al., 2006). Both the cholinergic and the non-cholinergic components are thought to play a key role in switching the neocortex into an arousal state characterized by high-frequency EEG activity, particularly in the gamma band (30–80 Hz) (Detari, 2000; Detari et al., 1999; Jones, 2008; Lee et al., 2005; Lin et al., 2006). Second, in agreement with the state-dependence of basal forebrain neurons across sleep stages demonstrated in rodents, basal forebrain structures in humans exhibit significant changes in glucose metabolism or blood flow throughout the sleep–wake cycle (Braun et al., 1997; Nofzinger et al., 1997; Zaborszky et al., 2008). Third, experimental lesions of the NBM induce deficits in performance on a wide variety of tasks requiring selected attentional abilities (Dunnett et al., 1991; Wenk, 1997) and result in a slowing of EEG activity (Buzsaki et al., 1988; Buzsaki and Gage, 1989). Finally, electrical stimulation of these arousal populations has demonstrated a role in both EEG desynchronization (Belardetti et al., 1977; McLin et al., 2002; Metherate et al., 1992) and behavioural arousal (Grahnstedt and Ursin, 1980). Low awakening thresholds in sleeping animals and effective stimulation sites that elicit cortical activation have repeatedly been observed in the middle and ventral aspects of the GPi and subjacent NBM (Grahnstedt and Ursin, 1980; Metherate et al., 1992).

Hitherto, the contribution of basal forebrain populations to arousal has not been directly tested in humans, mainly due to the difficulty to assess these small subcortical structures (Baars, 1995). However, the nearby ventral posterolateral aspect of the GPi is commonly targeted in surgery for movement disorders (Vitek et al., 1998). Microelectrode recording and stimulation techniques that are regularly employed during pallidal interventions, may thus also provide important insights into functional contributions of the GPi/NBM area in a large-scale arousal-regulatory network between brainstem and cortex.

The present case report demonstrates and discusses the phenomenon of transient awakening from general anaesthesia induced by unilateral intraoperative DBS in the GPi/NBM area. The aim of the present study was twofold: (i) Our first goal was to determine the anatomical substrates involved in the arousal effect. To this end, we precisely delineated the stimulation sites using intraoperative microelectrode mapping and performed a stereotactic analysis for electrode localization on fused computerized tomography/magnetic resonance imaging (CT/MRI) data. (ii) The second goal was to study the behavioural and electrophysiological accompaniments of this arousal modulation. Therefore, we employed EEG and electrocardiographic (ECG) recordings as central and peripheral arousal indices, respectively. Some of the results of this study have been presented in abstract form (Moll et al., 2007).

Material and methods

Patient details

A 42-year-old female with a 27-year history of involuntary turning and twisting of the neck was presented for surgical evaluation. At the onset, she developed an abnormal head posture in conjunction with intermittently occurring tremulous head movements triggered by stress. Symptoms were present during and interfered with most daily activities, such as reading, walking or car driving. No other body parts were affected. Head tremor was alcohol sensitive for a few years, but maximum pharmacological treatment with various anti-tremor drugs (including benzodiazepines, anticholinergics, beta-blocker and L-Dopa) was largely ineffective. She also underwent psychotherapy which was unsuccessful. Other family members were not affected by movement disorders. The head tremor became increasingly severe and socially embarrassing during the last 3 years. Due to the disease progression, the patient

had to give up her position as a hotel receptionist and subsequently developed reactive depression. She was referred to our hospital in 2005 for further assessment and local botulinum toxin injections. On examination, the patient had a constant, irregular, slow (3-Hz) head tremor (primarily horizontal 'no-no' movements) at rest along with a 15° rotation of the head to the right and a slight tilt to the left. There was an elevation and forward displacement of the left shoulder. Head tremor was rated as severe (Score 4, amplitude > 2 cm) using the Fahn–Tolosa–Marín Tremor Rating Scale (range 0–4) (Fahn et al., 1988). Severity of cervical dystonia was scored 11 on the severity subscale of the Toronto Western Spasmodic Torticollis Rating Scale (range 0–35) (Consky and Lang, 1994). The patient was capable to suppress abnormal head movements by supporting the chin with both hands or by adopting an abnormal head position and posture. Apart from abnormal head movements and postures, neurological examination was unremarkable. Repeated administration of botulinum toxin was associated with side effects. She was therefore considered a suitable candidate for implantation of DBS electrodes. The patient provided written informed consent before the surgical intervention in February 2006. All procedures were approved by a local ethics committee and conducted in accordance with the declaration of Helsinki. Due to the severity of the head tremor, the stereotactic operation was performed under general anaesthesia.

Anaesthetic procedure

As a premedication before surgery, the patient received 7.5 mg midazolam. Venous and arterial cannulae were inserted for fluid and drug administration and monitoring of arterial blood pressure. General anaesthesia was induced with a bolus of 2 mg/kg propofol and maintained by application of 6 mg/kg/h propofol in combination with 0.25 μg/kg/min remifentanil. The patient was mechanically ventilated via an endotracheal tube with an oxygen–air mixture (FiO_2 0.5). Anaesthetic depth was constantly monitored throughout the operative course at regular intervals by an experienced anaesthesiologist and adequacy was deduced from clinical signs such as complete unresponsiveness, lack of spontaneous movements, stable heart rate (HR) and blood pressure. With the exception of stimulation-induced changes (see below), the patient did not respond to verbal commands, prodding or any other sensory stimuli, no spontaneous movements occurred and autonomic measures remained stable throughout the whole surgical procedure. The level of anaesthesia continued to be on a constant level after the test stimulation (including skin incision and trepanation of the skull on the second hemisphere), so that no adjustment of the anaesthetic drugs was necessary for the subsequent steps of the procedure.

Stereotactic intervention

Because the patient had tremulous cervical dystonia (and no 'pure' head tremor) the posteroventrolateral GPi instead of the ventrolateral thalamus was targeted. Details of the surgical procedure are reported elsewhere (Hamel et al., 2003). Briefly, a MRI-compatible Zamorano–Dujovny frame (Stryker Leibinger, Freiburg, Germany) was mounted on the patient's head and tightly secured with pins. Both gadolinium-enhanced volumetric T1 MRI and T2 weighted spin echo MRI sequences were acquired (1.5 Tesla Magnetom Sonata, Siemens, Erlangen, Germany) and fused with a CT scan (Somatom Plus 4, Siemens, Erlangen, Germany) using commercially available software (iPlan, BrainLAB Inc., Westchester, IL, USA). Except for a small non-specific lesion in the right subcortical white matter of the parietal operculum, the brain appeared regular and inconspicuous on acquired anatomical MRI scans. After determining a reference-line connecting the anterior and posterior commissure (AC-PC line, length 23.6 mm; width of the third ventricle < 3 mm), the GPi was targeted 20 mm lateral to the AC-PC line, 3 mm inferior and 3 mm anterior to the mid-commissural point on both sides. The approach angles for the left and right side, respectively were 32/23 degrees from the AC-PC line in the sagittal projection (rostral inclination), and 15/13

degrees from the vertical in the coronal projection. A burr hole was made anterior to the left and right coronal suture, the micromanipulator was mounted on the stereotactic frame and the appropriate target coordinates were adjusted.

Microelectrode recordings

Microelectrode recordings were performed with five parallel tracks arranged in a concentric array (MicroGuide, Alpha-Omega, Nazareth, Israel). Four outer platinum–iridium electrodes (impedances, 0.3–0.8 MegaOhm at 1000 Hz; FHC Inc., Bowdoinham, ME, USA) were separated by 2 mm from a central one which aimed at the theoretical target. Signals were amplified ($\times$ 20.000), bandpass-filtered (300–6000 Hz) and digitized (sampling rate: 24 kHz). Spike detection was performed offline using a voltage threshold method and single units were then separated by manual cluster selection in 3D feature space using principal component projections of the waveforms (Offline-Sorter, Plexon Inc., Dallas, TX, USA). Spiketrain-analysis was applied to well-isolated single cell activity sampled for at least 30 s or 1000 action potentials (Neuroexplorer, Nex Technologies, Littleton, MA, USA).

Test stimulation

Following microelectrode-guided delineation of pallidal boundaries and identification of the optic tract, we aimed to assess the relative proximity to the internal capsule by determining the thresholds of stimulation-induced muscle contractions (as evidenced by apparent limb movements and/or the appearance of EMG-activity) or eye deviations. To this end, monopolar test stimulation was performed at different depth levels (see below) using the uninsulated macrotip of the electrode (cathodal) against the respective guide tube (anodal). The stimulus intensity was graduated in volts. With a macrotip impedance of $\sim$1 kOhm, 1 V would generate a current of $\sim$1 mA. In each stimulation site, the amplitude was gradually increased in steps of 0.5 V up to 7 V over a period of approximately 2–3 min, always at a frequency of 130 Hz (impulse width, 60 μs). To assess the distance to motor fibres in the adjacent internal capsule, we also carried out low-frequency stimulation in the posterior and medial stimulation sites on each hemisphere (frequency, 4 Hz; impulse width, 100 μs). The interval between individual electrical stimulation periods varied, but always exceeded 30 s.

Electrophysiological monitoring and analysis

In parallel with the microrecording signals, a 32-channel system (AlphaMap, Alpha-Omega, Nazareth, Israel) was used to amplify and record EEG (amplification $\times$ 5.000; bandpass, 1–300 Hz), EMG (amplification $\times$ 2.000; bandpass, 5–1000 Hz) and ECG signals at a sampling rate of 3.000 Hz during the microrecording and stimulation periods. EEG was recorded from four scalp electrodes (Ag/AgCl cup electrodes filled with conductive gel; Nicolet Biomedical, Madison, WI, USA) approximately placed at Pz, Oz, C3 and C4 according to the international 10–20 system against the left earlobe as a common reference. Spectral power was calculated in 5 s windows with a 2.5 s overlap with a 0.5 s block size/frequency resolution of 2 Hz (Matlab, Mathworks Inc., Natick, MA, USA). All windows were normalized to the mean power in each frequency bin in the rest period (16 windows) between the two stimulation periods. The grey scale (Fig. 4A) therefore reflects the difference between this interim period and the stimulation periods, which can be clearly identified by the stimulation artefact at 130 Hz. To quantify and compare the spectral changes following stimulation at different brain sites, spectral power was calculated for a 65 s segment of EEG recorded from the occipital midline electrode (Oz) during stimulation with each of the five macrotips in the secondly operated right hemisphere. In each case, the data was taken from the end of the stimulation period where the stimulus magnitude was largest. Spectra were calculated with a 1 s block size/frequency resolution of 1 Hz. Each power spectrum was normalized to baseline, using power values calculated for a rest period (no stimulation) of the same length recorded between the stimulation epochs. The concurrent recording from a three-lead ECG and

multiple surface electrodes placed above selected muscles on both sides of the body (including sternocleidomastoid, biceps brachii, triceps brachii, deltoid, flexor digitorum superficialis, extensor digitorum communis, quadriceps, gastrocnemius and tibialis anterior muscle) allowed the assessment of stimulation-induced effects on the HR and muscle-activity, respectively. All results are given as the mean $\pm$ S.D.

Results

Microelectrode-guided delineation of the stimulation sites

Microelectrode recordings started 15 mm above the theoretical target and allowed a precise delineation of the external and internal pallidal segments. Sporadic putaminal activity was encountered close to the dorsal boundary of the GPe (Fig. 1A), confirming a lateral plane of at least 20 mm to midline (Vitek et al., 1998). The mapping of the internal medullary lamina allowed a further division of the GPi into its external and internal divisions GPie and GPii, respectively. Neurons from the GPii fired somewhat faster (18.8 ± 17.2 Hz, $n = 18$) than neurons of the GPie (13.7 ± 7.1 Hz, $n = 25$) and GPe (11.5 ± 9.2 Hz, $n = 24$), however, this difference was not significant (Student's t-test, $p > 0.1$). Figure 1A,B show representative striatal and pallidal recordings, respectively. The pallidal base was recognized by sparseness of neuronal activity, as the electrodes were moved to the adjacent subpallidal fibre-field. Figure 1C provides a depth profile with a synopsis of all recording sites from both hemispheres. To assess the distance to the neighbouring optic tract, changes in background neuronal activity were examined during brief light stimuli applied with a torch in darkened conditions. At a depth level of 5 mm below AC-PC (2 mm below the pallidal base), the central and anterior electrodes on the left side showed increases and decreases of background neuronal activity, which followed the onset and offset of the transient light stimuli, respectively. In the right hemisphere, only the medial electrode displayed optic tract activity 6 mm below AC-PC. Following offline rectification, these responses could readily be visualized (Fig. 2A). The lack of recordings from both posterior trajectories indicated that these tracks traversed mainly fibre tracts of the adjacent internal capsule, being further substantiated by the identification of the microexcitable internal capsule in these positions (Fig. 2B, see below).

Behavioural arousal

Following characterization of light responses, test stimulation was carried out on each of the five microelectrodes at two different depth levels on the left (2 and 4 mm below AC-PC) and one depth level on the right side (4 mm below AC-PC), adding up to a total of 15 tested sites. We observed that stimulation in 6 out of 15 tested sites led to reproducible behavioural expressions of wakefulness without detectable signs of conscious awareness. Stimulation elicited enduring bilateral opening of the eyelids with the eyes in a near conjugate position (Fig. 3B), whereas in the absence of stimulation the patient's eyes were closed (Fig. 3A) and presented a divergent strabismus. When stimulation was carried out with intensities below the threshold for persistent eye opening, phasic behavioural arousal with transient eye opening in response to auditory or tactile stimuli could also be induced. The patient stereotypically opened the eyes with a short delay (700–1000 ms) in response to addressing the patient verbally or to pinching the patient's arms — indicating a stimulation-induced increased responsiveness to external stimuli. At all sites tested, the behavioural arousal persisted only during the course of stimulation and disappeared promptly with termination of stimulation, following which the patient could not be roused anymore by loud commands or any other stimuli. On the first operated left side, an arousal effect could be elicited by stimulation at two different sites: posterior electrode, 4 mm below AC-PC (threshold: 3.0 V) and anterior electrode, 2 mm below AC-PC (threshold: 2.0 V). On the right hemisphere, the arousal effect was elicited only with higher stimulus intensities at four different sites (depth level 4 mm below AC-PC): central (threshold: 5.0 V), medial (threshold:

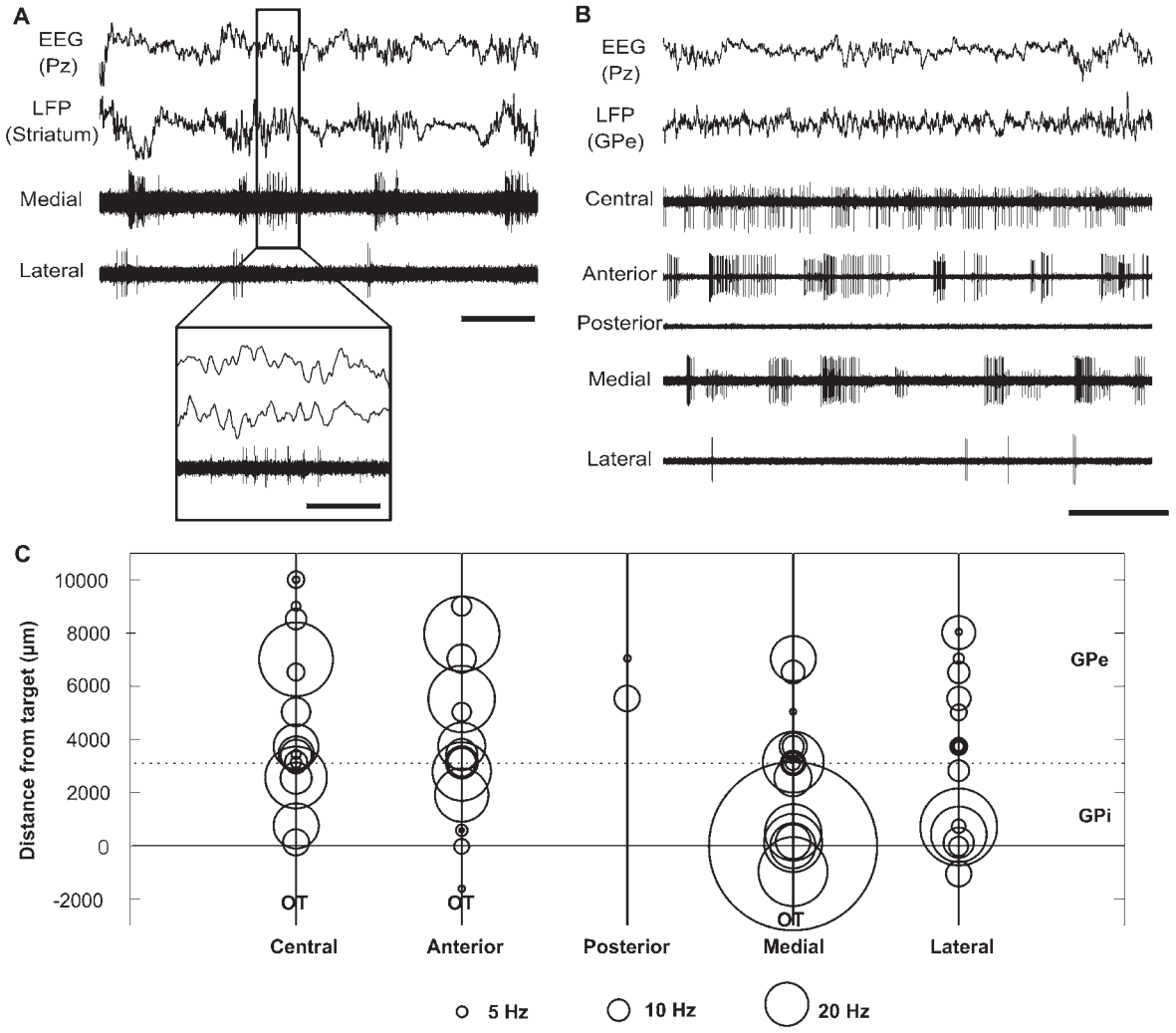


Fig. 1. Results of intraoperative microelectrode mapping. (A) Recording from the striatum, 12.7 mm above target. Note the burst-suppression pattern in the EEG and striatal LFP with alternating episodes of spindling activity and low-amplitude signals. Scale bar, 2 s. The two recorded striatal units fire at spindle onset and are completely silent during low-amplitude periods of EEG/LFP activity. Inset shows spindling-related activity of the striatal unit recorded from the medial track in the alpha-frequency range (10–12 Hz). Scale bar, 500 ms. (B) Representative example of microelectrode recordings from the GP of the left hemisphere (2.3 mm above the pallidal base). Central, anterior and medial tracks exhibit an irregular, uncorrelated bursting pattern. The lateral electrode picks up striatal cellular activity, while the posterior track traverses fibres of the internal capsule. Scale bar, 2 s. (C) Synopsis of mapping results (data from both hemispheres pooled). Activity-depth profiles are given for each microelectrode track, with circles representing the location and mean firing rate (circle size) of the recorded cell. The virtual absence of cellular activity in the posterior tracks suggests a course traversing the internal capsule. OT, optic tract.

5.7 V), posterior (threshold 4.5 V) and lateral (threshold: 7 V). Low-frequency stimulation (frequency 4 Hz, impulse width, 100 µs) did not lead to behavioural, cortical or autonomic activation at any of the tested sites (not shown).

Cortical activation

The described stimulation-induced behavioural arousal was associated with global low-voltage high-frequency activity in the EEG. The EEG

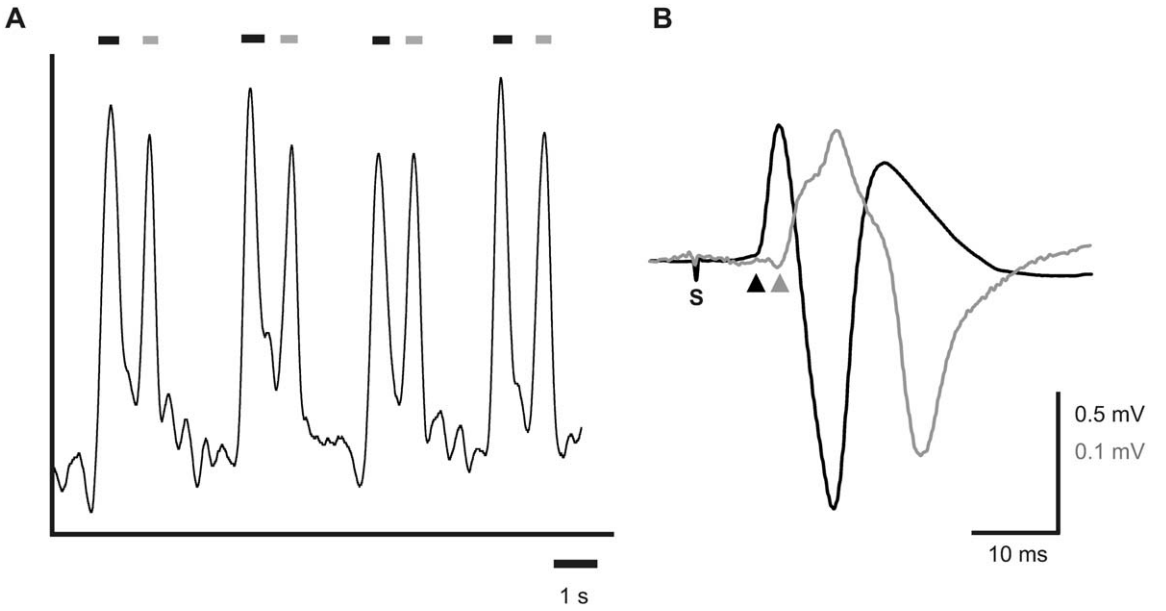


Fig. 2. Physiological identification of anatomical landmarks. (A) Optic tract response at a depth level of 5 mm below AC-PC; left hemisphere, medial electrode. The graph displays the time course of multi-unit activity after offline rectification and smoothing. Note the increases and decreases of background neuronal activity associated with transient light stimuli. Black and grey bars indicate movements of the torch onto and away from the pupil, respectively. (B) Motor-evoked potentials in the left m. sternocleidomastoideus (black) and m. biceps brachii (grey) following electrical stimulation of motor fibres in the right internal capsule, 2 mm below AC-PC plane, with low frequency. Latencies are 7 ms for the sternocleidomastoid (black arrowhead) and 9.5 ms for the biceps muscle (grey arrowhead), respectively. S, stimulus artefact. Note the difference of the two graphs in amplitude scaling.

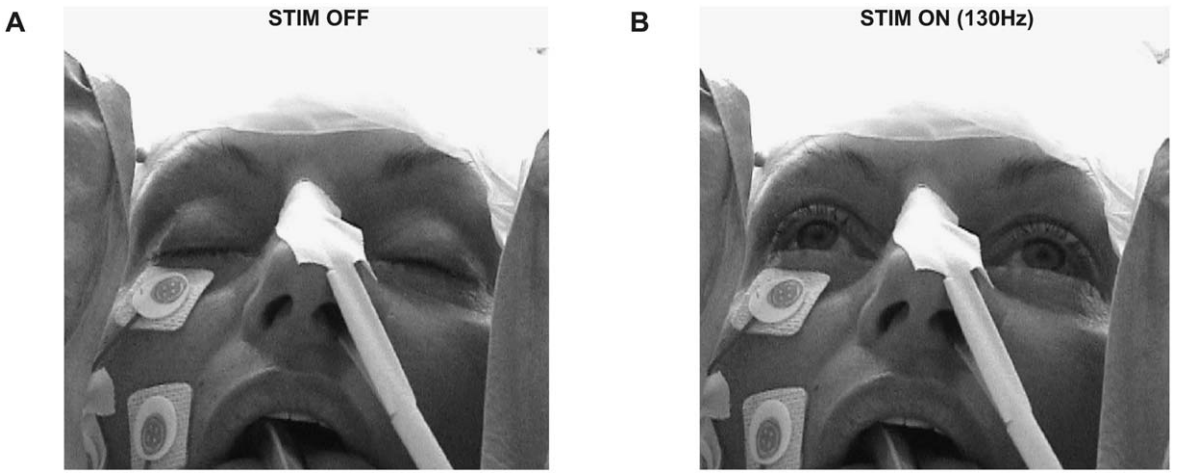


Fig. 3. Behavioural arousal. Photographs of the stimulation-induced behavioural effect. (A) Patient without stimulation. (B) Arousal reaction consisting of sustained eye opening during suprathreshold electrical stimulation of the left anterior electrode with 130 Hz at 2 V. Note the near conjugate position of the eyes. Patient consent has been obtained to publish this figure.

desynchronization showed a bilateral scalp distribution. Power spectral analysis showed that 130 Hz DBS was correlated with increased power at beta (>20 Hz) and gamma-frequencies (>40 Hz), the augmentation of which was in close correspondence with behavioural arousal. Figure 4A,B show spectrograms computed for a continuous EEG recording from an electrode placed above the left sensorimotor cortex (corresponding approximately to position C3 in the standard 10–20 system) during high-frequency stimulation of the medial and posterior electrodes in the first operated left hemisphere, respectively. Stimulation of the medial test-electrode (the first stimulation period), which did not lead to behavioural arousal, produced little change in the power at any frequency. Subsequent stimulation of the posterior test-electrode, which caused behavioural arousal with sustained eye opening at a threshold of approximately 3 V, led to an increase in power in the higher gamma-frequency range (>60 Hz), the magnitude of which increased with the intensity of stimulation. The fact that this increase was not seen during identical stimulation using the medial electrode, around 1.5 mm away, makes it highly unlikely that the change in spectral content of the EEG was an artefact of the electrical stimulation. Stimulation-induced power changes were observed to be especially pronounced in the delta (1–4 Hz) and higher gamma-frequency range (60–95 Hz). Minor power changes occurred in other frequency bands (theta, alpha and beta, not shown). Figure 5 shows a comparison between stimulation-induced power changes of the occipital midline EEG (Oz) in the delta band (1–4 Hz; left panel) and the higher gamma band (60–95 Hz; right panel) during stimulation of the five different trajectories on the second (right) hemisphere. Gamma-band power increases were greater at depth stimulation sites that also produced behavioural arousal. Changes in the gamma band were generally larger in magnitude than those in the delta band. A decrease in delta-power was observed in the two instances, where DBS led to both behavioural and autonomic activation (posterior and lateral trajectory).

Autonomic and electromyographic activation

In 6 of the 15 tested positions, electrical stimulation led to a significant autonomic activation, as revealed by a transient HR increase of 9 ± 2 beats min^{-1} (bpm) compared to the baseline HR (Student's paired *t*-test, $p = 0.01$, $n = 6$). In four of these six sites, stimulation produced autonomic activation without behavioural or EEG arousal, respectively. As Fig. 4B illustrates, the HR increase was particularly pronounced, when stimulation was associated with behavioural and EEG arousal (increase of 15.5 ± 3.5 bpm; 2/6 stimulation sites): Stimulation of the medial trajectory (Fig. 4B; first stimulation period, left section) on the first operated left hemisphere and 3 mm below AC-PC failed to induce a clinical and electrophysiological arousal response and did not increase the patient's HR. However, an EMG response of the contralateral biceps muscle was obtained upon electrical stimulation in this position, confirming the proximity of the medial trajectory to motor fibres running in the posterior limb of the internal capsule. In contrast, during stimulation of the posterior trajectory (Fig. 4B; second stimulation period, right section) with similar parameters (pulse-width, 60 μs; frequency, 130 Hz; amplitude stepwise increased from 0.5 to 5 V), the EMG remained silent. In this position, stimulation evoked behavioural as well as EEG arousal and was accompanied by a transient increase of the patient's pulse from 55 to 70 bpm. The arousal effect ceased abruptly after stimulation was discontinued and HR returned to baseline values. On the second operated right hemisphere, the topographic relationship of medial and posterior stimulation sites to the microexcitable internal capsule was different. High-frequency stimulation of the medial trajectory (4 mm below the AC-PC plane) did not lead to EMG changes, whereas stimulation of the posterior trajectory induced tetanic contractions of different contralateral arm (m. extensor digitorum communis, threshold: 5.0 V; m. biceps brachii, threshold: 5.5 V) and neck muscles (contralateral sternocleidomastoid muscle, threshold: 5.5 V). Using low-frequency stimulation in this

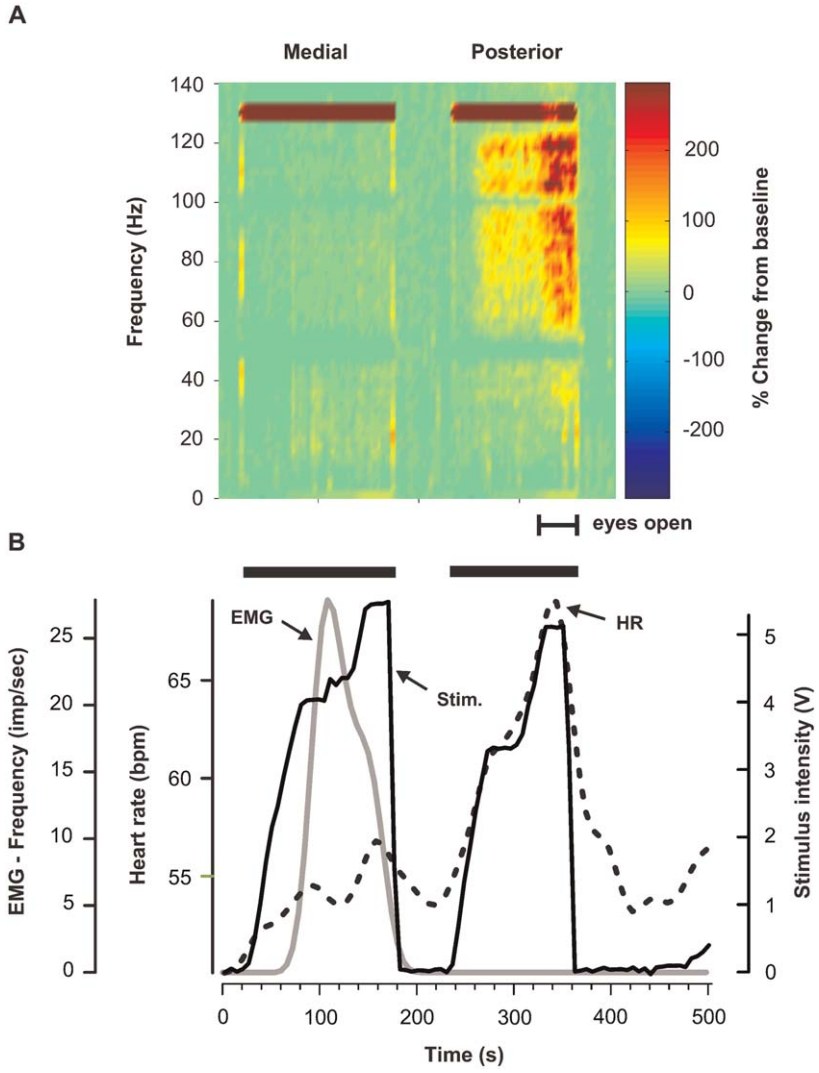


Fig. 4. Electroencephalographic and autonomic arousal. (A) Spectrogram showing the EEG power changes over the ipsilateral sensorimotor cortical area (C3) at different frequencies (*y*-axis) during stimulation of the medial and posterior test-electrode relative to a baseline derived from a 30 s prestimulation period (left hemisphere, 4 mm below AC-PC). While no cortical power changes occur during stimulation of the medial electrode, a strong power increase in the higher gamma band (>60 Hz) can be seen during stimulation of the posterior electrode, which is associated with behavioural arousal. (B) Concurrent changes in heart rate (HR, dashed line; green in the web version) and EMG-activity (grey; blue in the web version). The grey (blue in the web version) line indicates the firing frequency of a single muscle fibre that was recorded from the right m. biceps brachii. The solid black (dashed in the web version) line indicates the strength of stimulation at the medial and posterior electrode, respectively. DBS of the medial trajectory, which did not result in neither cortical nor expressions of behavioural arousal, did not significantly alter the patient's heart rate. The stimulation-related discharge of the muscle fibre indicates current spread to nearby motor fibres in the internal capsule. These fibres were not activated, when the posterior electrode was stimulated. Strong autonomic arousal was associated with cortical and behavioural arousal in this position.

posterior stimulation site, motor-evoked potentials occurred in the contralateral biceps and sternocleidomastoid muscle with a latency of $\sim$9.5 and $\sim$7 ms, respectively (threshold: 5.5 V; see Fig. 2B). With the exception of stimulation-induced changes, no spontaneous movements occurred (as evidenced by clinical evaluation and silent EMG recordings) throughout the operative

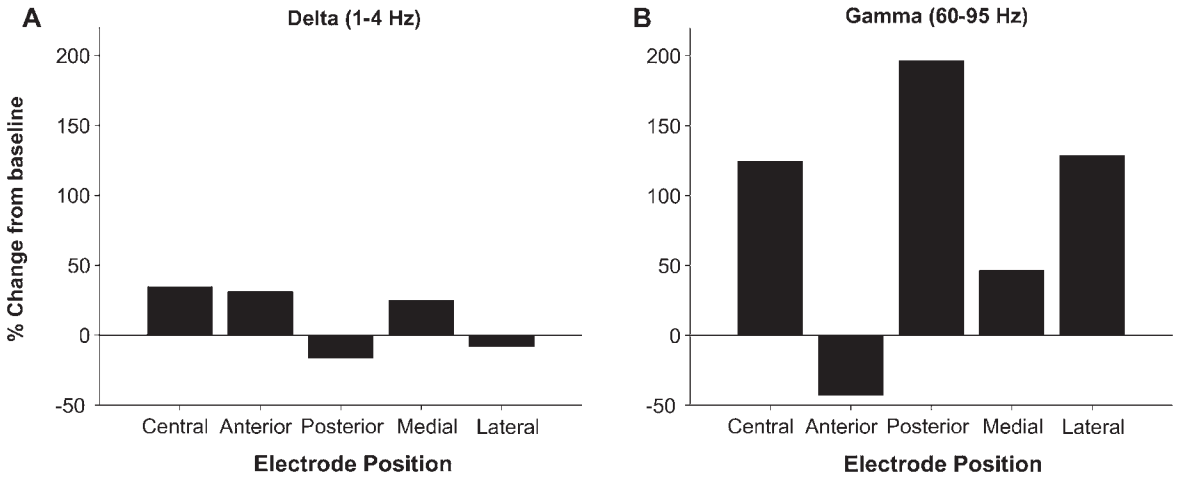


Fig. 5. Stimulation-induced power changes during GPi/NBM DBS. Power changes in the occipital midline EEG (Oz), induced by high-frequency stimulation of different electrode positions in the second (right) hemisphere. Left and right panel show the power changes occurring in the delta and gamma band, respectively.

Table 1. Results of intraoperative deep brain stimulation testing

Hemi-sphere	Depth below AC-PC	Track	Behavioural arousal	EEG arousal	Autonomic arousal	EMG activation
Left	2 mm	Central	No	No	Yes	No
		Anterior	Yes/2.0 V	Yes	No	No
		Posterior	No	No	No	Yes/3.2 V
		Medial	No	No	No	No
		Lateral	No	No	No	No
Left	4 mm	Central	No	No	Yes	No
		Anterior	No	No	Yes	No
		Posterior	Yes/3.0 V	Yes	No	No
		Medial	No	No	No	Yes/3.5 V
		Lateral	No	No	Yes	No
Right	4 mm	Central	Yes/5.0 V	Yes	No	Yes/5.2 V
		Anterior	No	No	No	Yes/6.0 V
		Posterior	Yes/4.5 V	Yes	Yes	Yes/5.5 V
		Medial	Yes/5.7 V	Yes	No	Yes/7.0 V
		Lateral	Yes/7.0 V	Yes	Yes	Yes/7.0 V

course. Table 1 provides a detailed overview of stimulation-related effects for each position of the stimulation electrodes.

Stereotactic reconstruction of the stimulation sites

In order to validate the final electrode positions, a stereotactic CT scan was performed postoperatively and fused with the preoperative MRI. It confirmed the correct position of the DBS electrodes within the GPi, the stereotactic coordinates of the ventral most contacts relative to the mid-commissural point (lateral, anterior, inferior) being $x = 19.6\,\text{mm}$, $y = 2.3\,\text{mm}$, $z = 4.3\,\text{mm}$ for the left and $x = 20\,\text{mm}$, $y = 2\,\text{mm}$, $z = 5\,\text{mm}$ for the right hemisphere (Fig. 6B,E). Correlation of the electrode position with corresponding sections of a stereotactic atlas (Schaltenbrand and Bailey,

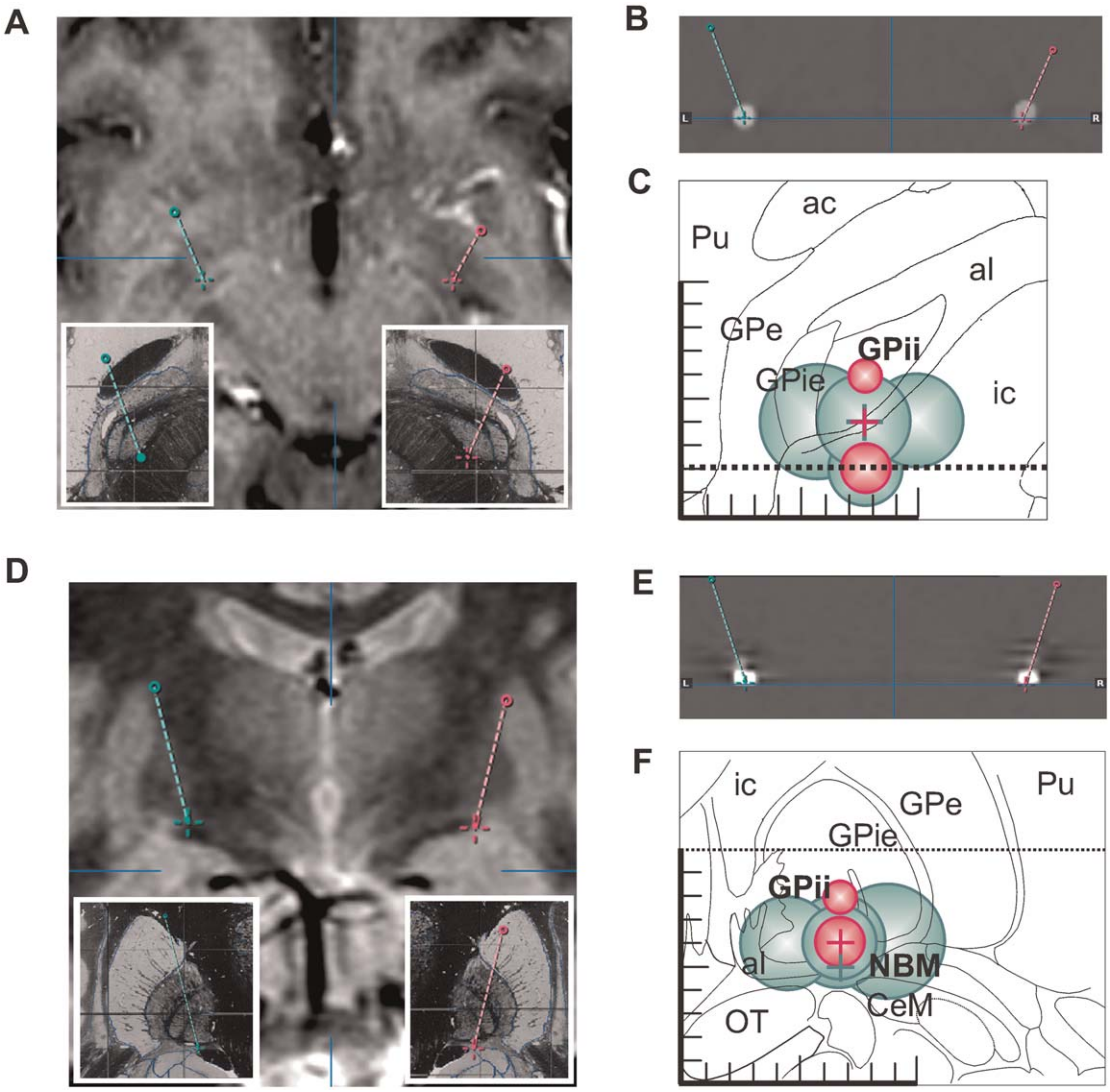


Fig. 6. Stereotactic reconstruction. Stereotactic reconstruction of stimulation sites in the horizontal (A–C) and frontal plane (D–F), respectively. (A) Horizontal T1-weighted MR section with planned target sites at the pallidal base. Insets show the trajectory superimposed on corresponding horizontal sections of the Schaltenbrand/Bailey atlas (Schaltenbrand and Bailey, 1959). (B) Planned trajectory superimposed on a postoperatively acquired horizontal stereotactic CT scan. Note the correspondence with the artefact derived from the implanted DBS electrode. (C) Reconstruction of peripallidal stimulation sites that led to behavioural arousal, with the assumed radial current spread superimposed on a corresponding horizontal atlas section. Note that stimulation results from both hemispheres are superimposed (dark grey, left hemisphere [red in the web version]; light grey, right hemisphere [green in the web version]). Scale bar is 10 mm. Dotted line indicates the midcommissural level. Abbreviations: ac, anterior commissure; al, ansa lenticularis; NBM, ncl. basalis Meynert; CeM, centromedial amygdaloid nucleus; GPe, external pallidal segment; GPie, lateral part of the internal pallidal segment; GPii, medial part of the internal pallidal segment; ic, internal capsule; Pu, putamen. (D) Assumed trajectory course superimposed on a frontal T2-weighted MR section. Note the proximity of the target sites to the optic tract. Insets depict the stereotactic trajectory drawn on a corresponding frontal section of the stereotactic atlas of Schaltenbrand and Bailey (1959). (E) Postoperative stereotactic CT scan, frontal reconstruction. Confirmation of the correct placement of the DBS electrode through superposition of the planned trajectory on the electrode artefact. (F) Reconstruction of arousal-associated stimulation sites and assumed current spread in the frontal plane. Abbreviations as in panel C.

1959) revealed the correct position of the quadropolar electrode with the most inferior contact placed just below the posterolateral pallidal base (Fig. 6).

Postoperative course

The central trajectory was chosen for permanent implantation of the quadropolar DBS electrodes (model DBS 3389, Medtronic Inc., Minneapolis, MN, USA) on both sides. Intraoperatively, bipolar stimulation of the ventral most contact ('0-', cathodal) against the dorsal most contact ('3+', anodal; pulse-width, 60 μs; frequency, 130 Hz) elicited an arousal effect at 5.5 V on the left, but not on the right side. Upon stimulation with higher voltages (>6 V), conjugate eye deviation was observed on the right side. Despite stimulation with even higher intensities (up to 7 V), no capsular affection could be provoked on either side. Upon awakening from anaesthesia after the operation, the patient was interviewed but reported no explicit recollection of the intraoperative arousal episodes. Dystonic head tremor re-occurred immediately. Initially, chronic DBS was started with monopolar stimulation of the most distal contacts ('0-' and '4-' cathodal vs. case+anodal) on both sides (amplitude, 2 V; pulse-width, 90 μs; frequency, 130 Hz) which led to an immediate, but not complete cessation of tremor. Stimulation-induced changes in the level of consciousness could not be reproduced postoperatively because dysarthria occurred at higher intensities (>3.5 V), limiting the range of stimulation. Subsequent follow-up programming sessions revealed that monopolar stimulation of the second most distal contacts ('1' and '5') against the case was more efficient and provided a broader therapeutic window for stimulation. Permanent stimulation of this contact (amplitude, 2.2 V; pulse-width, 90 μs; frequency, 145 Hz) did not lead to any recognizable alteration of the patient's vigilance status or sleep–wake rhythm. However, the patient displayed complete tremor suppression after 2 days (score 0 on the Fahn–Tolosa–Marín Tremor Rating Scale) and near-complete resolution of torticollis (score 4 on the Toronto Western Spasmodic Torticollis Rating Scale) after 1 week. In contrast, discontinuation of DBS resulted in immediate tremor recurrence and was not tolerated because of discomfort from rapidly recurring cervical dystonia. This beneficial stimulation effect has remained stable for more than 24 months, further adding to the notion that bilateral GPi stimulation is effective in suppressing dystonic head tremor.

Discussion

The key novel finding of the present case study is that acute unilateral high-frequency stimulation of the GPi/NBM area evoked a paradoxical arousal reaction, strong enough to transiently reverse general anaesthesia. Our case offered the unusual opportunity to study the functional contribution of a circumscribed region in the subpallidal basal forebrain area to the induction and maintenance of anaesthesia-induced unconsciousness in humans. Considering the difficulty to study the small subcortical sources involved in controlling arousal and behavioural responsiveness physiologically in the human brain, these data are of particular interest. The observations presented in this paper demonstrate an important functional contribution of the GPi/NBM area in a large-scale regulatory network between brainstem and cortex that determines the level of wakefulness and the activation state of the human brain.

An increase of the stimulation amplitude led to a gradual increase in the patient's responsiveness to external sensory stimuli, which covered the full spectrum of arousal levels from complete unresponsiveness (without stimulation), transient behavioural arousal (at subthreshold stimulation values) to persistent behavioural arousal at higher stimulation intensities. Notably, the patient did not show any behavioural signs indicative of conscious awareness during or after these intraoperative arousal episodes, including a lack of explicit recall postoperatively. Thus, electrical stimulation produced a wakeful state without awareness in our patient, to some degree similar to patients that are in a persistent vegetative state following brain injury (Jennett and Plum, 1972). This stimulation-induced dissociation of

wakefulness from awareness is remarkable, since typically, an impairment in arousal is closely linked with an impairment in awareness in most pharmacologically induced and disease-related states of unconsciousness (Laureys, 2005).

Intraoperative arousal effects are only rarely observed, despite the fact that the posteroventral lateral GPi is commonly targeted in surgery for different movement disorders and test stimulation is used intraoperatively in virtually every operation to determine stimulation-induced side effects. However, arousal reactions may be missed because (i) most stereotactic interventions are carried out with the patient awake, (ii) arousal reactions are not specifically provoked and (iii) the NBM is typically spared in pallidal surgery (Vitek et al., 1998). Umbach (1977), in a series of 175 pallidal interventions, reported an incidence of arousal effects seen under high-frequency stimulation below 1%. Therefore, an intraoperative arousal effect may be a rare event during pallidal surgery, possibly attributable to interindividual anatomical differences or to procedural details of surgery and anaesthesia. However, the beneficial clinical course of the described patient indicates that a stimulation-induced arousal reaction occurring during pallidal surgery is not indicative of incorrect electrode placement.

As is the case for any single-case report, a concern is the extent to which the results of the present study may be due to individual peculiarities such as, for example pre-existing structural alterations. There was no evidence in the patient's MRI and CT scans for anatomical abnormalities or damage in the region of interest that could account for the observed stimulation effects. Moreover, typical patterns of cellular activity were regularly encountered during microelectrode recordings from striatal and pallidal sites (Vitek et al., 1998) — with the comparably low firing rates of pallidal units being best explained by the effects of anaesthesia with propofol/remifentanyl (Hutchison et al., 2003). Evidently, one variable of critical importance in the present study may be the level of anaesthesia. It has been demonstrated in animal studies that the threshold for electrical brain stimulation to produce arousal and EEG desynchronization depends on the sleep stage (Grahnstedt and Ursin, 1980). More recently, the critical role of anaesthetic depth for the arousal-threshold has been shown in patients during propofol-induced sedation or general anaesthesia. Whereas i.v. application of epinephrine changed the arousal-level in sedated patients, it had no effect on patients under general anaesthesia (Shin et al., 2004). In our patient, adequacy of surgical anaesthesia was repeatedly ascertained and maintained on a constant level throughout the whole course of the operative procedure, with a propofol dosage typically used for general anaesthesia (Dunnet et al., 1994). There were no autonomic signs of inadequate anaesthesia (lacrimation, flushing, sweating) throughout the operation. With the exception of stimulation-induced increases in responsiveness, the patient did not respond to verbal or tactile stimuli during any part of the operation. Taken together, it seems plausible to attribute the observation of transient reversal of general anaesthesia to the modulatory effects of DBS on an arousal-regulating structure located just below the GPi, rather than to alternative explanations such as individual biovariability in the patient's response to anaesthetic drugs.

Therefore, the discussion will focus on neurofunctional mechanisms and structures underlying the observed stimulation-induced arousal reaction. In this respect, the localization of the stimulating electrode is of critical importance. The conjunction of intraoperative microelectrode mapping and postoperative stereotactic neuroimaging allowed us to determine the precise localization of the stimulation sites within the fibre area between GPi and NBM. We consider first the possible effects of DBS on pallidal outflow which funnels at the base of the pallidum before converging and crossing the posterior limb of the internal capsule (Patil et al., 1998). It is reasonable to assume that a greater number of pallidofugal signals were modulated by DBS in the outflow tracts than at their origin, since these pallidofugal fibre systems are more closely packed than the neurons from which they originate. Amongst other targets in the subthalamic and thalamic areas, the main pallidal outflow projects to the intralaminar thalamic nuclei (Parent and

Parent, 2004), which activate widespread neocortical territories. Inhibition of pallidal input to the intralaminar thalamus, through high-frequency stimulation, could therefore activate the thalamo-cortical system and thus, provide a first plausible interpretation of the non-specific arousal effect and induction of high-frequency rhythms in the EEG. In line with this interpretation, the observed behavioural arousal in our patient resembled very much the, Weckeffekt' originally described by Jung and Hassler who observed partial arousal in mildly sedated patients undergoing stereotaxy upon electrical stimulation of intralaminar thalamic nuclei (Hassler, 1957; Hassler et al., 1960; Jung, 1954; Jung and Hassler, 1960). In addition, the observed electrocorticographic arousal has more recently been described following DBS of the intralaminar thalamus (Velasco et al., 1997, 2006). A recent report demonstrated unexpected awakening from anaesthesia in rats upon attempts to induce lesions in the intralaminar thalamus with ibotenic acid (Stienen et al., 2008). These observations further stress the importance of the intralaminar thalamus as a crucial nodal point that is involved in the regulation of arousal and anaesthetic-induced unconsciousness.

The observed arousal reaction with conjugate gaze and simultaneous opening of both eyes is strongly reminiscent of reticular activation. Stimulation of the mesencephalic reticular formation with 100–300 Hz produces behavioural expressions associated with electrocortical activation and alerting of enduring persistence (Moruzzi and Magoun, 1949). Moreover, reticular stimulation is apt to facilitate intracortical information processing by enhancing stimulus-specific synchrony in the gamma-frequency range (Munk et al., 1996). In our patient, subpallidal DBS induced a clear coordination of lid and eye position. Pathways controlling both the levator palpebrae tonus and the activation of rectus muscles run in close association with the ascending arousal system through the paramedian tegmentum of the upper brainstem (Schmidtke and Buttner-Ennever, 1992). The marked sensitivity of the eyelid position to electrical stimulation in our patient supports the well established intimate relationship between eyelid movements and level of alertness (Kennard and Glaser, 1964). In line with improvements of apraxia of lid opening seen following pallidal DBS (Goto et al., 1997, 2000), our observations demonstrate that descending inputs from the GPi/NBM area are implicated in the supranuclear control of the levator palpebrae tonus. The fact that stimulation was effective in both hemispheres implies that such descending control is exerted bilaterally. Further support for a downstream activation or disinhibition of the brainstem reticular formation may be derived from the observation that sensory stimulation of different modalities, in addition to subthreshold electrical stimulation, led to behavioural arousal. Neurons in the reticular formation of the pons and medulla are innervated by multiple bifurcating and collateral axons of ascending sensory systems. They possess the capacity to respond to stimuli in more than one sensory modality with broad receptive fields (Scheibel et al., 1955) and are thus uniquely positioned to contribute to generalized arousal (Pfaff et al., 2008).

Pallidal efferent pathways descend along the pallidotegmental tract to target cells of the pedunculopontine tegmental (PPT) nucleus (Shink et al., 1997), which is part of the ascending arousal system (Datta and Siwek, 1997; Jones, 2005). Similar to activation of the thalamo-cortical system as described above, DBS-induced inhibition of pallidal outflow could also activate the PPT, which has been considered an interface between the basal ganglia and the reticular formation (Inglis and Winn, 1995).

An alternative interpretation of electrical stimulation near the pallidal base has to take into account the close proximity of neighbouring structures. The current spread using monopolar macrostimulation at current strengths similar to those in this study can roughly be estimated to 2–5 mm (Follett and Mann, 1986; McIntyre et al., 2004). Stimulation may therefore have implicated neighbouring systems in the sublenticular substantia innominata to some extent, in particular the NBM, the widespread cholinergic projections of which have long been implicated in cortical arousal (Detari et al., 1999; Richardson and DeLong, 1988).

The magnocellular basal forebrain complex releases acetylcholine to a number of cortical regions (Jones, 2005). Acetylcholine serves to potentiate neuronal responsivity and thereby facilitate information processing throughout cortical systems (Metherate et al., 1992). In the EEG, electrical stimulation of the NBM induces low amplitude fast oscillations in the gamma-frequency range (Jones, 2004; McLin et al., 2002; Metherate et al., 1992). By providing a steady background of cortical activity, the basal forebrain corticopetal system has been proposed as an important role in mediating cortical arousal and attention (Buzsaki and Gage, 1989). Besides its direct projections to the cerebral cortex, the thalamopetal component of NBM efferents to the reticular thalamic nucleus may provide an alternative pathway for cortical arousal (Heimer, 2000; Steriade and Buzsaki, 1990). Similar to the cholinergic reticulo-thalamic projection, an activation of this route may abolish spindles and slow wave activity in thalamo-cortical systems — leading to a facilitated transthalamic processing of sensory information and an enhancement of high-frequency activities in the EEG (Steriade and Buzsaki, 1990; Steriade et al., 1990). In addition to cortical arousal, autonomic activation has also been demonstrated following electrical stimulation of the NBM (McLin et al., 2002).

The descending NBM projections to sleep–wake related structures in the brainstem may account for the reticular component of behavioural arousal as discussed above (Grove, 1988; Semba, 2000; Semba et al., 1989). Moreover, recent lesioning studies have pointed out the involvement of the basal forebrain cholinergic system in mediating the effects of general (propofol) anaesthesia (Laalou et al., 2008; Pain et al., 2000). It is therefore conceivable, that the arousal effect seen in our patient involved direct stimulation of the posterior sublenticular extension of the NBM (cell group Ch4p) (Mesulam et al., 1983), which consists of several smaller cell aggregates (Zaborszky et al., 2008) of disseminated cholinergic cell groups embedded within the white matter laminae that surround the GP, within the internal capsule or within the ansa lenticularis (Hedreen et al., 1984; Mesulam, 1995; Saper and Chelimsky, 1984). The somewhat diffuse anatomical organization of the posterior Ch4 compartments could help to explain the different arousal thresholds of discrete stimulation sites tested in this study. Importantly, the posterior Ch4 subdivision is commonly confined by two landmark structures which have also been physiologically identified in the present study, that is where the optic tract attaches the internal capsule. Moreover, the centre of gravity of these cell groups is similar to the stereotactic coordinates used in this study (Zaborszky et al., 2008). Surprisingly little is known concerning stimulation effects of the NBM in humans, because it is currently not a target structure for DBS surgery and current surgical strategies aim to spare this neighbouring structure in pallidal surgery (Vitek et al., 1998). Two single case studies of basal nucleus DBS failed to describe clinical or electroencephalographic responses (Engel et al., 2002; Turnbull et al., 1985).

Finally, direct activation of the neighbouring centromedial amygdala or amygdalofugal pathways through volume conduction may constitute yet another possible mechanism subserving the behavioural arousal seen in our patient. The central nucleus of the amygdala is involved in the control of brainstem arousal systems and may increase vigilance by lowering neuronal threshold in sensory systems (Cardinal et al., 2002; Davis and Whalen, 2001). The electrocorticographic response following electrical stimulation of these sublenticular amygdaloid nuclei is in many ways similar, although not identical with the arousal response as elicited by stimulation of the brainstem reticular formation (Belardetti et al., 1977; Feindel and Gloor, 1954). The centromedial amygdala lies approximately 3 mm below the pallidal base (i.e. 7–8 mm below AC-PC). Given the fact that an arousal effect was elicited 2 mm below AC-PC with voltages as low as 2 V on the anterior track of the first stimulated left hemisphere, the possibility that the amygdala was involved in this stimulation effect is not very likely. Furthermore, a recent report of a dislocated pallidal DBS electrode into the left amygdaloid region described mood changes in a patient with dystonia, but did not report on

abnormalities of arousal or behavioural responsiveness associated with unilateral high-frequency stimulation of the amygdala (Piacentini et al., 2008).

Taken together, it seems most plausible to attribute the observed stimulation effect to direct stimulation of the posterior extension of the NBM rather than to a modulation of pallidofugal or amygdaloid pathways and related nuclei. The evidence supporting this conjecture can be summarized as follows. First, disinhibition of the cortico-striato-pallido-thalamo-cortical loop by modulation of increased pallidal outflow, while an attractive hypothesis, lacks experimental validation (Braun et al., 1997; Schiff, 2008; Schiff and Posner, 2007). However, there is strong experimental evidence demonstrating the important role of the NBM in cortical activation (Buzsaki and Gage, 1989; Detari et al., 1999; Dringenberg and Olmstead, 2003; Lee et al., 2005; Metherate et al., 1992; Semba, 1991; Steriade and Buzsaki, 1990). In contrast to the NBM, the GPi cannot be considered a classical site for the induction of cortical activation. Second, the abovementioned routes by which inhibition of pallidal outflow may cause cortical activation are based on the assumption of increased pallidal inhibition — however, our microelectrode recordings clearly show reduced levels of pallidal activity in terms of their discharge rate, rendering this possibility unlikely. Third, the GPi is a rather homogenous nucleus, while the Ch4p compartment consists of several small cell aggregates — potentially explaining the spatial dispersion of effective stimulation sites (Zaborszky et al., 2008). Fourth, the autonomic arousal response is a clue suggesting the involvement of the NBM, since NBM stimulation causes autonomic arousal and alters HR (McLin et al., 2002), whereas GPi stimulation does not (Thornton et al., 2002). Finally, basal forebrain cholinergic neurons (including the cholinergic NBM) have been demonstrated to mediate part of the sedative/hypnotic effects of general anaesthesia with propofol (Laalou et al., 2008; Pain et al., 2000).

Disruption of the arousal-regulatory pathways implicated in the present study may result in abnormally low levels of consciousness (i.e. reduced wakefulness) and problems with arousal, potentially explaining clinically related symptoms like fatigue and hypersomnia which have been reported following pallidal surgery (Hua et al., 2003). Moreover, it has been demonstrated that lesions at the pallidal base may disrupt frontal-subcortical circuits and produce behavioural changes associated with apathy and a reduced vigilance level, such as akinetic mutism (Mega and Cohenour, 1997). A further elucidation of the intimate anatomical and functional relationships between pallidal outflow and neighbouring basal forebrain systems, in particular the NBM, may therefore be of clinical importance.

Acknowledgments

The authors are grateful to the patient, who gave written informed consent for publication of this report, including the figures in this paper. A.K.E. acknowledges support by grants from the European Union (NEST-PATH-043457, MRTN-CT-2005-019247), the German Federal Ministry of Education and Research (01GA0301) and the Volkswagen Foundation (I/76697).

References

Alkire, M. T., Haier, R. J., & Fallon, J. H. (2000). Toward a unified theory of narcosis: Brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. *Consciousness and Cognition*, *9*, 370–386.

Baars, B. J. (1995). Tutorial commentary: Surprisingly small subcortical structures are needed for the state of waking consciousness, while cortical projection areas seem to provide perceptual contents of consciousness. *Consciousness and Cognition*, *4*, 159–162.

Belardetti, F., Borgia, R., & Mancia, M. (1977). Prosencephalic mechanisms of ECoG desynchronization in cerveau isole cats. *Electroencephalography and Clinical Neurophysiology*, *42*, 213–225.

Braun, A. R., Balkin, T. J., Wesenten, N. J., Carson, R. E., Varga, M., Baldwin, P., et al. (1997). Regional cerebral blood flow throughout the sleep-wake cycle. An $H_2(15)O$ PET study. *Brain*, *120*(Pt 7), 1173–1197.

Buzsaki, G., Bickford, R. G., Ponomareff, G., Thal, L. J., Mandel, R., & Gage, F. H. (1988). Nucleus basalis and thalamic control of neocortical activity in the freely moving rat. *Journal of Neuroscience*, *8*, 4007–4026.

Buzsaki, G., & Gage, F. H. (1989). The cholinergic nucleus basalis: A key structure in neocortical arousal. *EXS*, *57*, 159–171.

Cardinal, R. N., Parkinson, J. A., Hall, J., & Everitt, B. J. (2002). Emotion and motivation: The role of the amygdala, ventral striatum, and prefrontal cortex. *Neuroscience and Biobehavioral Reviews*, *26*, 321–352.

Consky, E. S., & Lang, A. E. (1994). Clinical assessments of patients with cervical dystonia. In J. Jankovic & M. Hallett (Eds.), *Therapy with botulinum toxin* (pp. 211–237). New York: Marcel Dekker.

Datta, S., & Siwek, D. F. (1997). Excitation of the brain stem pedunculopontine tegmentum cholinergic cells induces wakefulness and REM sleep. *Journal of Neurophysiology*, *77*, 2975–2988.

Davis, M., & Whalen, P. J. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry*, *6*, 13–34.

Detari, L. (2000). Tonic and phasic influence of basal forebrain unit activity on the cortical EEG. *Behavioural Brain Research*, *115*, 159–170.

Detari, L., Rasmusson, D. D., & Semba, K. (1999). The role of basal forebrain neurons in tonic and phasic activation of the cerebral cortex. *Progress in Neurobiology*, *58*, 249–277.

Dringenberg, H. C., & Olmstead, M. C. (2003). Integrated contributions of basal forebrain and thalamus to neocortical activation elicited by pedunculopontine tegmental stimulation in urethane-anesthetized rats. *Neuroscience*, *119*, 839–853.

Dunnet, J. M., Prys-Roberts, C., Holland, D. E., & Browne, B. L. (1994). Propofol infusion and the suppression of consciousness: Dose requirements to induce loss of consciousness and to suppress response to noxious and non-noxious stimuli. *British Journal of Anaesthesia*, *72*, 29–34.

Dunnett, S. B., Everitt, B. J., & Robbins, T. W. (1991). The basal forebrain-cortical cholinergic system: Interpreting the functional consequences of excitotoxic lesions. *Trends in Neurosciences*, *14*, 494–501.

Dutton, R. C., Smith, W. D., & Smith, N. T. (1995). Wakeful response to command indicates memory potential during emergence from general anesthesia. *Journal of Clinical Monitoring*, *11*, 35–40.

Engel, A. K., Moll, C. K. E., Debener, S., Gielen, F., Lenartz, D., Kluge, T., et al. (2002). *Microelectrode recordings in the human basal forebrain: A single case study*. Abstract Viewer and Itinerary Planner, Vol. Program No. 780.14. Society for Neuroscience, Online, Washington, DC.

Fahn, S., Tolosa, E., & Marín, C. (1988). Clinical rating scale for tremor. In J. Jankovic & E. Tolosa (Eds.), *Parkinson's disease and movement disorders* (pp. 225–234). Baltimore, MD: Urban and Schwarzenberg.

Feindel, W., & Gloor, P. (1954). Comparison of electrographic effects of stimulation of the amygdala and brain stem reticular formation in cats. *Electroencephalography and Clinical Neurophysiology Supplement*, *6*, 389–402.

Fiset, P., Paus, T., Daloze, T., Plourde, G., Meuret, P., Bonhomme, V., et al. (1999). Brain mechanisms of propofol-induced loss of consciousness in humans: A positron emission tomographic study. *Journal of Neuroscience*, *19*, 5506–5513.

Follett, K. A., & Mann, M. D. (1986). Effective stimulation distance for current from macroelectrodes. *Experimental Neurology*, *92*, 75–91.

Francesconi, W., Muller, C. M., & Singer, W. (1988). Cholinergic mechanisms in the reticular control of transmission in the cat lateral geniculate nucleus. *Journal of Neurophysiology*, *59*, 1690–1718.

Franks, N. P. (2008). General anaesthesia: From molecular targets to neuronal pathways of sleep and arousal. *Nature Reviews Neuroscience*, *9*, 370–386.

Goto, S., Kihara, K., Hamasaki, T., Nishikawa, S., Hirata, Y., & Ushio, Y. (2000). Apraxia of lid opening is alleviated by pallidal stimulation in a patient with Parkinson's disease. *European Journal of Neurology*, *7*, 337–340.

Goto, S., Kunitoku, N., Soyama, N., Yamada, K., Okamura, A., Yoshikawa, M., et al. (1997). Posteroventral pallidotomy in a patient with parkinsonism caused by hypoxic encephalopathy. *Neurology*, *49*, 707–710.

Grahnstedt, S., & Ursin, R. (1980). Awakening thresholds for electrical brain stimulation in five sleep-waking stages in the cat. *Electroencephalography and Clinical Neurophysiology*, *48*, 222–229.

Grove, E. A. (1988). Efferent connections of the substantia innominata in the rat. *The Journal of Comparative Neurology*, *277*, 347–364.

Hamel, W., Fietzek, U., Morsnowski, A., Schrader, B., Weinert, D., Muller, D., et al. (2003). Subthalamic nucleus stimulation in Parkinson's disease: Correlation of active electrode contacts with intraoperative microrecordings. *Stereotactic and Functional Neurosurgery*, *80*, 37–42.

Hassler, R. (1957). *Weckeffekte und delirante Zustände durch elektrische Reizungen bzw. Ausschaltungen im menschlichen Zwischenhirn*. Bruxelles: Prèmièr Congrès International des Sciències Neurologiquès, pp. 179–181.

Hassler, R., Ore, G. D., Dieckmann, G., Bricolo, A., & Dolce, G. (1969). Behavioural and EEG arousal induced by stimulation of unspecific projection systems in a patient with post-traumatic apallic syndrome. *Electroencephalography and Clinical Neurophysiology*, *27*, 306–310.

Hassler, R., Riechert, T., Mundinger, F., Umbach, W., & Ganglberger, J. A. (1960). Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. *Brain*, *83*, 337–350.

Hedreen, J. C., Struble, R. G., Whitehouse, P. J., & Price, D. L. (1984). Topography of the magnocellular basal forebrain system in human brain. *Journal of Neuropathology and Experimental Neurology*, *43*, 1–21.

Heimer, L. (2000). Basal forebrain in the context of schizophrenia. *Brain Research Brain Research Reviews*, *31*, 205–235.

Horner, R. L., Sanford, L. D., Pack, A. I., & Morrison, A. R. (1997). Activation of a distinct arousal state immediately after spontaneous awakening from sleep. *Brain Research*, *778*, 127–134.

Housepian, E. M., & Purpura, D. P. (1963). Electrophysiological studies of subcortical-cortical relations in man. *Electroencephalography and Clinical Neurophysiology*, *15*, 20–28.

Hua, Z., Guodong, G., Qinchuan, L., Yaqun, Z., Qinfen, W., & Xuelian, W. (2003). Analysis of complications of radiofrequency pallidotomy. *Neurosurgery*, *52*, 89–99. discussion 99–101.

Hutchison, W. D., Lang, A. E., Dostrovsky, J. O., & Lozano, A. M. (2003). Pallidal neuronal activity: Implications for models of dystonia. *Annals of Neurology*, *53*, 480–488.

Inglis, W. L., & Winn, P. (1995). The pedunculopontine tegmental nucleus: Where the striatum meets the reticular formation. *Progress in Neurobiology*, *47*, 1–29.

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet*, *1*, 734–737.

Jones, B. E. (2004). Activity, modulation and role of basal forebrain cholinergic neurons innervating the cerebral cortex. *Progress in Brain Research*, *145*, 157–169.

Jones, B. E. (2005). From waking to sleeping: Neuronal and chemical substrates. *Trends in Pharmacological Sciences*, *26*, 578–586.

Jones, B. E. (2008). Modulation of cortical activation and behavioral arousal by cholinergic and orexinergic systems. *Annals of the New York Academy of Sciences*, *1129*, 26–34.

Jung, R. (1954). Correlation of bioelectrical and autonomic phenomena with alterations of consciousness and arousal in man. In E. D. Adrian, F. Bremer, & H. H. Jasper (Eds.), *Brain mechanisms and consciousness* (pp. 310–339). Oxford: Blackwell Scientific Publications.

Jung, R., & Hassler, R. (1960). The extrapyramidal motor system. In H. W. Magoun (Ed.), *Neurophysiology* (Vol. 2, pp. 863–927). Washington, D.C.: American Physiological Society.

Katayama, Y., Tsubokawa, T., Yamamoto, T., Hirayama, T., Miyazaki, S., & Koyama, S. (1991). Characterization and modification of brain activity with deep brain stimulation in patients in a persistent vegetative state: Pain-related late positive component of cerebral evoked potential. *Pacing and Clinical Electrophysiology*, *14*, 116–121.

Keifer, J. (2003). Sleep and anesthesia. In J. F. Antognini, E. E. Carstens, & D. E. Raines (Eds.), *Neural mechanisms of anesthesia* (pp. 65–74). Totowa, NJ: Humana Press.

Kennard, D. W., & Glaser, G. H. (1964). An analysis of eyelid movements. *The Journal of Nervous and Mental Disease*, *139*, 31–48.

Laalou, F. Z., de Vasconcelos, A. P., Oberling, P., Jeltsch, H., Cassel, J. C., & Pain, L. (2008). Involvement of the basal cholinergic forebrain in the mediation of general (propofol) anesthesia. *Anesthesiology*, *108*, 888–896.

Laureys, S. (2005). The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences*, *9*, 556–559.

Lee, M. G., Hassani, O. K., Alonso, A., & Jones, B. E. (2005). Cholinergic basal forebrain neurons burst with theta during waking and paradoxical sleep. *Journal of Neuroscience*, *25*, 4365–4369.

Lee, M. G., Manns, I. D., Alonso, A., & Jones, B. E. (2004). Sleep-wake related discharge properties of basal forebrain neurons recorded with micropipettes in head-fixed rats. *Journal of Neurophysiology*, *92*, 1182–1198.

Lin, S. C., Gervasoni, D., & Nicolelis, M. A. (2006). Fast modulation of prefrontal cortex activity by basal forebrain noncholinergic neuronal ensembles. *Journal of Neurophysiology*, *96*, 3209–3219.

McIntyre, C. C., Mori, S., Sherman, D. L., Thakor, N. V., & Vitek, J. L. (2004). Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. *Clinical Neurophysiology*, *115*, 589–595.

McLin, D. E., III, Miasnikov, A. A., & Weinberger, N. M. (2002). The effects of electrical stimulation of the nucleus basalis on the electroencephalogram, heart rate, and respiration. *Behavioral Neuroscience*, *116*, 795–806.

Mega, M. S., & Cohenour, R. C. (1997). Akinetic mutism: Disconnection of frontal-subcortical circuits. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *10*, 254–259.

Mesulam, M. M. (1995). Cholinergic pathways and the ascending reticular activating system of the human brain. *Annals of the New York Academy of Sciences*, *757*, 169–179.

Mesulam, M. M., Mufson, E. J., Wainer, B. H., & Levey, A. I. (1983). Central cholinergic pathways in the rat: An overview based on an alternative nomenclature (Ch1-Ch6). *Neuroscience*, *10*, 1185–1201.

Metherate, R., Cox, C. L., & Ashe, J. H. (1992). Cellular bases of neocortical activation: Modulation of neural oscillations by the nucleus basalis and endogenous acetylcholine. *Journal of Neuroscience*, *12*, 4701–4711.

Moll, C. K. E., Sharott, A., Buhmann, C., Hidding, U., Zittel, S., Westphal, M., et al. (2007). Intraoperative arousal reaction due to electrical stimulation of the globus pallidus. *Acta Physiologica*, *189*, P20-L1-01.

Moruzzi, G., & Magoun, H. W. (1949). Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology*, *1*, 455–473.

Munk, M. H., Roelfsema, P. R., Konig, P., Engel, A. K., & Singer, W. (1996). Role of reticular activation in the modulation of intracortical synchronization. *Science*, *272*, 271–274.

Nofzinger, E. A., Mintun, M. A., Wiseman, M., Kupfer, D. J., & Moore, R. Y. (1997). Forebrain activation in REM sleep: An FDG PET study. *Brain Research*, *770*, 192–201.

Pain, L., Jeltsch, H., Lehmann, O., Lazarus, C., Laalou, F. Z., & Cassel, J. C. (2000). Central cholinergic depletion induced by 192 IgG-saporin alleviates the sedative effects of propofol in rats. *British Journal of Anaesthesia*, *85*, 869–873.

Parent, M., & Parent, A. (2004). The pallidofugal motor fiber system in primates. *Parkinsonism & Related Disorders*, *10*, 203–211.

Patil, A. A., Hahn, F., Sierra-Rodriguez, J., Traverse, J., & Wang, S. (1998). Anatomical structures in the Leksell pallidotomy target. *Stereotactic and Functional Neurosurgery*, *70*, 32–37.

Pfaff, D., Ribeiro, A., Matthews, J., & Kow, L. M. (2008). Concepts and mechanisms of generalized central nervous system arousal. *Annals of the New York Academy of Sciences*, *1129*, 11–25.

Piacentini, S., Romito, L., Franzini, A., Granato, A., Broggi, G., & Albanese, A. (2008). Mood disorder following DBS of the left amygdaloid region in a dystonia patient with a dislodged electrode. *Movement Disorders*, *23*, 147–150.

Pinault, D., & Deschenes, M. (1992). Muscarinic inhibition of reticular thalamic cells by basal forebrain neurones. *Neuroreport*, *3*, 1101–1104.

Richardson, R. T., & DeLong, M. R. (1988). A reappraisal of the functions of the nucleus basalis of Meynert. *Trends in Neuroscience*, *11*, 264–267.

Saper, C. B., & Chelimsky, T. C. (1984). A cytoarchitectonic and histochemical study of nucleus basalis and associated cell groups in the normal human brain. *Neuroscience*, *13*, 1023–1037.

Schaltenbrand, G., & Bailey, P. (1959). *Introduction to stereotaxis with an atlas of the human brain*. Stuttgart: Georg Thieme Verlag.

Schaltenbrand, G., Spuler, H., Wahren, W., & Wilhelmi, A. (1973). Vegetative and emotional reactions during electrical stimulation of deep structures of the brain during stereotactic procedures. *Zeit-schrift fur Neurologie*, *205*, 91–113.

Scheibel, M., Scheibel, A., Mollica, A., & Moruzzi, G. (1955). Convergence and interaction of afferent impulses on single units of reticular formation. *Journal of Neurophysiology*, *18*, 309–331.

Schiff, N. D. (2008). Central thalamic contributions to arousal regulation and neurological disorders of consciousness. *Annals of the New York Academy of Sciences*, *1129*, 105–118.

Schiff, N. D., Giacino, J. T., Kalmar, K., Victor, J. D., Baker, K., Gerber, M., et al. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, *448*, 600–603.

Schiff, N. D., & Plum, F. (2000). The role of arousal and ''gating'' systems in the neurology of impaired consciousness. *Journal of Clinical Neurophysiology*, *17*, 438–452.

Schiff, N. D., & Posner, J. B. (2007). Another ''Awakenings''. *Annals of Neurology*, *62*, 5–7.

Schmidtke, K., & Buttner-Ennever, J. A. (1992). Nervous control of eyelid function. A review of clinical, experimental and pathological data. *Brain*, *115*(Pt 1), 227–247.

Semba, K. (1991). The cholinergic basal forebrain: A critical role in cortical arousal. In T. C. Napier, P. W. Kalivas, & I. Hanin (Eds.), *The basal forebrain: Anatomy to function* (pp. 197–218). New York: Plenum Press.

Semba, K. (2000). Multiple output pathways of the basal forebrain: Organization, chemical heterogeneity, and roles in vigilance. *Behavioural Brain Research*, *115*, 117–141.

Semba, K., Reiner, P. B., McGeer, E. G., & Fibiger, H. C. (1989). Brainstem projecting neurons in the rat basal forebrain: Neurochemical, topographical, and physiological distinctions from cortically projecting cholinergic neurons. *Brain Research Bulletin*, *22*, 501–509.

Shin, H. W., Ban, Y. J., Lee, H. W., Lim, H. J., Yoon, S. M., & Chang, S. H. (2004). Arousal with iv epinephrine depends on the depth of anesthesia. *Canadian Journal of Anaesthesia*, *51*, 880–885.

Shink, E., Sidibe, M., & Smith, Y. (1997). Efferent connections of the internal globus pallidus in the squirrel monkey: II. Topography and synaptic organization of pallidal efferents to the pedunculopontine nucleus. *The Journal of Comparative Neurology*, *382*, 348–363.

Steriade, M. (1996). Arousal: Revisiting the reticular activating system. *Science*, *272*, 225–226.

Steriade, M., & Buzsaki, G. (1990). Parallel activation of thalamic and cortical neurons by brainstem and basal forebrain cholinergic systems. In M. Steriade & D. Biesold (Eds.), *Brain cholinergic systems* (pp. 3–64). New York: Oxford University Press.

Steriade, M., Gloor, P., Llinas, R. R., Lopes de Silva, F. H., & Mesulam, M. M. (1990). Report of IFCN Committee on Basic Mechanisms. Basic mechanisms of cerebral rhythmic activities. *Electroencephalography and Clinical Neurophysiology*, *76*, 481–508.

Steriade, M., & McCarley, R. W. (2005). *Brain control of wakefulness and sleep*. New York: Plenum Publishers.

Steriade, M., Timofeev, I., & Grenier, F. (2001). Natural waking and sleep states: A view from inside neocortical neurons. *Journal of Neurophysiology*, *85*, 1969–1985.

Stienen, P. J., van Oostrom, H., & Hellebrekers, L. J. (2008). Unexpected awakening from anaesthesia after hyperstimulation of the medial thalamus in the rat. *British Journal of Anaesthesia*, *100*, 857–859.

Thornton, J. M., Aziz, T., Schlugman, D., & Paterson, D. J. (2002). Electrical stimulation of the midbrain increases heart rate and arterial blood pressure in awake humans. *Journal of Physiology*, *539*, 615–621.

Turnbull, I. M., McGeer, P. L., Beattie, L., Calne, D., & Pate, B. (1985). Stimulation of the basal nucleus of Meynert in senile dementia of Alzheimer's type. A preliminary report. *Applied Neurophysiology*, *48*, 216–221.

Umbach, W. (1961). Vegetative reactions in electrical excitation and exclusion in subcortical brain structures in man. *Acta Neurovegetativa (Wien)*, *23*, 225–245.

Umbach, W. (1977). Vegetative Phänomene bei stereotaktischen Hirneingriffen. In A. Sturm & W. Birkmayer (Eds.), *Klinische pathologie des vegetativen nervensystems* (Vol. 2, pp. 1078–1128). Stuttgart: Gustav Fischer Verlag.

Velasco, M., Velasco, F., Jimenez, F., Carrillo-Ruiz, J. D., Velasco, A. L., & Salin-Pascual, R. (2006). Electrocortical and behavioral responses elicited by acute electrical stimulation of inferior thalamic peduncle and nucleus reticularis thalami in a patient with major depression disorder. *Clinical Neurophysiology*, *117*, 320–327.

Velasco, M., Velasco, F., Velasco, A. L., Brito, F., Jimenez, F., Marquez, I., et al. (1997). Electrocortical and behavioral responses produced by acute electrical stimulation of the human centromedian thalamic nucleus. *Electroencephalography and Clinical Neurophysiology*, *102*, 461–471.

Vitek, J. L., Bakay, R. A., Hashimoto, T., Kaneoke, Y., Mewes, K., et al. (1998). Microelectrode-guided pallidotomy: Technical approach and its application in medically intractable Parkinson's disease. *Journal of Neurosurgery*, *88*, 1027–1043.

Wenk, G. L. (1997). The nucleus basalis magnocellularis cholinergic system: One hundred years of progress. *Neurobiology of Learning and Memory*, *67*, 85–95.

Yamamoto, T., Katayama, Y., Oshima, H., Fukaya, C., Kawamata, T., & Tsubokawa, T. (2002). Deep brain stimulation therapy for a persistent vegetative state. *Acta Neurochirurgica Supplementum*, *79*, 79–82.

Zaborszky, L., Hoemke, L., Mohlberg, H., Schleicher, A., Amunts, K., & Zilles, K. (2008). Stereotaxic probabilistic maps of the magnocellular cell groups in human basal forebrain. *Neuroimage.*

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 11

Consciousness and epilepsy: why are complex-partial seizures complex?

Dario J. Englot[1] and Hal Blumenfeld[1,2,*]

[1]*Department of Neurology, Yale University School of Medicine, New Haven, CT, USA*
[2]*Departments of Neurobiology and Neurosurgery, Yale University School of Medicine, New Haven, CT, USA*

Abstract: Why do complex-partial seizures in temporal lobe epilepsy (TLE) cause a loss of consciousness? Abnormal function of the medial temporal lobe is expected to cause memory loss, but it is unclear why profoundly impaired consciousness is so common in temporal lobe seizures. Recent exciting advances in behavioral, electrophysiological, and neuroimaging techniques spanning both human patients and animal models may allow new insights into this old question. While behavioral automatisms are often associated with diminished consciousness during temporal lobe seizures, impaired consciousness without ictal motor activity has also been described. Some have argued that electrographic lateralization of seizure activity to the left temporal lobe is most likely to cause impaired consciousness, but the evidence remains equivocal. Other data correlates ictal consciousness in TLE with bilateral temporal lobe involvement of seizure spiking. Nevertheless, it remains unclear why bilateral temporal seizures should impair responsiveness. Recent evidence has shown that impaired consciousness during temporal lobe seizures is correlated with large-amplitude slow EEG activity and neuroimaging signal decreases in the frontal and parietal association cortices. This abnormal decreased function in the neocortex contrasts with fast polyspike activity and elevated cerebral blood flow in limbic and other subcortical structures ictally. Our laboratory has thus proposed the ''network inhibition hypothesis,'' in which seizure activity propagates to subcortical regions necessary for cortical activation, allowing the cortex to descend into an inhibited state of unconsciousness during complex-partial temporal lobe seizures. Supporting this hypothesis, recent rat studies during partial limbic seizures have shown that behavioral arrest is associated with frontal cortical slow waves, decreased neuronal firing, and hypometabolism. Animal studies further demonstrate that cortical deactivation and behavioral changes depend on seizure spread to subcortical structures including the lateral septum. Understanding the contributions of network inhibition to impaired consciousness in TLE is an important goal, as recurrent limbic seizures often result in cortical dysfunction during and between epileptic events that adversely affects patients' quality of life.

Keywords: cortex; EEG; fMRI; septal nuclei; slow waves; attention; temporal lobe epilepsy; thalamus

Introduction

Consciousness has been an exceeding difficult concept to define for researchers, clinicians, and

*Corresponding author.
Tel.: 203 785-3928; Fax: 203 737-2538;
E-mail: hal.blumenfeld@yale.edu

DOI: 10.1016/S0079-6123(09)17711-7

philosophers alike. This is likely because consciousness is a complex phenomenon which encompasses various different processes. Plum and Posner (1980) have suggested that it is important to distinguish between the *level* of consciousness and the *content* of consciousness. The content of consciousness can be described as the substrate on which consciousness acts, and is composed of all other neural systems hierarchically organized into parallel sensory and motor systems that receive inputs, generate outputs, and perform internal processing on multiple levels (Blumenfeld, 2002). In turn, the level of consciousness also has multiple components, which can be summarized as the maintenance of three distinct but related processes: (i) the awake, alert state; (ii) attention; and (iii) awareness of self and environment (Blumenfeld, 2002, 2009). To study the neurobiological mechanisms of the awake, alert state necessary for consciousness, previous investigators have utilized various models such as sleep, coma, deep anesthesia, brain lesions, and epilepsy.

Generalized seizure disorders in humans, such as absence (petite mal) and tonic-clonic (grand mal) epilepsy, involve a pathological pattern of synchronous neuronal discharges in extensive networks throughout the brain, resulting in a loss of consciousness (Blumenfeld, 2005). Absence seizures are a form of generalized epilepsy in children characterized by rhythmic 3–4 Hz "spike-wave" discharges on electroencephalogram (EEG) produced by pathophysiological corticothalamic interactions (Avoli and Gloor, 1982; Blumenfeld and McCormick, 2000). These events are associated with brief 5–10 s episodes of unresponsiveness that have significant effects on a child's attentional abilities both during and between events (Levav et al., 2002; Mirsky and Van Buren, 1965). Conversely, generalized tonic-clonic seizures are characterized by fast excitatory discharges synchronously affecting neuronal networks in numerous brain regions, producing several minutes of unconsciousness and abnormal convulsive activity of widespread muscle groups (Blumenfeld et al., 2009; Morrell, 1993; Zifkin and Dravet, 2007).

It is perhaps not surprising that generalized seizures, involving extensive dysfunction of cortical and subcortical brain regions, cause significant impairments of consciousness. In temporal lobe epilepsy (TLE), however, seizures often originate from focal structures within the mesial temporal lobe, and frequently do not secondarily generalize or propagate to distal cortical areas. Yet, despite confinement of epileptic discharges to the temporal lobe and related limbic structures, seizures in TLE often cause a loss of consciousness. Understanding the mechanisms of impaired consciousness and cortical dysfunction during temporal lobe seizures has important clinical implications, as impaired consciousness causes motor vehicle accidents, drownings, poor work and school performance, and social stigmatization resulting in a major negative impact on patient quality of life (Drazkowski, 2007; Jacoby et al., 2005; Kobau et al., 2008; Sperling, 2004). In addition, previous investigations of TLE patients have found neocortical deficits including gray matter atrophy (Bonilha et al., 2006) and hypometabolism between seizures (Diehl et al., 2003; Nelissen et al., 2006), which may be related to neuropsychological sequelae and chronic cognitive impairments frequently suffered by these individuals (Helmstaedter and Kockelmann, 2006; Hermann et al., 1997; Laurent and Arzimanoglou, 2006). An appreciation of the long-range network effects of temporal lobe seizures on the neocortex may lead to a better grasp of epileptic mechanisms and a further understanding of the brain region interactions that underlie the conscious state. In this review, we will summarize previous investigations of TLE in humans and animal models, discuss what they suggest about the mechanisms of impaired consciousness during temporal lobe seizures, and advocate directions to further our understanding of this important problem.

The network inhibition hypothesis in TLE

Epilepsy is a debilitating neurological disorder that affects approximately 1% of the population in developed countries such as the United States (Devinsky, 2004). TLE is one of the most common epileptic disorders, characterized by seizures that frequently originate in limbic structures of the

medial temporal lobe, such as the hippocampus and the amygdala (Engel, 1987; Williamson et al., 1993). As the temporal lobe is the most common site of origin of focal epileptic discharges, it has been suspected to be the most epileptogenic brain region (Engel et al., 2007). The etiology of TLE is frequently idiopathic, but it can also result from malignancy, trauma, infections, and vascular malformations (Engel and Williamson, 2007; Engel et al., 2007). Recurrent temporal lobe seizures often produce significant pathological changes, such as hippocampal sclerosis in two-thirds of patients, and can propagate from limbic structures to the temporal neocortex and other regions (Babb, 1987; de Lanerolle and Lee, 2005; Gloor, 1991; Williamson et al., 1993).

While discharges in TLE can propagate distally to produce a secondarily generalized tonic-clonic seizure, most temporal lobe seizures in patients taking anticonvulsant medications do not secondarily generalize. Thus, seizures in TLE are typically characterized as one of two major subtypes of partial seizures: complex-partial seizures, which result in a diminished level of consciousness during (ictal) and after (postictal) the event, and simple-partial seizures, which do not interfere with consciousness (ILAE, 1981). This clinical distinction is based primarily on symptomatology, and the neurobiological underpinnings of the divergent effects on consciousness seen in complex versus simple-partial seizures are not well understood. Various ideas have been proposed to explain how complex-partial seizures impair consciousness (Yu and Blumenfeld, 2008). Some evidence suggests that the laterality or bilaterality of temporal lobe involvement may be a primary determining factor of ictal alertness (Gloor et al., 1980; Hoffmann et al., 2008; Lux et al., 2002). Nevertheless, it has also been argued that one should not mistake postictal amnesia of the seizure — a probable result of bilateral temporal lobe dysfunction — with unconsciousness that also entails diminished responsiveness (Gloor, 1986). Therefore, another hypothesis is that while seizure lateralization may indeed be correlated with altered alertness in TLE, loss of consciousness more directly results from aberration of subcortical and brainstem structures that are necessary for maintaining the awake-alert state. As a sleep-like slow rhythm is frequently observed in frontal and parietal cortical regions during complex-partial seizures, our laboratory has hypothesized that ''ictal neocortical slow activity'' reflects remote effects of limbic seizures on other parts of the brain, resulting in a depressed cortical state responsible for the deficits in consciousness seen in TLE patients (Blumenfeld et al., 2004a, b). Figure 1 illustrates our ''network inhibition hypothesis,'' in which we postulate that consciousness is lost during complex-partial temporal lobe seizures because of seizure spread to midline subcortical and brainstem structures, leading in turn to bilateral cortical deactivation (Blumenfeld, 2009; Blumenfeld and Taylor, 2003; Norden and Blumenfeld, 2002). Evidence addressing this and other mechanistic theories of impaired consciousness in complex-partial TLE has been uncovered in previous behavioral, electrographic, and neuroimaging studies of temporal lobe seizures in both human patients and animal models of epilepsy.

Behavioral semiology of temporal lobe seizures

While simple-partial temporal lobe seizures are frequently characterized by autonomic and/or psychic symptoms and epigastric sensations, complex-partial seizures of the temporal lobe often begin with an inhibition of purposeful motor activity and elicitation of automatic behavioral manifestations that are associated with unresponsiveness (ILAE, 1989). These automaton-like behaviors, termed ''automatisms,'' are typically manifested as repetitive orofacial movements such as lip-smacking, chewing, and swallowing that are not related to external stimuli in the individual's environment (Penfield, 1950). They can also manifest as ''ambulatory automatisms'' of the limbs or dystonic posturing ictally (Leung et al., 2000; Marks and Laxer, 1998).

Escueta et al. (1977) completed one of the earliest combined video-EEG analyses of complex-partial seizures and their behavioral correlates in TLE patients. The authors identified three clinical phases during most of the 76 seizures recorded,

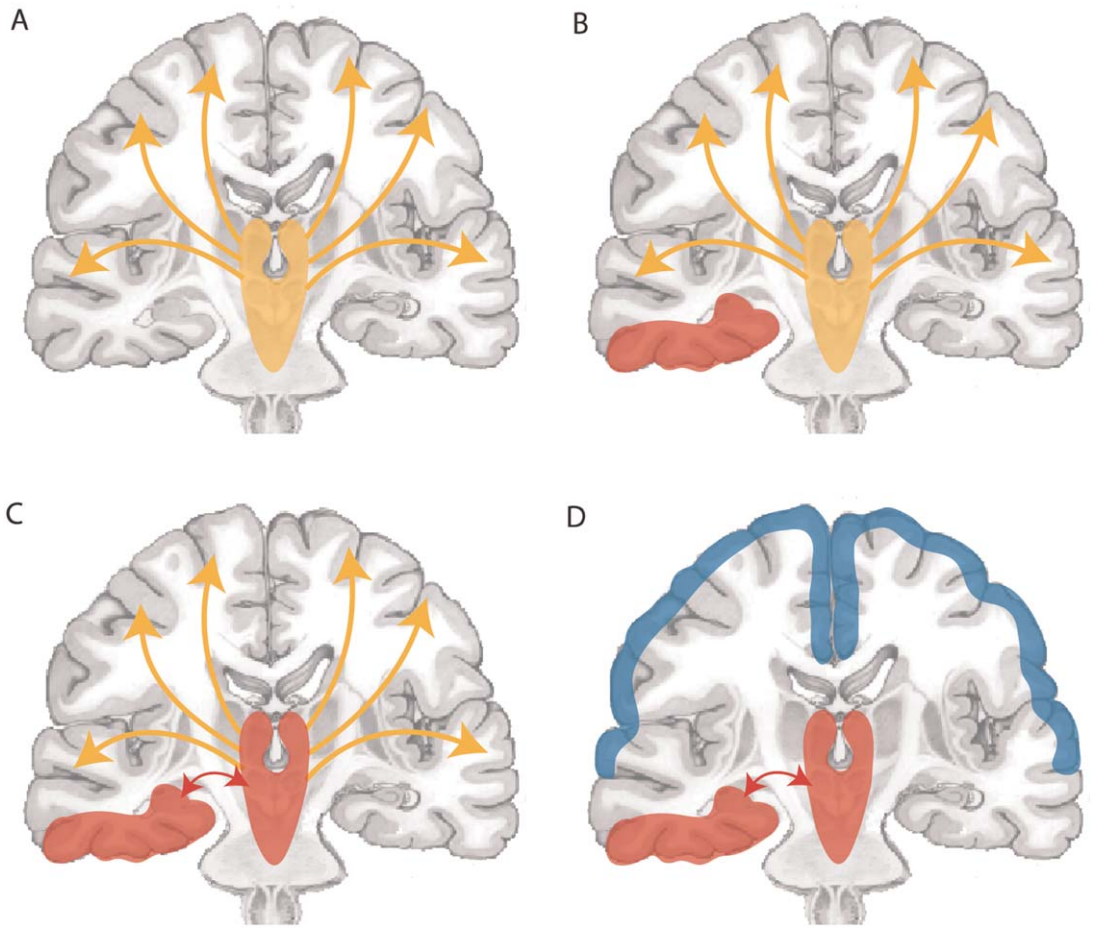


Fig. 1. Network inhibition hypothesis for loss of consciousness in complex-partial seizures. (A) Under normal conditions, the upper brainstem-diencephalic activating systems interact with the cerebral cortex to maintain normal consciousness. (B) A focal seizure involving the mesial temporal lobe unilaterally. (C) Propagation of seizure activity from the mesial temporal lobe to midline subcortical structures. (D) Disruption of the normal activating functions of the midline subcortical structures, together with the resulting depressed activity in bilateral regions of the frontoparietal association cortex, leads to loss of consciousness. Adapted with permission from Blumenfeld and Taylor (2003). Please see online version of this article for full color figure.

beginning with a motionless stare early in the event, followed by stereotypical movements, and with loss of consciousness later in the seizure (Escueta et al., 1977). Another study of 72 hippocampal or amygdalar seizures found that motionless staring or oroalimentary automatisms were the first behavioral manifestations during the majority of events (60%), with fewer seizures beginning with nonfocal discrete movements, perseverative stereotyped automatisms, or vocalizations (Maldonado et al., 1988). In general, whereas automatisms and other behavioral manifestations usually emerge early in a complex-partial seizure, while responsiveness may remain intact, consciousness in TLE is most profoundly affected late in the seizure and during the postictal period (Blumenfeld and Taylor, 2003). Rarely, automatisms have been described during simple-partial temporal lobe seizures with spared consciousness (Alarcon et al., 1998). For instance, one large investigation of 123 TLE patients reported that 7 individuals experienced prominent automatisms such as lip-smacking and swallowing without a loss of consciousness (Ebner et al., 1995).

Many patients report experiencing an ''aura'' at the beginning of a partial temporal lobe seizure, described as a warning symptom or vague signal of an impending event, likely representing early epileptiform activity below the threshold of scalp electrographic detection (Fried et al., 1995). One study of 96 seizures in 19 patients with stereotactic depth electrode implantation found that 67% of unilateral temporal lobe seizures began with an aura, while motionless stares, automatisms, and head-body turning were each manifested in approximately one-quarter of seizures (Quesney, 1986). In addition to auras preceding the epileptic event, psychic phenomena have been described in some patients during limbic seizures. In 1898, John Hughlings Jackson noted that medial temporal lobe seizures can result in a ''dreamy state,'' characterized by dramatic memory-like hallucinations such as déjà vu — the perception that one has previously experienced identical circumstances to the present situation (Jackson and Colman, 1898). After noting that certain patients with implanted intracranial electrodes experience these psychic phenomena during simple-partial seizures, Bancaud et al. (1994) reproduced these sensations of a dreamy state by electrically stimulating the anterior hippocampus, amygdala, or temporal neocortex. More severe psychotic symptoms or affective disturbances, such as hallucinations or intense emotional experiences, have also been described ictally in some individuals during temporal lobe seizures (Ardila, 1990; Boylan, 2002).

Following complex-partial temporal lobe seizures, patients often experience a postictal state of impaired consciousness, confusion, and amnesia of the event (Gloor, 1986). Blum et al. (1996) studied 23 epileptic patients to assess the individuals' insight into seizure occurrence and frequency. Looking at both complex-partial and secondarily generalized events, the authors observed that only one-quarter of patients always endorsed having had a seizure immediately after they regained consciousness, and 30% of individuals never acknowledged experiencing a documented seizure. Although not all seizures in this report originated from temporal lobe foci, those that did were most likely to be associated with postictal amnesia (Blum et al., 1996). Another investigation found a positive correlation between amnesia for previously documented auras and seizure severity, further suggesting that increased levels of temporal dysfunction may be more likely to produce postictal amnesia (Schulz et al., 1995).

Behavioral manifestations during limbic epileptic events in TLE patients raise interesting questions about whether loss of consciousness in temporal lobe seizures results from: (i) a progressive spread of excitatory epileptic discharges to other brain regions, such as the neocortex, or (ii) long-range depressive effects, dissimilar from seizure propagation, that suppress distant cortical and subcortical brain structures critical for vigilance. Electrophysiological and neuroimaging explorations of diminished ictal responsiveness in TLE have focused on correlating deficits in responsiveness with temporal lobe lateralization of seizure activity, and more recently have characterized the effects of limbic seizures on bilateral cortical and subcortical networks necessary for maintaining consciousness.

EEG correlates of impaired consciousness in human TLE

Limbic seizures originate from mesial temporal structures on either the left or right side of the brain. Lateralization of behavioral signs such as automatisms can provide insight into the side of seizure onset, albeit with some inconsistency (Saint-Hilaire and Lee, 2000). It has also been proposed that lateralization or bilaterality of temporal lobe seizures may be the predominant feature predicting either loss or preservation of consciousness ictally. Some have hypothesized that the left hemisphere, which is dominant for language in most humans, is primarily responsible for the conscious state (Albert et al., 1976; Ebner et al., 1995; Schwartz, 1967). One study utilizing the Wada test found that while temporary inactivation of the right hemisphere does not interfere with consciousness, impaired left hemispheric activity causes unresponsiveness to both verbal and somatic stimuli (Franczek et al., 1997). Correlating seizure lateralization with awareness

of the events, Inoue and Mihara (1998) found that TLE patients who were unaware of their seizures typically had onset of epileptic activity in the mesial temporal lobe of language-dominant (typically left) side. A more recent investigation similarly described that ictal behavioral arrest was more common during left-sided temporal seizures than those beginning on the right side (Hoffmann et al., 2008). Furthermore, Lux et al. (2002) looked at vocalizations during complex-partial seizures and reported that while patients with left temporal seizure activity had ictal memory loss and impairment of both expressive and receptive speech, those with seizure activity limited to the right temporal lobe rarely exhibited these impairments during the event. Another study examined ictal and postictal speech deficits in TLE and found that unintelligible vocalizations were more commonly associated with seizures originating in the language-dominant temporal lobe, while coherent speech was generally noted during discharges originating from the nondominant side (Gabr et al., 1989). Since involvement of the dominant temporal lobe more often causes language impairment, it is possible that apparent impaired consciousness could be an artifact of the testing procedures, which usually depend on responses to verbal questions and commands. This could lead to a bias in studies attempting to lateralize impaired consciousness in temporal lobe seizures, since nonverbal aspects of consciousness are more difficult to evaluate.

Another hypothesis is that unilateral temporal lobe seizure activity alone might not be sufficient to cause a loss of consciousness, and that bilateral limbic discharges are required to elicit unresponsiveness. Herbert Jasper (1964) was one of the first to propose that ictal automatisms and amnesia in TLE depend on seizure activity involving both temporal lobes. Gloor et al. (1980) described that 74% of temporal lobe seizures that resulted in a loss of consciousness showed bitemporal ictal involvement on EEG. Subsequently, several investigators have offered further evidence that seizures involving bilateral temporal lobe cortices are more likely to cause impairments in vigilance and responsiveness than those with unilateral localization (Bancaud et al., 1994; Inoue and Mihara, 1998; Pedley, 1992). These studies imply that bilaterality of temporal lobe involvement in TLE may be an important predictive factor of ictal impairment of consciousness. Nonetheless, while it may appear intuitive that bilateral temporal lobe dysfunction can result in amnesia due to aberrant limbic activity (Milner, 1972), temporal lobe structures are not often considered necessary for consciousness. This can be illustrated by the classic case of patient H.M. who was unable to form new memories after bilateral mesial temporal lobectomy, yet remained alert, responsive, and interactive — thus, ''conscious'' — postoperatively (Scoville and Milner, 1957). Might bilaterality of temporal lobe involvement represent a noncausal variable, correlated with impaired alertness during limbic seizures, but not the direct source of loss of consciousness? For instance, in one study by Munari et al. (1980), while complex-partial seizures did more commonly engage the temporal lobes bilaterally compared to simple-partial seizures, it was found that seizures with impaired consciousness were also approximately twice the duration of simple-partial events and were more likely to recruit structures outside of the temporal lobe. This implies that seizure severity and extratemporal involvement may also serve as predictors of ictal loss of consciousness in addition to temporal lobe laterality.

While the majority of electrographic studies of TLE have focused on temporal lobe localization of seizure activity, examining the effects of limbic discharges on other brain regions that are important for consciousness is an essential endeavor to further understand these problems. In patients with intracranial electrodes implanted in the thalamus, Bertashius (1991) found that thalamic nuclei were often affected by epileptic activity during temporal lobe seizures. More recently, Bartolomei and colleagues have observed that in patients with mesial TLE seizures, thalamocortical synchrony was specifically correlated with loss of consciousness ictally (Guye et al., 2006). Moreover, although epileptic discharges during temporal lobe seizures are typically characterized by fast, polyspike electrographic signals in both the seizure focus and loci

of propagation, slow EEG rhythms have also been uncovered in neocortical regions ictally in TLE. Specifically, several previous intracranial EEG studies have revealed large-amplitude slow oscillatory activity in frontal and parietal neocortical regions during complex-partial temporal lobe seizures (Eisenschenk et al., 2001; Franaszczuk et al., 1994; Lieb et al., 1991; Mayanagi et al., 1996). Despite the dissimilarity of these slow waves to fast seizure spiking, they have traditionally been interpreted as the spread of seizure activity to distal brain structures. In a recent intracranial EEG study of complex-partial temporal lobe seizures, our laboratory also found large-amplitude 1–2 Hz slow waves in the frontoparietal neocortices ictally, most prominent in the orbitofrontal cortex (Fig. 2) (Blumenfeld et al., 2004b). This slow activity in the association cortices during seizures was starkly contrasted with polyspike activity in the seizing temporal lobe, as it did not contain fast or sharp components characteristic of epileptic discharges (Fig. 2A–C). Furthermore, the neocortical slow activity persisted into the postictal period of impaired consciousness, and closely resembled the large-amplitude cortical oscillations typically seen during slow-wave sleep (Fig. 2D). These findings suggest that ictal neocortical slow activity, perhaps resulting from seizure spread to subcortical structures like the thalamus that are involved in cortical activation, may contribute to loss of consciousness during complex-partial seizures. Nevertheless, limited spatial sampling during human intracranial EEG studies of epilepsy restricts our understanding of distal brain effects during temporal lobe seizures. Further insight into the hypotheses addressing impaired consciousness in TLE has been achieved using neuroimaging techniques, which have served as critical tools to correlate ictal consciousness with involvement of anatomical regions throughout the brain.

Neuroimaging insights into impaired consciousness in human TLE

Why do complex-partial temporal lobe seizures cause unconsciousness even though EEG recordings typically show seizure activity confined to temporal cortex? As discussed previously, partial seizures in TLE often cause other functional deficits beyond those expected from local limbic impairment, such as repetitive automaton-like movements (Loddenkemper and Kotagal, 2005), dystonic posturing of the limbs (Marks and Laxer, 1998), and neuroendocrine changes (Bauer, 2001; Quigg et al., 2002). It has therefore been proposed that even when temporal lobe seizures do not propagate, they may cause remote dysfunction in other brain regions, leading to these disturbances and altered consciousness (Blumenfeld et al., 2004a, b; Van Paesschen et al., 2003). Several neuroimaging studies have investigated brain regions affected by limbic seizure activity. Of the functional imaging techniques available to study TLE, single photon emission computed tomography (SPECT) has advantages over positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), as the SPECT radiotracer can be injected during the seizure, with subsequent imaging performed after the event. This alleviates challenges related to movement artifact during seizures with other imaging methods (Englot and Blumenfeld, 2009; Kim et al., 2009).

Using SPECT, investigators have found increased cerebral blood flow (CBF) associated with epileptic activity in the temporal lobe on the side of seizure onset (Andersen et al., 1990; Bonte et al., 1983; Duncan et al., 1990). Other SPECT studies have shown bilateral involvement of the thalamus and upper brainstem during temporal lobe seizures (Hogan et al., 2006; Tae et al., 2005), with some providing evidence that impaired consciousness during these events is correlated with increased perfusion in these regions (Blumenfeld et al., 2004a; Lee et al., 2002; Mayanagi et al., 1996). Imaging results of thalamic involvement in TLE complement evidence of elevated activity in the thalamus ictally detected using intracranial EEG (Arthuis et al., 2009; Guye et al., 2006; Rosenberg et al., 2006), and of interictal thalamic atrophy or dysfunction often associated with mesial TLE (Chang et al., 2008; Gong et al., 2008; Hetherington et al., 2007; Labate et al., 2008; Natsume et al., 2003; Riederer et al., 2008).

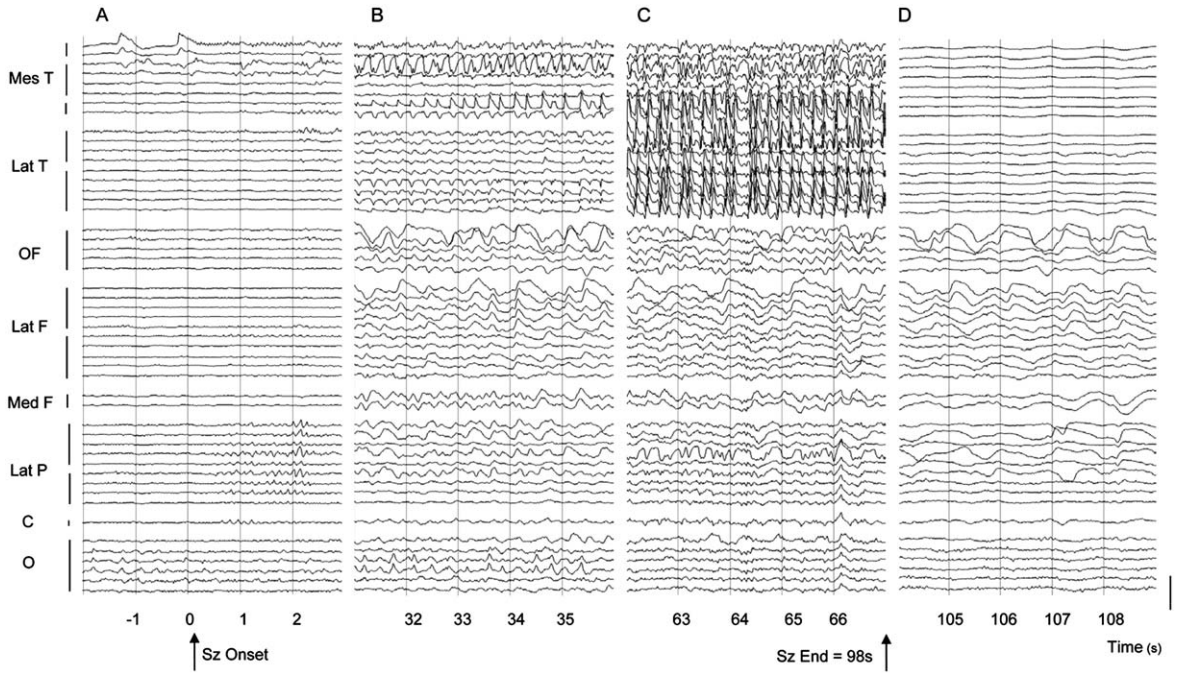


Fig. 2. Example of intracranial EEG recording during a mesial temporal seizure. (A) Seizure onset with low-voltage fast activity emerging from periodic spiking in the mesial temporal contacts. Later in this interval (0–30 s after seizure onset) spike-and-slow activity later appeared in the mesial as well as the lateral temporal contacts (not shown). (B) Sample from 30 to 60 s after seizure onset. Rhythmic spike and sharp wave activity continues in the temporal lobe, while the frontal and parietal contacts show large amplitude irregular slow-wave activity. (C) Sample from 60 to 90 s after seizure onset. Spike and polyspike-and-wave activity is present in the temporal lobe, with ongoing slow waves in the neocortex. (D) Postictal suppression is seen in temporal lobe contacts, with continued irregular slowing in the frontoparietal neocortex. Ipsilateral contacts only are shown. Bars along left margin indicate electrode contacts from different strips, rows, or depth electrodes in the indicated brain regions. Calibration bar on right is 1000 μV. Montage is referential to mastoid. Mes T, mesial temporal; Lat T, lateral temporal; OF, orbital frontal; Lat F, lateral frontal; Med F, medial frontal; Lat P, lateral parietal; C, perirolandic (pre- and post-central gyri); O, occipital. Adapted with permission from Blumenfeld et al. (2004b).

Given these findings, it is possible that medial diencephalic and brainstem connections known to be important for arousal may contribute to behavioral arrest during complex-partial seizures of the temporal lobe.

In addition to revealing areas of increased perfusion ictally in TLE, some neuroimaging studies have also shown *reduced* CBF in frontal and parietal cortices during complex-partial seizures, simultaneous to increases in the seizing temporal lobe (Chang et al., 2002; Menzel et al., 1998; Rabinowicz et al., 1997). For instance, Van Paesschen et al. (2003) performed ictal SPECT during complex-partial seizure in 24 patients with intractable mesial TLE. The authors observed temporal lobe hyperperfusion ipsilateral to seizures onset that was inversely associated with hypoperfusion in the frontal lobes during scans in all patients. In another recent SPECT investigation, our laboratory reported that neocortical decreases in CBF during complex-partial temporal lobe seizures were associated with deficits in consciousness, as no reductions were seen on average during simple-partial temporal lobe seizures (Fig. 3) (Blumenfeld et al., 2004a). Specifically, statistical parametric maps of complex-partial seizures indicated CBF elevations in the temporal lobe on the side of seizure onset, as well as midline subcortical-diencephalic structures, while CBF was diminished in widespread frontal and parietal association cortices ictally (Fig. 3A). However, widespread bilateral CBF decreases in

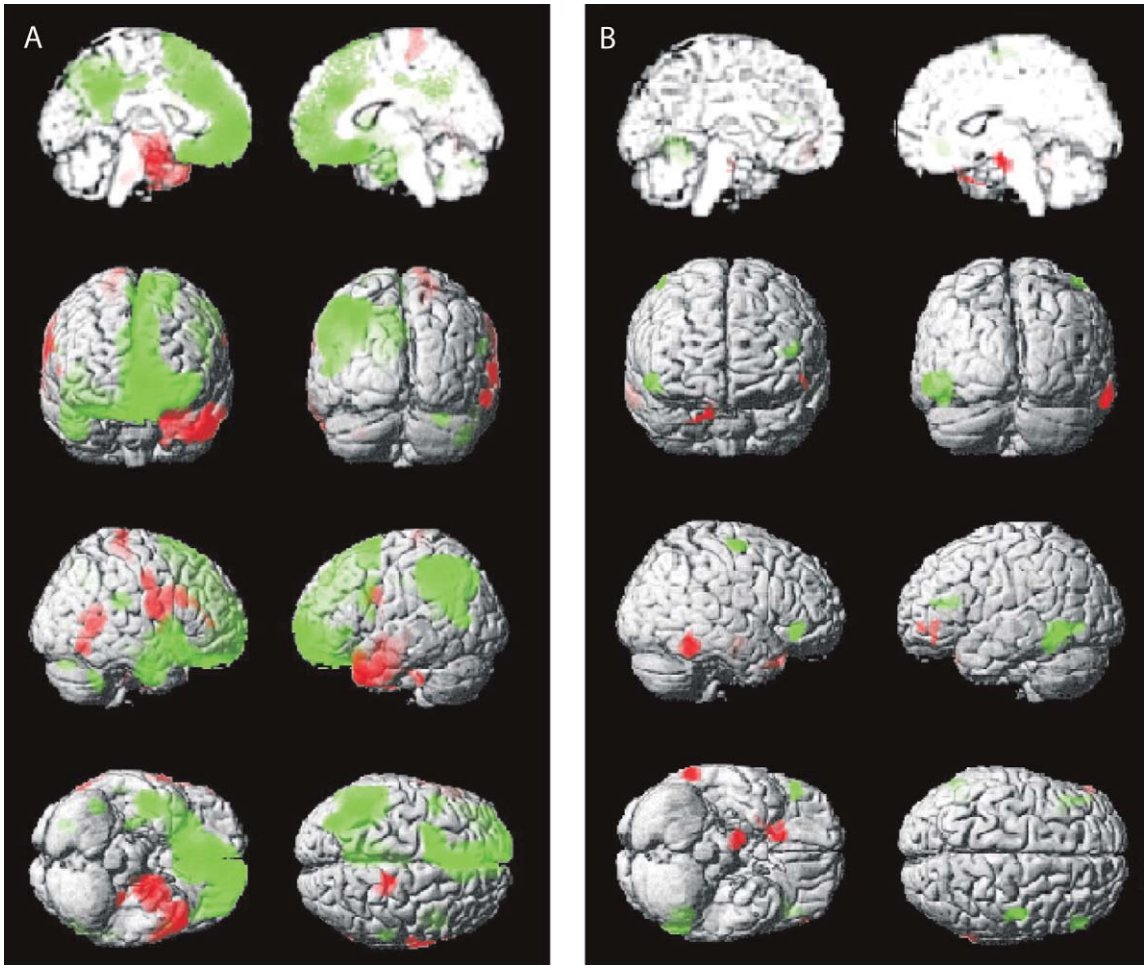


Fig. 3. Complex-partial, but not simple-partial, temporal lobe seizures are associated with significant CBF decreases in frontoparietal neocortical regions. Statistical parametric maps depict CBF increases in red and decreases in green. Changes ipsilateral to seizure onset are shown on the left side of the brain, and contralateral changes on the right side of the brain (combining patients with left and right onset seizures). (A) Complex-partial seizures arising from the temporal lobe are associated with significant CBF increases and decreases in widespread brain regions. Sixty to ninety seconds after seizure onset, increases occur mainly in the ipsilateral temporal lobe, while decreases occur in the ipsilateral > contralateral frontal and parietal association cortex ($n = 8$). (B) Simple-partial seizures arising from the temporal lobe are not associated with widespread CBF changes ($n = 6$). For (A) and (B), extent threshold, $k = 425$ voxels (voxel size $= 2 \times 2 \times 2$ mm). Height threshold, $P = 0.01$. Equivalently, only voxel clusters greater than 1 cm^3 in volume and with Z scores greater than 2.33 are displayed. Adapted with permission from Blumenfeld et al. (2004a). Please see online version of this article for full color figure.

the higher-order association cortices were not present during simple-partial seizures (Fig. 3B). SPECT signal decreases during complex-partial seizures were seen in the same frontoparietal cortical regions as ictal neocortical slow activity (Fig. 2). In addition, like neocortical slow oscillations, cortical hypoperfusion was observed during both the ictal and postictal periods of temporal lobe seizures, when consciousness remains impaired (Blumenfeld et al., 2004a, b).

The above neuroimaging and electrophysiological findings raise the question: is ictal unconsciousness in TLE more directly related to deactivation of the frontoparietal neocortex following ictal recruitment of subcortical regions, rather than being caused by the spread of

excitatory seizure activity to bilateral temporal or association cortices? In some respects, this possibility echoes ideas of 19th-century neurologist John Hughlings Jackson, who after observing several epileptic seizures, proposed that consciousness is impaired when higher cortical function becomes disorganized and lacks integrative ability (Jackson et al., 1931). Jackson considered the ''highest nervous centers'' to be the substrata of consciousness, representing complex cortical regions responsible for the coordination of various inputs and outputs throughout the body, and he hypothesized that impaired consciousness resulted when discharges engaged these regions. Jackson proposed that if a seizure begins in a subordinate structure or series of structures, consciousness will be lost if this discharge spread to alter higher-order processes, or if a sufficiently large number of subordinate structures become recruited (Jackson et al., 1931; Yamauchi, 1998).

Neuroimaging and EEG characterizations of cortical activity during complex-partial temporal seizures raise many interesting questions regarding loss of consciousness during these events. For instance, involvement of which subcortical structures is important in the production of ictal neocortical slow rhythms? Does the phenomenon result from an active inhibitory process directly affecting the cortex, or from disruption of normal neocortical activation, allowing the cortex to temporarily resort to a depressed state resembling coma, deep anesthesia, or sleep (Cowan and Wilson, 1994; Haider et al., 2006; Steriade et al., 1993)? Or, in contrast, do ictal neocortical slow rhythms simply represent the propagation of excitatory seizure activity to distal cortical regions? To further address these issues, it is useful to discuss invasive recordings of neuronal activity recorded in animal models of TLE.

Network effects of temporal lobe seizures in animal models

While human studies of neurological disease possess the greatest validity, animal models of TLE activity allow controlled mechanistic studies which can be valuable in understanding both network effects and behavioral manifestations associated with complex-partial seizures. Behavioral correlates of electrographic temporal lobe seizures have been extensively studied in rodent models of TLE. For instance, the classic scale created by Ronald Racine (1972) allows investigators to rate behavioral limbic seizures from those including only mild manifestations such as staring and behavioral arrest (class 0) or facial automatisms (class 1) to those with more prominent convulsions characterized by head nodding (class 2) or progressively worsening clonic activity (classes 3–5). Thus, animal behavior during Racine class 0 or 1 seizures resembles the semiology associated with human complex-partial temporal lobe seizures.

Similar to human investigations, several rat studies of TLE have shown involvement of the thalamus during partial limbic seizures (Bertram et al., 2001, 2008; Blumenfeld et al., 2007; Englot et al., 2008). Significant neuronal loss has been described in the medial, dorsal, and rhomboid thalamic nuclei associated with limbic seizures, with lidocaine-mediated inhibition of the midline thalamus reducing the duration of epileptic discharges (Bertram et al., 2001). Also, as discussed below, our laboratory has described bilateral involvement of the thalamus on fMRI during electrically stimulated limbic seizures (Englot et al., 2008).

How might aberrant activity in the thalamus and other subcortical structures that are important for alertness lead to a loss of consciousness? One possibility is that these regions may help propagate excitatory activity directly to the neocortex. Alternatively, our network inhibition hypothesis proposes that seizure activity in one part of the brain, particularly the mesial temporal lobe, may cause inhibition of normal subcortical activating systems, and thereby indirectly deactivate frontoparietal cortical regions necessary for consciousness. Given the inherent network properties of the central nervous system, intense activation of one region might result in functional changes in adjacent or remote areas, even without spread of excitation to these other areas. Common examples in which increased activity in one cortical region can cause an inhibitory surround include

normal visual or somatosensory processing (Angelucci et al., 2002; Brumberg et al., 1996; Derdikman et al., 2003; McCasland et al., 1991; Sengpiel et al., 1997). Some animal studies have provided evidence that a similar process may occur in epilepsy focally, such as in abnormal surround inhibition adjacent to cortical seizure foci (Collins, 1978; Prince and Wilder, 1967; Schwartz and Bonhoeffer, 2001). However, in TLE the affected frontoparietal neocortex does not lie immediately adjacent to the mesial temporal lobe, suggesting that more complex long-range network mechanisms may play a role.

Our laboratory recently performed a multimodal study of ictal neocortical slow oscillations during partial limbic seizures in both lightly anesthetized and awake-behaving rats (Englot et al., 2008). We observed that spontaneous partial limbic seizures in awake-behaving animals were associated with fast 9–12 Hz fast polyspike seizure activity in hippocampal EEG, as expected. However, in the frontal cortex, we observed large amplitude 1–3 Hz slow waves (Fig. 4A) that more closely resembled slow-wave sleep oscillations (Fig. 4A, bottom right) than seizure spiking. These partial seizures were associated with mild behavioral manifestations such as behavioral arrest and facial automatism (Racine class 0–1), differing dramatically from convulsive activity seen during secondarily generalized seizures in the same animals — the latter of which were associated with fast polyspike activity in the frontal cortex (Englot et al., 2008).

Electrically stimulated partial hippocampal seizures in lightly anesthetized animals also revealed similar patterns of local field potential (LFP) fast activity and large population spikes in multiunit activity (MUA) seen in the hippocampus ictally (Fig. 4B). This activity differed from decreased firing with Up and Down states of neuronal firing in the frontal cortex ictally, which resembled Up and Down states seen during deep anesthesia (Fig. 4B, bottom right). These Up and Down states appeared similar to neocortical firing patterns commonly seen in other studies of cortical depression, such as during deep sleep and anesthesia (Cowan and Wilson, 1994; Haider et al., 2006; Steriade et al., 1993).

CBF measurements using laser Doppler flowmetry (LDF) showed that while cortical seizure propagation (i.e., secondary generalization) was associated with elevated CBF, cortical perfusion decreased during partial seizures with ictal slow activity (Englot et al., 2008). Finally, fMRI recordings of electrically stimulated partial seizures revealed decreased blood oxygen level dependent (BOLD) signal in the orbital frontal cortex ictally, contrasted by elevations in the hippocampus, as well as the septal nuclei and thalamus (Fig. 5). These studies complement electrophysiology and neuroimaging investigations of human TLE to further suggest that ictal neocortical slow activity is associated with diminished neocortical activity, not excitatory seizure propagation to the cortex.

The mechanistic differences between cortical polyspike propagation during secondarily generalized seizures versus ictal neocortical slow activity during complex-partial seizures are not fully understood. The pathways responsible for secondary generalization of temporal lobe seizures have been previously studied (Bertashius, 1991; Gloor et al., 1993; Spencer et al., 1987; Wilson et al., 1990). Some have suggested that the orbitofrontal cortex plays an important role in cortical seizure propagation (Lieb et al., 1991; Wilson and Engel, 1993), possessing a high degree of functional connectivity with the hippocampus in TLE (Catenoix et al., 2005; Wilson and Engel, 1993). It is thus possible that exploitation of normal circuits connecting the hippocampus and neocortex, which are important for memory storage (Lavenex and Amaral, 2000; Thierry et al., 2000), can contribute to abnormal cortical activity in limbic epilepsy. Perhaps the orbitofrontal cortex acts as gateway for neocortical propagation of epileptic discharges, maintaining a diminished state of function during smaller complex-partial seizures that is overwhelmed by exceedingly intense excitation during secondarily generalized limbic seizures.

Neuroimaging studies of limbic seizures in rats provide preliminary insight into brain regions which may play a role in ictal neocortical slow activity. In addition to hippocampal excitation, we observed fMRI BOLD increases in the medial thalamus

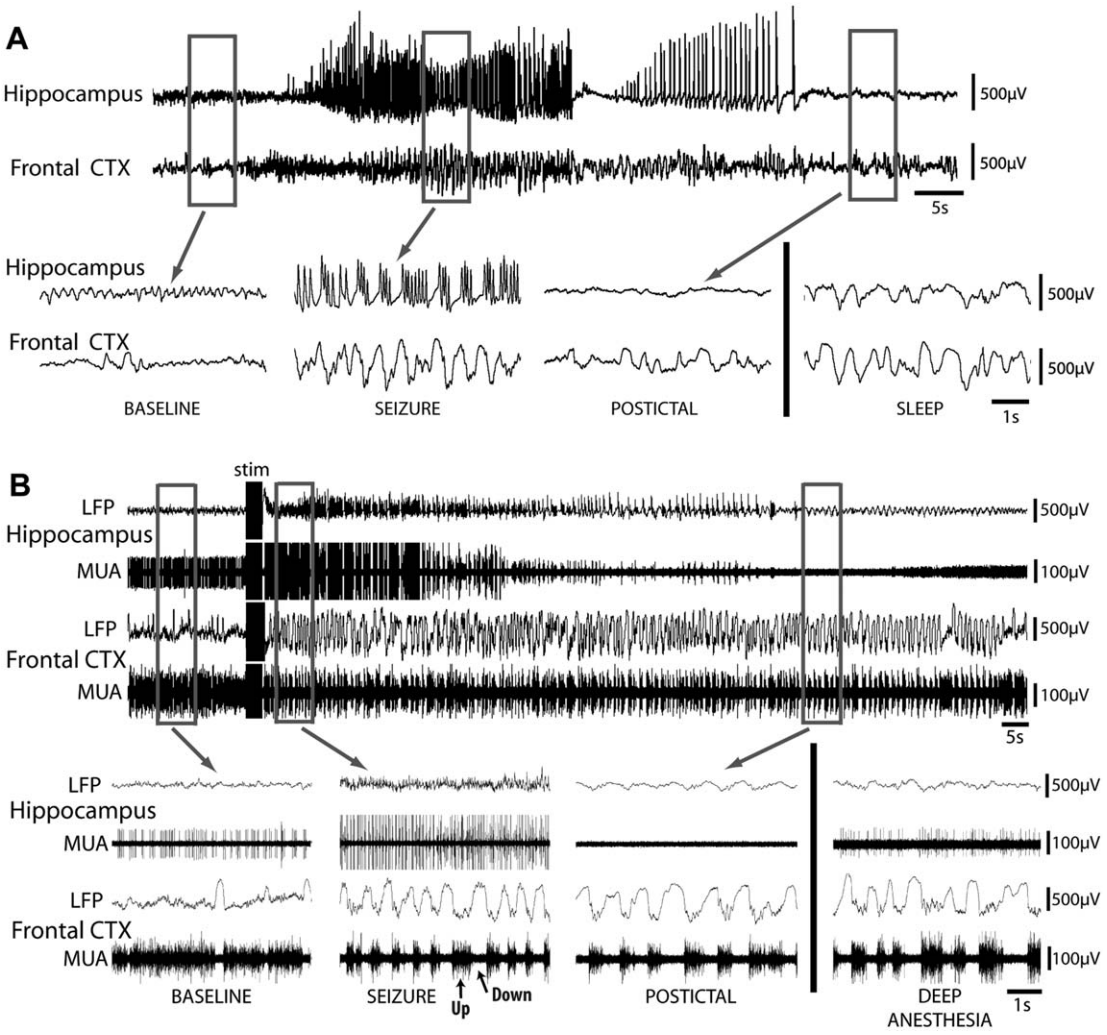


Fig. 4. Partial limbic seizures in rats produce ictal neocortical slow waves in the orbitofrontal cortex (CTX). (A) Local field potentials (LFP) in the hippocampus and orbitofrontal cortex during a spontaneous partial seizure associated with behavioral arrest in an awake-behaving rat. Hippocampal recordings reveal large-amplitude, fast polyspike activity during the seizure, while frontal cortical recordings show large-amplitude 1–3 Hz slow waves during and after the seizure without considerable propagation of fast spike activity. Ictal neocortical slow activity resembles large-amplitude slow rhythms seen in the frontal cortex during an episode of natural sleep, recorded in the same animal at a different time (bottom, right). LFP recordings are filtered 0.3–100 Hz. (B) Example of LFP and multiunit activity (MUA) recordings during an electrically stimulated partial seizure in a lightly anesthetized rat. During baseline, recordings show a stable theta rhythm in hippocampal LFP and low-voltage beta activity with occasional slow waves in the orbitofrontal cortex (see also inset). MUA recordings reveal relatively stable neuronal firing in both areas. During the seizure, hippocampal LFP recordings show 9–10 Hz fast polyspike activity ictally associated with population spikes in MUA recordings. Population spikes are often up to 10 times larger in amplitude than individual baseline units and are thus shown truncated here. In the orbitofrontal cortex, 1–2 Hz large-amplitude slow waves are seen in LFP recordings, associated with Up and Down states (arrows) of neuronal firing in MUA recordings. No fast polyspike activity is present in the frontal cortex LFPs. After the seizure, hippocampal activity is depressed whereas frontal slow oscillations persist postictally. Recordings from the same rat under deep anesthesia at a different time are also shown (bottom right), during which slow activity is present in the frontal cortex. LFP recordings are filtered 0.1–100 Hz and MUA recordings are filtered 400 Hz–20 kHz. Adapted with permission from Englot et al. (2008).

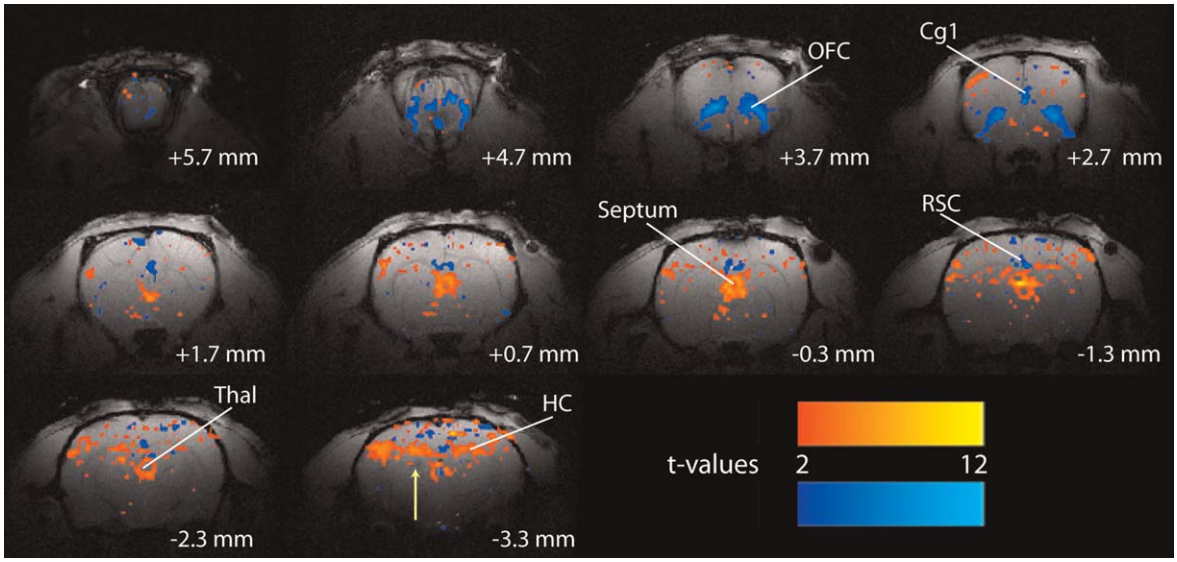


Fig. 5. Example of BOLD increases and decreases during an electrically stimulated partial limbic seizure. During partial limbic seizures, BOLD fMRI signal increases are observed in the hippocampus, thalamus, and septal nuclei. Prominent BOLD decreases are seen in the orbitofrontal, anterior cingulate, and retrosplenial/posterior cingulate cortices. The arrow signifies the hippocampal electrode artifact. *t*-maps are shown for the first 30 s of seizure activity (10 consecutive fMRI images acquired every 3 s) versus 30 s baseline and are superimposed on high-resolution anatomical images. Slices are shown from anterior to posterior, with approximate coordinates relative to bregma (Englot et al., 2008). Color bars indicate *t*-values for increases (warm colors) and decreases (cold colors). The display threshold is $t = 2$. Cg1, anterior cingulate cortex; HC, hippocampus; OFC, orbitofrontal cortex; RSC, retrosplenial/posterior cingulate cortex; Thal, thalamus. Adapted with permission from Englot et al. (2008). Please see online version of this article for full color figure.

during partial limbic seizures (Fig. 5). Given the similarities between ictal slow activity and cortical slow waves that occur during slow-wave sleep, perhaps similar reductions in subcortical arousal systems contribute to this phenomenon (Gervasoni et al., 2004; Jones, 2002; Steriade et al., 1991). We also saw considerable activations in the lateral septum during partial limbic seizures (Fig. 5) which were larger and more consistent than changes in any other region, and peaked relatively early compared to signal fluctuations in other areas (Englot et al., 2008). The septum is an anterior and medial region in the basal forebrain which can be divided into several subregions. The lateral septal nuclei consist mainly of GABAergic inhibitory neurons, while the medial septal nuclei consist mainly of cholinergic neurons (Colom, 2006). The lateral septal nuclei receive their major inputs from the hippocampal formation, and then project heavily to the medial septum–diagonal band of Broca complex, as well as to various hypothalamic areas, the mammillary complex, the ventral tegmental area, and other regions in the basal forebrain (Colom et al., 2006; Irle and Markowitsch, 1986; Mesulam and Mufson, 1984; Risold and Swanson, 1997). GABAergic neurons in the lateral septum are, therefore, poised to produce widespread inhibition in a variety of subcortical structures. The septum is considered a nodal point where ascending non-rhythmic inputs from the brainstem and hypothalamus are converted into rhythmical signals, which are then transmitted to the hippocampus and neocortex (Bland and Colom, 1993; Bland et al., 1994; Vertes and Kocsis, 1997). Thus, the septal nuclei play an important role in regulating normal hippocampal rhythms (Cavazos et al., 1997; Colom, 2006), and may also contribute anti-epileptogenic effects by preventing hyperexcitable limbic states (Colom et al., 2006; Colom and Garrido-Sanabria, 2007). This introduces a few novel questions: does the septum also contribute to the production of rhythmic ictal neocortical slow

activity, or does it play an important inhibitory role in limiting limbic seizure propagation?

During preliminary mechanistic studies in the rat, we applied focal electrical stimuli to three regions showing fMRI activation during partial limbic seizures — the dorsal hippocampus, mediodorsal thalamus, and lateral septum (Englot et al., 2009). Our goal was to mimic ''seizure'' activity in each region individually, without actually producing a seizure that would propagate to the other regions. Interestingly, while stimulations of the hippocampus and medial thalamus did not result in notable behavioral alterations or cortical electrographic effects, stimulating the lateral septum did produce large-amplitude 1–3 Hz slow oscillations in the frontal cortex and behavioral arrest resembling changes during ictal neocortical slow activity (Englot et al., 2009). Furthermore, by preventing lateral septal recruitment in hippocampal seizures via surgical transection of the fornix — the primary white matter tract that permits hippocampal-septal communication — both neocortical slow oscillations and behavioral arrest were abolished during limbic seizures (Englot et al., 2009). These findings allow novel insights into a potential role of septal activity in the production of ictal neocortical slow waves and diminished responsiveness during complex-partial temporal lobe seizures.

The network inhibition hypothesis revisited

As proposed in our network inhibition hypothesis (Fig. 1), it is possible that ictal aberration of normal activity in subcortical arousal systems may contribute to unconsciousness during complex-partial temporal lobe seizures. Some attention has been directed toward the importance of thalamocortical interactions in this phenomenon, but the intense lateral septal involvement during partial limbic seizures in rats has led us to also consider a possible role for the septum in eliciting ictal neocortical slow activity. While the majority of neurons in the lateral septal nuclei are inhibitory cells that release gamma-aminobutyric acid (GABA), no direct projections to orbitofrontal cortex have been found, to our knowledge (Colom et al., 2006; Risold and Swanson, 1997). However, previous animal studies have suggested that the lateral septum does project to other regions involved in normal cortical activation, such as the hypothalamus and basal forebrain (Cirino and Renaud, 1985; Irle and Markowitsch, 1986; Mesulam and Mufson, 1984; Varoqueaux and Poulain, 1999), in addition to its most prominent projections to the medial septum (Colom et al., 2006; Risold and Swanson, 1997). It is thus possible that lateral septal activation, such as during limbic seizures or electrical stimulation, may result in increased inhibition of the basal forebrain or hypothalamic regions, leading secondarily to diminished cortical excitation. First we consider a relatively simple model. For instance, many projections in the basal forebrain release acetylcholine onto the neocortex — a major source of cortical activation in the awake state (Duque et al., 2000). Might lateral septal neurons inhibit these nearby acetylcholinergic projections, leading secondarily to a loss of cortical activation?

As depicted schematically in Figure 6, human and animal results to date have led us to hypothesize about numerous potential mechanistic contributions to ictal neocortical slow activity during complex-partial temporal lobe seizures. For instance, it is possible that during a partial limbic seizure, abnormal excitation of the hippocampus produces lateral septal activation via glutamatergic projections traveling in the fornix (Fig. 6A). This may in turn lead to inhibition of the nucleus basalis by GABAergic projections from the lateral septum, which then results in diminished acetylcholinergic activation of the frontal cortex by the nucleus basalis. Receiving less excitatory input, the neocortex defaults to an inhibited state, allowing slow oscillatory activity to emerge, and behavior to become diminished. Interestingly, past studies have shown that lesions of the nucleus basalis in the rat produce large-amplitude slow oscillations in the neocortex (Bringmann, 1996; Buzsaki et al., 1988), resembling cortical slow waves seen during sleep and partial limbic seizures. However, aberration of normal thalamocortical interactions are also likely to affect cortical states, as are changes in other

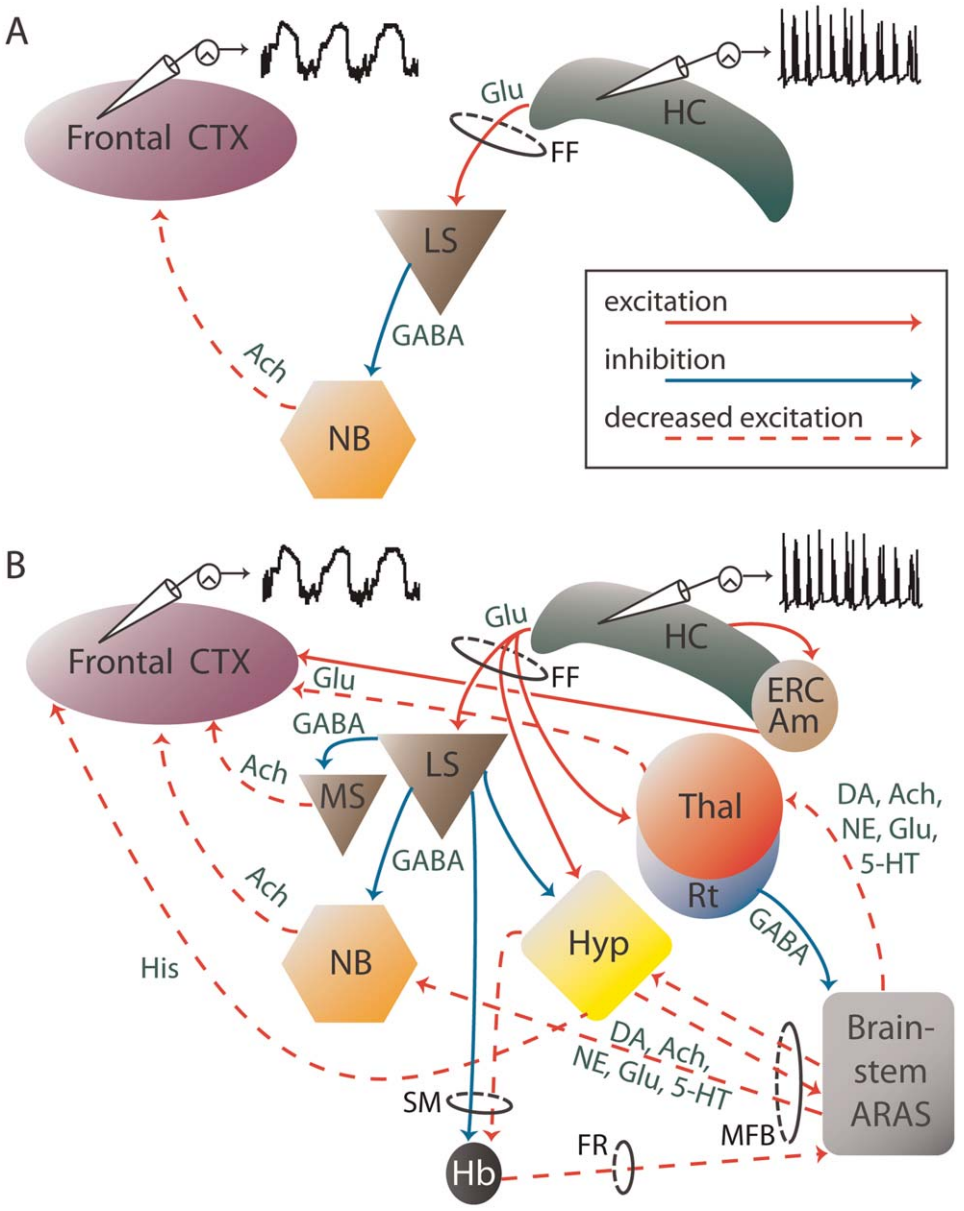


Fig. 6. Schematic diagram illustrating possible network mechanisms of ictal neocortical slow activity. (A) A simplified schematic diagram, showing that excitation of the hippocampus during a seizure may activate the lateral septum via glutamatergic projections in the fornix. This leads in turn to GABAergic inhibition of the nucleus basalis, which then results in diminished acetylcholinergic activation of the frontal cortex by the nucleus basalis, and thus allows the cortex to enter a depressed state associated with ictal neocortical slow activity. (B) A more complex diagram based on (A), adding other network changes that may contribute to ictal neocortical slow oscillations during hippocampal seizure activity. These mechanisms include the inhibitory influence of the lateral septum and the thalamic reticular nucleus onto subcortical structures and the ascending reticular activation system. This in turn leads to decreased excitatory input to the frontal neocortex by various activating structures, such as the thalamus, hypothalamus, and the nucleus basalis — ultimately resulting in cortical depression. Anatomical structures are labeled with black lettering, while neurotransmitters are listed in green. Recordings in the hippocampus and frontal cortex show example LFPs in each region. 5-HT, serotonin; Ach, acetylcholine; AM, amygdala; ARAS, ascending reticular activation system; CTX, cortex; DA, dopamine; ERC, entorhinal cortex; FF, fimbria-fornix; FR, fasciculus retroflexus; GABA, gamma-aminobutyric acid; Glu, glutamate; Hb, habenula; HC, hippocampus; His, histamine; MFB, medial forebrain bundle; LS, lateral septum; MS, medial septum; NB, nucleus basalis; NE, norepinephrine; Rt, thalamic reticular nucleus; SM, stria medullaris, Thal, thalamus. Please see online version of this article for full color figure.

brain regions known to be important in arousal which we have not yet explored. Therefore, it is important to broaden our mechanistic hypothesis to encompass other possible network alterations.

Figure 6B illustrates several additional structures and pathways that may contribute to ictal neocortical slow activity. These potential mechanisms include GABAergic inhibitory influence from regions that may be activated by limbic seizure activity — including the lateral septum and the thalamic reticular nucleus — onto subcortical and brainstem structures which play a role in arousal. For instance, the ascending reticular activating system of the rostral brainstem is comprised of several cell populations important for wakefulness. These include serotonergic neurons in the dorsal raphe (Richerson, 2004), norepinephrine-containing projections from the locus coeruleus (Berridge and Foote, 1996), dopamine release from the pedunculopontine tegmental region and the substantia nigra pars compacta (Dunbar et al., 1992; Dzirasa et al., 2006), acetylcholinergic fibers from the pontomesencephalic tegmentum (Jones, 2008; Woolf and Butcher, 1986), as well as several glutamatergic projections (Jones, 2003). Alterations in these regions during temporal lobe seizures could result from inhibitory signals from the reticular thalamic nucleus (Parent and Steriade, 1984; Steriade et al., 1984), or from diminished excitatory impulses originating from the hypothalamus (Baev et al., 1985; Purves et al., 1992) or habenula (Cuello et al., 1978; Irle et al., 1984) — areas which receive projections from the septal region (Kawaja et al., 1990; Risold and Swanson, 1997).

It is known that projections from the ascending reticular formation convey arousal signals to the cortex primarily through the basal forebrain, thalamus, and hypothalamus (Siegel, 2004). In turn, the hypothalamus provides excitatory input to the neocortex via histaminergic projections in the pre-optic region of the anterior hypothalamus (Lin et al., 1994), and hypocretin/orexin neurons in the posterior hypothalamus (Sakurai, 2005; Saper et al., 2001). The hypothalamus also sends input to brainstem activating regions through the habenula via the stria medullaris and subsequent fasciculus retroflexus (Blander and Wise, 1989; Goto et al., 2005; Semba and Fibiger, 1992). Hence, it is possible that the hypothalamus contributes to the behavioral and neocortical effects of partial limbic seizures, perhaps by providing less cortical or brainstem excitation after becoming inhibited by lateral septal projections (Staiger and Wouterlood, 1990; Varoqueaux and Poulain, 1999), or alternatively through aberration of normal function by direct seizure propagation (Bastlund et al., 2005; Quigg et al., 1999; Silveira et al., 2000).

Another important structure to consider in the mechanism of ictal neocortical slow oscillations is the amygdaloid complex. The amygdala has been shown to play a significant role in epileptiform activity of the temporal lobe (Aroniadou-Anderjaska et al., 2008; Klueva et al., 2003; McIntyre and Gilby, 2008) as well as modulation of arousal signals in both local (Pare and Gaudreau, 1996; Velasco et al., 1989) and distant cortical regions (Dringenberg and Vanderwolf, 1996; Stock et al., 1981). There is some evidence that the amygdala may play a notable role in acetylcholinergic neocortical activation (Dringenberg and Vanderwolf, 1996). Furthermore, given shared connections between the amygdaloid complex and septum via fibers in the stria terminalis and amygdalofugal pathways (Leonard and Scott, 1971), it is important to consider possible effects of convergent signals from septal and hippocampal regions onto the amygdala in modulating neocortical rhythms during limbic seizures. The entorhinal cortex is also a major afferent and efferent pathway to the hippocampus (Chrobak et al., 2000; McIntyre and Gilby, 2008), and could therefore contribute in important ways to spread of ictal activity to both cortical and subcortical structures, and to modulation of neocortical activity.

Finally, the possible role of the medial septum in ictal neocortical slow activity requires further investigation. In addition to the well-known hippocampal connections, the medial septum–diagonal band of Broca complex does have some cholinergic cortical projections, albeit mostly to posterior cortical regions (Gaykema et al., 1990), and previous rat studies have suggested that medial septal lesions may impair performance in

attention-related tasks (Brandner and Schenk, 1998).

In summary, a large number of subcortical structures could potentially contribute to behavioral changes during limbic seizures, and further investigations will be crucial as the network underpinnings of ictal neocortical slow activity continue to be unraveled.

Future directions

The human and animal studies of TLE summarized here provide characterization and preliminary insight into the mechanistic underpinnings of impaired consciousness and ictal neocortical slow rhythms during complex-partial temporal lobe seizures. However, much remains unknown about how focal seizure activity in the temporal lobe leads to a loss of consciousness ictally, and additional investigations — including studies in animal models within which mechanistic interventions are feasible — are needed to further elucidate this problem.

It will be beneficial in future studies to perform invasive measurements of neuronal activity in awake-behaving animals, during which behavior can be studied simultaneously. One mechanistic possibility we have discussed is that lateral septal involvement in partial seizures may result in inhibition of the acetylcholinergic activating system in the nucleus basalis via GABAergic septal projections, leading secondarily to neocortical depression. Further experiments addressing this hypothesis should include electrophysiological recordings from the nucleus basalis during limbic seizures to determine if the firing of acetylcholinergic neurons is indeed suppressed. We should also determine whether stimulation of the nucleus basalis prevents ictal neocortical slow rhythms during seizures by diminishing inhibitory influence from the lateral septum onto the basal forebrain. Direct measurements of changes in neurotransmitter levels in the neocortex during partial seizures represent another key direction, as they may provide further insight into the neurophysiological underpinnings of ictal cortical changes. Utilizing microdialysis or recent voltammetric biosensor techniques (Parikh et al., 2007; Rutherford et al., 2007) may be useful in detecting cortical neurotransmitter fluctuations during ictal neocortical slow activity. Moreover, surgical and pharmacological interventions geared toward preventing distal effects of complex-partial seizures in animals are likely to be fruitful. While in preliminary rat experiments, preventing lateral septal recruitment during electrically stimulated limbic seizures via fornix transection diminished both the electrographic and behavioral correlates of ictal neocortical slow oscillations, the utilization of more localized, reversible methods to prevent subcortical discharges during seizures should be considered. Also, in vivo intracellular recordings of pyramidal neurons in neocortical regions affected by ictal slow waves might permit supplementary insight into whether ictal neocortical slow activity is associated with diminished excitatory postsynaptic potentials, which would suggest decreased levels of excitatory neurotransmitters, or increased inhibitory postsynaptic potentials, implying elevated inhibitory neurotransmission in the cortex.

Animal fMRI studies can produce high spatial resolution images of structures affected by temporal lobe seizures, but potentially important regions have not yet been visualized ictally. Future scans should examine in particular areas important for neocortical activation that have also been shown to be involved in limbic seizures, such as the hypothalamus, amygdala, and upper brainstem, which are difficult to image with surface coils and will therefore require more innovative technical advances. Additional exploration should include electrophysiological recordings, stimulations, and inactivations of these structures during partial limbic seizures.

Although modeling consciousness in animal studies bears obvious limitations, complex-partial seizures in humans interfere with the most basic level of consciousness — the awake, alert state — which we believe can be reasonably modeled in basic research. For example, the behavioral correlates of ictal neocortical slow activity in rats include decreased locomotion and behavioral arrest. While quantitative measurements of performance using controlled behavioral tasks during

limbic seizures have not yet been pursued, these will be important to include in upcoming investigations. For instance, simple response-time and Pavlovian conditioning tasks can be utilized to test both attention (responding to a stimulus) and learning (conditioning of a stimulus) during ictal neocortical slow activity in rats.

To translate this work into the human arena, additional human studies will be necessary as well. Further intracranial studies prospectively evaluating human behavior with both widespread cortical (Blumenfeld et al., 2004b) and subcortical (Arthuis et al., 2009; Guye et al., 2006) electrophysiological measurements will be necessary to more fully identify the specific anatomical regions and activity patterns associated with behavioral impairment. Prospective, standardized, and quantitative methods for patient assessment, including computerized and manually administered testing batteries are needed, which should be continuously available to enhance the quality and quantity of behavioral data obtained in conjunction with electrophysiological studies. Treatment of impaired consciousness in epilepsy will continue to be aimed first and foremost at preventing seizures. However, in some patients, stopping all seizures is not feasible, so treatments that can at least prevent impaired consciousness during seizures will be beneficial. Thus, ultimately, therapeutic interventions such as disconnection procedures, neurostimulation, or medication trials may soon become possible, with the goal of preventing impaired consciousness during partial seizures.

Conclusions: the consciousness system and TLE

In the mid-20th century, Wilder Penfield and Herbert Jasper hypothesized that the brainstem and diencephalon play critical roles in integrating brain activity across both cerebral hemispheres (Jasper, 1991; Penfield, 1958). It was observed that most epileptic patients suffered little to no impairment of consciousness after wide resection of cerebral cortical structures or the corpus callosum, although applying pressure to the brainstem resulted in immediate and reversible loss of consciousness (Penfield, 1958). Penfield and Jasper deduced that the neuroanatomical basis of consciousness involved more than the cerebral cortex, already known to be the seat of various cognitive processes (Jasper, 1991). They argued that the ''indisputable substratum'' of consciousness was rooted in diencephalic and upper brainstem regions. Jasper (1964) also posited that activation of only the amygdala and hippocampus was insufficient to induce automatisms, and the impairment of consciousness required the involvement of widespread subcortical structures. Furthermore, neurochemical studies suggested the presence of diffuse ascending modulatory systems that project from the diencephalon and brainstem that interact with, but are anatomically separate from, the sensory and motor systems (Jasper, 1991). Work summarized in this review, examining both human TLE patients and animal models, suggests that functional aberration of these same networks may also underlie ictal neocortical slow activity and loss of consciousness during complex-partial temporal lobe seizures. As we have discussed, factors which may increase the likelihood of network aberration during partial temporal lobe seizures include: (i) lateralization of discharges to the dominant hemisphere, (ii) bilateral temporal lobe involvement, (iii) increased seizure length and severity, and (iv) dysfunction of subcortical structures important for arousal.

Although the full mechanisms of ictal neocortical slow activity in TLE remain unknown, progress to date allows us to expand upon the ideas of Jasper and Penfield and define a ''consciousness system'' within which dysfunction during epileptic seizures results in temporary loss of the awake, alert state. We propose that the consciousness system includes (i) the upper brainstem, (ii) subcortical structures such as the medial thalamus and basal forebrain region (possibly including the septal nuclei), (iii) anterior and posterior interhemispheric regions (cingulate, medial frontal cortex, and precuneus/retrosplenial cortex), and (iv) lateral frontal and parietal association cortices (Blumenfeld, 2009). It is likely that when seizure activity significantly disrupts normal activity in these areas, consciousness is

adversely affected secondary to either cortical seizure propagation, as in primary-generalized, or secondarily generalized seizures, or neocortical deactivation, as in complex-partial temporal lobe seizures. In contrast, epileptic events that do not involve regions in the consciousness system, such as simple-partial temporal lobe seizures, do not cause a loss of consciousness. While significant questions remain regarding the mechanisms of impaired consciousness during partial temporal lobe seizures, recent advances in our understanding of ictal neocortical slow activity and related network effects will help guide future studies geared toward preventing the adverse neocortical effects of complex-partial seizures.

Acknowledgments

This work was supported by NIH R01 NS049307 (HB) and F30 NS59074 (DJE), a Donaghue Foundation Investigator Award (HB), and by the Betsy and Jonathan Blattmachr family.

References

Alarcon, G., Elwes, R. D. C., Polkey, C. E., & Binnie, C. D. (1998). Ictal oroalimentary automatisms with preserved consciousness: Implications for the pathophysiology of automatisms and relevance to the international classification of seizures. *Epilepsia*, *39*, 1119–1122.

Albert, M. L., Silverberg, R., Reches, A., & Berman, M. (1976). Cerebral dominance for consciousness. *Archives of Neurology*, *33*, 453–454.

Andersen, A. R., Waldemar, G., Dam, M., Fuglsang-Frederiksen, A., Herning, M., & Kruse-Larsen, C. (1990). SPECT in the presurgical evaluation of patients with temporal lobe epilepsy — A preliminary report. *Acta Neurochirurgica Supplementum*, *50*, 80–83.

Angelucci, A., Levitt, J. B., & Lund, J. S. (2002). Anatomical origins of the classical receptive field and modulatory surround field of single neurons in macaque visual cortical area V1. *Progress in Brain Research*, *136*, 373–388.

Ardila, A. (1990). Partial cognitive seizures. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *2*, 175–182.

Aroniadou-Anderjaska, V., Fritsch, B., Qashu, F., & Braga, M. F. (2008). Pathology and pathophysiology of the amygdala in epileptogenesis and epilepsy. *Epilepsy Research*, *78*, 102–116.

Arthuis, M., Valton, L., Regis, J., Chauvel, P., Wendling, F., Naccache, L., et al. (2009). Impaired consciousness during temporal lobe seizures is related to increased long-distance cortical-subcortical synchronization. *Brain*, *132*, 2091–2101.

Avoli, M., & Gloor, P. (1982). Interaction of cortex and thalamus in spike and wave discharges of feline generalized penicillin epilepsy. *Experimental Neurology*, *76*, 196–217.

Babb, T. L., & Brown, W. J. (1987). Pathological findings in epilepsy. In J. Engel, Jr. (Ed.), *Surgical treatments of the epilepsies* (pp. 511–540). New York: Raven Press.

Baev, K. V., Berezovskii, V. K., Kebkalo, T. G., & Savos'kina, L. A. (1985). Projections of neurons of the hypothalamic locomotor region to brain stem and spinal cord structures in the cat. *Neirofiziologiia*, *17*, 817–823.

Bancaud, J., Brunet-Bourgin, F., Chauvel, P., & Halgren, E. (1994). Anatomical origin of deja vu and vivid 'memories' in human temporal lobe epilepsy. *Brain*, *117*, 71–90.

Bastlund, J. F., Jennum, P., Mohapel, P., Penschuck, S., & Watson, W. P. (2005). Spontaneous epileptic rats show changes in sleep architecture and hypothalamic pathology. *Epilepsia*, *46*, 934–938.

Bauer, J. (2001). Interactions between hormones and epilepsy in female patients. *Epilepsia*, *42*(Suppl. 3), 20–22.

Berridge, C. W., & Foote, S. L. (1996). Enhancement of behavioral and electroencephalographic indices of waking following stimulation of noradrenergic beta-receptors within the medial septal region of the basal forebrain. *Journal of Neuroscience*, *16*, 6999–7009.

Bertashius, K. M. (1991). Propagation of human complex-partial seizures: A correlation analysis. *Electroencephalography and Clinical Neurophysiology*, *78*, 333–340.

Bertram, E. H., Mangan, P. S., Zhang, D., Scott, C. A., & Williamson, J. M. (2001). The midline thalamus: Alterations and a potential role in limbic epilepsy. *Epilepsia*, *42*, 967–978.

Bertram, E. H., Zhang, D., & Williamson, J. M. (2008). Multiple roles of midline dorsal thalamic nuclei in induction and spread of limbic seizures. *Epilepsia*, *49*, 256–268.

Bland, B. H., & Colom, L. V. (1993). Extrinsic and intrinsic properties underlying oscillation and synchrony in limbic cortex. *Progress in Neurobiology*, *41*, 157–208.

Bland, B. H., Oddie, S. D., Colom, L. V., & Vertes, R. P. (1994). Extrinsic modulation of medial septal cell discharges by the ascending brainstem hippocampal synchronizing pathway. *Hippocampus*, *4*, 649–660.

Blander, A., & Wise, R. A. (1989). Anatomical mapping of brain stimulation reward sites in the anterior hypothalamic area: Special attention to the stria medullaris. *Brain Research*, *483*, 12–16.

Blum, D. E., Eskola, J., Bortz, J. J., & Fisher, R. S. (1996). Patient awareness of seizures. *Neurology*, *47*, 260–264.

Blumenfeld, H. (2002). *Neuroanatomy through clinical cases*. Sunderland, MA: Sinauer Associates Publishers, Inc.

Blumenfeld, H. (2005). Consciousness and epilepsy: Why are patients with absence seizures absent? *Progress in Brain Research*, *150*, 271–286.

Blumenfeld, H. (2009). Epilepsy and consciousness. In S. Laureys & G. Tononi (Eds.), *The neurology of consciousness: Cognitive neuroscience and neuropathology*. New York, NY: Elsevier.

Blumenfeld, H., & McCormick, D. A. (2000). Corticothalamic inputs control the pattern of activity generated in thalamocortical networks. *The Journal of Neuroscience*, *20*, 5153–5162.

Blumenfeld, H., McNally, K. A., Vanderhill, S. D., Paige, A. L., Chung, R., Davis, K., et al. (2004a). Positive and negative network correlations in temporal lobe epilepsy. *Cerebral Cortex*, *14*, 892–902.

Blumenfeld, H., Rivera, M., McNally, K. A., Davis, K., Spencer, D. D., & Spencer, S. S. (2004b). Ictal neocortical slowing in temporal lobe epilepsy. *Neurology*, *63*, 1015–1021.

Blumenfeld, H., Rivera, M., Vasquez, J. G., Shah, A., Ismail, D., Enev, M., et al. (2007). Neocortical and thalamic spread of amygdala kindled seizures. *Epilepsia*, *48*, 254–262.

Blumenfeld, H., & Taylor, J. (2003). Why do seizures cause loss of consciousness? *The Neuroscientist*, *9*, 301–310.

Blumenfeld, H., Varghese, G. I., Purcaro, M. J., Motelow, J. E., Enev, M., McNally, K. A., et al. (2009). Cortical and subcortical networks in human secondarily generalized tonic-clonic seizures. *Brain*, *132*, 999–1012.

Bonilha, L., Rorden, C., Appenzeller, S., Coan, A. C., Cendes, F., & Li, L. M. (2006). Gray matter atrophy associated with duration of temporal lobe epilepsy. *NeuroImage*, *32*, 1070–1079.

Bonte, F. J., Devous, M. D., Sr., Stokely, E. M., & Homan, R. W. (1983). Single-photon tomographic determination of regional cerebral blood flow in epilepsy. *American Journal of Neuroradiology*, *4*, 544–546.

Boylan, L. S. (2002). Peri-ictal behavioral and cognitive changes. *Epilepsy and Behavior*, *3*, 16–26.

Brandner, C., & Schenk, F. (1998). Septal lesions impair the acquisition of a cued place navigation task: Attentional or memory deficit? *Neurobiology of Learning and Memory*, *69*, 106–125.

Bringmann, A. (1996). Behaviour-related effects of nicotine on slow EEG waves in basal nucleus-lesioned rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *353*, 168–174.

Brumberg, J. C., Pinto, D. J., & Simons, D. J. (1996). Spatial gradients and inhibitory summation in the rat whisker barrel system. *Journal of Neurophysiology*, *76*, 130–140.

Buzsaki, G., Bickford, R. G., Ponomareff, G., Thal, L. J., Mandel, R., & Gage, F. H. (1988). Nucleus basalis and thalamic control of neocortical activity in the freely moving rat. *The Journal of Neuroscience*, *8*, 4007–4026.

Catenoix, H., Magnin, M., Guenot, M., Isnard, J., Mauguiere, F., & Ryvlin, P. (2005). Hippocampal-orbitofrontal connectivity in human: An electrical stimulation study. *Clinical Neurophysiology*, *116*, 1779–1784.

Cavazos, J. E., Wang, C. J., Sitoh, Y. Y., Ng, S. E., & Tien, R. D. (1997). Anatomy and pathology of the septal region. *Neuroimaging Clinics of North America*, *7*, 67–78.

Chang, C. P., Yen, D. J., Yu, S. M., Liu, R. S., Chang, H. F., Hsieh, H. J., et al. (2008). Unilateral thalamic hypometabolism in patients with temporal lobe epilepsy. *Journal of the Formosan Medical Association*, *107*, 567–571.

Chang, D. J., Zubal, I. G., Gottschalk, C., Necochea, A., Stokking, R., Studholme, C., et al. (2002). Comparison of statistical parametric mapping and SPECT difference imaging in patients with temporal lobe epilepsy. *Epilepsia*, *43*, 68–74.

Chrobak, J. J., Lorincz, A., & Buzsaki, G. (2000). Physiological patterns in the hippocampo-entorhinal cortex system. *Hippocampus*, *10*, 457–465.

Cirino, M., & Renaud, L. P. (1985). Influence of lateral septum and amygdala stimulation on the excitability of hypothalamic supraoptic neurons. An electrophysiological study in the rat. *Brain Research*, *326*, 357–361.

Collins, R. C. (1978). Use of cortical circuits during focal penicillin seizures: An autoradiographic study with [14C]deoxyglucose. *Brain Research*, *150*, 487–501.

Colom, L. V. (2006). Septal networks: Relevance to theta rhythm, epilepsy and Alzheimer's disease. *Journal of Neurochemistry*, *96*, 609–623.

Colom, L. V., Garcia-Hernandez, A., Castaneda, M. T., Perez-Cordova, M. G., & Garrido-Sanabria, E. R. (2006). Septo-hippocampal networks in chronically epileptic rats: Potential antiepileptic effects of theta rhythm generation. *Journal of Neurophysiology*, *95*, 3645–3653.

Colom, L. V., & Garrido-Sanabria, E. (2007). Modulation of normal and altered hippocampal excitability states by septal networks. *Journal of Neuroscience Research*, *85*, 2839–2843.

Cuello, A. C., Emson, P. C., Paxinos, G., & Jessell, T. (1978). Substance P containing and cholinergic projections from the habenula. *Brain Research*, *149*, 413–429.

Cowan, R. L., & Wilson, C. J. (1994). Spontaneous firing patterns and axonal projections of single corticostriatal neurons in the rat medial agranular cortex. *Journal of Neurophysiology*, *71*, 17–32.

de Lanerolle, N. C., & Lee, T. S. (2005). New facets of the neuropathology and molecular profile of human temporal lobe epilepsy. *Epilepsy and Behavior*, *7*, 190–203.

Derdikman, D., Hildesheim, R., Ahissar, E., Arieli, A., & Grinvald, A. (2003). Imaging spatiotemporal dynamics of surround inhibition in the barrels somatosensory cortex. *Journal of Neuroscience*, *23*, 3100–3105.

Devinsky, O. (2004). Diagnosis and treatment of temporal lobe epilepsy. *Reviews in Neurological Diseases*, *1*, 2–9.

Diehl, B., LaPresto, E., Najm, I., Raja, S., Rona, S., Babb, T., et al. (2003). Neocortical temporal FDG-PET hypometabolism correlates with temporal lobe atrophy in hippocampal sclerosis associated with microscopic cortical dysplasia. *Epilepsia*, *44*, 559–564.

Drazkowski, J. (2007). An overview of epilepsy and driving. *Epilepsia*, *48*(Suppl. 9), 10–12.

Dringenberg, H. C., & Vanderwolf, C. H. (1996). Cholinergic activation of the electrocorticogram: An amygdaloid activating system. *Experimental Brain Research*, *108*, 285–296.

Dunbar, J. S., Hitchcock, K., Latimer, M., Rugg, E. L., Ward, N., & Winn, P. (1992). Excitotoxic lesions of the pedunculopontine tegmental nucleus of the rat. II. Examination of eating and drinking, rotation, and reaching and grasping following unilateral ibotenate or quinolinate lesions. *Brain Research*, *589*, 194–206.

Duncan, R., Patterson, J., Hadley, D. M., Wyper, D. J., McGeorge, A. P., & Bone, I. (1990). Tc99m HM-PAO single photon emission computed tomography in temporal lobe epilepsy. *Acta Neurologica Scandinavica*, *81*, 287–293.

Duque, A., Balatoni, B., Detari, L., & Zaborszky, L. (2000). EEG correlation of the discharge properties of identified neurons in the basal forebrain. *Journal of Neurophysiology*, *84*, 1627–1635.

Dzirasa, K., Ribeiro, S., Costa, R., Santos, L. M., Lin, S. C., Grosmark, A., et al. (2006). Dopaminergic control of sleep-wake states. *The Journal of Neuroscience*, *26*, 10577–10589.

Ebner, A., Dinner, D. S., Noachtar, S., & Luders, H. (1995). Automatisms with preserved responsiveness: A lateralizing sign in psychomotor seizures. *Neurology*, *45*, 61–64.

Eisenschenk, S., Gilmore, R. L., Cibula, J. E., & Roper, S. N. (2001). Lateralization of temporal lobe foci: Depth versus subdural electrodes. *Clinical Neurophysiology*, *112*, 836–844.

Engel, J. (1987). Outcome with respect to epileptic seizures. In J. Engel (Ed.), *Surgical treatment of the epilepsies* (pp. 553–571). New York, NY: Raven Press.

Engel, J., & Williamson, P. D. (2007). Limbic seizures. In J. Engel & T. A. Pedley (Eds.), *Epilepsy: A comprehensive textbook* (pp. 541–552). Philadelphia, PA: Lippincott Williams & Wilkins.

Engel, J., Williamson, P. D., & Wieser, H. G. (2007). Mesial temporal lobe epilepsy with hippocampal sclerosis. In J. Engel & T. A. Pedley (Eds.), *Epilepsy: A comprehensive textbook* (pp. 2479–2486). Philadelphia, PA: Lippincott Williams & Wilkins.

Englot, D. J., & Blumenfeld, H. (2009). Functional MRI in basic epilepsy research. In P. Schwartzkroin (Ed.), *Encyclopedia of basic epilepsy research*. London, UK: Elsevier.

Englot, D. J., Mishra, A. M., Mansuripur, P. K., Herman, P., Hyder, F., & Blumenfeld, H. (2008). Remote effects of focal hippocampal seizures on the rat neocortex. *The Journal of Neuroscience*, *28*, 9066–9081.

Englot, D. J., Modi, B., Mishra, A. M., DeSalvo, M., Hyder, F., & Blumenfeld, H. (2009). Cortical deactivation induced by subcortical network dysfunction in limbic seizures. In review.

Escueta, A. V., Kunze, U., Waddell, G., Boxley, J., & Nadel, A. (1977). Lapse of consciousness and automatisms in temporal lobe epilepsy: A videotape analysis. *Neurology*, *27*, 144–155.

Franaszczuk, P. J., Bergey, G. K., & Kaminski, M. J. (1994). Analysis of mesial temporal seizure onset and propagation using the directed transfer function method. *Electroencephalography and Clinical Neurophysiology*, *91*, 413–427.

Franczek, S., Demakis, G. J., Pennell, E. B., DeBose, C., & Gilmore, R. L. (1997). Revisited: Cerebral dominance for consciousness. *Electroencephalography and Clinical Neurophysiology*, *102*, 24P–25P.

Fried, I., Spencer, D. D., & Spencer, S. S. (1995). The anatomy of epileptic auras: Focal pathology and surgical outcome. *Journal of Neurosurgery*, *83*, 60–66.

Gabr, M., Luders, H., Dinner, D., Morris, H., & Wyllie, E. (1989). Speech manifestations in lateralization of temporal lobe seizures. *Annals of Neurology*, *25*, 82–87.

Gaykema, R. P., Luiten, P. G., Nyakas, C., & Traber, J. (1990). Cortical projection patterns of the medial septum-diagonal band complex. *The Journal of Comparative Neurology*, *293*, 103–124.

Gervasoni, D., Lin, S. C., Ribeiro, S., Soares, E. S., Pantoja, J., & Nicolelis, M. A. (2004). Global forebrain dynamics predict rat behavioral states and their transitions. *The Journal of Neuroscience*, *24*, 11137–11147.

Gloor, P. (1986). Consciousness as a neurological concept in epileptology: A critical review. *Epilepsia*, *27*(Suppl. 2), S14–S26.

Gloor, P. (1991). Mesial temporal sclerosis: Historical background and overview from a modern perspective. In H. Luders (Ed.), *Epilepsy surgery* (Vol. 77, pp. 689–702). New York, NY: Raven Press.

Gloor, P., Olivier, A., & Ives, J. (1980). Loss of consciousness in temporal lobe epilepsy: Observations obtained with stereotaxic depth electrode recordings and stimulations. In R. Canger, F. Angeleri, & J. K. Penry (Eds.), *Advances in epileptology: The XIth Epilepsy International Symposium* (pp. 349–353). New York, NY: Raven Press.

Gloor, P., Salanova, V., Olivier, A., & Quesney, L. F. (1993). The human dorsal hippocampal commissure. An anatomically identifiable and functional pathway. *Brain*, *116*, 1249–1273.

Gong, G., Concha, L., Beaulieu, C., & Gross, D. W. (2008). Thalamic diffusion and volumetry in temporal lobe epilepsy with and without mesial temporal sclerosis. *Epilepsy Research*, *80*, 184–193.

Goto, M., Canteras, N. S., Burns, G., & Swanson, L. W. (2005). Projections from the subfornical region of the lateral hypothalamic area. *The Journal of Comparative Neurology*, *493*, 412–438.

Guye, M., Regis, J., Tamura, M., Wendling, F., McGonigal, A., Chauvel, P., et al. (2006). The role of corticothalamic coupling in human temporal lobe epilepsy. *Brain*, *129*, 1917–1928.

Haider, B., Duque, A., Hasenstaub, A. R., & McCormick, D. A. (2006). Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. *Journal of Neuroscience*, *26*, 4535–4545.

Helmstaedter, C., & Kockelmann, E. (2006). Cognitive outcomes in patients with chronic temporal lobe epilepsy. *Epilepsia*, *47*(Suppl. 2), 96–98.

Hermann, B. P., Seidenberg, M., Schoenfeld, J., & Davies, K. (1997). Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Archives of Neurology*, *54*, 369–376.

Hetherington, H. P., Kuzniecky, R. I., Vives, K., Devinsky, O., Pacia, S., Luciano, D., et al. (2007). A subcortical network of dysfunction in TLE measured by magnetic resonance spectroscopy. *Neurology*, *69*, 2256–2265.

Hoffmann, J. M., Elger, C. E., & Kleefuss-Lie, A. A. (2008). Lateralizing value of behavioral arrest in patients with temporal lobe epilepsy. *Epilepsy and Behavior*, *13*, 634–636.

Hogan, R. E., Kaiboriboon, K., Bertrand, M. E., Rao, V., & Acharya, J. (2006). Composite SISCOM perfusion patterns in right and left temporal seizures. *Archives of Neurology*, *63*, 1419–1426.

ILAE. (1981). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*, *22*, 489–501.

ILAE. (1989). Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*, *30*, 389–399.

Inoue, Y., & Mihara, T. (1998). Awareness and responsiveness during partial seizures. *Epilepsia*, *39*, 7–10.

Irle, E., & Markowitsch, H. J. (1986). Afferent connections of the substantia innominata/basal nucleus of Meynert in carnivores and primates. *Journal für Hirnforschung*, *27*, 343–367.

Irle, E., Sarter, M., Guldin, W. O., & Markowitsch, H. J. (1984). Afferents to the ventral tegmental nucleus of Gudden in the mouse, rat, and cat. *The Journal of Comparative Neurology*, *228*, 509–541.

Jackson, J., & Colman, W. (1898). Case of epilepsy with tasting movements and 'dreamy state' — Very small patch of softening in the left uncinate gyrus. *Brain*, *21*, 580–590.

Jackson, J. H., Taylor, J., Holmes, G., & Walshe, F. (1931). *Selected writings of John Hughlings Jackson*. London: Hodder and Stoughton.

Jacoby, A., Snape, D., & Baker, G. A. (2005). Epilepsy and social identity: The stigma of a chronic neurological disorder. *Lancet Neurology*, *4*, 171–178.

Jasper, H. H. (1964). Some physiological mechanisms involved in epileptic automatisms. *Epilepsia*, *5*, 1–20.

Jasper, H. H. (1991). Current evaluation of the concepts of centrencephalic and cortico-reticular seizures. *Electroencephalography and Clinical Neurophysiology*, *78*, 2–11.

Jones, B. E. (2003). Arousal systems. *Frontiers in Bioscience*, *8*, s438–s451.

Jones, B. E. (2008). Modulation of cortical activation and behavioral arousal by cholinergic and orexinergic systems. *Annals of the New York Academy of Sciences*, *1129*, 26–34.

Jones, E. G. (2002). Thalamic circuitry and thalamocortical synchrony. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *357*, 1659–1673.

Kawaja, M. D., Flumerfelt, B. A., & Hrycyshyn, A. W. (1990). Synaptic organization of septal projections in the rat medial habenula: A wheat germ agglutinin-horseradish peroxidase and immunohistochemical study. *Synapse*, *6*, 45–54.

Kim, S. H., Zubal, I. G., & Blumenfeld, H. (2009). Epilepsy localization by ictal and interictal SPECT. In R. Van Heertum, M. Ichise, & R. S. Tikofsky (Eds.), *Functional cerebral SPECT and PET imaging*. Philadelphia, PA: Lippincott Williams & Wilkins.

Klueva, J., Munsch, T., Albrecht, D., & Pape, H. C. (2003). Synaptic and non-synaptic mechanisms of amygdala recruitment into temporolimbic epileptiform activities. *European Journal of Neuroscience*, *18*, 2779–2791.

Kobau, R., Zahran, H., Thurman, D. J., Zack, M. M., Henry, T. R., Schachter, S. C., et al. (2008). Epilepsy surveillance among adults — 19 states, Behavioral Risk Factor Surveillance System, 2005. *MMWR Surveillance Summaries*, *57*, 1–20.

Labate, A., Cerasa, A., Gambardella, A., Aguglia, U., & Quattrone, A. (2008). Hippocampal and thalamic atrophy in mild temporal lobe epilepsy: A VBM study. *Neurology*, *71*, 1094–1101.

Laurent, A., & Arzimanoglou, A. (2006). Cognitive impairments in children with nonidiopathic temporal lobe epilepsy. *Epilepsia*, *47*(Suppl. 2), 99–102.

Lavenex, P., & Amaral, D. G. (2000). Hippocampal-neocortical interaction: A hierarchy of associativity. *Hippocampus*, *10*, 420–430.

Lee, K. H., Meador, K. J., Park, Y. D., King, D. W., Murro, A. M., Pillai, J. J., et al. (2002). Pathophysiology of altered consciousness during seizures: Subtraction SPECT study. *Neurology*, *59*, 841–846.

Leonard, C. M., & Scott, J. W. (1971). Origin and distribution of the amygdalofugal pathways in the rat: An experimental neuroanatomical study. *Journal of Comparative Neurology*, *141*, 313–329.

Leung, L. S., Ma, J., & McLachlan, R. S. (2000). Behaviors induced or disrupted by complex partial seizures. *Neuroscience and Biobehavioral Reviews*, *24*, 763–775.

Levav, M., Mirsky, A. F., Herault, J., Xiong, L., Amir, N., & Andermann, E. (2002). Familial association of neuropsychological traits in patients with generalized and partial seizure disorders. *Journal of Clinical and Experimental Neuropsychology*, *24*, 311–326.

Lieb, J. P., Dasheiff, R. B., & Engel, J., Jr. (1991). Role of the frontal lobes in the propagation of mesial temporal lobe seizures. *Epilepsia*, *32*, 822–837.

Lin, J. S., Sakai, K., & Jouvet, M. (1994). Hypothalamo-preoptic histaminergic projections in sleep-wake control in the cat. *European Journal of Neuroscience*, *6*, 618–625.

Loddenkemper, T., & Kotagal, P. (2005). Lateralizing signs during seizures in focal epilepsy. *Epilepsy and Behavior*, *7*, 1–17.

Lux, S., Kurthen, M., Helmstaedter, C., Hartje, W., Reuber, M., & Elger, C. E. (2002). The localizing value of ictal consciousness and its constituent functions: A video-EEG study in patients with focal epilepsy. *Brain*, *125*, 2691–2698.

Maldonado, H. M., Delgado-Escueta, A. V., Walsh, G. O., Swartz, B. E., & Rand, R. W. (1988). Complex partial seizures of hippocampal and amygdalar origin. *Epilepsia*, *29*, 420–433.

Marks, W. J., Jr., & Laxer, K. D. (1998). Semiology of temporal lobe seizures: Value in lateralizing the seizure focus. *Epilepsia*, *39*, 721–726.

Mayanagi, Y., Watanabe, E., & Kaneko, Y. (1996). Mesial temporal lobe epilepsy: Clinical features and seizure mechanism. *Epilepsia*, *37*(Suppl. 3), 57–60.

McCasland, J. S., Carvell, G. E., Simons, D. J., & Woolsey, T. A. (1991). Functional asymmetries in the rodent barrel cortex. *Somatosensory and Motor Research*, *8*, 111–116.

McIntyre, D. C., & Gilby, K. L. (2008). Mapping seizure pathways in the temporal lobe. *Epilepsia*, *49*(Suppl. 3), 23–30.

Menzel, C., Grunwald, F., Klemm, E., Ruhlmann, J., Elger, C. E., & Biersack, H. J. (1998). Inhibitory effects of mesial temporal partial seizures onto frontal neocortical structures. *Acta Neurologica Belgica*, *98*, 327–331.

Mesulam, M. M., & Mufson, E. J. (1984). Neural inputs into the nucleus basalis of the substantia innominata (Ch4) in the rhesus monkey. *Brain*, *107*(1), 253–274.

Milner, B. (1972). Disorders of learning and memory after temporal lobe lesions in man. *Clinical Neurosurgery*, *19*, 421–446.

Mirsky, A. F., & Van Buren, J. M. (1965). On the nature of the ''absence'' in centrencephalic epilepsy: A study of some behavioral, electroencephalographic, and autonomic factors. *Electroencephalography and Clinical Neurophysiology*, *18*, 334–348.

Morrell, M. J. (1993). Differential diagnosis of seizures. *Neurologic Clinics*, *11*, 737–754.

Munari, C., Bancaud, J., Bonis, A., Stoffels, C., Szikla, G., & Talairach, J. (1980). Impairment of consciousness in temporal lobe seizures: A stereoelectroencephalographic study. In R. Canger, F. Angeleri, & J. K. Penry (Eds.), *Advances in epileptology: The XIth Epilepsy International Symposium* (pp. 111–114). New York: Raven Press.

Natsume, J., Bernasconi, N., Andermann, F., & Bernasconi, A. (2003). MRI volumetry of the thalamus in temporal, extratemporal, and idiopathic generalized epilepsy. *Neurology*, *60*, 1296–1300.

Nelissen, N., Van Paesschen, W., Baete, K., Van Laere, K., Palmini, ., Van Billoen, H., et al. (2006). Correlations of interictal FDG-PET metabolism and ictal SPECT perfusion changes in human temporal lobe epilepsy with hippocampal sclerosis. *NeuroImage*, *32*, 684–695.

Norden, A. D., & Blumenfeld, H. (2002). The role of subcortical structures in human epilepsy. *Epilepsy and Behavior*, *3*, 219–231.

Pare, D., & Gaudreau, H. (1996). Projection cells and interneurons of the lateral and basolateral amygdala: Distinct firing patterns and differential relation to theta and delta rhythms in conscious cats. *The Journal of Neuroscience*, *16*, 3334–3350.

Parent, A., & Steriade, M. (1984). Midbrain tegmental projections of nucleus reticularis thalami of cat and monkey: A retrograde transport and antidromic invasion study. *The Journal of Comparative Neurology*, *229*, 548–558.

Parikh, V., Kozak, R., Martinez, V., & Sarter, M. (2007). Prefrontal acetylcholine release controls cue detection on multiple timescales. *Neuron*, *56*, 141–154.

Pedley, T. (1992). Classifications of seizures and epilepsy. In S. Resor & H. Kutt (Eds.), *The medical treatment of epilepsy* (p. 8). New York, NY: Informa Health Care.

Penfield, W. (1950). Epileptic automatism and the centrencephalic integrating system. *Research Publications: Association for Research in Nervous And Mental Disease*, *30*, 513–528.

Penfield, W. (1958). Centrencephalic integrating system. *Brain*, *81*, 231–234.

Plum, F., & Posner, J. B. (1980). *The diagnosis of stupor and coma*. Philadelphia, PA: Davis.

Prince, D. A., & Wilder, B. J. (1967). Control mechanisms in cortical epileptogenic foci. ''Surround'' inhibition. *Archives of Neurology*, *16*, 194–202.

Purves, D., Augustine, G., Fitzpatrick, D., Katz, L., Williams, S., McNamara, J., et al. (1992). *Emotions. Neuroscience*. Sunderland, MA: Sinauer Associates Publishers, Inc.

Quesney, F. (1986). Clinical and EEG features of complex partial seizures of temporal lobe origin. *Epilepsia*, *27*, S27–S45.

Quigg, M., Clayburn, H., Straume, M., Menaker, M., & Bertram, E. H., III (1999). Hypothalamic neuronal loss and altered circadian rhythm of temperature in a rat model of mesial temporal lobe epilepsy. *Epilepsia*, *40*, 1688–1696.

Quigg, M., Kiely, J. M., Shneker, B., Veldhuis, J. D., & Bertram, E. H., III (2002). Interictal and postictal alterations of pulsatile secretions of luteinizing hormone in temporal lobe epilepsy in men. *Annals of Neurology*, *51*, 559–566.

Rabinowicz, A. L., Salas, E., Beserra, F., Leiguarda, R. C., & Vazquez, S. E. (1997). Changes in regional cerebral blood flow beyond the temporal lobe in unilateral temporal lobe epilepsy. *Epilepsia*, *38*, 1011–1014.

Racine, R. J. (1972). Modification of seizure activity by electrical stimulation. II. Motor seizure. *Electroencephalography and Clinical Neurophysiology*, *32*, 281–294.

Richerson, G. B. (2004). Serotonergic neurons as carbon dioxide sensors that maintain pH homeostasis. *Nature Reviews. Neuroscience*, *5*, 449–461.

Riederer, F., Lanzenberger, R., Kaya, M., Prayer, D., Serles, W., & Baumgartner, C. (2008). Network atrophy in temporal lobe epilepsy: A voxel-based morphometry study. *Neurology*, *71*, 419–425.

Risold, P. Y., & Swanson, L. W. (1997). Connections of the rat lateral septal complex. *Brain Research. Brain Research Reviews*, *24*, 115–195.

Rosenberg, D. S., Mauguiere, F., Demarquay, G., Ryvlin, P., Isnard, J., Fischer, C., et al. (2006). Involvement of medial pulvinar thalamic nucleus in human temporal lobe seizures. *Epilepsia*, *47*, 98–107.

Rutherford, E. C., Pomerleau, F., Huettl, P., Stromberg, I., & Gerhardt, G. A. (2007). Chronic second-by-second measures of l-glutamate in the central nervous system of freely moving rats. *Journal of Neurochemistry*, *102*, 712–722.

Saint-Hilaire, J. M., & Lee, M. A. (2000). Localizing and lateralizing value of epileptic symptoms in temporal lobe epilepsy. *Canadian Journal of Neurological Sciences*, *27*(Suppl. 1), S1–S5. discussion S20-1.

Sakurai, T. (2005). Roles of orexin/hypocretin in regulation of sleep/wakefulness and energy homeostasis. *Sleep Medicine Reviews*, *9*, 231–241.

Saper, C. B., Chou, T. C., & Scammell, T. E. (2001). The sleep switch: Hypothalamic control of sleep and wakefulness. *Trends in Neuroscience*, *24*, 726–731.

Schulz, R., Luders, H. O., Noachtar, S., May, T., Sakamoto, A., Hothausen, H., et al. (1995). Amnesia of the epileptic aura. *Neurology*, *45*, 231–235.

Schwartz, B. (1967). Hemispheric dominance and consciousness. *Acta Neurologica Scandinavica*, *43*, 513–525.

Schwartz, T. H., & Bonhoeffer, T. (2001). In vivo optical mapping of epileptic foci and surround inhibition in ferret cerebral cortex. *Nature Medicine*, *7*, 1063–1067.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, *20*, 11–21.

Semba, K., & Fibiger, H. C. (1992). Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: A retro- and antero-grade transport and immunohistochemical study. *The Journal of Comparative Neurology*, *323*, 387–410.

Sengpiel, F., Sen, A., & Blakemore, C. (1997). Characteristics of surround inhibition in cat area 17. *Experimental Brain Research*, *116*, 216–228.

Siegel, J. (2004). Brain mechanisms that control sleep and waking. *Naturwissenschaften*, *91*, 355–365.

Silveira, D. C., Klein, P., Ransil, B. J., Liu, Z., Hori, A., Holmes, G. L., et al. (2000). Lateral asymmetry in activation of hypothalamic neurons with unilateral amygdaloid seizures. *Epilepsia*, *41*, 34–41.

Spencer, S. S., Williamson, P. D., Spencer, D. D., & Mattson, R. H. (1987). Human hippocampal seizure spread studied by depth and subdural recording: The hippocampal commissure. *Epilepsia*, *28*, 479–489.

Sperling, M. R. (2004). The consequences of uncontrolled epilepsy. *CNS Spectrums*, *9*, 98–101, 106–9.

Staiger, J. F., & Wouterlood, F. G. (1990). Efferent projections from the lateral septal nucleus to the anterior hypothalamus in the rat: A study combining phaseolus vulgaris-leucoagglutinin tracing with vasopressin immunocytochemistry. *Cell Tissue Research*, *261*, 17–23.

Steriade, M., Dossi, R. C., Pare, D., & Oakson, G. (1991). Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proceedings of the National Academy of Sciences of the United States of America*, *88*, 4396–4400.

Steriade, M., Nunez, A., & Amzica, F. (1993). A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: Depolarizing and hyperpolarizing components. *Journal of Neuroscience*, *13*, 3252–3265.

Steriade, M., Parent, A., & Hada, J. (1984). Thalamic projections of nucleus reticularis thalami of cat: A study using retrograde transport of horseradish peroxidase and fluorescent tracers. *The Journal of. Comparative Neurology*, *229*, 531–547.

Stock, G., Rupprecht, U., Stumpf, H., & Schlor, K. H. (1981). Cardiovascular changes during arousal elicited by stimulation of amygdala, hypothalamus and locus coeruleus. *Journal of the Autonomic Nervous System*, *3*, 503–510.

Tae, W. S., Joo, E. Y., Kim, J. H., Han, S. J., Suh, Y. L., Kim, B. T., et al. (2005). Cerebral perfusion changes in mesial temporal lobe epilepsy: SPM analysis of ictal and interictal SPECT. *Neuroimage*, *24*, 101–110.

Thierry, A. M., Gioanni, Y., Degenetais, E., & Glowinski, J. (2000). Hippocampo-prefrontal cortex pathway: Anatomical and electrophysiological characteristics. *Hippocampus*, *10*, 411–419.

Van Paesschen, W., Dupont, P., Van Driel, G., Van Billoen, H., & Maes, A. (2003). SPECT perfusion changes during complex partial seizures in patients with hippocampal sclerosis. *Brain*, *126*, 1103–1111.

Varoqueaux, F., & Poulain, P. (1999). Projections of the mediolateral part of the lateral septum to the hypothalamus, revealed by Fos expression and axonal tracing in rats. *Anatomia Embryologia (Berlin)*, *199*, 249–263.

Velasco, J. M., Fernandez de Molina, A., & Perez, D. (1989). Suprarhinal cortex response to electrical stimulation of the lateral amygdala nucleus in the rat. *Experimental Brain Research*, *74*, 168–172.

Vertes, R. P., & Kocsis, B. (1997). Brainstem-diencephalo-septohippocampal systems controlling the theta rhythm of the hippocampus. *Neuroscience*, *81*, 893–926.

Williamson, P. D., French, J. A., Thadani, V. M., Kim, J. H., Novelly, R. A., Spencer, S. S., et al. (1993). Characteristics of medial temporal lobe epilepsy: II. Interictal and ictal scalp electroencephalography, neuropsychological testing, neuroimaging, surgical results, and pathology. *Annals of Neurology*, *34*, 781–787.

Wilson, C. L., & Engel, J., Jr. (1993). Electrical stimulation of the human epileptic limbic cortex. *Advances in Neurology*, *63*, 103–113.

Wilson, C. L., Isokawa, M., Babb, T. L., & Crandall, P. H. (1990). Functional connections in the human temporal lobe. I. Analysis of limbic system pathways using neuronal responses evoked by electrical stimulation. *Experimental Brain Research*, *82*, 279–292.

Woolf, N. J., & Butcher, L. L. (1986). Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. *Brain Research Bulletin*, *16*, 603–637.

Yamauchi, T. (1998). Impairment of consciousness during epileptic seizures with special reference to neuronal mechanisms. *Epilepsia*, *39*, 16–20.

Yu, L., & Blumenfeld, H. (2009). Theories of impaired consciousness in epilepsy. *Annals of the New York Academy of Sciences*, 1157, 48–60.

Zifkin, B. G., & Dravet, C. (2007). Generalized tonic-clonic seizures. In J. Engel & T. A. Pedley (Eds.), *Epilepsy: A comprehensive textbook* (pp. 353–362). Philadelphia, PA: Lippincott Williams & Wilkins.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 12

You are only coming through in waves: wakefulness variability and assessment in patients with impaired consciousness

Tristan Bekinschtein[1,2,*], Victor Cologan[3], Brigitte Dahmen[3] and Diego Golombek[4]

[1]*MRC Cognition and Brain Sciences Unit, Cambridge, UK*
[2]*Impaired Consciousness Research Group, University of Cambridge, UK*
[3]*Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium*
[4]*Chronobiology Lab, University of Quilmes/CONICET, Buenos Aires, Argentina*

Abstract: The vegetative state (VS) is defined as a condition of wakefulness without awareness. Being awake and being asleep are two behavioral and physiological manifestations of the daily cycles of vigilance and metabolism. International guidelines for the diagnosis of VS propose that a patient fulfills criteria for wakefulness if he/she exhibits cycles of eye closure and eye opening giving the impression of a preserved sleep–wake cycle. We argue that these criteria are insufficient and we suggest guidelines to address wakefulness in a more comprehensive manner in this complex and heterogeneous group of patients. Four factors underlying wakefulness, as well as their interactions, are considered: arousal/responsiveness, circadian rhythms, sleep cycle, and homeostasis. The first refers to the arousability and capacity to, consciously or not, respond to external stimuli. The second deals with the circadian clock as a synchronizer of physiological functions to environmental cyclic changes. The third evaluates general sleep patterns, while homeostasis refers to the capacity of the body to regulate its internal state and maintain a stable condition. We present examples of reflex responses, activity rhythms, and electroencephalographic (EEG) measurements from patients with disorders of consciousness (DOC) to illustrate these factors of wakefulness. If properly assessed, they would help in the evaluation of consciousness by informing when and in which context the patient is likely to exhibit maximal responsiveness. This evaluation has the potential to improve diagnosis and treatment and may also add prognostic value to the multimodal assessment in DOC.

Keywords: disorders of consciousness; wakefulness; circadian rhythms; arousal variability; sleep patterns; homeostasis

*Corresponding author.
Tel.: +44 (0)1223 355294 (ext. 531); Fax: +44 (0)1223 359062;
E-mail: tristan.bekinschtein@mrc-cbu.cam.ac.uk

DOI: 10.1016/S0079-6123(09)17712-9

> It could be worst/I could be alone/I could be locked in here on my own. Like a stone that certainly drops/and it never stops/I could be lost or I could be saved. Calling out from beneath the waves.
>
> (*Crests of waves, Coldplay*, 2002)

Wakefulness

Every morning most people in this world wake up (Dylan, 1979; Jewel, 1995; Brown, 1970). Waking up is composed of several processes, of which the most obvious is that of regaining consciousness. However, the process of waking up starts well before we regain consciousness, since our internal circadian clock unconsciously times our body rhythms to be prepared for future events. Before the actual time of waking up, both body temperature and some hormone levels (e.g., cortisol) rise, while other nocturnal variables decrease (e.g., melatonin), thus preparing the arousal system to leave the arms of Morpheus — the god of sleep. But what happens if this highly synchronized process is disrupted by brain injury? Is it possible to ''wake up'' without regaining consciousness?

Wakefulness is a key feature in the diagnosis of disorders of consciousness (DOC), but it is rarely assessed in full and is commonly taken for granted (Multi-Society Task Force on PVS, 1994). The vegetative state (VS) was originally defined as ''wakefulness without awareness'' (Jennett and Plum, 1972) and is now widely acknowledged by both the scientific and medical communities and even by the general public (*The Sunday Times*, 2007). In disorder of consciousness patients, wakefulness refers to ''preserved sleep-wake cycles in patients without awareness.'' We propose that this definition is insufficient to describe wakefulness in full and does not help the clinician in determining the state of the patient in the intensive care unit (ICU) (during the acute state) nor during the postacute and chronic states. Despite the considerable experience gained in the 1980s and 1990s, the Multi-Society Task Force on PVS (1994) did not improve or extend the definition, nor proposed any thorough approach to the assessment of wakefulness in DOC patients.

The Multi-Society Task Force on PVS (1994) created a consensus statement summarizing the current knowledge of the medical aspects of the persistent VS in adults and children. It stated that ''The vegetative state can be diagnosed according to the following criteria: (1) no evidence of awareness of self or environment and an inability to interact with others; (2) no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli; (3) no evidence of language comprehension or expression; (4) intermittent wakefulness manifested by the presence of sleep-wake cycles; (5) sufficiently preserved hypothalamic and brain-stem autonomic functions to permit survival with medical and nursing care; (6) bowel and bladder incontinence; and (7) variably preserved cranial-nerve reflexes (pupillary, oculocephalic, corneal, vestibulo-ocular, and gag) and spinal reflexes.'' While the first three points deal with the *awareness* part of the definition, points (4)–(7) refer to the criteria in terms of *wakefulness* and *responsiveness*. In the course of this chapter we will attempt to show that point (4) is rarely addressed, point (5) is partially tested concerning brainstem, but not hypothalamic autonomic functions, point (6) is seldom or never tested, and, finally, point (7) (the only *wakelfulness* variable frequently tested in the neurological examination) is not enough to define wakefulness in DOC.

Since the ''wakefulness'' part of the definition is loosely defined and rarely discussed in the literature, we will make it the focus of this chapter. We argue that a new framework is needed to characterize wakefulness in DOC patients, and that the main concepts of wakefulness to bear in mind will be (1) arousal/responsiveness, (2) sleep patterns, (3) circadian rhythms, and (4) homeostasis. Indeed, these four concepts are well defined and widely accepted and, in addition, they provide objective criteria to define bonafide measures in clinical practice. We will also propose a few simple tests and measurements to try to characterize the different factors of wakefulness. Moreover, since these factors are

heavily interconnected, when measuring one physiological parameter, usually several factors are scrutinized.

Arousal and the intensity of responses

Arousal is defined as a state of responsiveness to sensory stimulation (Mosby's Medical Dictionary, 2009) and a condition of sensory alertness. The difference between responsiveness and sensory alertness is that the former refers to the capacity of the system to respond while the latter is the threshold at which sensory stimuli can affect the system. A patient in VS may be alert from a sensory point of view but unable to control his/her responsiveness and therefore fail to react to incoming stimuli albeit spared capacity to process them.

The arousal system can be considered at three levels: (1) an upper level encompassing cerebral cortex and white matter; (2) a middle level including thalamus and upper brainstem; and (3) a lower level encompassing lower midbrain and pons. Although the upper level does not seem to be necessary to sustain arousal and is instead linked to awareness, brain damage at any of these levels may result in coma or various arousal alterations (Brenner, 2005; Evans, 2002). Moreover, arousal has been related to performance by the Yerkes–Dodson Law, which dictates that performance increases with arousal up to a point where it starts to decay (inverted U-shaped curve) (Yerkes and Dodson, 1908). The classic approach of arousal in the transition from sleep to wake proposes that arousal will slowly increase from the stages of slow-wave sleep (SWS) to stages 2 and 1, and increases even more when fully awake. However, it takes time to reach a full arousal level since sleep inertia carries a low arousal lag into the wake state; not surprisingly, performance in different tasks increases with ''more wakefulness'' (more arousal). Nevertheless, the arousal curve is not the same for all tasks, and there seems to be a distinction between cognitive tasks and automatic tasks. The former seems to require lower arousal for more difficult or intellectually challenging tasks (the subject needs to concentrate on the material), while automatic tasks require higher arousal levels for activities involving endurance and persistence (the subject needs higher and sustained motivation) (Teigen, 1994). For the purposes of defining arousal in an allegedly unconscious or minimally conscious subject, we should keep in mind that responsiveness and sensory alertness could be severely impaired in this population. The responses to be assessed to establish arousal levels in these patients should be kept simple to avoid misinterpretations.

For the clinician the challenge is to define a few simple bedside tests that may inform about the level of arousal of the DOC patient before starting a full neurological, behavioral, cognitive, or neurophysiological assessment. One approach has been to relate pain to autonomic arousal. By taking measures of pulse rate, skin conductance, and skin temperature, it may be possible to measure the physiological arousal caused by experiencing pain (Rhudy et al., 2008). It is also possible to measure brain activity by EEG in order to determine the extent to which an individual is experiencing pain. Responses to nociceptive stimuli are frequently assessed in DOC behavioral scales (Coma recovery scale-revised (CRS-R), GCS, SMART, WHIM) and can be easily recorded when taking measures of pulse rate, skin conductance, and skin temperature. These more sensitive methods to measure internal parameters have the potential of mapping the autonomic reactions to the stimuli but also provide the opportunity to assess arousal using objective and quantifiable methods.

Another evaluation, although rarely used in DOC, concerns arousal organization, which is linked to sleep–wake organization. A general ''basic-rest activity cycle'' (BRAC) has been defined and proposed to occur during both sleep and wakefulness stages (Kleitman, 1982). In other temporal scales, arousal can be defined as fast simultaneous changes in the EEG along with autonomic and somatic activity (Halasz et al., 2004). Compared to healthy individuals, patients with DOC do not exhibit the normal arousal alternations also known as ''standard cyclical alternating patterns'' (Freedman et al., 2001).

In these patients, changes in brain activation may be very slow, lasting a number of seconds or even minutes, and are not always rhythmic. These arousal alternations are often more extreme than in the healthy brain and may even be life-threatening, especially those occurring in the vegetative system (e.g., involving cerebrospinal fluid pressure increases, see Evans, 2002). The contrast between the extreme changes in sleep microstructure in the damaged brain as compared to the normal brain indicates the profound impairment in arousal control mechanisms in DOC.

A systematic approach to test arousal (responsiveness) variability in a simple manner would be to assess one particular reflex in the course of several hours. If the stimulus is frequently presented in a short period of time, it could lead to habituation effects; but if it is repeated one time every 30 s for 2 h, the response could unmask waves of different arousability levels. Figure 1 depicts eyeblink reflex responses to an air puff to the cornea in three DOC patients. Although the first few trials evidenced habituation effects, after stabilization, waves of responses varying in strength and latency appeared sporadically, illustrating how variable arousal can be in different DOC patients.

Sleep patterns (or how to assess brain network functions)

It has been proposed that one of the functions of sleep is to restore general homeostasis (including, more specifically, subcortical brain structures) (Hobson, 1996), and to stabilize the synaptic weight of recent neural connections (Gilestro et al., 2009). Accordingly, the lack of sleep cycles in DOC might predict a lower probability of recovery.

Sleep is usually characterized by the adoption of a typical posture and the absence of response to external stimuli due to transient but reversible periods of unconsciousness which, in healthy individuals, are accompanied by well-defined EEG changes (Rechtschaffen & Kales, 1968). The present section focuses on the importance of neurophysiology for the evaluation of sleep in DOC, in relation with diagnostic and prognostic criteria. However, it will be stressed that in DOC the electrophysiological definition of wakefulness and sleep is problematic because oscillations recorded by EEG no longer reflect the same cellular mechanisms as in normal physiological sleep. For example, large amplitude slow waves do not necessarily indicate deep nonrapid eye movement (NREM) or ‘SWS as they do in normal sleeping individuals. Indeed, a clear definition of sleep stage criteria (and therefore sleep staging) remains to be established in DOC. We will first review the available data on sleep in coma and VS in order to propose some specific recommendations. Unfortunately, there are no studies on sleep in minimaly conscious state (MCS), probably due to the recent definition of this state of consciousness (Giacino et al., 2002).

Although it is well-known that sleep abnormalities are extremely common in critically ill patients (Parthasarathy and Tobin, 2004; Cabello et al., 2007), their mechanisms and distinctive features remain poorly understood. From a behavioral point of view, normal sleep is usually preceded by the search for a safe place and a progressive but reversible decrease in response to external stimuli, as well a decrease in motor activity. In DOC, assessing these behavioral criteria is challenging.

One way to indirectly monitor sleep–wake cycles and circadian rhythms inexpensively and over long time periods is to record motor activity with a wrist actimeter. Motor activity measured with an actimeter has shown to be correlated to sleep detection in polysomnography (DeSouza et al., 2003; Berger et al., 2008) and can give a better account of the total sleep time than sleep diaries, even though sleep periods and variables such as sleep onset latency might be overestimated (Ancoli-Israel et al., 2003). Especially for patient groups, for whom traditional sleep monitoring such as polysomnography might not be applicable and rest-activity cycles should be evaluated over longer time periods such as weeks or months, actimetry can serve as a potential alternative (Morgenthaler et al., 2007). Actimetry has been used to investigate rest–activity cycles in

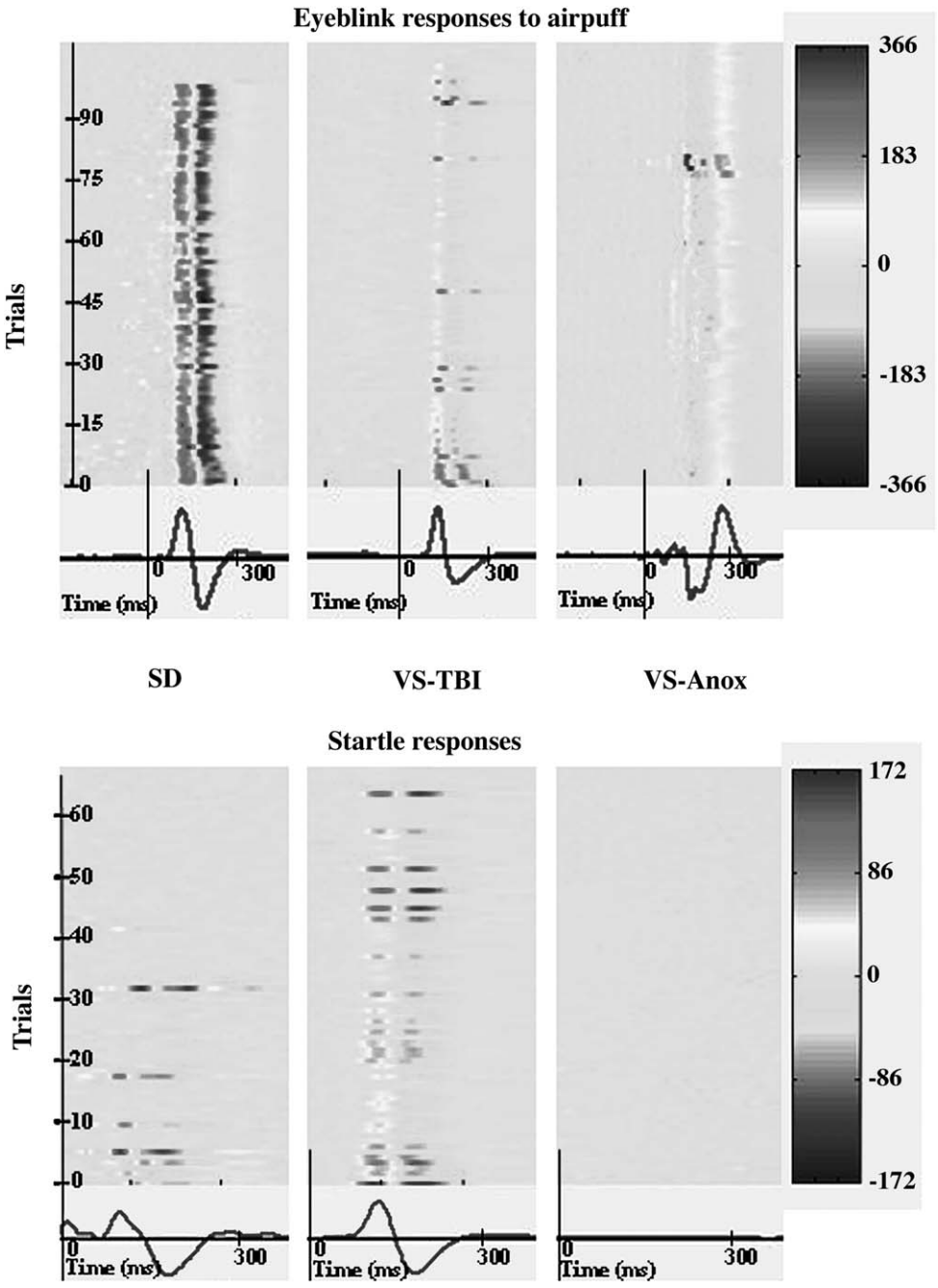


Fig. 1. Arousal changes reflected eyeblink variability to an airpuff and a startle tone. Top graph: electromyographic eyeblink responses to an airpuff to the cornea in a severely disabled (SD) patient (left), a VS patient of TBI origin (middle), and a VS patient of anoxic origin (right). Lower graph: electromyographic eyeblink responses to a loud noise burst in the same patients. Each plot is a raster of 60–100 trials occurring every 12–18 s. SD and VS-TBI patients showed habituation effects in the first 10–15 trials, while patient VS-anoxic showed no habituation effects. Nevertheless, SD patient showed nearly no changes after the 20th trial, while the two VS patients exhibited big changes in responsiveness suggesting changes in arousal. The bottom graph shows changes for SD and VS-TBI but no response for the patient from anoxic origin.

different psychiatric and neurologic patient groups as for example depression (e.g., Benedetti et al., 2008) or dementia (e.g., Werth et al., 2002; Paaivilainen et al., 2005). Furthermore, it has been used to evaluate treatment effects of nonpharmacological (e.g., Alessi et al., 2005) or pharmacological intervention (e.g., Daurat et al., 2000) to restore rest–activity rhythms. Recently, its feasibility has also been demonstrated for tetraplegic patients (Spivak et al., 2007). We recorded actimetry data in DOC patients to try to assess its feasibility to detect a near 24-h rhythm as a marker of a spared circadian clock and sleep–wake cycle across several days. Averaged movement data of a healthy control, an MCS patient, and a VS patient across 24 h are displayed in Fig. 2. What is evident from this figure is a clear sleep–wake cycle in the healthy control, as indicated by the increased movement during the day and the reduction during the hours of night. In the MCS patient this pattern is less clear but also detectable (at least indicating a rest–wake cycle), while it is also identifiable but even more deteriorated in the VS patient.

From a physiological point of view, normal sleep is associated with well-defined cycles, stages, arousals, and microstructures (e.g., K-complexes, spindles). In DOC the existence of such polysomnographic (PSG) elements is a matter of debate. Another characteristic aspect of sleep is its regulation by homeostatic and circadian processes. In DOC the available evidence for such regulators is scarce. As we will show in the subsequent section, circadian rhythms may be severely disrupted in DOC and, therefore, the evaluation of circadian rhythmicity should be evaluated independently from sleep since it may well be the case that a DOC patient shows sleep patterns sparsely along the day without apparent circadian control.

Early studies on coma suggested that the presence of EEG patterns resembling sleep may be reliable markers for a favorable outcome (Bergamasco et al., 1968; Chatrian et al., 1963). It was reported that sleep patterns become more complex during rehabilitation therapy, paralleling cognitive recovery (Ron et al., 1980). Some authors have used standard sleep criteria to analyze PSG data in DOC (Oksenberg et al., 2001). However, as many forms of brain damage may result in a relatively similar clinical state of unconsciousness, and cerebral activity changes in DOC may differ substantially from physiological sleep patterns, those criteria are probably not applicable for sleep staging in severely brain damaged patients. We suggest these scoring criteria need to be adapted for the study of sleep–wake patterns in DOC. To this end the visual adaptive scoring system, which describes vigilance levels with a higher resolution (Himanen and Hasan, 2000), or the analysis of microarousals (Halasz et al., 2004) may be useful alternatives.

In coma the EEG often shows a generalized slowing in the delta or theta range. Other EEG patterns that can be encountered include alpha-coma, burst-suppression, and epileptic-like activity (Brenner, 2005). No differentiation between normal and pathological slow sleep waves have been described. However, continuous delta activity in coma should not be mistaken for normal SWS. Coma can be considered as a dysregulation of the brain's arousal system caused by diffuse brain damage or by focal brainstem lesions (Adams et al., 2000). Some earlier studies have also indicated that sleep spindles may carry prognostic information. It was subsequently shown that the presence of spindle activity after hypoxic or anoxic injury does not always indicate a good outcome. However, the absence of spindles or EEG background reactivity does predict a poor outcome (Hulihan and Syna, 1994). A more recent study supports these findings in comatose children and concludes that the reappearance of sleep patterns and sleep spindles is a sign of a good prognosis. In traumatic coma, these sleep elements are more frequently observed than in anoxic cases (Cheliout-Heraut et al., 2001).

It is assumed that spindle coma represents a combination of physiological sleep and coma, the latter accounting for the failure of arousal. In humans, the pathophysiological mechanism of spindle coma is presumed to be the preservation of pontine raphe nuclei and thalamocortical circuits subserving sleep spindle activity, together with the impairment of ascending reticular

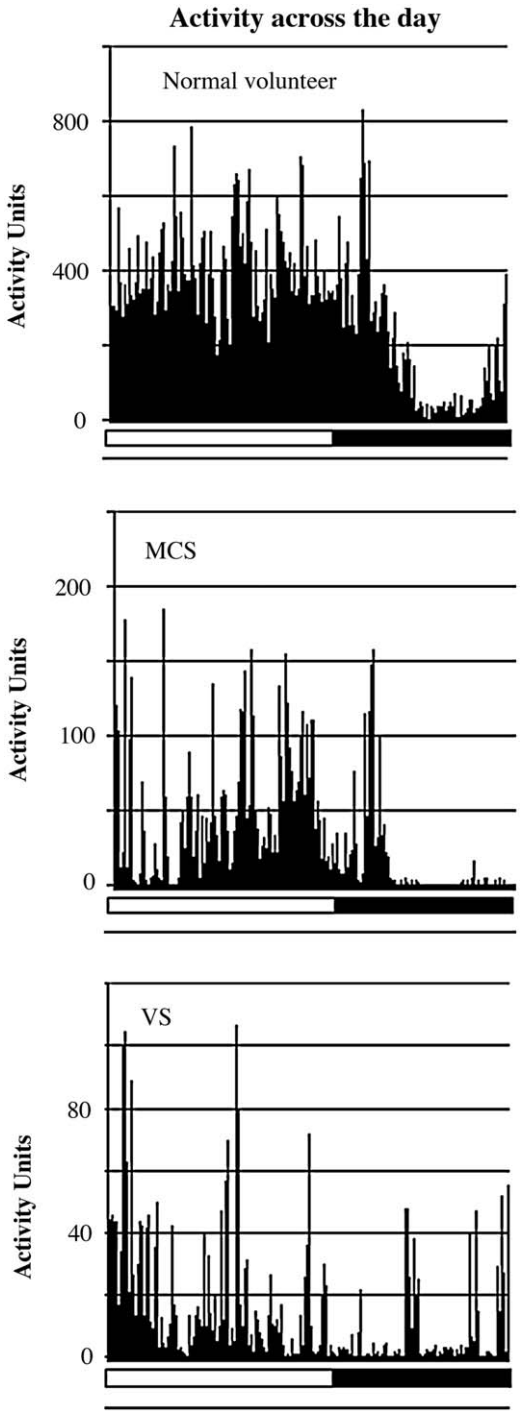


Fig. 2. Wrist activity may reveal circadian rhythmicity and sleep–wake cycling in DOC patients. Actigraphy watches measured ballistic movements in one arm in each participant for five consecutive days. While the normal volunteer (top graph) and the MCS patient (middle graph) show clear differences between day (white stripes) and night (black stripes), the VS patient shows a weaker effect (nonetheless still significant), albeit with a significantly lower effect size. The VS patient showed also more variability between days suggesting a weaker control of the circadian clock.

activating pathways at the midbrain level that maintain wakefulness (Britt et al., 1980; Britt, 1981; Seet et al., 2005). The predictability of different levels of sleep–wake organization in traumatic coma was compared to other indexes such as neuroradiological findings, age, or Glasgow Coma Scale (GCS) scores (Valente et al., 2002). It is interesting that PSG recordings were better predictors of outcome when compared to the GCS scores. NREM sleep elements such as K-complexes and sleep spindles as well as rapid eye movement (REM) sleep elements alternating with NREM sleep elements were also indicators of a better outcome. In contrast, a poor outcome was indicated for patients who had only monophasic EEG or an absence of sleep elements.

Compared to a healthy control group, only minor sleep alterations were found in nine traumatic patients with good outcome and no sleep patterns were found in one permanent VS patient (Giubilei et al., 1995). In another study it was reported that patients "in the last remission stages" went through all sleep stages with an increase of total sleep time in comparison to patients "in the first remission stages" of VS (D'Aleo et al., 1994b). As discussed above, spindle activity may be related to both injury severity and recovery. Evidence of spindles, although always reduced in density and duration, was found in 11 out of 20 traumatic and 3 out of 10 hypoxic VS patients (D'Aleo et al., 1994a). In addition, the authors showed an increase of spindle density from 5 to 12 per minute paralleling the clinical recovery of traumatic patients. As what has been shown for coma, these results suggest spindles as potential markers of good outcome in VS, but more studies are warranted.

Other authors focused on REM sleep in VS patients. An early study has shown the occurrence of nystagmus in wake and REM stages of six vegetative patients (Gordon and Oksenberg, 1993). The same authors also showed both a degradation of REM sleep and specific phasic events such as the number of REMs in 11 traumatic VS patients (Oksenberg et al., 2001). These findings might reflect possible damage or dysregulation in the pedunculopontine tegmental cholinergic structures in VS. Nevertheless, other phasic events such as sleep-related erections (Oksenberg et al., 2000) seem to be preserved. At present, no correlation between REM parameters and recovery from VS has been founded. However, it is clear that the more the comatose patient's brain activity resembles normal healthy sleep, the better the prognosis. It appears that there may be indicators of good outcome such as spindles, phasic arousal activity, and conservation of sleep stages. This would justify the use of PSG in the clinical routine. Disruptions of sleep patterns and NREM phasic events (e.g., spindles) are often found in the early stage of coma. Given that human spindle generators are located in the thalamus, it is tempting to hypothesize that the absence of spindles in coma results from the interruption of either the ascending reticular thalamocortical pathway or of thalamocortical loops. The absence of sleep–wake cycles seems associated with brainstem or hypothalamus dysfunction, and preliminary evidence suggests this may be associated with a poor outcome.

Since DOC patients do not show the normal behavioral, physiological, and regulatory signs of sleep, the characterization of their putative sleep–wake cycles is a challenging issue. Support for the presence of homeostatic sleep regulation in DOC could be provided by sleep deprivation protocols (e.g., by maintaining their eyes open) in which EEG comparisons could be performed. Another criterion for sleep state is an increased arousal threshold. If between different EEG patterns in DOC patients, arousal threshold changes significantly, this might be signaling sleep staging and therefore some degree of sleep preservation. Arousal level can be measured with auditory stimuli and EEG or with other reflexes, as we show in Fig. 1.

Overall, in the reviewed literature, data on patients' sleep appear to be insufficient and standardized methods were rarely used to assess behaviorally the level of consciousness. In summary, large cohort studies of well-documented VS patients are needed to (1) provide a better understanding of the presence (or absence)

of sleep–wake cycles in VS (and MCS), and (2) to reveal more detailed relationships between brain injury, sleep parameters, and clinical outcome.

In conclusion, the study of sleep is of particular interest in DOC with various different etiologies as it can provide relationships between neurophysiological measures and functional neuroanatomy, whereas waking patterns in noncomatose patients only indicate the persistence of the reticular activating system. As an example, spindles may reflect the preserved functional integrity of the thalamus; SWS and REM sleep may reflect residual functioning of brainstem nuclei; and the circadian organization of sleep patterns are informative of residual hypothalamic functioning. Nevertheless, the analysis of waking EEG, filtered for muscular artefacts (which are often exacerbated in DOC) and eyeblinks may also yield useful diagnostic and prognostic information. To illustrate this point we show in Fig. 3 two patients with very different sleep structure. Patient 1 shows no EEG differences between the night hours (represented by the horizontal gray bar) and the day hours, and no eye-movement differences, despite his diagnosis of VS and subsequent evolution to MCS a few months later. On the other side, patient 2 was in MCS at the time of the assessment and showed a relatively well-structured sleep rhythm for a severe brain injury patient. This patient also showed a difference between day and night electrooculography (EOG) (and in electrocardiographic recordings)

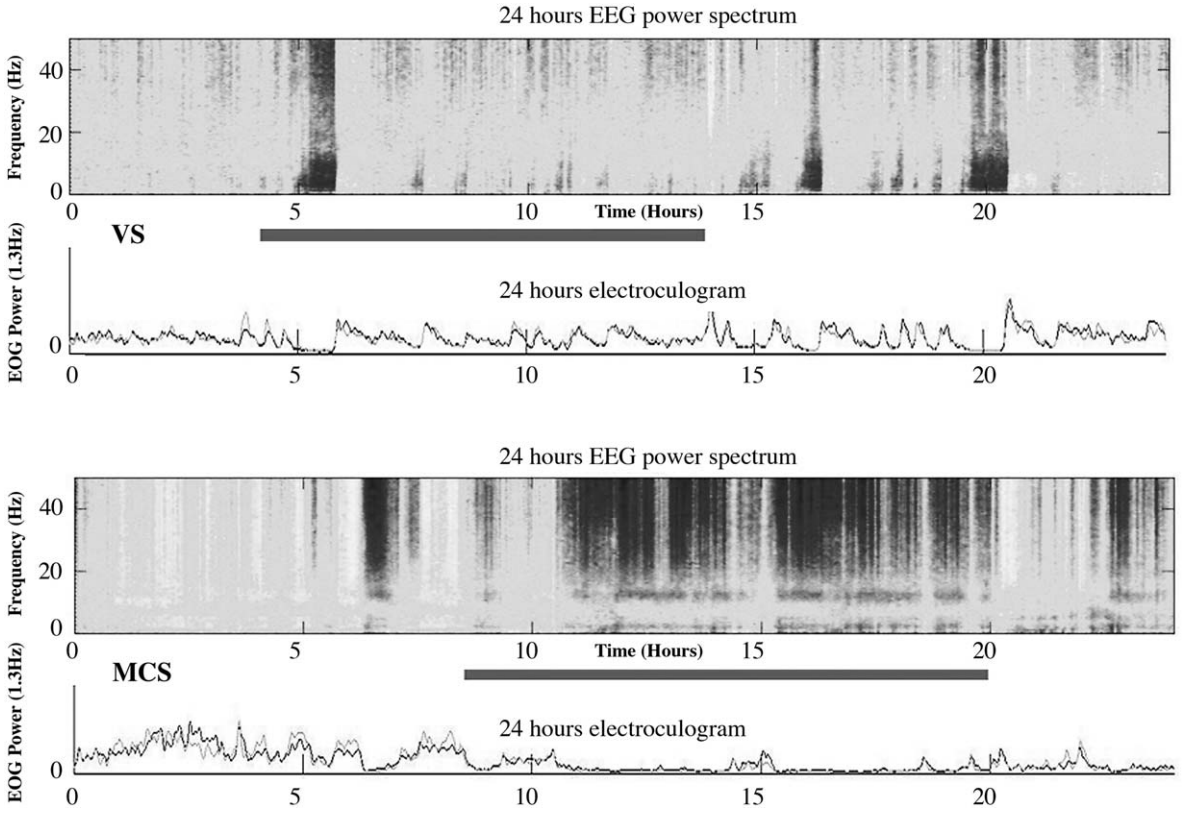


Fig. 3. 24-h EEG and EOG reveal sleep patterns preservation in DOC patients. Top graph: VS patient without sleep patterns or differences between day and night times (horizontal bar signals lights off). Bottom graph: MCS patient exhibiting clear differences in EEG and EOG between day and night times.

patterns suggesting spared functioning not only in the thalamocortical loop but in brainstem structures too.

Circadian rhythms (or when is it best to test for consciousness)

Together with evidence of eye opening, the presence of a sleep–wake cycle defines the threshold for the progression from a comatose state (Multi-Society Task Force on PVS, 1994) to VS or MCS (Report of a working party of the Royal College of Physicians, 2003). However, despite the importance of a sleep–wake cycle for differential diagnosis, there is very little empirical evidence that DOC patients actually exhibit sleep phenomena or display a circadian rhythm. Sleep–wake cycles are typically inferred by behavioral observations of long periods of eye closure.

A true cycle would only be possible if the clock in the brain is functioning properly. Circadian rhythms are endogenously generated by a biological clock located in the hypothalamic suprachiasmatic nuclei (SCN). SCN lesions eliminate such rhythms in physiology and behavior, while transplants of the nuclei restore rhythmicity to many variables. However, this master clock is actually the organizer of the activity of ''peripheral'' clocks which are present in most tissues (Reppert and Weaver, 2002). The circa-24 h (circadian) activity of the SCN is coupled through neural and humoral pathways with output relay stations that control rhythmic behavior and physiology (Buijs et al., 2006). One of the key features of circadian rhythms is their plasticity in terms of entrainment to the environment by adjusting to daily cues or ''zeitgeber''. The most important of these signals is the light–dark cycle, which is transduced through a retinohypothalamic tract leading to a cascade of neurochemical and genetic changes in the SCN (Golombek et al., 2003). This entrainment-SCN-output pathway regulates chronobiological parameters, including the timing of the sleep–wake cycle (Zee and Manthena, 2007). Circadian entrainment is achieved through a retinohypothalamic photoreception system led by retinal cells that give rise to an unconscious neural pathway independent from ''normal'' vision (Brainard and Hanifin, 2005).

Circadian and diurnal rhythms in mental performance in normal subjects have been described extensively (see Blatter and Cajochen, 2007; Carrier and Monk, 2000; Monk et al., 1997; Valdez et al., 2008; Waterhouse et al., 2001). Indeed, the diurnal variation in cognitive, mental, and physical abilities is fundamental for the determination of risk levels in different tasks and activities (Åkerstedt, 2007; Dinges, 1995; Folkard, 1990; Waterhouse et al., 2001) as well as for educational prospects (Golombek and Cardinali, 2008; Cajochen et al., 2004). There are several variables that confer interindividual variability to circadian variation in cognitive tasks. One of them is the preferred/innate habits of temporality or chronotype, that is, the tendency toward morningness or eveningness in an individual's behavior and physiology (Horne and Ostberg, 1976; Zavada et al., 2005). Extreme morning or evening chronotypes are accompanied by concomitant changes in physiological and behavioral variables (i.e., body temperature or melatonin onset, mental performance tasks), and there have been suggestions of specific polymorphisms in clock genes underlying such chronotypes (Allebrandt and Roenneberg, 2008). However, there is no profound insight into the relationship of chronotypes (even in their extreme form) and subtle changes in consciousness levels throughout the day.

On the contrary, there is strong evidence of diurnal changes in self-rated subjective feelings and mental performance tasks in normal subjects, which usually correlate with the endogenous cycle of body temperature (e.g., Blatter and Cajochen, 2007; Folkard, 1990). Indeed, mental performance is significantly worse in sleep deprivation conditions and during the night (Monk et al., 1997). It is important to state that these changes are related to the two main mechanisms responsible for the sleep–wake cycle, that is, the homeostatic (fatigue) component and the circadian (endogenous) proclivity to wakefulness or sleep (Beersma and Gordijn, 2007; Boivin et al., 1997; Borbely, 1982).

Although sleep states and, certainly, pharmacological manipulations, have traditionally been linked to different consciousness levels (Broughton, 1982; Cantero and Atienza, 2005; Tung and Mendelson, 2004), no formal approach to circadian modulation of consciousness or, on the other hand, circadian alterations in altered consciousness states has been performed, except for a few studies in patients with different degrees of brain damage. In this aspect, core body temperature rhythms are significantly affected by both impaired physical activity and brain lesions (Takekawa et al., 2002) and, more importantly, circadian rhythms have been associated with diagnosis and neurological findings in patients with altered consciousness states derived from brain damage (Dauch and Bauer, 1990). The pineal hormone melatonin, which is controlled by the circadian clock and might serve as one of its humoral outputs, has been proposed as a putative regulator of diverse plastic events in the brain, ultimately related to conscious mental processing (Bob and Fedor-Freybergh, 2008).

A handful of studies have shown 24-h variability (or lack of) in different physiological parameters in patients with impaired consciousness. Although none of them can be considered circadian studies but day–night variations (with only one day of measurements), they are still informative for our purposes. One study reported day–night brain state differences (Isono et al., 2002) in 8 out of 12 VS patients using continuous EEG; the remaining 4 patients showed the same EEG pattern during day and night. Three other studies measured blood pressure, heart rate, temperature and urinary excretion hormones, blood pressure and heart rate (Fukudome et al., 1996), and growth hormone, prolactin and cortisol, finding significant day–night changes in body temperature and urine hormones but not in blood pressure (Pattoneri et al., 2005). DOC patients showed significantly lower day–night difference in blood pressure as compared to normal volunteers, and alterations in the rhythm of hormonal levels (Vogel et al., 1990). These results point to a large variability in DOC patients in their ability to react to external temporal variations and suggests that a subpopulation might have the circadian system disrupted.

Another condition that results in impaired consciousness due to profound organic failure is severe sepsis, one of the principal causes of mortality and morbidity in ICUs. Mortality rates are consistently estimated as between 30% and 40% (Friedman et al., 1998). The systemic response to major infections involves massive inflammation, coagulation, and antifibrinolytic mechanisms ultimately leading to organ dysfunction. In addition, sepsis-related encephalopaties are common causes for altered consciousness states, ranging from sleep alterations to semiconscious vegetative or comatose situations (Davies et al., 2006, Sanap and Worthley, 2002; Papadopoulos et al., 2000). Moreover, circadian rhythm disruption, often exaggerated in ICU environments, probably helps in the development of disease (Herdegen, 2002). In addition, circadian disruptions of temperature and activity rhythms are predictors of mortality rates in murine septic models (Vlach et al., 2000). A recent report suggests that an environment deprived of circadian cues (e.g., no strong light–dark cycle) — which closely resembles the situation in most ICUs during recovery from sepsis significantly impairs survival in animal models of disease (Carlson and Chiu, 2008).

Endocrine circadian rhythms are also severely disrupted in septic patients (Mundigler et al., 2002; Bornstein et al., 1988; Joosten et al., 2000; Dennhardt et al., 1989). In particular, cyclic melatonin secretion, which is usually interpreted as a close indicator of the hands of the circadian clock, is impaired in critically ill patients due to the nature of the disease, continuous drug administration, and loss of external zeitgeber cues (Mundigler et al., 2002). Chronic illness, including sepsis and most situations which require a prolonged stay in ICUs, results in sleep disruption and deprivation which in turn is a strong morbid factor decreasing quality of life and potential recovery (Friese et al., 2009; Weinhouse and Schwab, 2006). It has also been suggested that exogenous melatonin treatment might be effective for treating sleep and circadian dysfunction in chronically ill patients (Bourne and Mills, 2006).

Rhythm robustness could be used as a predictor for disease severity, including mortality rates, in septic patients (Joosten et al., 2000).

Taking these ideas into consideration we have performed studies in a murine model of sepsis (by endotoxin — LPS — administration) and found that not only LPS toxic effect is time-dependent, but also that the eventual outcome in terms of morbidity and mortality is modulated by the circadian state of the animal (Marpegan et al., 2009). In addition, when analyzing circadian rhythms in temperature, blood pressure, and heart rate in septic patients, there is a clear correlation between rhythm amplitude and robustness and the degree of sepsis severity and survival rate (Katz et al., 2002).

In short, circadian rhythms could be a good prognostic marker in the acute phase of DOC but also a good measure of the physiological state of the patient in general. The first step is to obtain a rhythm that may represent the output of the clock, and second, to measure the circadian system capacity to react to external stimuli. We have recently measured skin temperature for two weeks in a small group of patients in an attempt to characterize true rhythmicity beyond 24 h (Bekinschtein et al., accepted). This study showed preserved circadian rhythmicity in two traumatic brain injury (TBI) patients, but no true rhythms in three patients of anoxic origin. Figure 2 shows patterns of activity variation (wrist actigraphy) in a normal volunteer, an MCS patient, and a VS patient. Although significantly smaller, the difference between day and night activity was significant even in the low-activity VS patient. Following these first few attempts of characterize the circadian patterns in DOC patients, we propose skin temperature measurements and wrist actigraphy as easy-to-use methods to address long-term rhythms in these patients, and melatonin or cortisol sampling to further test other outputs of the central clock. To define whether patients do really come through in waves and how rhythmic these are, we suggest: (1) at least four days of recording of continuous temperature and motor activity, and (2) three days (and nights) blood sampling every 6 h (with a higher sampling frequency at critical times) to assess cortisol and melatonin day–night differences. These measurements, together with 24-h EEG, should give enough information on whether there are rhythms and if behavioral assessment should be planned accordingly.

Homeostasis (or the search for balance in severe brain injury)

Immediately after a brain insult, a restoration of the basic bodily functions will be intended, by mechanical and/or chemical means. Severely injured patients frequently have a general unbalance of the whole homeostatic regulation of the body (Varon and Fromm, 2001). Those patients who are stabilized, can breathe by themselves, and have a regular heart function might appear homeostatically regulated but may as well still have lesions in the hypothalamus, pituitary gland, or other organs or tissues, putting them at a higher risk of contracting disease (Katikireddy and Kuschner, 2006a). Sometimes homeostasis assessment becomes a detective-like work wherein glucose levels, hydration, sweating, temperature, and urine composition are be tested regularly.

Several common illnesses, including diabetes, dehydration, gout, and central hyper- or hypothermia, may appear when a patient is homeostatically unbalanced (Katikireddy and Kuschner, 2006a, b). In most cases the treatment is symptomatic, and it is difficult to reach a stable point since these patients tend to deteriorate with time and it becomes more difficult to restore homeostasis. In this specific patient population, homeostasis assessment determines the optimal time to measure response capacity both in terms of arousal and in terms of conscious behavior. A metabolic imbalance has a huge impact on arousal and behavior and may hinder the true cognitive capacity of the patient by decreasing responsiveness.

To illustrate this point we present the case of a VS patient with a large brainstem and

hypothalamic (spreading to the left thalamus) lesion. The patient's autonomic failure makes the behavioral assessment extremely difficult. The patient does not close her eyelids anymore and suffers from extreme sweating attacks lasting 40–90 min. During these attacks her right-hand withdrawal responses are higher than when she is not in the autonomic storm. Her temperature rhythm and heartbeat proved to be very arrhythmic and she had a variation in Coma Recovery Scores between 3 and 8 in six consecutive assessments along three days (one in the morning and one in the afternoon). These results demonstrate the difficulty in determining her responsiveness and advocate for a full wakefulness assessment before a diagnostic decision regarding the level of awareness in DOC is achieved.

After brain insult some TBI patients may develop homeostatic imbalance (Sacho and Childs, 2008). It has been suggested that either excitatory center/s located in the upper brainstem and diencephalon drive paroxysms or that the causative brainstem/diencephalic centers are inhibitory in nature, with damage releasing excitatory spinal cord processes (excitatory/inhibitory ratio model) (Baguley et al., 2008). Dysautonomic attacks seem to be more closely associated with mesencephalic rather than diencephalic damage. Many reports suggest that paroxysmal episodes can be triggered by environmental events.

The remaining question is what to test for homeostasis assessment. Unlike arousal, circadian rhythms, or sleep patterns, homeostasis is considered more frequently in DOC. Temperature, blood pressure, and glucose levels are assessed regularly. But the levels of hydration, hormones, and electrolytes (potassium, calcium, and sodium) are not tested, although they might certainly impact the patient's responsiveness. We propose that the patient should be assessed by an endocrinologist in the early postacute period to define a set of tests to be taken regularly to keep in mind homeostatic variations in the course of a day or a week. This could avoid conflicting reports arising from a homeostatic imbalance on the responsiveness levels of the patient and therefore reduce the level of misdiagnosis (Andrews et al., 1996).

Assessment of wakefulness

The following recommendations may serve as a reference for clinicians involved in the examination and treatment of patients with DOC. They are based on our clinical experience with this patient population and the current state of knowledge about wakefulness from a clinical point of view.

Some of the recommendations for the accurate behavioral assessment of DOC patients (Majerus et al., 2005) may also apply to the evaluation of wakefulness:

- The patient should be healthy.
- The patient should be in a good nutritional state.
- Sedating drugs should be withdrawn whenever possible.
- Complications and consequences of neurological imbalance should be prevented.
- Controlled posture is important.

While these recommendations are certainly fundamental for the assessment of awareness, they also have a direct implication on the proposed four factors underlying wakefulness. Indeed, health is an issue at stake, since these patients are prone to infections and if this is the case the wakefulness assessment may be informative to decide whether it is worth to continue with a full behavioral and/or physiological assessment. A similar criterion applies to nutritional state: checking homeostatic responses and arousal/responsiveness should indicate the body's metabolic state and its capacity to respond to external stimulation. In addition, control of spasticity and postures is important in the behavioral assessment, as it has been shown patients in VS and MCS score much higher when assessed at 85° at a tilt table as compared to bed position (Elliott et al., 2005). Most likely the ascending reticular activating system is stimulated by the

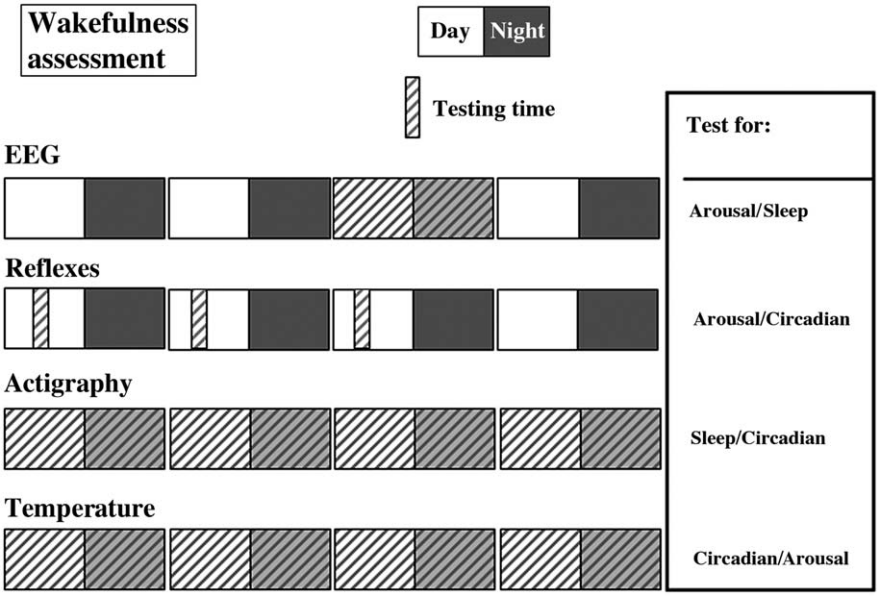


Fig. 4. Wakefulness assessment for DOC patients. For each test the proposed testing time is shown, as well as the factor it addresses.

change in position. In our opinion, any procedure that may increase arousal should be considered for DOC patients since it may unveil behaviors consistent with conscious awareness in VS patients or capacity to communicate in MCS patients.

For a full understanding of the wakefulness capacity of a DOC patient, we propose a series of tests to assess arousal, circadian rhythms, and sleep patterns. We recommend starting this assessment when the patient is systemically healthy and homeostatically stable. Figure 4 shows a summary of the tests proposed and when to start each measure. Arousal is behaviorally stratified in the CRS-R scale ranging from ''unarousable'' to ''attention''; however, this is useful for an initial test but does not inform about arousal variability in the patient. To this aim we propose to choose one reflex in the patient that can be rated (i.e., very low, low, medium, high, very high responses) and to assess it systematically (every 5 min) in the course of 2–3 h for at least three days (testing at the same day and time). This approach should inform about the variability in arousal both within and between days.

To test for circadian control we propose to continuously record a simple variable for several days. To define if the central clock in the brain is functioning, the external environment should be controlled, in particular temperature and light–dark variations. We have shown that skin temperature and motor activity may be easy to test and have the capacity to unveil the day-to-day variability. Both methods are cheap and require minimal maintenance, and if rhythms are assessed for at least four days, the clock capacity to be entrained can be determined. This test, together with the arousal assessment, will give an indication on when it is best to test for awareness in order to increase the likelihood of obtaining the maximal responses from each DOC patient.

Sleep evaluation may be indicative of the degree of damage in different brain networks. A 24-h EEG assessment may relate to reticular activating function if state transitions are present; spindles may reflect the preserved functional integrity of the thalamus; and SWS and REM

sleep may reflect residual functioning of brainstem nuclei.

Conclusion

In the second part of the report from the Muti-Society Task Force on PVS (1994), recovery is divided into two dimensions: recovery of consciousness and recovery of function. The first one refers to the capacity to detect awareness (emergence from VS), and the second deals with the patient's capacity to communicate, to learn, and to perform adaptative tasks. Surprisingly there is no mention of the capacity to recover from decreased wakefulness or the problems caused by lower and/or erratic responsiveness in the assessment of recovery of consciousness or recovery of function. As we pointed out in this chapter, wakefulness may not appear as a key aspect in the evaluation of DOC patients, but the level of wakefulness may act as an enabling condition for conscious processing (Dehaene and Changeaux, 2004).

The clear relationship between circadian rhythms and sleep states (Winfree, 1982) could and should be extended to different conscious states. Although it is difficult to measure fatigue (as the homeostatic process of sleep) in DOC patients, it is possible to measure some physiological variables that are under circadian control and, in the process, responsiveness variability (changes in arousal) can be obtained. For the assessment of wakefulness and awareness, the temperature rhythm (if found) could be a good starting point to decide when, during the day, it is best to assess the cognitive processing of the patient. The understanding of the relationships between arousal, circadian rhythms, and sleep in DOCs is essential from a descriptive point of view and, most importantly, as putative diagnostic and prognostic tools that might help to aid therapeutic alternatives.

If the patient is homeostatically stable the combination of arousal, circadian, and sleep assessments can account for most of the aspects of wakefulness in DOC patients. Knowing when the patient does seem to be more active, more responsive, and fully awake may decrease the misdiagnosis (false negatives) of true MCS patients classified as VS and true severely disabled patients classified as MCS. The detailed assessment of wakefulness — whether coming through in waves, in tides, or completely absent — will help in the characterization of this neglected aspect of consciousness and may have prognostic value for DOC patients.

Acknowledgments

We thank the patients and their families for their participation. We specially thank Dr. Laureys, Dr. Delorme, Dr. Manes, and Dr. Owen for helping in our research with DOC patients. We also thank Thanh Dang-Vu for providing the normal volunteer actigraphy data. We (the authors) declare having no conflicts of interest. TB is supported by an IIF Marie Curie Fellowship, VC by FRIA-FNRS, BD by the German National Merit Foundation, and DG by CONICET, ANPCyT and Universidad de Quilmes.

References

Adams, J. H., Graham, D. I., & Jennett, B. (2000). The neuropathology of the vegetative state after an acute brain insult. *Brain*, *123*, 1327–1338.

Åkerstedt, T. (2007). Altered sleep/wake patterns and mental performance. *Physiology and Behavior*, *90*, 209–218.

Alessi, C., Martin, J. L., Webber, A. P., Kim, E. C., Harker, J. O., & Josephson, K. R. (2005). Randomized, controlled trial of a nonpharmacological intervention to improve abnormal sleep/wake patterns in nursing home residents. *JAGS*, *53*, 803–810.

Allebrandt, K. V., & Roenneberg, T. (2008). The search for circadian clock components in humans: New perspectives for association studies. *Brazilian Journal of Medical and Biological Research*, *41*, 716–721.

Ancoli-Israel, S., Cole, R., Alessi, C., Chambers, M., Moorcroft, W., & Pollak, C. P. (2003). The role of actigraphy in the study of sleep and circadian rhythm. *Sleep*, *26*, 342–359.

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *BMJ*, *313*, 13–16.

Baguley, I. J., Heriseanu, R. E., Cameron, I. D., Nott, M. T., & Slewa-Younan, S. (2008). A critical review of the pathophysiology of dysautonomia following traumatic brain injury. *Neurocritical Care*, *8*, 293–300.

Beersma, D., & Gordijn, M. (2007). Circadian control of the sleep–wake cycle. *Physiology and Behavior*, *90*, 190–195.

Bekinschtein, T. A., Golombek, D. A., Simonetta, S. H., Coleman, M. R., & Manes, F. F. (in press). Circadian rhythms in the vegetative state.

Benedetti, F., Radaelli, D., Bernasconi, A., Dallaspezia, S., Falini, A., Scotti, G., Lorenzi, C., Colombo, C., & Smeraldi, E. (2008). Clock genes beyond the clock: CLOCK genotype biases neural correlates of moral valence decision in depressed patients. *Genes Brain Behavior*, *7*(1), 20–25.

Bergamasco, B., Bergamini, L., Doriguzzi, T., & Sacerdote, I. (1968). The sleep cycle in coma: Prognostic value. *Electroencephalography and Clinical Neurophysiology*, *25*, 87.

Berger, A. M., Wielgus, K. K., Young-McCaughan, S., Fischer, P., Farr, L., & Lee, K. A. (2008). Methodological challenges when using actigraphy in research. *Journal of Pain and Symptom Management*, *36*, 191–199.

Blatter, K., & Cajochen, C. (2007). Circadian rhythms in cognitive performance: Methodological constraints, protocols, theoretical underpinnings. *Physiology and Behavior*, *90*, 196–208.

Bob, P., & Fedor-Freybergh, P. (2008). Melatonin, consciousness, and traumatic stress. *Journal of Pineal Research*, *44*, 341–347.

Boivin, D., Czeisler, C., Dijk, D. J., Duffy, C., Folkard, S., Minors, D., et al. (1997). Complex interaction of the sleep–wake cycle and circadian phase modulates self-rated subjective feelings in healthy subjects. *Archives of General Psychiatry*, *54*, 145–152.

Borbely, A. (1982). Sleep regulation: Circadian rhythm and homeostasis. In D. Ganten & D. Pfaff (Eds.), *Sleep. Clinical and experimental aspects* (pp. 83–104). Berlin: Springer Verlag.

Bornstein, S. R., Licinio, J., Tauchnitz, R., Engelmann, L., Negrao, A. B., Gold, P., et al. (1988). Plasma leptin levels are increased in survivors of acute sepsis: Associated loss of diurnal rhythm, in cortisol and leptin secretion. *The Journal of Clinical Endocrinology and Metabolism*, *83*, 280–283.

Bourne, R. S., & Mills, G. H. (2006). Melatonin: Possible implications for the postoperative and critically ill patient. *Intensive Care Medicine*, *32*, 371–379.

Brainard, G. C., & Hanifin, J. P. (2005). Photons, clocks, and consciousness. *Journal of Biological Rhythms*, *20*, 314–325.

Brenner, R. P. (2005). The interpretation of the EEG in stupor and coma. *Neurologist*, *11*, 271–284.

Britt, C. W., Jr. (1981). Nontraumatic ''spindle coma'': Clinical, EEG, and prognostic features. *Neurology*, *31*, 393–397.

Britt, C. W., Jr., Raso, E., & Gerson, L. P. (1980). Spindle coma, secondary to primary traumatic midbrain hemorrhage. *Electroencephalographic Clinical Neurophysiology*, *49*, 406–408.

Broughton, R. (1982). Human consciousness and sleep/waking rhythms: A review and some neuropsychological considerations. *Journal of Clinical Neuropsychology*, *4*, 193–218.

Brown, J. (1970). ''Get up.'' From the single ''Get Up (I Feel Like Being A) Sex Machine''. Live at the Bell Auditorium (USA).

Buijs, R. M., Scheer, F. A., Kreier, F., Yi, C., Bos, N., Goncharuk, V. D., et al. (2006). Organization of circadian functions: Interaction with the body. *Progress in Brain Research*, *153*, 341–360.

Cabello, B., Parthasarathy, S., & Mancebo, J. (2007). Mechanical ventilation: Let us minimize sleep disturbances. *Current Opinion in Critical Care*, *13*, 20–26.

Cajochen, C., Knoblauch, V., Wirz-Justice, A., Kräuchi, K., Graw, P., & Wallach, D. (2004). Circadian modulation of sequence learning under high and low sleep pressure conditions. *Behavioural Brain Research*, *151*, 167–176.

Cantero, J. L., & Atienza, M. (2005). The role of neural synchronization in the emergence of cognition across the wake–sleep cycle. *Review of Neuroscience*, *6*, 69–83.

Carlson, D. E., & Chiu, W. C. (2008). The absence of circadian cues during recovery from sepsis modifies pituitary–adrenocortical function and impairs survival. *Shock*, *29*, 127–132.

Carrier, J., & Monk, T. (2000). Circadian rhythms of performance: new trends. *Chronobiology International*, *17*, 719–732.

Chatrian, G. E., White, L. E., Jr., & Daly, D. (1963). Electroencephalographic patterns resembling those of sleep in certain comatose states after injuries to the head. *Electroencephalography and Clinical Neurophysiology*, *15*, 272–280.

Cheliout-Heraut, F., Rubinsztajn, R., Ioos, C., & Estournet, B. (2001). Prognostic value of evoked potentials and sleep recordings in the prolonged comatose state of children. Preliminary data. *Neurophysiologie Clinique*, *31*, 283–292.

D'Aleo, G., Bramanti, P., Silvestri, R., Saltuari, L., Gerstenbrand, F., & Di Perri, R. (1994a). Sleep spindles in the initial stages of the vegetative state. *Italian Journal of Neurological Sciences*, *15*, 347–351.

D'Aleo, G., Saltuari, L., Gerstenbrand, F., & Bramenti, P. (1994b). Sleep in the last remission stages of vegetative state of traumatic nature. *Functional Neurology*, *9*, 189–192.

Dauch, W. A., & Bauer, S. (1990). Circadian rhythms in the body temperatures of intensive care patients with brain lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, *53*, 345–347.

Daurat, A., Benoit, O., & Buguet, A. (2000). Effects of zopiclone on the rest/activity rhythm after a westward flight across five time zones. *Psychopharmacology*, *149*, 241–245.

Davies, N. W., Sharief, M. K., & Howard, R. S. (2006). Infection-associated encephalopathies: Their investigation, diagnosis, and treatment. *Journal of Neurology*, *253*, 833–845.

Dehaene, S., & Changeux, J. P. (2004). Neural mechanisms for access to consciousness. In M. Gazzaniga (Ed.), *The cognitive neurosciences*. (3rd ed., volume in press).

Dennhardt, R., Gramm, H. J., Meinhold, K., & Voigt, K. (1989). Patterns of endocrine secretion during sepsis. *Progress in Clinical and Biological Research*, *308*, 751–756.

DeSouza, L., Benedito-Silva, A. A., Noguiera Pires, M. L., Poyares, D., Tufik, S., & Calil, H. M. (2003). Further validation of actigraphy in sleep studies. *Sleep*, *26*, 81–85.

Dinges, D. (1995). An overview of sleepiness and accidents. *Journal of Sleep Research*, *4*(Suppl. 2), 4–14.

Dylan, B. (1979). ''When you gonna wake up?'' From the Album ''Slow Train Coming''. CMS Digital Studios (California, USA).

Elliott, L., Coleman, M., Shiel, A., Wilson, B. A., Badwan, D., Menon, D., et al. (2005). Effect of posture on levels of arousal and awareness in vegetative and minimally conscious state patients: A preliminary investigation. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*, 298–299.

Evans, B. M. (2002). What does brain damage tell us about the mechanisms of sleep? *Journal of the Royal Society of Medicine*, *95*, 591–597.

Folkard, S. (1990). Circadian performance rhythms: Some practical and theoretical implications. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *327*, 543–553.

Freedman, N. S., Gazendam, J., Levan, L., Pack, A. I., & Schwab, R. J. (2001). Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *American Journal of Respiratory and Critical Care Medicine*, *163*, 451–457.

Friedman, G., Eliezer, S., & Vincet, J. L. (1998). Has the mortality of septic shock changed with time? *Critical Care Medicine*, *26*, 2078–2086.

Friese, R. S., Bruns, B., & Sinton, C. M. (2009). Sleep deprivation after septic insult increases mortality independent of age. *Journal of Trauma*, *66*, 50–54.

Fukudome, Y., Abe, I., Saku, Y., Matsumura, K., Sadoshima, S., Utunomiya, H., et al. (1996). Circadian blood pressure in patients in a persistent vegetative state. *American Journal of Physiology*, *270*, 1109–1114.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*, 349–353.

Gilestro, G. F., Tononi, G., & Cirelli, C. (2009). Widespread changes in synaptic markers as a function of sleep and wakefulness in Drosophila. *Science*, *324*, 109–112.

Giubilei, F., Formisano, R., Fiorini, M., Vitale, A., Faroni, J., Toni, D., et al. (1995). Sleep abnormalities in traumatic apallic syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, *58*, 484–486.

Golombek, D. A., & Cardinali, D. P. (2008). Mind, brain, education and biological timing. *Mind, Brain and Education*, *2*, 1–6.

Golombek, D. A., Ferreyra, G. A., Agostino, P. V., Murad, A. D., Rubio, M. F., Pizzio, G. A., et al. (2003). From light to genes: Moving the hands of the circadian clock. *Frontiers in Bioscience*, *8*, 285–293.

Gordon, C. R., & Oksenberg, A. (1993). Spontaneous nystagmus across the sleep–wake cycle in vegetative state patients. *Electroencephalography and Clinical Neurophysiology*, *86*, 132–137.

Halasz, P., Terzano, M., Parrino, L., & Bodizs, R. (2004). The nature of arousal in sleep. *Journal of Sleep Research*, *13*, 1–23.

Herdegen, J. J. (2002). Intensive care unit sleep disruption: Can the cycle be restored? *Critical Care Medicine*, *30*, 709–710.

Himanen, S. L., & Hasan, J. (2000). Limitations of Rechtschaffen and Kales. *Sleep Medicine Reviews*, *4*, 149–167.

Hobson, J. A. (1996). How the brain goes out of its mind. *Endeavour*, *20*, 86–89.

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness in human circadian rhythms. *International Journal of Chronobiology*, *4*, 97–110.

Hulihan, J. F., Jr., & Syna, D. R. (1994). Electroencephalographic sleep patterns in post-anoxic stupor and coma. *Neurology*, *44*, 758–760.

Isono, M., Wakabayashi, Y., Fujiki, M. M., Kamida, T., & Kobayashi, H. (2002). Sleep cycle in patients in a state of permanent unconsciousness. *Brain Injury*, *16*, 705–712.

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet*, *7753*, 734–737.

Jewel, A. (1995). From the Album ''Pieces of You''. Atlantic (New York, USA).

Joosten, K. F., de Kleijn, E. D., Westerterp, M., de Hoog, M., Eijck, F. C., Hop, W. C. J., et al. (2000). Endocrine and metabolic responses in children with meningoccocal sepsis: Striking differences between survivors and nonsurvivors. *The Journal of Clinical Endocrinology and Metabolism*, *85*, 3746–3753.

Katikireddy, C. K., & Kuschner, W. G. (2006a). Critical care medicine update: Essentials for the nonintensivist, part 2. *Comprehensive Therapy*, *32*, 82–89.

Katikireddy, C. K., & Kuschner, W. G. (2006b). Critical care medicine update: Essentials for the nonintensivist, part 1. *Comprehensive Therapy*, *32*, 74–81.

Katz, M. E., Grizzo, M. E., Salim, M., Gonzalez Ley, B., Merino, D., Golombek, D. A., et al. (2002). Sleep-wake cycle after renal transplant and cyclosporin treatment (abst.). *Transplantation*, *74*(4), 760.

Kleitman, N. (1982). Basic rest–activity cycle 22 years later. *Sleep*, *5*, 311–317.

Majerus, S., Gill-Thwaites, H., Andrews, K., & Laureys, S. (2005). Behavioral evaluation of consciousness in severe brain damage. *Progress in Brain Research*, *150*, 397–413.

Marpegan, L., Leone, M. J., Katz, M. E., Sobrero, P., Bekinschtein, T. A., & Golombek, D. A. (in press). Diurnal variation in endotoxin-induced mortality in mice: Correlation with proinflammatory factors.

Monk, T., Buysse, D., Reynolds, C., Berga, S., Jarrett, D., Begley, A., et al. (1997). Circadian rhythms in human performance and self-rated subjective feelings under constant conditions. *Journal of Sleep Research*, *6*, 9–18.

Morgenthaler, T., Alessi, C., Friedman, L., Owens, J., Kapur, V., Boehlecke, B., et al. (2007). Practice parameters for the use of actimetry in the assessment of sleep and sleep disorders: An update for 2007. *Sleep*, *30*, 519–529.

Mosby's Medical Dictionary. (2009). 8th edn. San Diego: Elsevier Inc.

Multi-Society Task Force on PVS. (1994). Medical aspects of the persistent vegetative state (1 and 2). *The New England Journal of Medicine*, *330*, 1572.

Mundigler, G., Delle-Karth, G., Koreny, M., Zehetgruber, M., Steindl-Munda, P., Marktl, W., et al. (2002). Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Critical Care Medicine*, *30*, 536–540.

Oksenberg, A., Arons, E., Sazbon, L., Mizrahi, A., & Radwan, H. (2000). Sleep-related erections in vegetative state patients. *Sleep*, *23*, 953–957.

Oksenberg, A., Gordon, C., Arons, E., & Sazbon, L. (2001). Phasic activities of rapid eye movement sleep in vegetative state patients. *Sleep*, *24*, 703–706.

Paaivilainen, P., Korhonen, I., Lotjonen, J., Cluitmans, L., Julha, M., Sarela, A., et al. (2005). Circadian activity rhythm in demented and non-demented nursing-home residents measured by telemetric actigraphy. *Journal of Sleep Research*, *14*, 61–68.

Papadopoulos, M. C., Davies, D. C., Moss, R. F., Tighe, D., & Bennett, E. D. (2000). Pathophysiology of septic encephalopathy: A review. *Critical Care Medicine*, *28*, 3019–3024.

Parthasarathy, S., & Tobin, M. J. (2004). Sleep in the intensive care unit. *Intensive Care Medicine*, *30*, 197–206.

Pattoneri, P., Tirabassi, G., Pela, G., Astorri, E., Mazzuchi, A., & Borghetti, A. (2005). Circadian blood pressure and heart rate changes in patients in a persistent vegetative state after traumatic brain injury. *Journal of Clinical Hypertension (Greenwich)*, *7*, 734–739.

Rechtschaffen, A., & Kales, A. (1968). *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects*. Bethesda, MD: US Dept. of Health, Education, and Welfare, p. 12.

Reppert, S. M., & Weaver, D. R. (2002). Coordination of circadian timing in mammals. *Nature*, *418*, 935–941.

Rhudy, J. L., Williams, A. E., McCabe, K. M., Russell, J. L., & Maynard, L. J. (2008). Emotional control of nociceptive reactions (ECON): Do affective valence and arousal play a role?. *Pain*, *136*, 250–261.

Ron, S., Algom, D., Hary, D., & Cohen, M. (1980). Time-related changes in the distribution of sleep stages in brain injured patients. *Electroencephalography and Clinical Neurophysiology*, *48*, 432–441.

Sacho, R. H., & Childs, C. (2008). The significance of altered temperature after traumatic brain injury: An analysis of investigations in experimental and human studies: Part 2. *British Journal of Neurosurgery*, *22*, 497–507.

Sanap, M. N., & Worthley, L. I. (2002). Neurologic complications of critical illness: Part I. Altered states of consciousness and metabolic encephalopathies. *Critical Care and Resuscitation*, *4*, 119–132.

Seet, R. C., Lim, E. C., & Wilder-Smith, E. P. (2005). Spindle coma from acute midbrain infarction. *Neurology*, *64*, 2159–2160.

Spivak, E., Oksenberg, A., & Catz, A. (2007). The feasibility of sleep assessment by actigraph in patients with tetraplegia. *Spinal Cord*, *45*, 765–770.

Takekawa, H., Miyamoto, M., Miyamoto, T., Yokota, N., & Hirata, K. (2002). Alteration of circadian periodicity in core body temperatures of patients with acute stroke. *Psychiatry and Clinical Neuroscience*, *56*, 221–222.

Teigen, K. H. (1994). Yerkes-Dodson: A law for all Seasons. *Theory and Psychology*, *4*(4), 525–547.

The Sunday Times. (2007). 40% of coma patients in a 'vegetative state' may be misdiagnosed, says a new report. Available at: http://www.timesonline.co.uk/tol/life_and_style/health/article3004892.ece

Tung, A., & Mendelson, W. B. (2004). Anesthesia and sleep. *Sleep Medicine Reviews*, *8*, 213–225.

Valdez, P., Reilly, T., & Waterhouse, J. (2008). Rhythms in mental performance. *Mind, Brain and Education*, *2*, 7–16.

Valente, M., Placidi, F., Oliveira, A. J., Bigagli, A., Morghen, I., Poietti, R., et al. (2002). Sleep organization pattern as a prognostic marker at the subacute stage of post-traumatic coma. *Clinical Neurophysiology*, *113*, 1798–1805.

Varon, J., & Fromm, R. E. (2001). *Handbook of practical critical care medicine*. Berlin: Springer.

Vlach, K. D., Boles, J. W., & Stiles, B. G. (2000). Telemetric evaluation of body temperature and physical activity as predictors of mortality in a murine model of staphylococcal enterotoxic shock. *Journal of Comparative Medicine*, *50*, 160–166.

Vogel, H. P., Kroll, M., Fritschka, E., & Quabbe, H. J. (1990). Twenty-four-hour profiles of growth hormone, prolactin and cortisol in the chronic vegetative state. *Clinical Endocrinology (Oxford)*, *33*, 631–643.

Waterhouse, J., Minors, D., Åkerstedt, T., Reilly, T., & Atkinson, G. (2001). Rhythms of human performance. In J. Takahashi, F. Turek, & R. Moore (Eds.), *Handbook of behavioral neurobiology: Circadian clocks* (pp. 571–601). New York: Kluwer Academic/Plenum Publishers.

Weinhouse, G. L., & Schwab, R. J. (2006). Sleep in the critically ill patient. *Sleep*, *29*, 707–716.

Werth, E., Savaskan, E., Knoblauch, V., Fontana Gasio, P., Van Someren, E. J. W., Hock, C., et al. (2002). Decline in long-term circadian rest-activity cycle organization in a patient with dementia. *Journal of Geriatric Psychiatry and Neurology*, *15*, 55–59.

Winfree, A. T. (1982). The tides of human consciousness: Descriptions and questions. *American Journal of Physiology*, *242*, R163–R166.

Yerkes, R. M., & Dodson, J. D. (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of Comparative Neurology and Psychology*, *18*, 459–482.

Zavada, A., Gordijn, M. C., Beersma, D. G., Daan, S., & Roenneberg, T. (2005). Comparison of the Munich Chronotype Questionnaire with the Horne–Ostberg's Morningness–Eveningness Score. *Chronobiology International*, *22*, 267–278.

Zee, P. C., & Manthena, P. (2007). The brain's master circadian clock: Implications and opportunities for therapy of sleep disorders. *Sleep Medicine Reviews*, *11*, 59–70.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 13

Disorders of consciousness: further pathophysiological insights using motor cortex transcranial magnetic stimulation

Natallia Lapitskaya[1,2,*], Martin R. Coleman[3], Joergen Feldbaek Nielsen[1], Olivia Gosseries[2] and Alain Maertens de Noordhout[4]

[1]*Neurorehabilitation Research Department, Hammel Neurorehabilitation and Research Centre, Hammel, Denmark*
[2]*Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium*
[3]*Impaired Consciousness Research Group, Wolfson Brain Imaging Centre, University of Cambridge, UK*
[4]*Neurology Department, University of Liège, Centre Hospitalier Regional de la Citadelle, Liège, Belgium*

Abstract: Transcranial magnetic stimulation (TMS) is a noninvasive means of investigating the function, plasticity, and excitability of the human brain. TMS induces a brief intracranial electrical current, which produces action potentials in excitable cells. Stimulation applied over the motor cortex can be used to measure overall excitability of the corticospinal system, somatotopic representation of muscles, and subsequent plastic changes following injury. The facilitation and inhibition characteristics of the cerebral cortex can also be compared using the modulatory effect of a conditioning stimulus preceding a test stimulus. So called paired-pulse protocols have been used in humans and animals to assess GABA (γ-amino-butyric acid)-ergic function and may have a future role directing therapeutic interventions. Indeed, repetitive magnetic stimulation, where intracranial currents are induced by repetitive stimulation higher than 1 Hz, has been shown to modulate brain responses to sensory and cognitive stimulation. Here, we summarize information gathered using TMS with patients in coma, vegetative state, and minimally conscious state. Although in the early stages of investigation, there is preliminary evidence that TMS represents a promising tool by which to elucidate the pathophysiological sequelae of impaired consciousness and potentially direct future therapeutic interventions. We will discuss the methodology of work conducted to date, as well as debate the general limitations and pitfalls of TMS studies in patients with altered states of consciousness.

Keywords: coma; vegetative state; minimally conscious state; brain injury; transcranial magnetic stimulation; repetitive transcranial magnetic stimulation

Introduction

Over the past two decades, transcranial magnetic stimulation (TMS) has provided fascinating insight into the mechanisms and consequences of

*Corresponding author.
Tel.: +45 8762 3573; Fax: +45 8762 3305;
E-mail: natallia.lapitskaya@hammel.rm.dk

DOI: 10.1016/S0079-6123(09)17713-0

cortical plasticity in the intact and damaged human brain (e.g., see Siebner and Rothwell, 2003). However, very few studies have focused on severe brain injury and disorders of consciousness (DOC), specifically, the conditions of coma, vegetative state (VS), and minimally conscious state (MCS). This chapter provides a brief introduction to the technique of TMS, before summarizing information gathered using TMS in DOC. Although in the early stages of investigation, there is preliminary evidence to suggest that TMS represents a promising tool by which to elucidate the pathophysiological sequelae of impaired consciousness and potentially direct future therapeutic interventions. We will discuss the methodology of work conducted to date, as well as debate the general limitations and pitfalls of TMS studies in patients with DOC. Finally, we will also suggest possible areas of future TMS investigation with these challenging patients.

General principles of TMS

TMS represents a noninvasive, generally pain free, means of stimulating the cerebral cortex (Barker and Jalinous, 1985). In classic TMS experiments, a plastic-coated coil of wire is placed over the scalp, through which a powerful and rapidly changing current is passed, to create a magnetic field that penetrates the cranium and neuronal membrane, to produce excitatory or inhibitory postsynaptic potentials (reviewed in Di Lazzaro et al., 2004). In most experiments, stimulation is delivered to the primary motor cortex, and motor evoked potentials (MEPs) are recorded from a muscle using surface electromyography electrodes. TMS may activate, inhibit, or interfere with the activity of various cortico-cortical and cortico-subcortical networks according to the parameters of stimulation. Stimulation site, coil orientation, biphasic versus monophasic stimulation, stimulus intensity, and frequency can all be used to manipulate the resulting changes to the cerebrum, including how long these changes continue for after stimulation has ceased.

Single- and paired-pulse TMS

Single-pulse TMS (spTMS) can be applied to the motor cortex to determine motor threshold and generate input–output curves. Motor threshold refers to the lowest TMS intensity required to evoke MEPs in a target muscle in 50% of trials. Provided spinal motor neuronal excitability is stable, motor threshold is believed to represent a measure of membrane excitability in pyramidal neurons (Ziemann et al., 1996). Single TMS pulses of progressively increasing intensity applied to the motor cortex can be used to generate a recruitment curve. The resulting modulation of MEP amplitude to increasing intensity of TMS pulses appears to provide a measure of excitatory feedback to corticospinal efferent output, which may be glutamatergically mediated (Kaelin-Lang et al., 2002; Prout and Eisen, 1994). By using a paired-pulse TMS paradigm, activation of intracortical inhibitory neurons within the motor cortex is possible (Kujirai et al., 1993). It is suggested that an inhibitory phenomenon takes place at the cortical level (Di Lazzaro et al., 1998) and is the result of the firing of GABAergic interneurons within motor cortex (Boroojerdi et al., 2001; Ziemann et al., 1996). The functional connectivity between the sensory and the primary motor cortex can also be described by TMS. Afferent input (i.e., electrical stimulation of the digital or median nerves) is shown to modify the excitability of the motor cortex induced by TMS with a complex time course (Maertens de Noordhout et al., 1992; Tokimura et al., 2000). This inhibitory phenomenon is termed as ‘‘short latency afferent inhibition’’ and is thought to be regulated by muscarinic cholinergic circuits (Di Lazzaro et al., 2002). Functional connectivity between the two cerebral hemispheres can be studied by transcallosal TMS (Ferbert et al., 1992) by applying a conditioning stimulus to one hemisphere while applying a test stimulus to the other hemisphere. Transcallosal output gives rise to inhibition of the contralateral primary motor cortex (Gerloff et al., 1998; Meyer et al., 1995; Wassermann et al., 1991).

Repetitive and paired associative TMS

Single and paired pulses guarantee a high temporal precision (in the milliseconds range). If a train of multiple pulses is applied at a particular frequency, the stimulation is called repetitive TMS (rTMS). In contrast to spTMS, multiple pulses have more prolonged effects on the brain. The nature of the aftereffects depends on the number, intensity, and frequency of stimulation pulses. For example, stimulation at frequencies lower than 1 Hz reduces cortex excitability (Chen et al., 1997; Romero et al., 2002), while stimulation at frequencies higher than 1 Hz tends to increase cortical excitability (Berardelli et al., 1998). The duration of such excitability shift depends on the duration of the rTMS exposure, that is, the number of rTMS trains applied and the intertrain interval. Changes in excitability of the neuraxis observed during rTMS appear complex (reviewed in Fitzgerald et al., 2006) and require both studies in humans and in animal models to explore the underlying mechanisms. In contrast, paired associative stimulation has accumulated reasonable evidence for a role of synaptic mechanisms that might relate to long-term potentiation (LTP) and long-term depression (LTD)-like effects. Paired associative stimulation was first described by Stefan et al. (2000). The median nerve is activated by bipolar electrical stimulation at the wrist, and spTMS is applied to the hand representation of the contralateral primary motor cortex through a focal figure-of-eight coil. The interstimulus interval is either set to 25 ms (Stefan et al., 2000) or adjusted to the individual N20-latency (plus 2 ms) of the median nerve somatosensory evoked potential (Ziemann et al., 2004). LTP-like plasticity, induced by paired associative stimulation, is measured as a long-term increase (>30 min) of the MEP in the target muscle (Stefan et al., 2000) or by an increase in the slope of the MEP intensity curve (Meunier et al., 2007; Rosenkranz et al., 2007). Finally, Huang et al. (2005) have recently described a rapid method to modulate excitability in the motor cortex, termed as ''theta burst stimulation.'' The protocol uses short bursts of low intensity (80% of active motor threshold), high-frequency (50 Hz) pulses, repeated at 5 Hz—the frequency of the theta rhythm in the electroencephalogram. Epidural recordings suggest that continuous theta burst stimulation has its major effect on the synapse between the interneurones responsible for the indirect I_1 wave and the corticospinal neurones (Di Lazzaro et al., 2005). Different patterns of delivery of theta burst stimulation (continuous vs. intermittent) produce opposite effects on synaptic efficiency of the stimulated motor cortex (Di Lazzaro et al., 2008; Huang et al., 2005).

TMS in DOC

Despite widespread use of TMS techniques in neuroscience, very few TMS investigations have been conducted in acute and chronic DOC (reviewed in Lapitskaya et al., 2009). The majority of TMS work with DOC has been undertaken to determine whether TMS has the ability to predict outcome from coma at an early stage or to evaluate whether TMS is able to assess corticospinal motor function more precisely than the clinical examination. No studies have been published so far considering TMS as a tool for investigating pathophysiology aspects of DOC.

The prognostic utility of TMS in coma

To date four empirical studies have focused on whether TMS can predict outcome in coma. Ying et al. (1992) examined 23 comatose patients (11 traumatic, 12 non-traumatic) within 2–20 days of coma onset and found no relationship between the integrity of MEPs and outcome as measured by the Glasgow Outcome Scale (Jennett and Bond, 1975). Similarly, Facco et al. (1991) investigated 22 comatose patients (13 traumatic, 9 non-traumatic) within 1 week of coma onset and found no relationship between the integrity of MEPs and outcome. A similar finding was also obtained from 30 patients with acute brainstem lesions. Schwarz et al. (2000) used spTMS to record MEPs from a group of patients, whom they

described as having decreased consciousness (described clinically as comatose, stuporous, and somnolent), having been admitted to the accident and emergency department. However, no correlation was found between MEPs and Glasgow Outcome Scale score 3 months post-ictus. In contrast, Zentner and Rohde (1992) performed spTMS with 39 comatose patients (etiology not available) within 3 days of insult, and found that MEPs presence was weakly correlated with the patients Glasgow Outcome Scale score 3 months and 2 years later.

In summary, TMS studies to date have failed to identify a clear prognostic utility. One of the limitations of the classic MEP in the clinical setting appears to be its absence in some patients with good outcome. A transient absence of MEPs in comatose patients may be due to reversible damage of motor pathways or decreased excitability due to treatment (e.g., sedation, antiepileptic drugs). When cortical excitability is decreased, the single magnetic stimulus might not be strong enough to excite the motor cortex even with the maximal stimulator output; therefore facilitation techniques should be applied in comatose patients. The commonly used technique in healthy volunteers of voluntary muscle contraction is not possible in unresponsive patients—thus other techniques (e.g., painful stimulation prior to the TMS; double or repetitive pulse paradigms) have to be used.

The prognostic utility of TMS in VS and MCS

Patients in VS have ''awakened'' from their coma (e.g., they open their eyes on stimulation or spontaneously), but remain unaware of self or environment (e.g., they show only reflex motor responses) (Jennett and Plum, 1972). In contrast, patients in MCS show limited but clearly discernible evidence of awareness of self or environment (i.e., reproducible responses to command, pursuit eye movement, etc.). The emergence of MCS is characterized by the recovery of functional communication or use of objects (Giacino et al., 2002). Despite the fact that misdiagnosis of these patients is still frequent in clinical practice (e.g., Schnakers et al., 2006, 2009), the diagnosis of MCS often leads to a better outcome than VS.

To date only three studies have assessed VS and MCS patients with TMS. It should be mentioned that consciousness impairment in the published patient populations is not well defined, as the studies were conducted before the introduction of the MCS criteria (Giacino et al., 2002). Moosavi et al. (1999) applied spTMS to the hand and leg motor area in 19 patients; 6–76 months after severe anoxic brain injury. Eleven patients were consistently unresponsive to simple verbal commands and multimodality sensory stimulation (VS), while eight patients were able to respond with reliable movements such as gaze directed selection of ''yes'' or ''no'' signs (MCS). However, none of the patients were able to make isolated finger or thumb movements. Moosavi et al. were unable to elicit MEPs from any muscle in two of the eleven unresponsive, VS patients. Whether the MEPs' absence can be attributed to the focal damage in the respective motor areas remains speculative, as the authors do not present any imaging data on these patients. In the remaining patients, the nonresponsive (VS) patient group differed from the responsive (MCS) patient group in having a higher threshold, longer duration, and greater irregularity in the form of the response, while the threshold, form, and latency of MEPs from the responsive (MCS) group were similar to healthy control subjects.

The second study to investigate VS patients with TMS was conducted by Mazzini et al. (1999), who used TMS to monitor recovery. Mazzini examined MEPs from upper and lower limbs in 27 patients in the subacute period (about 2 months after injury) and then at 6 and 12 months post-ictus. Patients were either comatose or in the VS at the first examination, while five patients remained VS 1 year after the trauma and one died at the end of the follow-up. During the study period, the authors observed an overall trend toward an increase of amplitude and decrease of latency of MEPs. MEPs from upper and lower limbs progressively normalized in all patients, and at 1 year after trauma, only 12% of patients had mild abnormalities in MEP responses. The differences between basal MEP scores and those at

12 months after trauma did not correlate with the Glasgow Coma Scale at the time of injury and the duration of coma. Similarly, no association was found between MEP amplitude or latency at the first examination and outcome, measured by Glasgow Outcome Scale.

Nevertheless, a concomitant increase in MEP amplitude and clinical recovery has been observed in a single case study. Crossley et al. (2005) investigated the relationship between cognitive and behavioral ability and spTMS elicited MEPs. In their case study, recovery from the traumatic coma was monitored using the Wessex Head Injury Matrix (Shiel et al., 2000). Clinical and TMS examinations were performed at 4 weeks post-injury, when the patient showed signs of arousal and alertness (eyes open briefly, attention held momentarily by dominant stimulus), and 12 months later, when the patient was reported to be fully awake and conscious. TMS conducted at 12 months showed an increase in the MEP amplitude in comparison to the recording at 4 weeks, consistent with clinical improvement.

In summary, the results support the idea that a degree of cortical functional integrity is present in post-comatose patients, even in those who are clinically diagnosed as being in a nonresponsive state. Despite the absence of voluntary movements, TMS elicited MEP responses in the majority of severely brain-damaged patients, and a trend toward an increase of amplitude and decrease of latency of MEPs could be observed during the recovery period.

Possible confounding variables influencing TMS results in DOC

A variety of factors might have effects on the cortical excitability parameters obtained with TMS in DOC patients.

(1) Medication is one of the main pitfalls when interpreting TMS results in DOC patients. TMS is thought to activate the corticospinal neurons transsynaptically (Di Lazzaro et al., 2003), and is more susceptible than transcranial electrical stimulation to inhibitory drug effects, but on the other hand, could have a higher sensitivity to detect superficial, presynaptic lesions. Chronic DOC patients have been weaned off sedation, but many remain on anticonvulsants, antispasticity and analgesic drugs, benzodiazepines, central nervous system stimulants, and antidepressants. While some information has been gathered on how individual drugs influence TMS (reviewed in Paulus et al., 2008), the effects of different combinations of drugs used in severely injured and bedridden patients remains unclear.

(2) Currents induced in the healthy brain by TMS flow parallel to the plane of the stimulation coil, that is, approximately parallel to the brain's cortical surface when the stimulation coil is held tangentially to the scalp (Saypol et al., 1991). This results in preferential activation of neural elements oriented horizontally, that is, parallel to the cortical surface (Amassian et al., 1990; Day et al., 1987). This notion is not unchallenged (Edgley et al., 1990) and is highly dependent on stimulation intensity, coil orientation, sulcal pattern, conductivity of neighboring tissue, and orientation of nerve fibers (Maccabee et al., 1993). In DOC patients, one usually needs higher stimulation intensities to elicit an MEP. The site within the motor system at which decreased excitability occurs, however, is unclear. In the case of severe brain injury, a combination of primary and secondary lesions directly destroy or compress brain tissue and produce local and remote effects on the brain (Plum and Posner, 1983), while diffuse axonal injury causes shearing injuries to the cerebral white matter (Povlishock, 1993). The excitability patterns after brain damage may be as much due to the site and type of damage as to the changes in activity across the undamaged brain.

(3) The amplitude of the MEP is not only dependent on TMS intensity, but is also greatly influenced by factors that affect corticospinal excitability. The excitability of the postsynaptic corticospinal neuron

may be decreased or increased, possibly relating to changes in extrinsic input to the motor cortex. The magnitude of the intracortical inhibition and facilitation varies depending on the degree of contraction of the target muscle—a critical variable to control for in paired-pulse TMS studies. For example, voluntary contraction of the target muscle enhances excitability at the spinal level and facilitates the responses to TMS (Hess et al., 1986; Thompson et al., 1991). Mental imagery of contraction of the same target muscle results in a similar facilitation of MEPs. Cincotta et al. (1999) reported a case of locked-in syndrome due to a large pontine infarction. One month after the attack, no MEPs could be recorded from either the right upper or lower limb. In contrast, MEPs were obtained from the left hand, although with a prolonged latency and reduced amplitude. When the patient was requested to mentally perform an abduction of her paralyzed left little finger, the latency and the amplitude of these responses improved as compared with the relaxed condition. Although in this patient no control condition was investigated to rule out the possibility that MEP changes might depend upon the patient's arousal level, it seems reasonable to conclude that motor imagery played a major role in determining this facilitation.

(4) The amplitude and the latency of the MEP reflect not only the integrity of the corticospinal tract, but also the excitability of nerve roots and the conduction along the peripheral motor pathway to the muscles. Patients with dysfunction at any level along the corticospinal pathway may show abnormal MEPs, while the presence of intact MEPs suggests integrity of the pyramidal tract. Pronounced lengthening of central motor conduction time suggests demyelination of pathways, while a low-amplitude response, with little delay or absence of response, is more suggestive of loss of neurons or axons. The spectrum of neuromuscular problems in the severely brain injured patient is broad, especially in the acute stage of coma. In the intensive care unit, 70% of patients with systemic inflammatory response syndrome suffer from critical illness polyneuropathy (Witt et al., 1991). Axonal motor neuropathy and neuromuscular junction dysfunction, due to administration of neuromuscular blocking agents and steroids, myopathy (diffuse, type II muscle fibers atrophy, thick-filament myopathy, necrotizing myopathy), and atrophy of the muscles due to prolonged immobility, might affect both amplitude and latency of MEPs (Zifko et al., 1998).

(5) Maintenance of a constant scalp position with the stimulating coil is critically important in TMS studies because a small change in the position can greatly affect the MEP amplitude. VS patients are, by definition, unable to follow instructions, and adjustment to the robotic coil positioning cannot always be maintained, so TMS experiments often require manual coil positioning, which is difficult over a long session.

In summary, TMS results in DOC should be interpreted with some caution. At present, there is some indication TMS may provide a useful measure of excitability in the targeted cortex and its connections.

Directions for future research

The last 10 years have been witnessed to important advances in our understanding of DOC. Structural brain imaging studies demonstrate that the behavioral level ultimately achieved by a patient following severe brain injury cannot be simply graded by the degree of diffuse axonal and direct ischemic brain damage (Giacino et al., 2006). Changes in cerebral metabolism and excitability of brain areas remote from a lesion have been reported in animals and humans and implicated as mechanisms relevant for functional recovery (Andrews, 1991; Seitz et al., 1999). The underlying mechanisms involve the unmasking of existing, but latent, horizontal

connections (Sanes and Donoghue, 2000) or modulation of synaptic efficacy such as LTP or LTD (Cooke and Bliss, 2006). The neurotransmitter systems involved in mediating these effects include the inhibitory GABAergic (Hess et al., 1996b; Hess and Donoghue, 1994) as well as the excitatory glutamatergic system with activation of *N*-methyl-d-aspartate receptors (Hess et al., 1996a). Single-pulse stimulation paradigms do not seem to provide sufficient information about the integrity of inhibitory and excitatory networks in DOC. However, paired-pulse and repetitive stimulation paradigms might identify signs of preserved brain connectivity in noncommunicative brain-damaged patients. Transcallosal inhibition (Takeuchi et al., 2006) and short latency afferent inhibition (Fujiki et al., 2006) are worthy of further investigation in DOC as they are potent connectivity markers.

In addition, rTMS modulates cortical excitability beyond the duration of the rTMS trains themselves. Particularly tantalizing is the possibility that modulation of cortical excitability by rTMS might have therapeutic applications in DOC conditions. At present, there are no proven treatments for promoting recovery from DOC. Inspiration could be picked up from multifarious studies in major depressive disorders (Fregni et al., 2006; Gross et al., 2007; Pascual-Leone et al., 1998), cognitive (reviewed in Miniussi et al., 2008) and motor (reviewed in Edwards and Fregni, 2008) rehabilitation in stroke, traumatic brain injury, and neurodegenerative disorders. Indeed, in a recent case study, Pape et al. (2009) described the results of a safety and efficacy study that examined a therapeutic rTMS protocol for persons with severe traumatic brain injury. A 6-week rTMS protocol (30 sessions) was delivered to a 26-year-old man who remained in VS 10 months after severe traumatic brain injury. Stimulation was directed over the right dorsolateral prefrontal cortex. Neurobehavioral assessments were obtained at baseline, every fifth rTMS session, and at a 6-week follow-up. There were no adverse events related to the provision of rTMS treatment. A trend toward significant neurobehavioral gains was temporally related to the provision of rTMS. Although it is too early to conclude that rTMS might have any therapeutic application, it is possible rTMS could modify cortical excitability. Indeed, theta burst stimulation paradigms are of particular interest in DOC, as they seem to facilitate long-lasting cortical excitability changes (inhibitory and excitatory) after very short stimulation sessions. Furthermore, noninvasive brain stimulation, integrated with EEG and neuroimaging techniques, may provide a means to investigate a range of stimulation sites (i.e., occipital and frontal areas, precuneus, etc.) and parameters for deep brain stimulation in order to facilitate cognitive recovery (Schiff et al., 2007) in DOC.

Here, we have briefly reviewed some of the ways in which TMS could be applied to evaluate cortical excitability in DOC. Although early empirical studies suggest that TMS has very little prognostic utility, the more recent application of rTMS, particularly theta burst, suggests it may have a therapeutic role, promoting changes in cortical excitability. At present, the field of neurorehabilitation lacks evidence-based treatments for promoting cognitive recovery in DOC, and thus it is hoped more studies utilizing TMS will be seen in the near future.

Acknowledgments

NL is supported by a research fellowship from the European Neurological Society and the Danish Medical Research Council. OG is research fellow at the Fonds de la Recherche Scientifique (FRS). This work was supported by European Commission (DISCOS, Mindbridge and COST) and James McDonnell Foundation.

References

Amassian, V. E., Quirk, G. J., & Stewart, M. (1990). A comparison of corticospinal activation by magnetic coil and electrical stimulation of monkey motor cortex. *Electroencephalography and Clinical Neurophysiology*, *77*, 390–401.

Andrews, R. J. (1991). Transhemispheric diaschisis. A review and comment. *Stroke*, *22*, 943–949.

Barker, A. T., & Jalinous, R. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet*, *1*, 1106–1107.

Berardelli, A., Inghilleri, M., Rothwell, J. C., Romeo, S., Curra, A., Gilio, F., et al. (1998). Facilitation of muscle evoked responses after repetitive cortical stimulation in man. *Experimental Brain Research*, *122*, 79–84.

Boroojerdi, B., Battaglia, F., Muellbacher, W., & Cohen, L. G. (2001). Mechanisms influencing stimulus-response properties of the human corticospinal system. *Clinical Neurophysiology*, *112*, 931–937.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., et al. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, *48*, 1398–1403.

Cincotta, M., Tozzi, F., Zaccara, G., Borgheresi, A., Lori, S., Cosottini, M., et al. (1999). Motor imagery in a locked-in patient: Evidence from transcranial magnetic stimulation. *Italian Journal of Neurological Sciences*, *20*, 37–41.

Cooke, S. F., & Bliss, T. V. P. (2006). Plasticity in the human central nervous system. *Brain*, *129*, 1659–1673.

Crossley, M., Shiel, A., Wilson, B., Coleman, M. R., Gelling, L., Fryer, T., et al. (2005). Monitoring emergence from coma following severe brain injury in an octogenarian using behavioural indicators, electrophysiological measures and metabolic studies: A demonstration of the potential for good recovery in older adults. *Brain Injury*, *19*, 729–737.

Day, B. L., Thompson, P. D., Dick, J. P., Nakashima, K., & Marsden, C. D. (1987). Different sites of action of electrical and magnetic stimulation of the human brain. *Neuroscience Letters*, *75*, 101–106.

Di Lazzaro, V., Oliviero, A., Pilato, F., Mazzone, P., Insola, A., Ranieri, F., et al. (2003). Corticospinal volleys evoked by transcranial stimulation of the brain in conscious humans. *Neurological Research*, *25*, 143–150.

Di Lazzaro, V., Oliviero, A., Pilato, F., Saturno, E., Dileone, M., Mazzone, P., et al. (2004). The physiological basis of transcranial motor cortex stimulation in conscious humans. *Clinical Neurophysiology*, *115*, 255–266.

Di Lazzaro, V., Oliviero, A., Profice, P., Saturno, E., Pilato, F., Insola, A., et al. (1998). Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. *Electroencephalography and Clinical Neurophysiology*, *109*, 397–401.

Di Lazzaro, V., Oliviero, A., Tonali, P. A., Marra, C., Daniele, A., Profice, P., et al. (2002). Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. *Neurology*, *59*, 392–397.

Di Lazzaro, V., Pilato, F., Dileone, M., Profice, P., Oliviero, A., Mazzone, P., et al. (2008). The physiological basis of the effects of intermittent theta burst stimulation of the human motor cortex. *Journal of Physiology (London)*, *586*, 3871–3879.

Di Lazzaro, V., Pilato, F., Saturno, E., Oliviero, A., Dileone, M., Mazzone, P., et al. (2005). Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *Journal of Physiology (London)*, *565*, 945–950.

Edgley, S. A., Eyre, J. A., Lemon, R. N., & Miller, S. (1990). Excitation of the corticospinal tract by electromagnetic and electrical stimulation of the scalp in the macaque monkey. *Journal of Physiology (London)*, *425*, 301–320.

Edwards, D., & Fregni, F. (2008). Modulating the healthy and affected motor cortex with repetitive transcranial magnetic stimulation in stroke: Development of new strategies for neurorehabilitation. *NeuroRehabilitation*, *23*, 3–14.

Facco, E., Baratto, F., Munari, M., Dona, B., Casartelli Liviero, M., Behr, A. U., et al. (1991). Sensorimotor central conduction time in comatose patients. *Electroencephalography and Clinical Neurophysiology*, *80*, 469–476.

Ferbert, A., Priori, A., Rothwell, J. C., Day, B. L., Colebatch, J. G., & Marsden, C. D. (1992). Interhemispheric inhibition of the human motor cortex. *Journal of Physiology (London)*, *453*, 525–546.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology*, *117*, 2584–2596.

Fregni, F., Boggio, P. S., Nitsche, M. A., Marcolin, M. A., Rigonatti, S. P., & Pascual-Leone, A. (2006). Treatment of major depression with transcranial direct current stimulation. *Bipolar Disorders*, *8*, 203–204.

Fujiki, M., Hikawa, T., Abe, T., Ishii, K., & Kobayashi, H. (2006). Reduced short latency afferent inhibition in diffuse axonal injury patients with memory impairment. *Neuroscience Letters*, *405*, 226–230.

Gerloff, C., Cohen, L. G., Floeter, M. K., Chen, R., Corwell, B., & Hallett, M. (1998). Inhibitory influence of the ipsilateral motor cortex on responses to stimulation of the human cortex and pyramidal tract. *Journal of Physiology (London)*, *510*, 249–259.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*, 349–353.

Giacino, J. T., Hirsch, J., Schiff, N., & Laureys, S. (2006). Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Archives of Physical Medicine and Rehabilitation*, *87*, S67–S76.

Gross, M., Nakamura, L., Pascual-Leone, A., & Fregni, F. (2007). Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatrica Scandinavica*, *116*, 165–173.

Hess, C. W., Mills, K. R., & Murray, N. M. F. (1986). Magnetic stimulation of the human brain-facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. *Neuroscience Letters*, *71*, 235–240.

Hess, G., Aizenman, C. D., & Donoghue, J. P. (1996a). Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. *Journal of Neurophysiology*, *75*, 1765–1778.

Hess, G., Aizenman, C. D., & Donoghue, J. P. (1996b). Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. *Journal of Neurophysiology*, *75*, 1765–1778.

Hess, G., & Donoghue, J. P. (1994). Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps. *Journal of Neurophysiology*, *71*, 2543–2547.

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron*, *45*, 201–206.

Jennett, B., & Bond, M. (1975). Assessment of outcome after severe brain damage. *Lancet*, *1*, 480–484.

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet*, *1*, 734–737.

Kaelin-Lang, A., Luft, A. R., Sawaki, L., Burstein, A. H., Sohn, Y. H., & Cohen, L. G. (2002). Modulation of human corticomotor excitability by somatosensory input. *Journal of Physiology (London)*, *540*, 623–633.

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., et al. (1993). Corticocortical inhibition in human motor cortex. *Journal of Physiology (London)*, *471*, 501–519.

Lapitskaya, N., Delvaux, V., Overgaard, M., Nielsen, F., Maertens de Noordhout, A., Moonen, G., et al. (2009). Transcranial magnetic stimulation in disorders of consciousness. *Reviews in the Neurosciences*, *20* (3–4), in press.

Maccabee, P. J., Amassian, V. E., Eberle, L. P., & Cracco, R. Q. (1993). Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in vitro—Locus of excitation. *Journal of Physiology (London)*, *460*, 201–219.

Maertens de Noordhout, A., Rothwell, J. C., Day, B. L., Dressler, D., Nakashima, K., Thompson, P. D., et al. (1992). Effect of digital nerve stimuli on responses to electrical or magnetic stimulation of the human brain. *Journal of Physiology (London)*, *447*, 535–548.

Mazzini, L., Pisano, F., Zaccala, M., Miscio, G., Gareri, F., & Galante, M. (1999). Somatosensory and motor evoked potentials at different stages of recovery from severe traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *80*, 33–39.

Meunier, S., Russmann, H., Simonetta-Moreau, M., & Hallett, M. (2007). Changes in spinal excitability after PAS. *Journal of Neurophysiology*, *97*, 3131–3135.

Meyer, B. U., Roricht, S., Voneinsiedel, H. G., Kruggel, F., & Weindl, A. (1995). Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. *Brain*, *118*, 429–440.

Miniussi, C., Cappa, S. F., Cohen, L. G., Floel, A., Fregni, F., Nitsche, M. A., et al. (2008). Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. *Brain Stimulation*, *1*, 326–336.

Moosavi, S. H., Ellaway, P. H., Catley, M., Stokes, M. J., & Haque, N. (1999). Corticospinal function in severe brain injury assessed using magnetic stimulation of the motor cortex in man. *Journal of Neurological Sciences*, *164*, 179–186.

Pape, T., Rosenow, J., Lewis, G., Ahmed, G., Walker, M., Guernon, A., et al. (2009). Repetitive transcranial magnetic stimulation-associated neurobehavioral gains during coma recovery. *Brain Stimulation*, *2*, 22–35.

Pascual-Leone, A., Tormos, J. M., Keenan, J., Tarazona, F., Canete, C., & Catala, M. D. (1998). Study and modulation of human cortical excitability with transcranial magnetic stimulation. *Journal of Clinical Neurophysiology*, *15*, 333–343.

Paulus, W., Classen, J., Cohen, L. G., Large, C. H., Di Lazzaro, V., Nitsche, M., et al. (2008). State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. *Brain Stimulation*, *1*, 151–163.

Plum, F., & Posner, J. B. (1983). *The diagnosis of stupor and coma*. Philadelphia, PA: Davis FA.

Povlishock, J. T. (1993). Pathobiology of traumatically induced axonal injury in animals and man. *Annals of Emergency Medicine*, *22*, 980–986.

Prout, A. J., & Eisen, A. A. (1994). The cortical silent period and amyotrophic lateral sclerosis. *Muscle and Nerve*, *17*, 217–223.

Romero, J. R., Anschel, D., Sparing, R., Gangitano, M., & Pascual-Leone, A. (2002). Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. *Clinical Neurophysiology*, *113*, 101–107.

Rosenkranz, K., Kacar, A., & Rothwell, J. C. (2007). Differential modulation of motor cortical plasticity and excitability in early and late phases of human motor learning. *Journal of Neuroscience*, *27*, 12058–12066.

Sanes, J. N., & Donoghue, J. P. (2000). Plasticity and primary motor cortex. *Annual Review of Neuroscience*, *23*, 393–415.

Saypol, J. M., Roth, B. J., Cohen, L. G., & Hallett, M. (1991). A theoretical comparison of electric and magnetic stimulation of the brain. *Annals of Biomedical Engineering*, *19*, 317–328.

Schiff, N. D., Giacino, J. T., Kalmar, K., Victor, J. D., Baker, K., Gerber, M., et al. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, *448*, 600–603.

Schnakers, C., Giacino, J., Kalmar, K., Piret, S., Lopez, E., Boly, M., et al. (2006). Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Annals of Neurology*, *60*, 744–745.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., Moonen, G., et al. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, *9* (July 21), 35.

Schwarz, S., Hacke, W., & Schwab, S. (2000). Magnetic evoked potentials in neurocritical care patients with acute brainstem lesions. *Journal of Neurological Sciences*, *172*, 30–37.

Seitz, R. J., Azari, N. P., Knorr, U., Binkofski, F., Herzog, H., & Freund, H. J. (1999). The role of diaschisis in stroke recovery. *Stroke*, *30*, 1844–1850.

Shiel, A., Horn, S. A., Wilson, B. A., Watson, M. J., Campbell, M. J., & McLellan, D. L. (2000). The wessex head injury matrix (WHIM) main scale: A preliminary report on a scale to assess and monitor patient recovery after severe head injury. *Clinical Rehabilitation*, *14*, 408–416.

Siebner, H. R., & Rothwell, J. (2003). Transcranial magnetic stimulation: New insights into representational cortical plasticity. *Experimental Brain Research*, *148*, 1–16.

Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain*, *123*, 572–584.

Takeuchi, N., Ikoma, K., Chuma, T., & Matsuo, Y. (2006). Measurement of transcallosal inhibition in traumatic brain injury by transcranial magnetic stimulation. *Brain Injury*, *20*, 991–996.

Thompson, P. D., Day, B. L., Crockard, H. A., Calder, I., Murray, N. M. F., Rothwell, J. C., et al. (1991). Intraoperative recordings of motor tract potentials at the cervicomedullary junction following scalp electrical and magnetic stimulation of the motor cortex. *Journal of Neurology, Neurosurgery, and Psychiatry*, *54*, 618–623.

Tokimura, H., Di Lazzaro, V., Tokimura, Y., Oliviero, A., Profice, P., Insola, A., et al. (2000). Short latency inhibition of human hand motor cortex by somatosensory input from the hand. *Journal of Physiology (London)*, *523*, 503–513.

Wassermann, E. M., Fuhr, P., Cohen, L. G., & Hallett, M. (1991). Effects of transcranial magnetic stimulation on ipsilateral muscles. *Neurology*, *41*, 1795–1799.

Witt, N. J., Zochodne, D. W., Bolton, C. F., Maison, F. G., Wells, G., Young, G. B., et al. (1991). Peripheral nerve function in sepsis and multiple organ failure. *Chest*, *99*, 176–184.

Ying, Z., Schmid, U. D., Schmid, J., & Hess, C. W. (1992). Motor and somatosensory evoked potentials in coma: Analysis and relation to clinical status and outcome. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*, 470–474.

Zentner, J., & Rohde, V. (1992). The prognostic value of somatosensory and motor evoked potentials in comatose patients. *Neurosurgery*, *31*, 429–434.

Ziemann, U., Iliac, T. V., Pauli, C., Meintzschel, F., & Ruge, D. (2004). Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *Journal of Neuroscience*, *24*, 1666–1672.

Ziemann, U., Lonnecker, S., Steinhoff, B. J., & Paulus, W. (1996). Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Annals of Neurology*, *40*, 367–378.

Zifko, U. A., Zipko, H. T., & Bolton, C. F. (1998). Clinical and electrophysiological findings in critical illness polyneuropathy. *Journal of Neurological Sciences*, *159*, 186–193.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 14

A perturbational approach for evaluating the brain's capacity for consciousness

Marcello Massimini[1,*], Melanie Boly[2], Adenauer Casali[1], Mario Rosanova[1] and Giulio Tononi[3]

[1]*Department of Clinical Sciences, University of Milan, Milan, Italy*
[2]*Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liege and CHU Hospital, Belgium*
[3]*Department of Psychiatry, University of Wisconsin, WI, USA*

Abstract: How do we evaluate a brain's capacity to sustain conscious experience if the subject does not manifest purposeful behaviour and does not respond to questions and commands? What should we measure in this case? An emerging idea in theoretical neuroscience is that what really matters for consciousness in the brain is not activity levels, access to sensory inputs or neural synchronization per se, but rather the ability of different areas of the thalamocortical system to interact causally with each other to form an integrated whole. In particular, the information integration theory of consciousness (IITC) argues that consciousness is integrated information and that the brain should be able to generate consciousness to the extent that it has a large repertoire of available states (*information*), yet it cannot be decomposed into a collection of causally independent subsystems (*integration*). To evaluate the ability to integrate information among distributed cortical regions, it may not be sufficient to observe the brain in action. Instead, it is useful to employ a perturbational approach and examine to what extent different regions of the thalamocortical system can interact causally (*integration*) and produce specific responses (*information*). Thanks to a recently developed technique, transcranial magnetic stimulation and high-density electroencephalography (TMS/hd-EEG), one can record the immediate reaction of the entire thalamocortical system to controlled perturbations of different cortical areas. In this chapter, using sleep as a model of unconsciousness, we show that TMS/hd-EEG can detect clear-cut changes in the ability of the thalamocortical system to integrate information when the level of consciousness fluctuates across the sleep–wake cycle. Based on these results, we discuss the potential applications of this novel technique to evaluate objectively the brain's capacity for consciousness at the bedside of brain-injured patients.

Keywords: coma; consciousness; transcranial magnetic stimulation; electroencephalography; information; integration

Evaluating a subject's level of consciousness

The bedside evaluation of patients affected by disorders of consciousness (DOC) relies on repeated behavioural observation by trained

*Corresponding author.
Tel.: +39 33 39 92 57 91; Fax: +39 02 48002084;
E-mail: marcello.massimini@unimi.it

DOI: 10.1016/S0079-6123(09)17714-2

personnel. During the examination, spontaneous and elicited behaviour in response to multisensory stimulation is recorded in accordance with specific scales (Giacino et al., 2004; Gill-Thwaites and Munday, 2004; Kalmar and Giacino, 2005; Shiel et al., 2000). Regardless of the scale employed, the examiner typically looks for (1) evidence of awareness of the self or of the environment, (2) evidence of sustained, reproducible, purposeful or voluntary response to tactile, auditory or noxious stimuli and (3) evidence of language comprehension and expression (Laureys et al., 2004). If none of these three defining behavioural features can be detected during careful and repeated evaluations, the subject is considered unconscious (Royal College of Physicians, 1994), while patients who show non-reflexive behaviour but are unable to communicate their thoughts and feelings are ascribed to a recently defined clinical entity, the minimally conscious state (Giacino et al., 2002). Thus, according to the clinical definition of consciousness, subjects are conscious if they can signal that this is the case. However, since in patients with severe brain injury motor responsiveness is often impaired, it may also happen that a subject is aware but unable to move or speak (Schnakers et al., 2009). Therefore, while detecting the presence of voluntary behaviour at the bedside is sufficient to infer that a subject is aware, its absence does not necessarily imply unconsciousness (Boly et al., 2007; Laureys et al., 2004; Monti et al., 2009).

Recently, the development of new neuroimaging protocols has made it possible to probe for signs of awareness even when subjects are completely unable to move (Boly et al., 2007; Owen and Coleman, 2008). For example, in a recent study (Owen and Coleman, 2008), a clinically vegetative, seemingly unresponsive patient was put in the scanner and asked to imagine playing tennis or navigating through her own apartment. Remarkably, the patient showed fMRI patterns of brain activation that were consistent and specific for the requested cognitive task, just like healthy subjects. This paradigmatic case demonstrates that the patient's ability to wilfully enter specific neural states upon request can be used to detect the presence of awareness even when motor outputs are absent. However, there still may be cases, such as in aphasia, akinetic mutism, catatonic depression or diffuse dopaminergic lesions, where a patient, although aware, may not be able to understand or be willing to respond (Boly et al., 2007). Moreover, because of frequent movement artefacts and because of possible alterations of the normal coupling of hemodynamics and neuronal firing (Rossini et al., 2004), acquiring and interpreting fMRI data is especially difficult in DOC patients (Giacino et al., 2006). Hence, the absence of volitional brain activity in the scanner, just like the absence of purposeful movements during a clinical examination, does not necessarily imply the absence of awareness.

The behavioural approach and the neuroimaging paradigm represent two different levels at which a communication can be established with a DOC patient (Owen et al., 2005). If an overt behaviour fails to signal consciousness, it is still possible to dig deeper by looking for purposeful neural activations. Both methods leave no doubts in case of a positive result: if the subjects respond, they are actually aware. Instead, a negative result leaves an open question.

Evaluating a brain's capacity for consciousness

In this chapter, we propose an additional level at which consciousness can be studied even when no communication whatsoever (behavioural or neural) can be established with the subject. This paradigm does not aim at probing the subject in order to elicit wilfull behaviours or neural activations; rather, it involves probing directly the subject's brain to gauge core properties that are theoretically relevant for consciousness. This option requires (1) starting from a theory that suggests which properties are fundamental for a physical system to give rise to conscious experience and (2) identifying and implementing a practical measuring method to weigh up these properties in a real brain. Here, we start with the information integration theory of consciousness (IITC) (Tononi, 2004, 2005, 2008), a theory that argues that consciousness is integrated

information and that a physical system should be able to generate consciousness to the extent that it can enter any of a large number of available states (*information*), yet it cannot be decomposed into a collection of causally independent subsystems (*integration*). Then, we devise a practical method to gauge the brain's capacity to integrate information. To do this we employ a combination of transcranial magnetic stimulation and electroencephalography (TMS/hd-EEG), a technique that allows stimulating directly different subsets of cortical neurons and recording the immediate reaction of the rest of the brain. Based on measurements performed in sleeping subjects (Massimini et al., 2005, 2007), we argue that this method represents an effective way to appreciate, at a general level, to what extent different regions of the thalamocortical system can interact globally (*integration*) to produce specific responses (*information*). Thus, instead of asking the subjects to wilfully perform different motor or cognitive tasks, we directly "ask" (with TMS) their thalamocortical system to enter different neural states and we assess (with hd-EEG) to what extent these states are integrated and specific. While this approach is not meant to tell whether a subject is actually conscious or not, it may represent a principled way to objectively weigh a brain's capacity for conscious experience.

Theoretical guidelines: the integrated information theory of consciousness

The IITC takes its start from phenomenology and, by making a critical use of thought experiments, argues that subjective experience *is* integrated information. Therefore, according to the IITC, any physical system will have subjective experience to the extent that it is capable of integrating information. In this view, experience, i.e. information integration, is a fundamental quantity that is, in principle, measurable, just as mass or energy is. Information and integration are, on the other hand, the very essence of subjective experience. Classically, information is the reduction of uncertainty among alternatives: when a coin falls on one of its two sides, it provides 1 bit of information, whereas a die falling on one of six faces provides $\sim$2.6 bits. But then having any conscious experience, even one of pure darkness, must be extraordinarily informative, because it rules out countless other experiences instead (think of all the frames of every possible movie). In other words, having any experience is like throwing a die with a trillion faces and identifying which number came up. On the other hand, every experience is an integrated whole that cannot be subdivided into independent components. For example, with an intact brain you cannot experience the left half of the visual field independently of the right half, or visual shapes independently of their colour. In other words, the die of experience is a single one; throwing multiple dice and combining the numbers will not help.

If the capacity for consciousness corresponds to the capacity to integrate information, then a physical system should be able to generate consciousness to the extent that it can discriminate among a large number of available states (*information*), yet it cannot be decomposed into a collection of causally independent subsystems (*integration*). How can one identify such an integrated system, and how can one measure its repertoire of available states? To measure the repertoire of different states that are available to a system, one can use the entropy function, but this way of measuring information is completely insensitive to whether the information is integrated. Thus, measuring entropy would not allow us to distinguish between one million photodiodes with a repertoire of two states each, and a single integrated system with a repertoire of $2^{1,000,000}$ states. To measure information integration, it is essential to know whether a set of elements constitutes a causally integrated system, or they can be broken down into a number of independent or quasi-independent subsets among which no information can be integrated.

Indeed, the theory claims that the level of consciousness of a physical system is related to the repertoire of different states (*information*) that can be discriminated by the system as a whole (*integration*). Thus, a measure of integrated information, called phi (Φ), has been proposed in order to quantify the information generated

when a system discriminates one particular state of its repertoire, above and beyond the information generated independently by its parts (Balduzzi and Tononi, 2008; Tononi, 2004).

As demonstrated through computer simulations, information integration is optimized (Φ is highest) if the elements of a complex are connected in such a way that they are both functionally specialized (connection patterns are different for different elements) and functionally integrated (all elements can be reached from all other elements of the network). If functional specialization is lost by replacing the heterogeneous connectivity with a homogeneous one, or if functional integration is lost by rearranging the connections to form small modules, the value of Φ decreases considerably (Tononi and Sporns, 2003).

According to the IITC, this is exactly why, among many structures of the brain, the thalamocortical system is so special for consciousness: it is naturally organized in a way that appears to emphasize at once both functional specialization and functional integration. Thus, it comprises a large number of elements that are functionally specialized, becoming activated in different circumstances (Bartels and Zeki, 2005). This is true at multiple spatial scales, from different cortical systems dealing with vision, audition, etc., to different cortical areas dealing with shape, colour, motion, etc., to different groups of neurons responding to different directions of motion. On the other hand, the specialized elements of the thalamocortical system are integrated through an extended network of intra- and inter-areal connections that permit rapid and effective interactions within and between areas (Engel et al., 2001).

But then, the theory also explicitly predicts that the fading of consciousness should be associated with either a reduction of integration within thalamocortical circuits (e.g. they could break down into causally independent modules) or a reduction in information (the repertoire of available states might shrink), or both. This specific prediction is however difficult to test in humans, since, in practice, Φ can only be measured rigorously for small, simulated systems. In the next section, we try to identify an empirical method to approximate a measure of the capacity for integrated information in a human brain.

Employing TMS/hd-EEG to evaluate thalamocortical integration and information capacity

Different methods have been proposed in order to infer on a subject's level of consciousness solely based on brain activity. Some of these methods, such as spectral analysis (Berthomier et al., 2007) and the proprietary ''bispectral index'' (Myles et al., 2004), seem to correlate empirically with consciousness but have no clear theoretical foundation. Other measures, such as neural complexity (Tononi et al., 1994) and causal density (Seth, 2005), are theoretically motivated (Seth et al., 2008) but have not yet been tested empirically. More or less explicitly, all these measures attempt to capture the coexistence of functional integration and functional differentiation in spontaneous (mainly hd-EEG) brain signals. Yet, to dependably appreciate the brain's capacity for consciousness (defined as integrated information), one should go beyond spontaneous activity levels or patterns of temporal correlation among distant neuronal groups (functional connectivity). First, this is because the repertoire of available states is, by definition, potential and, thus, not necessarily observable. Second, because it is difficult to say whether a system is actually integrated or not by just observing the spontaneous activity it generates. For example, observing time-varying, complex correlations among retinal neurons that are responding to a rich visual scene may lead one to the conclusion that the retina is both functionally specialized and functionally integrated. However, such complex spatial-temporal correlations do not imply that the retina *per se* has a capacity for consciousness. In fact, it is enough to perturb a few retinal elements and to record from the rest of the cells to realize that, to a large extent, the retina is actually composed of segregated modules that do not interact with each other. Indeed, the ability to integrate information can only be demonstrated

from a causal perspective; one must employ a perturbational approach (effective connectivity) and examine to what extent subsets of neurons can interact causally as a whole (*integration*) to produce responses that are specific for that particular perturbation (*information*). Moreover, one should probe causal interactions by directly stimulating the cerebral cortex to avoid possible subcortical filtering or gating. Finally, since causal interactions among thalamocortical neurons develop on a sub-second time scale (just as phenomenal consciousness does), it is very important to record the neural effects of the perturbation with the appropriate temporal resolution.

Thus, in practice, one should find a way to stimulate different subsets of cortical neurons and measure, with good spatial-temporal resolution, the effects produced by these perturbations in the rest of the thalamocortical system. Today, this measurement can be performed non-invasively in humans, thanks to the development of a novel electrophysiological technique, based on the combination of navigated TMS and high-density electroencephalography (Ilmoniemi et al., 1997) (Fig. 1). With TMS, the cerebral cortex is stimulated directly by generating a brief but strong magnetic pulse (<1 ms, 2 T) through a coil applied to the surface of the scalp. The rapid change in magnetic field strength induces a current flow in the tissue, which results in the activation of underlying neuronal population. The synchronous volley of action potential thus initiated propagates along the available connection pathways and can produce activations in target cortical regions. By integrating TMS with MR-guided infra-red navigation systems, it is also possible to render the perturbation controllable and reproducible, in most cortical regions. Finally, using multi-channel EEG amplifiers that are compatible with TMS (Virtanen et al., 1999) one

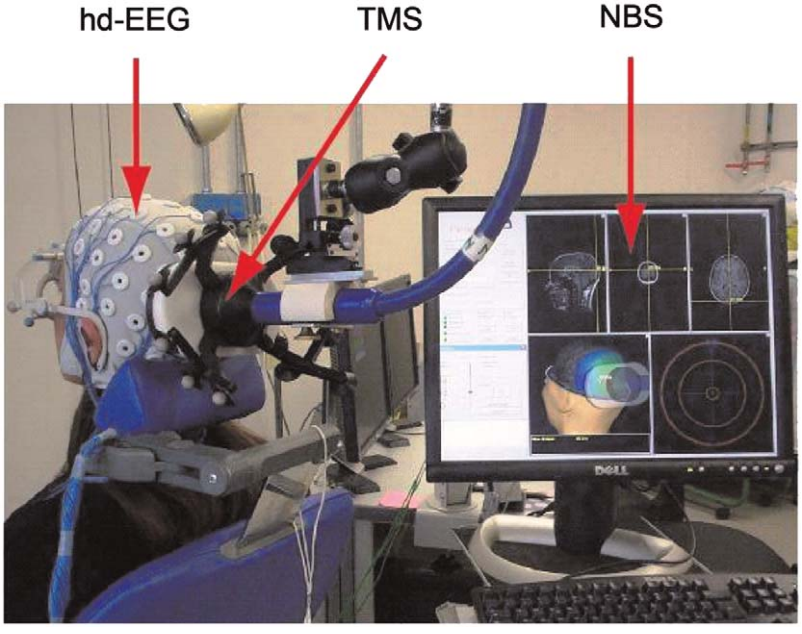


Fig. 1. TMS/hd-EEG setup. In this example, a subject is sitting on an ergonomic chair while TMS is targeted to the occipital cortex. The red arrows indicate, from left to right, the three fundamental elements that compose the set-up: (1) a cap for high-density (60 channels) hd-EEG recordings that is connected to a TMS-compatible amplifier; (2) a focal figure-of-eight stimulating coil (TMS), held in place by a mechanical arm; (3) the display of the navigated brain stimulation system (NBS). This system employs an infra-red camera (not visible in this picture) to navigate TMS on a 3D reconstruction of the subject's MRI. The location and the intensity of the electric field induced by TMS are estimated and displayed in real time. To prevent the subject from perceiving the click associated with the coil's discharge, noise masking is played through inserted earplugs. Please see online version of this article for full color figure.

can record, starting just a few milliseconds after the pulse, the impact of the perturbation on the stimulated target and in distant cortical areas. Indeed, the integrated use of neuro-navigation systems, TMS and multichannel TMS-compatible hd-EEG amplifiers together constitute a new brain scanning method in which stimulation is navigated into any desired brain target and the concurrently recorded scalp potentials are processed into source images of the TMS-evoked neuronal activation (Komssi and Kahkonen, 2006).

It is worth highlighting some of the specific advantages that TMS/hd-EEG may offer as a tool to probe the brain of DOC patients:

1. TMS-evoked activations are intrinsically causal (Paus, 2005). Thus, unlike methods based on temporal correlations, TMS/hd-EEG immediately captures the fundamental mechanism that underlies integration, i.e. the ability of different elements of a system to affect each other.
2. TMS/hd-EEG bypasses sensory pathways and subcortical structures to probe directly the thalamocortical system. Therefore, unlike peripherally evoked potentials and evoked motor activations, TMS/hd-EEG does not depend on the integrity of sensory and motor systems and can access any patient (deafferentated or paralysed). Moreover, with TMS one can stimulate most cortical areas (including associative cortices) employing several different parameters (intensity, angle, current direction), thus probing a vast repertoire of possible responses, above and beyond observable ongoing brain states.
3. TMS-evoked potentials can be recorded with millisecond resolution, a time scale that is adequate to capture effective synaptic interactions among neurons.
4. TMS/hd-EEG does not require the subject to be involved in a task and the observed activations are not affected either by the willingness of the patient to participate or by his effort and performance. Hence, this approach is well suited to assess the objective capacity of thalamocortical circuits independently on behaviour.
5. TMS/hd-EEG can be made portable in order to overcome the logistical and economic hurdles that may separate severely brain-injured patients from advanced imaging facilities.

Thus, at least in principle, TMS/hd-EEG may represent an appropriate tool to approximate a theoretical measure of consciousness at the patient's bedside. However, the question whether this technique may actually detect changes in the brain's capacity to integrate information can only be answered experimentally. For example, one should demonstrate that TMS-evoked activations are widespread (*integration*) and specific (*information*) in a conscious brain but that they become either local (revealing a loss of integration) or stereotypical (revealing a loss of information) when the same brain becomes unconscious. In the next section, we describe the results of experiments where TMS/hd-EEG was used to understand what changes in human thalamocortical circuits when consciousness fades upon falling asleep.

TMS/hd-EEG detects changes in the brain's capacity for integrated information during sleep

Sleep is the only time when healthy humans regularly lose consciousness. Subjects awakened during slow-wave sleep early in the night may report short, thought-like fragments of experience, or often nothing at all (Hobson et al., 2000). Sleep also exposes several interesting paradoxes about the relationships between consciousness and the brain. For instance, it was thought that the fading of consciousness during sleep was due to the brain shutting down. However, while metabolic rates decrease in some cortical areas, thalamocortical neurons remain active during slow-wave sleep also, with mean firing rates comparable to those of quiet wakefulness (Steriade et al., 2001). It was also hypothesized that sensory inputs are blocked during sleep and that they are necessary to sustain conscious

experience. However, we now know that, even during deep sleep, sensory signals continue to reach the cerebral cortex (Kakigi et al., 2003) where they are processed subconsciously (Portas et al., 2000). Gamma activity and synchrony have been viewed as possible correlates of consciousness and they were found to be low in slow-wave sleep (Cantero et al., 2004). However, they may be equally low in REM sleep, when subjective experience is usually vivid, and they can be high in anaesthesia (Vanderwolf, 2000). On the other hand, intracranial recordings show that gamma activity (Destexhe et al., 2007) and gamma-coherence (Bullock et al., 1995) persist during slow-wave sleep. Interestingly, similar paradoxes, where neural activity levels, access to sensory information and the degree of neural synchrony do not correlate with the level of consciousness, can be found in other conditions such as anaesthesia, epilepsy and DOC patients (Tononi and Laureys, 2008). In this sense, sleep represents a general model to learn what really matters for consciousness.

For this reason, in a series of recent experiments, we have employed TMS/hd-EEG to measure what changes in thalamocortical circuits during the transition from wakefulness into different stages of sleep (Massimini et al., 2005, 2007). Figure 2A shows the response obtained after stimulation of rostral premotor cortex in one subject during wakefulness. The black traces represent the voltage recorded from all scalp electrodes; the cortical currents associated with the main peaks of activity are depicted below. The circles on the cortical surface indicate the site of stimulation, while the cross highlights the location of maximal cortical activation. TMS, applied at an intensity corresponding to motor threshold, triggers, during wakefulness, a series of low-amplitude, high-frequency (25–30 Hz) waves of activity associated with cortical activations that propagate along long-range ipsilateral and transcallosal connections. Remarkably, the exactly same stimulation, applied 15 min later, during sleep stages 3 and 4, results in a very different picture (Fig. 2B). In this case, TMS triggers a larger, low-frequency wave, associated with a strong initial cortical activation that does not propagate to connected brain regions and dissipates rapidly. This finding is general and can be reproduced after the stimulation of different cortical areas, as long as the subjects are in slow-wave sleep stages 3 and 4. Thus, the cortical area that is directly engaged by TMS preserves its reactivity but behaves as an isolated module; in this way, TMS/hd-EEG reveals a clear-cut reduction of cortico-cortical integration occurring during sleep early in the night. Interestingly, during REM sleep late in the night, when dreams become long and vivid and the level of consciousness returns to levels close to wakefulness (despite the subject being almost paralysed), thalamocortical integration partially recovers and TMS triggers a more widespread and differentiated pattern of activation (Fig. 2C).

TMS/hd-EEG measurements not only indicate that during slow-wave sleep the thalamocortical system tends to break down into isolated modules (loss of integration), but also show that the ability of thalamocortical circuits to produce differentiated responses (information) is impaired. In Fig. 3, the responses to two different TMS perturbations (one applied to premotor cortex and the other one applied to visual cortex) are compared during wakefulness and slow-wave sleep. For each condition, the significant currents evoked by TMS are cumulated over the entire post-stimulus interval and are plotted on the cortical surface; on the right side of each cortical surface, the time course of the currents recorded from three selected areas are depicted. This example, as the one reported in the previous figure, confirms a clear-cut loss of integration during slow-wave sleep by showing that distant cortical areas cease to be causally affected by the initial perturbation. On the other hand, it also reveals a clear loss of response specificity. Thus, while during wakefulness the premotor and the visual cortex react to the stimulus with a pattern of activation which has a characteristic shape and frequency content (Rosanova et al., 2009), this distinction is clearly obliterated during sleep; the local response to TMS becomes, in both cases, a simple positive–negative wave.

Indeed, if the reactivity of the sleeping brain is systematically tested by applying TMS at different

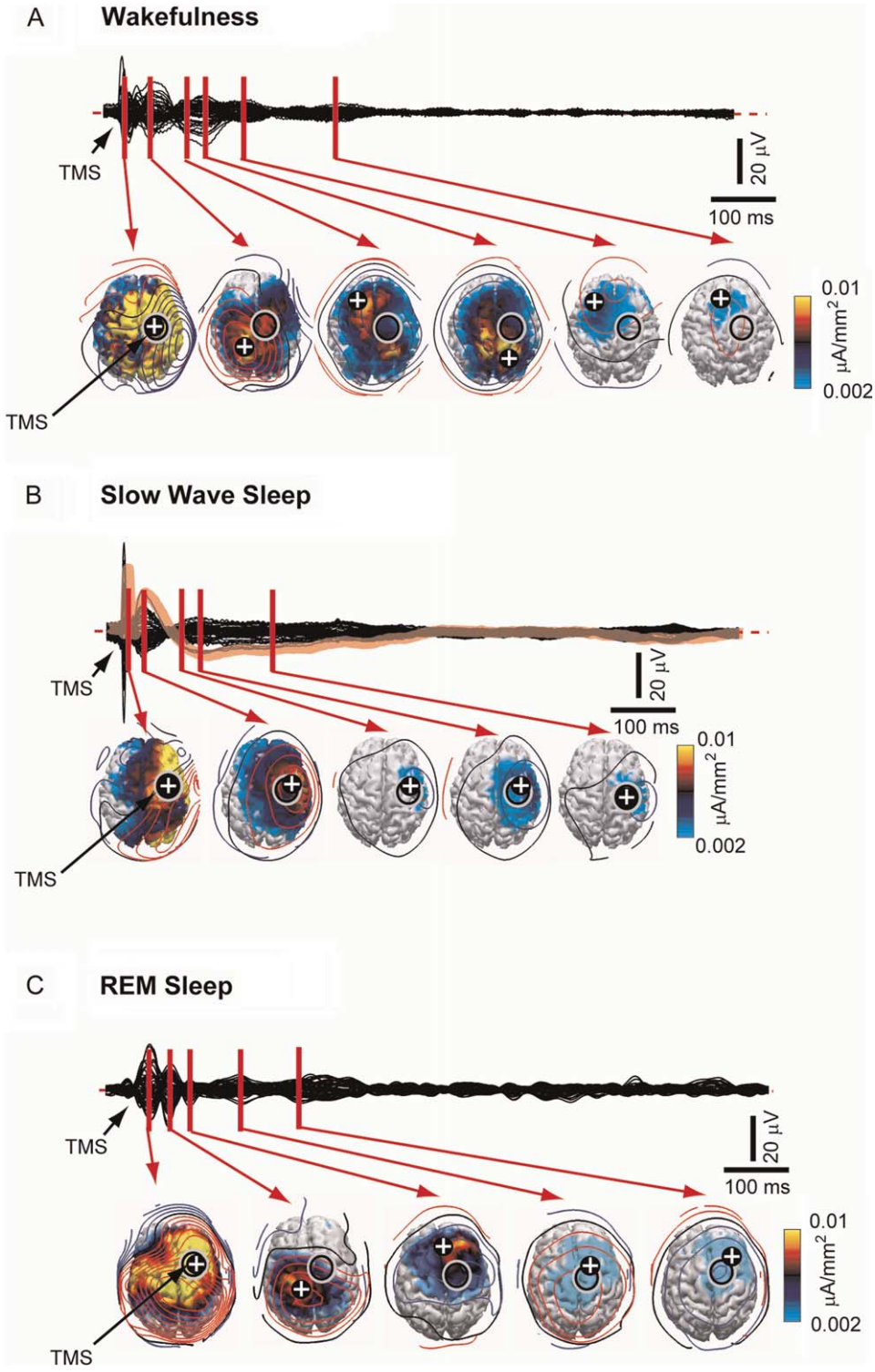


Fig. 2. Cortical responses to TMS across the sleep–wake cycle. hd-EEG voltages and current densities are shown from a representative subject in whom the premotor cortex was stimulated with transcranial magnetic stimulation (TMS) (black arrow). (A) During waking, stimulation evokes hd-EEG responses first near the stimulation site (circle; the cross is the site of maximum evoked current) and then, in sequence, at other cortical locations, producing a long-range pattern of activation. (B) During slow-wave sleep, the stimulus-evoked response remains local, indicating a loss of cortical integration. At the same time, the response recorded from the electrode located under the stimulator (thick red trace) becomes a positive wave followed by a negative rebound. (C) During REM sleep, effective connectivity among distant cortical areas recovers, indicating a significant resurgence of cortical integration (adapted with permission from Massimini et al., 2007). Please see online version of this article for full color figure.

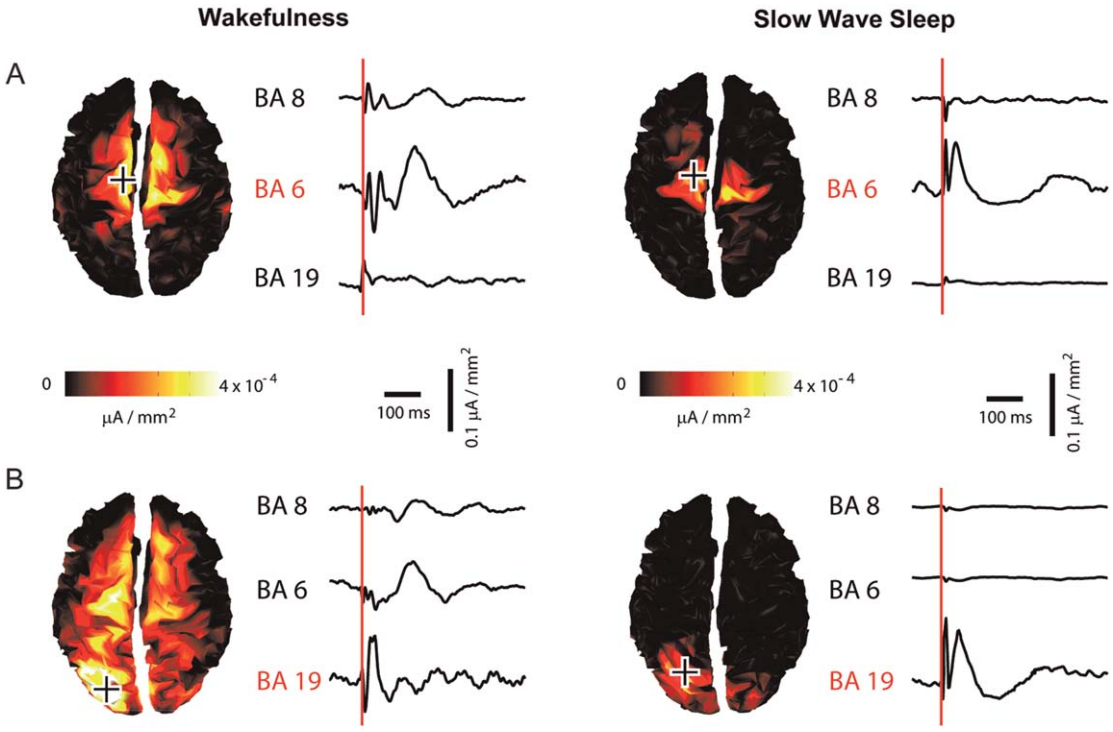


Fig. 3. Loss of cortical integration and differentiation during slow-wave sleep. TMS is applied to premotor cortex (A) and to visual cortex (B) during wakefulness (left panels) and during slow-wave sleep (right panels). After source modelling, non-parametric statistics is performed to detect the significant currents induced by TMS. For each condition, the significant currents recorded during the entire post-stimulus interval are plotted on the cortical surface; on the right side of each cortical surface, the time series of the currents recorded from three selected areas (Brodmann areas (BA) 8, 6 and 19) are depicted (the time of stimulation is marked by a red line). With the transition from wakefulness to slow-wave sleep, distant cortical areas cease to be causally affected by the initial perturbation, indicating a break-down of cortical integration. At the same time, cortical responses to TMS become stereotypical, indicating a loss of cortical differentiation. Please see online version of this article for full color figure.

intensities and in different cortical areas (Massimini et al., 2007), one invariably obtains a stereotypical response: a positive wave followed by a negative rebound (Fig. 3). Interestingly, this positive–negative component develops towards a full-fledged sleep slow wave when TMS is delivered at increasing intensities in a scalp region around the vertex (Massimini et al., 2007). The prominent negative component of TMS-evoked slow waves is very likely to be associated with a widespread hyperpolarization in a large population of cortical neurons, as is the case for spontaneous sleep slow waves (Cash et al., 2009; Massimini et al., 2004). Thus, it appears that the only way the sleeping brain can react to a direct cortical perturbation is by producing a slow wave that is either local (Fig. 2B) or global and non-specific (Fig. 4B).

What prevents the emergence of a differentiated long-range pattern of activation during sleep? It is likely that the mechanism underlying the impaired capacity of the sleeping brain for integrated information is the same mechanism that underlies the occurrence of spontaneous sleep slow-waves, that is bistability in thalamocortical circuits (Tononi and Massimini, 2008). Upon falling asleep, brainstem activating systems reduce their firing rates, thus increasing the influence of depolarization-dependent potassium currents in thalamic and cortical neurons (McCormick et al., 1993). Due to these currents, cortical neurons become bistable and inevitably tend to fall into a

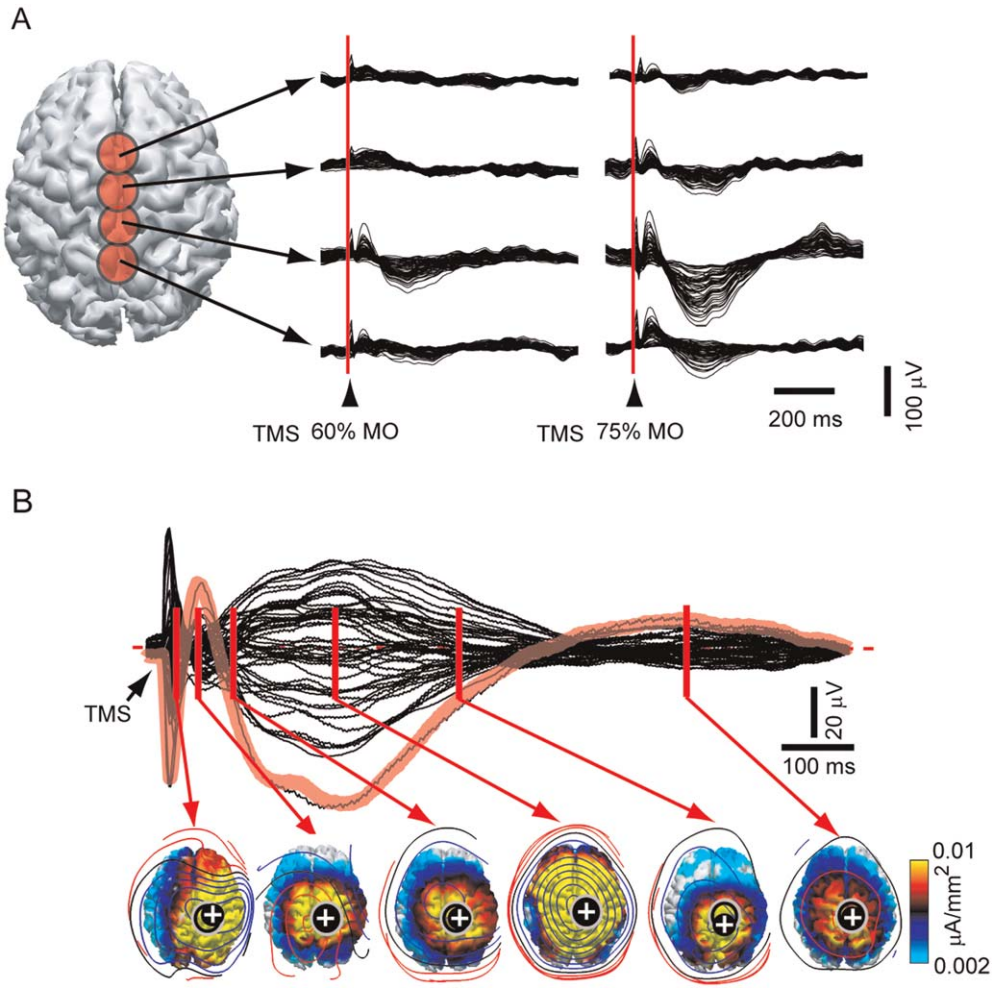


Fig. 4. The sleeping brain reacts to TMS by producing stereotypical responses that resemble spontaneous sleep slow-waves. (A) TMS is delivered at four midline sites along the posterior–anterior axis of the cortex (posterior parietal, sensorimotor, supplementary motor, rostral premotor). The brain response to TMS is probed, at each site, at two intensities (MO is maximum stimulator output). The average responses to 15 TMS trials recorded from all channels (referenced to the mastoid) are shown for each intensity and each cortical site. At all cortical sites, TMS evokes a positive component followed by a negative rebound that develops towards a full-fledged sleep slow-wave when stimulation is delivered at increasing intensities in a scalp region closer to the sensory-motor cortex. (B) In this region, TMS triggers a large negative deflection associated with long-lasting currents that spread like an oil-spot to the surrounding cortex, starting from a fixed local maximum. In this particular case, the brain's reaction to TMS becomes global but remains stereotypical and non-specific (adapted with permission from Massimini et al., 2007).

silent, hyperpolarized state (down-state) after a period of activation (up-state). This bistability provides the mechanism for the slow oscillations of sleep where large populations of cortical neurons spontaneously alternate between up- and down-states (Hill and Tononi, 2005). At the same time, due to bistability, any local activation, whether occurring spontaneously or induced by a stimulus (like TMS), eventually triggers a stereotypical down-state that, in turn, prevents the emergence of specific, long-range patterns of activation.

Altogether, TMS/hd-EEG measurements suggest that, during slow-wave sleep, the thalamo-cortical system, despite being active and reactive,

either breaks down in causally independent modules (producing a local down-state) or bursts into an explosive and non-specific response (producing a global down-state and a full-fledged hd-EEG slow-wave). In no case, during slow-wave sleep, does TMS result in a balanced, long-range, differentiated pattern of activation. The TMS/hd-EEG perturbational approach also suggests that intrinsic bistability in thalamocortical networks, the key mechanism responsible for the occurrence of the spontaneous slow oscillations of sleep, may be the reason why information integration is impaired in early NREM sleep (Massimini et al., 2009). While sleep and the associated bistability are physiological and reversible processes, pathological processes may similarly result in a modification of the brain's ability to integrate information and this modification may be similarly detected by TMS/hd-EEG. In the next section, we discuss the possible applications of TMS/hd-EEG at the bedside of DOC patients.

TMS/EEG in DOC patients: some predictions

Given the variety of brain lesions and conditions that are associated to DOC (Laureys et al., 2004, 2009), it is very difficult to predict what kind of results TMS/hd-EEG might give in individual DOC patients. However, an informed guess can be adopted at least in some specific cases. For instance, it is conceivable that TMS-evoked activations similar to the ones described during slow-wave sleep may also be found in patients that are in a coma caused by a lesion in the ascending reticular activating system. In these cases, one could predict that, due to bistability, TMS should trigger a stereotypically local, or global, slow wave, provided that thalamocortical circuits are fundamentally intact. Similarly, due to pathological bistability in cortical circuits (Hahn and Durand, 2001), large and stereotypical responses would be expected in patients that are in a status epilepticus. On the other hand, TMS should results in mostly local responses in cases where connectivity is generally impaired, such as in patients with diffuse axonal injury (Graham et al., 2005). What would happen, instead, when a coma patient opens her/his eyes, shows only reflexive behaviour (Schiff et al., 1999) and enters the vegetative state (Laureys and Boly, 2008)? In principle, the recovery of arousal, if not paralleled by recovery of awareness, should not be associated with significant changes in the ability of thalamocortical circuits to integrate information. In this sense, TMS-evoked activation is not expected to show relevant changes during the transition from coma to the vegetative state. Very different is the condition of locked-in patients (Plum and Posner, 1972) who awaken from their coma fully conscious (Schnakers et al., 2008) but completely paralysed, except for the ability to gaze upward; in this case, TMS should trigger more widespread and differentiated patterns of activation, just as it does during normal wakefulness or at most upon entering REM sleep, when subjects are conscious but almost paralysed.

The most important challenge for any objective measure of consciousness is proving itself capable of detecting a potential for residual cognition when no communication whatsoever can be established with the patient. This task is difficult by definition, since there is no behavioural reference to assess the subject's actual level of consciousness. Nevertheless, some strategies could be adopted to practically validate TMS/hd-EEG measures as a dependable marker of the brain's capacity for consciousness. First, one should demonstrate that using TMS/hd-EEG it is possible to identify significant differences between vegetative and minimally conscious patients concerning their brain's capacity for integrated information. A positive result in such a population study would indicate that TMS/hd-EEG is sensitive enough to objectify minimal changes in the brain's capacity for awareness. Second, one should demonstrate that the longitudinal TMS/hd-EEG measurements can predict the individual patient's outcome. For instance, it would be relevant to observe TMS-evoked cortical responses that progressively become more global and specific in the brain of intensive care patients shortly before they regain consciousness at the clinical level. Then, TMS/hd-EEG may be employed as a diagnostic/prognostic tool to evaluate covert consciousness and to foster evidence-based neuro-rehabilitation.

Future perspectives

We attempted at identifying an objective marker of consciousness that is theoretically grounded and practically measurable. The core message of this chapter is that using by TMS/hd-EEG it is possible to detect clear-cut changes in the capacity of human thalamocortical circuits to integrate information, a theoretical requirement to generate conscious experience, when the level of consciousness fluctuates across the sleep–wake cycle. The implication of this finding is that TMS/hd-EEG may be similarly employed to evaluate the brain's capacity for consciousness at the bedside of non-communicative patients. Clearly, before applying this technique to DOC patients, further steps need to be taken.

First, TMS/hd-EEG normative data have to be defined. Thus, several cortical areas must be systematically perturbed in healthy subjects in order to determine the specificity and the reproducibility of cortical responses to TMS. A similar assessment has been recently performed on a limited set of cortical areas (superior occipital lobule, precuneus and premotor) and has revealed patterns of TMS-evoked cortical activation that are specific for the stimulated site and reproducible across subjects (Rosanova et al., 2009). This database needs to be further extended including more cortical areas and subjects.

Second, a standard analysis procedure must be developed in order to extract from TMS/hd-EEG data synthetic indices that capture the brain's capacity for integration and differentiation. In fact, the results presented in this chapter are suggestive, but only qualitative. Different algorithms can be devised in order to quantify TMS/hd-EEG data in a way that is theoretically relevant. For instance, the extent of the brain area that is significantly engaged by TMS (Fig. 3) provides a simple measure of integration. Indeed, since TMS-evoked activations are intrinsically causal (Paus, 2005), it is warranted that the elements within this area are interacting effectively with each other and that the observed patterns of activations are not random. At this point, one could simply use measures related to entropy, or to algorithmic complexity, to summarize in one number the spatial–temporal differentiation of the deterministic activation produced by this integrated network. This number will be low for modular network, because, in this case, activity remains local, and will be equally low for networks with widespread homogeneous connectivity, because, all elements will respond in the same way. Only networks that are integrated and differentiated at the same time are likely to react to TMS with a response characterized by a high complexity value.

Third, the technique and the appropriate analysis procedure must be tested in conditions where consciousness is graded and abolished in a controlled fashion, such as during anaesthesia (Alkire et al., 2008). Specifically, it would be important to apply TMS/hd-EEG measures of integrated information while consciousness is altered using different anaesthetics (such as midazolam, propofol or ketamine) that act through diverse mechanisms and that are associated with variable patterns of spontaneous EEG activity. Certainly, a reliable marker should only correlate with the level of consciousness, whether this has been altered by physiological sleep, by one anaesthetic or another, or by a pathological process.

Acknowledgements

This work was supported by European grant STREP LSHM-CT-2205-51818 to Marcello Massimini. Melanie Boly is Research Fellow at the Belgian National Fund for Scientific Research (FNRS). We thank Andrea Soddu, Silvia Casarotto and Fabio Ferrarelli for their help and comments.

References

Alkire, M. T., Hudetz, A. G., & Tononi, G. (2008). Consciousness and anesthesia. *Science*, *322*, 876–880.

Balduzzi, D., & Tononi, G. (2008). Integrated information in discrete dynamical systems: Motivation and theoretical framework. *PLoS Computational Biology*, *4*, e1000091.

Bartels, A., & Zeki, S. (2005). The chronoarchitecture of the cerebral cortex. *Philosophical Transactions of the Royal*

Society of London. Series B, Biological Sciences, *360*, 733–750.

Berthomier, C., Drouot, X., Herman-Stoïca, M., Berthomier, P., Prado, J., Bokar-Thire, D., et al. (2007). Automatic analysis of single-channel sleep EEG: Validation in healthy individuals. *Sleep*, *30*, 1587–1595.

Boly, M., Coleman, M. R., Davis, M. H., Hampshire, A., Bor, D., Moonen, G., et al. (2007). When thoughts become action: An fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage*, *36*, 979–992.

Bullock, T. H., McClune, M. C., Achimowicz, J. Z., Iragui-Madoz, V. J., Duckrow, R. B., & Spencer, S. S. (1995). Temporal fluctuations in coherence of brain waves. *Proceedings of the National Academy of Sciences of the United States of America*, *92*, 11568–11572.

Cantero, J. L., Atienza, M., Madsen, J. R., & Stickgold, R. (2004). Gamma EEG dynamics in neocortex and hippocampus during human wakefulness and sleep. *Neuroimage*, *22*, 1271–1280.

Cash, S. S., Halgren, E., Dehghani, N., Rossetti, A. O., Thesen, T., Wang, C., et al. (2009). The human K-complex represents an isolated cortical down-state. *Science*, *324*, 1084–1087.

Destexhe, A., Hughes, S. W., Rudolph, M., & Crunelli, V. (2007). Are corticothalamic 'up' states fragments of wakefulness? *Trends in Neurosciences*, *30*, 334–342.

Engel, A. K., Fries, P., & Singer, W. (2001). Dynamic predictions: Oscillations and synchrony in top-down processing. *Nature Review, Neurosciences*, *2*, 704–716.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*, 349–353.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK coma recovery scale-revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation*, *85*, 2020–2029.

Giacino, J. T., Hirsch, J., Schiff, N., & Laureys, S. (2006). Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Archives of Physical Medicine and Rehabilitation*, *87*, S67–S76.

Gill-Thwaites, H., & Munday, R. (2004). The Sensory Modality Assessment and Rehabilitation Technique (SMART): A valid and reliable assessment for vegetative state and minimally conscious state patients. *Brain Injury*, *18*, 1255–1269.

Graham, D. I., Adams, J. H., Murray, L. S., & Jennett, B. (2005). Neuropathology of the vegetative state after head injury. *Neuropsychological Rehabilitation*, *15*, 198–213.

Hahn, P. J., & Durand, D. M. (2001). Bistability dynamics in simulations of neural activity in high-extracellular-potassium conditions. *Journal of Computational Neuroscience*, *11*, 5–18.

Hill, S., & Tononi, G. (2005). Modeling sleep and wakefulness in the thalamocortical system. *Journal of Neurophysiology*, *93*, 1671–1698.

Hobson, J. A., Pace-Schott, E. F., & Stickgold, R. (2000). Dreaming and the brain: Toward a cognitive neuroscience of conscious states. *The Behavioral and Brain Sciences*, *23*, 793–842. discussion 904–1121

Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Näätänen, R., et al. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport*, *8*, 3537–3540.

Kakigi, R., Naka, D., Okusa, T., Wang, X., Inui, K., Qiu, Y., et al. (2003). Sensory perception during sleep in humans: A magnetoencephalograhic study. *Sleep Medicine*, *4*, 493–507.

Kalmar, K., & Giacino, J. T. (2005). The JFK coma recovery scale - revised. *Neuropsychological Rehabilitation*, *15*, 454–460.

Komssi, S., & Kahkonen, S. (2006). The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. *Brain Research Reviews*, *52*, 183–192.

Laureys, S., & Boly, M. (2008). The changing spectrum of coma. *Nature Clinical Practice Neurology*, *4*, 544–546.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*, 537–546.

Laureys, S., Boly, M., Moonen, G., & Maquet, P. (2009). Coma. In L. Squire (Ed.), *Encyclopedia of neuroscience* Vol. 2, (pp. 1133–1142). Amsterdam: Elsevier.

Massimini, M., Huber, R., Ferrarelli, F., Hill, S., & Tononi, G. (2004). The sleep slow oscillation as a traveling wave. *The Journal of Neuroscience*, *24*, 6862–6870.

Massimini, M., Ferrarelli, F., Huber, R., Esser, S. K., Singh, H., & Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. *Science*, *309*, 2228–2232.

Massimini, M., Ferrarelli, F., Esser, S. K., Riedner, B. A., Huber, R., Murphy, M., et al. (2007). Triggering sleep slow waves by transcranial magnetic stimulation. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 8496–8501.

Massimini, M., Tononi, G., & Huber, R. (2009). Slow waves, synaptic plasticity and information processing: Insights from transcranial magnetic stimulation and high-density EEG experiments. *The European Journal of Neuroscience*, *29*, 1761–1770.

McCormick, D. A., Wang, Z., & Huguenard, J. (1993). Neurotransmitter control of neocortical neuronal activity and excitability. *Cerebral Cortex*, *3*, 387–398.

Monti, M. M., Coleman, M. R., & Owen, A. M. (2009). Neuroimaging and the vegetative state: Resolving the behavioral assessment dilemma? *Annals of New York Academy of Sciences*, *1157*, 81–89.

Myles, P. S., Leslie, K., McNeil, J., Forbes, A., & Chan, M. T. (2004). Bispectral index monitoring to prevent awareness during anaesthesia: The B-Aware randomised controlled trial. *Lancet*, *363*, 1757–1763.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2008). Detecting awareness in the vegetative state. *Annals of New York Academy of Sciences*, *1129*, 130–138.

Owen, A. M., Coleman, M. R., Menon, D. K., Berry, E. L., Johnsrude, I. S., Rodd, J. M., Davis, M. H., et al. (2005). Using a hierarchical approach to investigate residual

auditory cognition in persistent vegetative state. *Progress in Brain Research*, *150*, 457–471.

Paus, T. (2005). Inferring causality in brain images: A perturbation approach. *Philosophical Transactions of the Royal Society of London: Series B, Biological Sciences*, *360*, 1109–1114.

Plum, F., & Posner, J. B. (1972). The diagnosis of stupor and coma. *Contemporary Neurology Series*, *10*, 1–286.

Portas, C. M., Krakow, K., Allen, P., Josephs, O., Armony, J. L., & Frith, C. D. (2000). Auditory processing across the sleep-wake cycle: Simultaneous EEG and fMRI monitoring in humans. *Neuron*, *28*, 991–999.

Rosanova, M., Casali, A., Bellina, V., Resta, F., Mariotti, M., & Massimini, M. (2009). Natural frequencies of human corticothalamic circuits. *Journal of Neuroscience*, *29*(24), 7679–7685.

Rossini, P. M., Altamura, C., Ferretti, A., Vernieri, F., Zappasodi, F., Caulo, M., et al. (2004). Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? *Brain*, *127*, 99–110.

Royal College of Physicians. (1994). Medical aspects of the persistent vegetative state (1). The multi-society task force on PVS. *The New England Journal Medicine*, *330*, 1499–1508.

Schiff, N., Ribary, U., Plum, F., & Llinás, R. (1999). Words without mind. *Journal Cognitive Neuroscience*, *11*, 650–656.

Schnakers, C., Majerus, S., Goldman, S., Boly, M., Van Eeckhout, P., Gay, S., et al. (2008). Cognitive function in the locked-in syndrome. *Journal of Neurology*, *255*, 323–330.

Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., et al. (2009). Detecting consciousness in a total locked-in syndrome: An active event-related paradigm. *Neurocase*, 1–7.

Seth, A. K. (2005). Causal connectivity of evolved neural networks during behavior. *Network*, *16*, 35–54.

Seth, A. K., Dienes, Z., Cleeremans, A., Overgaard, M., & Pessoa, L. (2008). Measuring consciousness: Relating behavioural and neurophysiological approaches. *Trends in Cognitive Sciences*, *12*, 314–321.

Shiel, A., Horn, S. A., Wilson, B. A., Watson, M. J., Campbell, M. J., & McLellan, D. L. (2000). The Wessex Head Injury Matrix (WHIM) main scale: A preliminary report on a scale to assess and monitor patient recovery after severe head injury. *Clinical Rehabilitation*, *14*, 408–416.

Steriade, M., Timodeev, I., & Grenier, F. (2001). Natural waking and sleep states: A view from inside neocortical neurons. *Journal of Neurophysiology*, *85*, 1969–1985.

Tononi, G. (2004). An information integration theory of consciousness. *BMC Neuroscience*, *5*, 42.

Tononi, G. (2005). Consciousness, information integration, and the brain. *Progress in Brain Research*, *150*, 109–126.

Tononi, G. (2008). Consciousness as integrated information: A provisional manifesto. *The Biological Bulletin*, *215*, 216–242.

Tononi, G., & Laureys, S. (2008). The neurology of consciousness: An overview. In S. Laureys and G. Tononi (Eds.), *The Neurology of Consciousness* (pp. 375–411). Amsterdam: Elsevier.

Tononi, G., & Massimini, M. (2008). Why does consciousness fade in early sleep? *Annals of New York Academy of Sciences*, *1129*, 330–334.

Tononi, G., & Sporns, O. (2003). Measuring information integration. *BMC Neuroscience*, *4*, 31.

Tononi, G., Sporns, O., & Edelman, G. M. (1994). A measure for brain complexity: Relating functional segregation and integration in the nervous system. *Proceedings of the National Academy of Science of the United States of America*, *91*, 5033–5037.

Vanderwolf, C. H. (2000). Are neocortical gamma waves related to consciousness? *Brain Research*, *855*, 217–224.

Virtanen, J., Ruohonen, J., Näätänen, R., & Ilmoniemi, R. J. (1999). Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation. *Medical & Biological Engineering & Computing*, *37*, 322–326.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 15

Magnetic resonance spectroscopy and diffusion tensor imaging in coma survivors: promises and pitfalls ☆

Luaba Tshibanda[1,2], Audrey Vanhaudenhuyse[1], Damien Galanaud[3], Mélanie Boly[1], Steven Laureys[1,*] and Louis Puybasset[4]

[1]*Coma Science Group, Cyclotron Research Center and Neurology Department, University and University Hospital of Liège, Belgium*
[2]*Department of Neuroradiology, University Hospital of Liège, Belgium*
[3]*Department of Neuroradiology, Pitié-Salpêtrière Hospital, Paris, France*
[4]*Department of Anesthesiology-Reanimation, Pitié-Salpêtrière Hospital, Paris, France*

Abstract: The status of comatose patient is currently established on the basis of the patient-exhibited behaviors. Clinical assessment is subjective and, in 40% of patients, fails to distinguish vegetative state (VS) from minimally conscious states (MCS). The technologic advances of magnetic resonance imaging (MRI) have dramatically improved our understanding of these altered states of consciousness. The role of neuroimaging in coma survivors has increased beyond the simple evaluation of morphological abnormalities. The development of 1H-MR spectroscopy (MRS) and diffusion tensor imaging (DTI) provide opportunity to evaluate processes that cannot be approached by current morphologic MRI sequences. They offer potentially unique insights into the histopathology of VS and MCS. The MRS is a powerful noninvasive imaging technique that enables the in vivo quantification of certain chemical compound or metabolites as N-acetylaspartate (NAA), Choline (Cho), and Creatine (Cr). These biomarkers explore neuronal integrity (NAA), cell membrane turnover (Cho), and cell energetic function (Cr). DTI is an effective and proved quantitative method for evaluating tissue integrity at microscopic level. It provides information about the microstructure and the architecture of tissues, especially the white matter. Various physical parameters can be extracted from this sequence: the fractional anisotropy (FA), a marker of white matter integrity; mean diffusivity (MD); and the apparent diffusion coefficient (ADC) which can differentiate cytotoxic and vasogenic edema. The most prominent findings with MRS and DTI performed in traumatic brain-injured (TBI) patients in subacute phase are the reduction of the NAA/Cr ratio in posterior pons and the decrease of mean infratentorial and supratentorial FA except in posterior pons that enables to predict unfavorable outcome at 1 year from TBI with up to 86% sensitivity and 97% specificity. This review will focus on the interest of comatose patients MRI multimodal assessment with

☆ Luaba Tshibanda and Audrey Vanhaudenhuyse contributed equally to this work.

*Corresponding author.
Tel.: +32 4 366 23 16; Fax: +32 4 366 29 46;
E-mail: steven.laureys@ulg.ac.be

DOI: 10.1016/S0079-6123(09)17715-4

MRS and DTI. It will emphasize the advantages and pitfalls of these techniques in particular in predicting the coma survivors' outcome.

Keywords: traumatic brain injury; coma; diffusion tensor imaging; spectroscopy; prognosis; outcome

Introduction

Survivors of severe brain damage following traumatic brain injury (TBI), stroke, or anoxic/hypoxic encephalopathy may remain in an altered state of consciousness during several years. TBI is the most frequent etiology of severe brain damage among young and middle-aged adults (as compared to stroke and tumors in elderly subjects; Katz, 1997), leading to up to 14% of subsequently permanently vegetative patients (Celesia, 1993; Jennett, 2005; Payne et al., 1996). However, in about 5–10% of these TBI patients, anatomical lesions detected by classical morphological MRI (sequences such as T2*, FLAIR, and diffusion) are unable to explain their clinical status and to give clue about their chance of recovery. These patients present significant problems concerning diagnosis and misdiagnosis, prognosis, and therapy (Andrews et al., 1996; Childs and Mercer, 1996; Schnakers et al., 2009). The announcement of an optimistic outcome will increase the commitment of the team, while a pessimistic prognosis risks demobilizing and jeopardizing the potential recovery of the patient. Questions about end of life, aggressive therapy, limitation of care, and euthanasia often arise in such cases and lead to passionate debates among the medical staff, and sometimes more widely in the media and society. Therefore, neuroimaging techniques should be used not only to evaluate structural abnormality and detect TBI complications but also to reliably show the extent of brain damage in a clinical diagnostic and a therapeutic way and lead to a better understanding of the behavioral observations. In this review, we discuss recent developments in the use of proton magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) in the assessment of brain injury patients in particular after TBI due to the frequency of this etiology.

Imaging protocols

Magnetic resonance imaging (MRI) in coma survivors is routinely performed on 1.5 T or 3 T MR scanners. MRI assessment may often be limited by patient motion which can necessitate sedation; the risk of uncontrolled intracranial pressure occurring during the exam if performed when brain swelling is still present; unstable hemodynamic or respiratory condition, due to the limited monitoring available in the magnet; and artifacts generated by some metallic devices (most commonly intracranial pressure valves). In our view, a comprehensive patient MRI exploration should check both infra- and supratentorial structures, involved in arousal and awareness functions (Boly et al., 2008b). The ascending reticular activating system, located in the posterior part of the upper two-thirds of the brainstem is the primary arousal structure (Parvizi and Damasio, 2001; Plum and Posner, 1980). The evaluation of the patient's brain ability to generate awareness should include the assessment of the integrity of a large set of supratentorial structures, encompassing thalamus, basal forebrain, and fronto-parietal association cortices (Laureys et al., 1999; Parvizi and Damasio, 2001; Selden et al., 1998).

Classical morphological MRI was shown to poorly correlate with recovery of consciousness in severely brain-damaged patients. The fact that patients often develop progressive posttraumatic global brain atrophy (Table 1), despite the fact that initial morphologic imaging revealed only discrete findings or failed to show any pathology, also reflects the insufficiency of conventional imaging techniques to comprehensively evaluate the gravity of brain lesion in individual patients (Anderson et al., 1996; Gale et al., 1995; Gentry et al., 1988; Kelly et al., 1988). In particular, morphological MRI is not accurate for diagnosis

Table 1. Prognosis values of structural magnetic resonance imaging, magnetic resonance spectroscopy, diffusion weighted imaging and diffusion tensor imaging in altered state of consciousness patients

Authors	Number of patients	Diagnosis	Etiology	Interval	Main findings
Structural magnetic resonance imaging					
Firsching et al. (1998)	61	Coma; CGS $\leq$ 7 ($n = 61$)	TBI	$<$7 d	100% of mortality with bilateral pontine lesion, 2% with no brainstem lesion, 8% with unilateral or midline mesencephalon lesion, 8% with unilateral pons or medulla oblongata lesion, and 0% with lesion of the lower bilateral portions of medulla oblongata
Kampfl et al. (1998)	80	Vegetative state; CGS $\leq$ 8 ($n = 80$)	TBI	50 d, range 42–56	214-fold higher probability for not recovering with lesions in the corpus callosum and 7-fold with dorsolateral brainstem lesion
Paterakis et al. (2000)	24	Severe head injury; GCS $<$ 8 ($n = 19$); Moderate head injury; GCS 9–12 ($n = 5$)	TBI	$<$48 h	Good recovery when hemorrhagic DAI lesions; unfavorable outcome not associated with isolated nonhemorrhagic DAI lesions; 100% of unfavorable outcome when subcortical gray matter injury; subarachnoid hemorrhage not associated with favorable and unfavorable outcome
Carpentier et al. (2006)	40	Severe TBI; GCS 6$\pm$3 ($n = 40$)	TBI	17$\pm$11 d	Number of brainstem lesions: 4.3$\pm$3.3 for patients with GOS = 1–2, 1.9$\pm$1.5 for GOS = 3, 0.5$\pm$1.1 for GOS = 4–5
Magnetic resonance spectroscopy					
Choe et al. (1995)	10	Closed head injury; GCS 3–12 ($n = 10$)	TBI	132$\pm$134 d	Fronto-parietal white matter: positive correlation of NAA/Cr ratio with emergence of vegetative state
Friedman et al. (1999)	14	TBI; GCS 3–8 ($n = 7$), GCS 9–14 ($n = 5$), GCS NA ($n = 2$)	TBI	45$\pm$21 d	Occipito-parietal white and gray matter: patients with decreased NAA concentration have poor overall cognitive function at outcome
Garnett et al. (2000)	26	TBI; GCS 3–8 ($n = 9$), GCS 9–15 ($n = 17$)	TBI	12 d, range 3–35	Frontal white matter: GOS correlated with NAA/Cr ($r = 0.65$) and NAA/Cho ratio ($r = 0.58$); GOS did not correlate with Cho/Cr and Ins/Cr
Sinson et al. (2001)	30	TBI; GCS 3–15 ($n = 30$)	TBI	41 d, range 2–1129	Splenium: NAA/Cr ratio significantly lower in patients with $\leq$GOS = 1–4 (1.24$\pm$0.28 NAA/Cr ratio) than GOS = 5 (1.53$\pm$0.37 NAA/Cr ratio)
Uzan et al. (2003)	14	Vegetative state; GCS 4–7 ($n = 14$)	TBI	193$\pm$19 d	Thalamus: lower NAA/Cr ratio in permanent vegetative patients (1.17$\pm$0.25) than patients who recovered (1.8$\pm$0.26, $p < 0.001$); Cho/Cr ratio did not permit outcome differentiation
Carpentier et al. (2006)	40	Severe TBI; GCS 6$\pm$3 ($n = 40$)	TBI	17$\pm$11 d	Brainstem: NAA/Cr ratio showed significant difference between patients with GOS = 1–2 (1.68$\pm$0.4 NAA/Cr ratio) and GOS = 4–5 (2.1$\pm$0.3 NAA/Cr ratio)
Marino et al. (2007)	10	TBI; GCS 4–7 ($n = 7$), GCS 8–13 ($n = 3$)	TBI	48–72 h	Central brain: correlation of GOS with NAA ($r = -0.79$) and La ratio ($r = 0.79$)

Table 1. (*Continued*)

Authors	Number of patients	Diagnosis	Etiology	Interval	Main findings
Tollard et al. (2009)	43	Closed-head injury, GCS ≤ 7 ($n = 43$)	TBI	24 ± 11 d	Thalamus, lenticular nucleus, insular cortical gray matter, occipital white matter: NAA/Cr values at all sites lowest in patients with GOS = 1–3 (1.3 ± 0.3 NAA/Cr ratio) than with GOS = 4–5 (1.7 ± 0.4 NAA/Cr ratio)
Diffusion weighted imaging					
Schaefer (2004)	26	Closed head injury; GCS 10 ± 3 ($n = 26$)	TBI	<48 h	Correlation between number of lesions and outcome ($r = 0.662$); corpus callosum and outcome ($r = 0.513$); brainstem lesion and outcome ($r = 0.316$); basal ganglia/thalamus and outcome ($r = 0.179$)
Diffusion tensor imaging					
Huisman et al. (2004)	20	Head traumatic injury; GCS 9 ± 4 ($n = 20$)	TBI	<7 d	Splenium: correlation between outcome and ADC ($r = -0.599$), and outcome and FA ($r = -0.694$); internal capsule: correlation between outcome and FA ($r = -0.714$), no correlation between outcome and ADC ($r = -0.018$); thalamus/putamen: no correlation between outcome and FA and ADC
Tollard et al. (2009	43	Closed head injury; GCS ≤ 7 ($n = 43$)	TBI	24 ± 11 d	Pons, midbrain, temporal and occipital white matter, internal and external capsules, semioval center: FA significantly lower in patients with GOS 1–3 than with GOS 4–5 patients, except in the posterior pons; 86% sensitivity and 97% specificity for predicting outcome by combining MRS and DTI analysis
Perlbarg et al. (2009)	30	TBI with persistent disorder of consciousness; GCS 6 ± 4 ($n = 30$)	TBI	24 ± 11 d	FA significantly lower in GOS 1–3 than in GOS 4–5 and controls in right inferior longitudinal fasciculus, right cerebral peduncle, right posterior limb of the internal capsule and posterior corpus callosum

Notes: GCS, Glasgow Coma Scale; TBI, traumatic brain injury; NA, not available; d, days; h, hours; DAI, diffuse axonal injury; NAA, N-acetylaspartate; Cr, creatinine; Cho, choline; Ins, myo-inositol; GOS, Glasgow Outcome Scale; La, lactate; ADC, apparent diffusion coefficient; FA, fractional anisotropy.

or assessment of severity and extension of diffuse axonal injury (DAI). DAI consists in diffuse white matter damage, usually caused by the effect of brutal acceleration–deceleration and/or rotational forces; resulting in stretching, disruption, and separation of axons as the brain moves inside the skull and causing important morbidity and mortality (Adams et al., 1982; Strich, 1961; Gean, 1994; Murray et al., 1996). Morphological MRI assessments were however shown to be more sensitive and specific to assess the recovery of consciousness than computed tomodensitometry and electrophysiological tools (Wedekind et al., 1999).

Taking into account these considerations, conventional MRI cannot be considered as a reliable technique to assess brain-injured patients and predict their functional outcome. The lack of sensitivity of conventional MRI led to introduce new tools in the clinical assessment of comatose

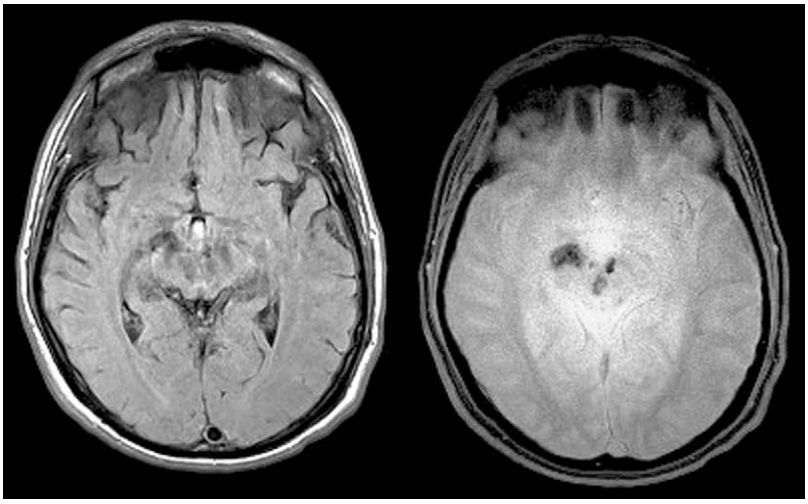


Fig. 1. Axial fluid attenuated inversion recovery (FLAIR) (left) and T2* (right) in a TBI minimally conscious patient. T2* sequence shows hyposignal in the midbrain suggestive of bleeding not clearly seen on FLAIR sequence.

patients such as positron emission tomography (PET; Beuthien-Baumann et al., 2003; Boly et al., 2008a; Laureys et al., 1999), functional MRI (fMRI; Boly et al., 2008b, Monti et al., 2009; Coleman et al., 2007; Owen et al., 2006), MRS (Cox, 1996), and DTI (Assaf and Pasternak, 2008; Voss et al. 2006). Preliminary studies suggest that these alternative functional and metabolic imaging methods could be more sensitive to detect brain damage immediately following TBI, and could thus be useful to monitoring longitudinal changes in brain function of non-communicative brain-damaged patients. In the future, they could play a crucial role in coma assessment, adding to a purely morphology-based imaging approach a more comprehensive evaluation of the patient's brain ability to generate consciousness, combining information on structure and function.

Conventional MRI protocol

In our view, in order to perform a comprehensive assessment of structural damage in individual coma patients, the morphologic MRI acquisitions should include noncontrast-enhanced sagittal T1, axial fluid attenuated inversion recovery (FLAIR), axial T2*, axial diffusion, coronal T2 sequences, and a 3D T1 weighted volume acquisition. In our centers, images are typically obtained with a section thickness of 5 mm (except for the 3D T1 which is millimetric). FLAIR sequence detects brain edema and contusion, epidural or subdural hematoma, subarachnoid hemorrhage, as well as the resulting herniation or hydrocephalus; while gradient echo-planar T2* weighted images are useful in detecting hemorrhage (Gerber et al., 2004; Scheid et al., 2003) (Fig. 1). The 3D T1 sequence provides information on the volume of the brain, and can be use during the follow up of patients. Indeed, severe and irreversible brain damage would lead to progressive brain atrophy, over a period of weeks to years (Trivedi et al., 2007).

Diffusion tensor imaging protocol

DTI is one of the most popular MRI techniques investigated in current brain-imaging research (Fig. 2). It is an extension of diffusion-weighted imaging (DWI) which is based on the principle that water molecule movement is restricted by barriers to diffusion in the brain depending on tissue organization. The acquisition protocol, image processing, analysis, and interpretation of DTI are now routinely performed in clinical conditions although it suffers from inherent

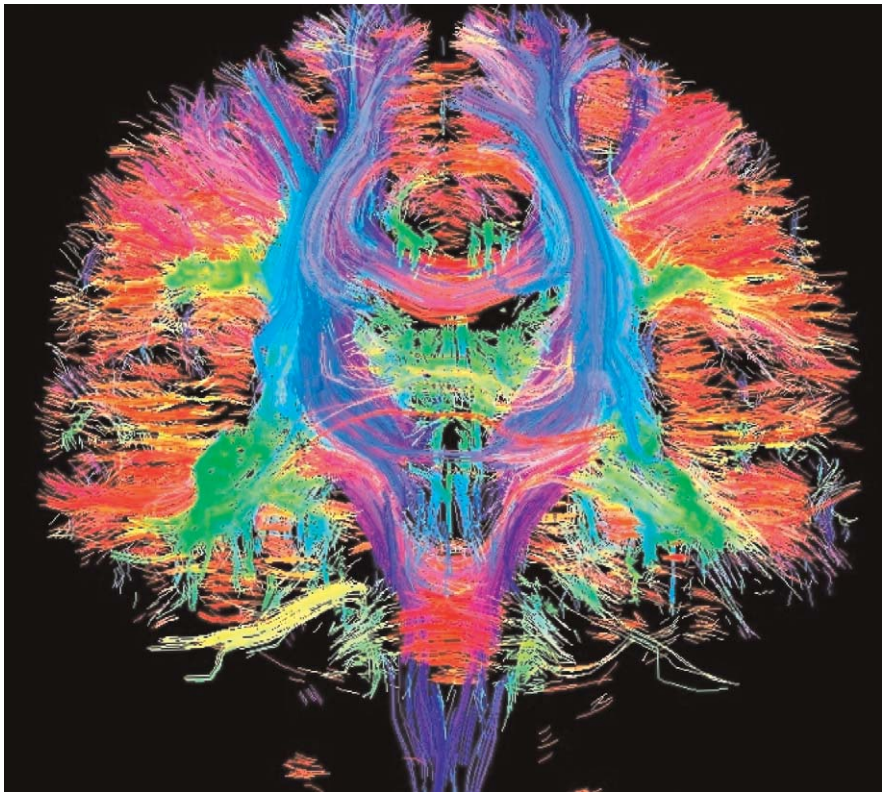


Fig. 2. Example of diffusion tensor imaging (DTI) obtained in a healthy volunteer, visualising the white matter tracts. Acquisition time: 4:51; TR/TE: 5700/90 ms; Resolution: 128×128; Slices: 40 transversal slices (2.0 mm thickness, 30% gap, interleaved); Voxel size: $1.8 \times 1.8 \times 2.0\,mm^3$; FoV: $230 \times 230\,mm^2$.

artifacts and limitations such as the partial volume effect and the inability of the model to cope with non-Gaussian diffusion. DTI imaging is classically performed in axial plane, using the following parameters: TR/TE, 8000/84.9 ms; 23 directions; diffusion *b* value, $700\,s/mm^2$; slice thickness, 5 mm; no gap; 20 slices; field of view, 32×32 cm; matrix, 128×128; and 2 averages (Tollard et al., 2009). DTI provides data that can be used to compute two basic properties: the overall amount of diffusion represented by the apparent diffusion coefficient (ADC) and the fractional anisotropy (FA) which enable visualization and characterization of white matter (WM) in two and three dimensions. The FA characterizes the anisotropic component, that is, degree and directionality of water diffusion. Determination of FA allows a quantification of WM density in vivo and gives information about its integrity (Liu et al., 1999; Melhem et al., 2000; Pierpaoli et al., 1996). In our protocol of data acquisition and analysis, symmetric rectangular regions of interest (ROI) are also used for the quantitative measures positioning at several sites including the anterior and posterior pons, right and left midbrain, the right and left WM of temporal lobe, occipital lobe, posterior limb of the internal capsule, external capsule, anterior and posterior semiovale centrum (Tollard et al., 2009).

DWI and DTI show anomalies invisible on current morphological MRI even on $T2^*$ sequence (Huisman et al., 2003) and can better assess the degree of neurological impairment than any other conventional MRI sequence (Shanmuganathan et al., 2004). DTI permits to identify specific fiber bundles such as the corpus

callosum and the long association fibers that include cingulum, superior and inferior longitudinal fascicules, uncinate fasciculus, superior and inferior fronto-occipital fascicules. Other fibers bundles can also be visualized: brainstem tracts, projection fibers such as corticospinal and corticothalamic fibers. DTI is an appropriate technique to assess microstructural WM damage that occurs in TBI, particularly since the pathophysiological mechanisms altering water diffusion anisotropy include DAI and intracranial hypertension. Several studies confirmed that DWI is a valuable technique to assess DAI (Arfanakis et al., 2002; Huisman et al., 2003; Liu et al., 1999) and showed that DTI is sensitive to damage in tissue that may appear normal on conventional MRI sequences (Arfanakis et al., 2002; Chan et al., 2003). Over conventional sequences commonly used to assess DAI (such as FLAIR, T2*, diffusion-weighted, and susceptibility weighted), DTI offers the advantages of a greater sensitivity and the availability of quantitative information.

Magnetic resonance spectroscopy protocol

MRS provides in vivo biochemical information. The metabolites that can be identified with proton MRS are dependent on the echo time (TE). At 1.5 T and 3 T, metabolites visualized utilizing intermediate-to-long TE (135–288 ms) include choline (Cho), creatine (Cr), N-acetylaspartate (NAA), and lactate (La). NAA is produced in the mitochondria of the neurons and transported into the neuronal cytoplasm and the axons. It is found in both gray and white matter in approximately equal quantities (Danielsen and Ross, 1999). In healthy subjects, there is an increase in NAA in gray matter from ventral to dorsal, and from the cerebral hemispheres to the spinal cord (Pouwels and Frahm, 1998). Several studies suggest NAA to be a brain osmolyte with possible reversible changes (Baslow et al., 2003, 2007; Moffett et al., 2007). It is considered as a marker of neuronal density and viability and functional status (Ebisu et al., 1994; Sullivan et al., 2001); its peak decrease when there is neuron suffering or loss. Choline is a metabolic marker of membrane synthesis and catabolism. MRS permits to detect free choline and phosphocholine, that is, those that are not incorporated into the macromolecules on the membrane surface (Ross and Michaelis, 1994). Its concentration is slightly greater in white than in gray matter. Its peak increases when there is greater membrane turnover, cell proliferation, or inflammatory process. Creatine is considered as a marker of the aerobic energy metabolism. It is assumed to be stable, hence is used for calculating metabolite ratios (NAA/Cr and Cho/Cr ratios). Lactate is at the limit of detectability in normal human brain using the routine spectroscopic techniques. However, under anaerobic glycolysis conditions, such as brain hypoxia, ischemia, or severe post-traumatic injury, lactate level may increase significantly.

In our view, a comprehensive MRS protocol to assess brain function in comatose patients should include single-voxel ^{1}H spectroscopy (SVS) placed on the posterior two-thirds of the pons (the parameters we typically use are: TR/TE, 1500/135 ms; matrix, 1×1; voxel thickness, 20 mm; and 96 averages) (Fig. 3) and an axial chemical shift imaging (CSI) at the level of the basal ganglia to include thalamus, insular cortex, and periventricular WM in the field of exploration (the parameters we typically use are: TR/TE, 1500/135 ms; field of view, 24×24 cm; matrix, 18×18; slice thickness, 15 mm; and NEX, 1) (Tollard et al., 2009) (Fig. 4). In our clinical practice, the SVS is usually performed in the pons for three reasons. First, the pons contains a large part of the ascending reticular activating system; second, the pons is often affected by DAIs not necessarily seen on FLAIR and T2* sequences; and third, the pons can be damaged from both primary and secondary cerebral injuries due to temporal lobe herniation (Carpentier et al., 2006). Patients with bilateral lesions of the protuberance on standard morphological MRI sequences have been reported with a 100% mortality rate (Firsching et al., 1998). Finally, MRS has a better sensitivity than T2*sequence in the detection of ischemic or hemorrhagic diffuse axonal lesions in TBI (Cecil et al., 1998).

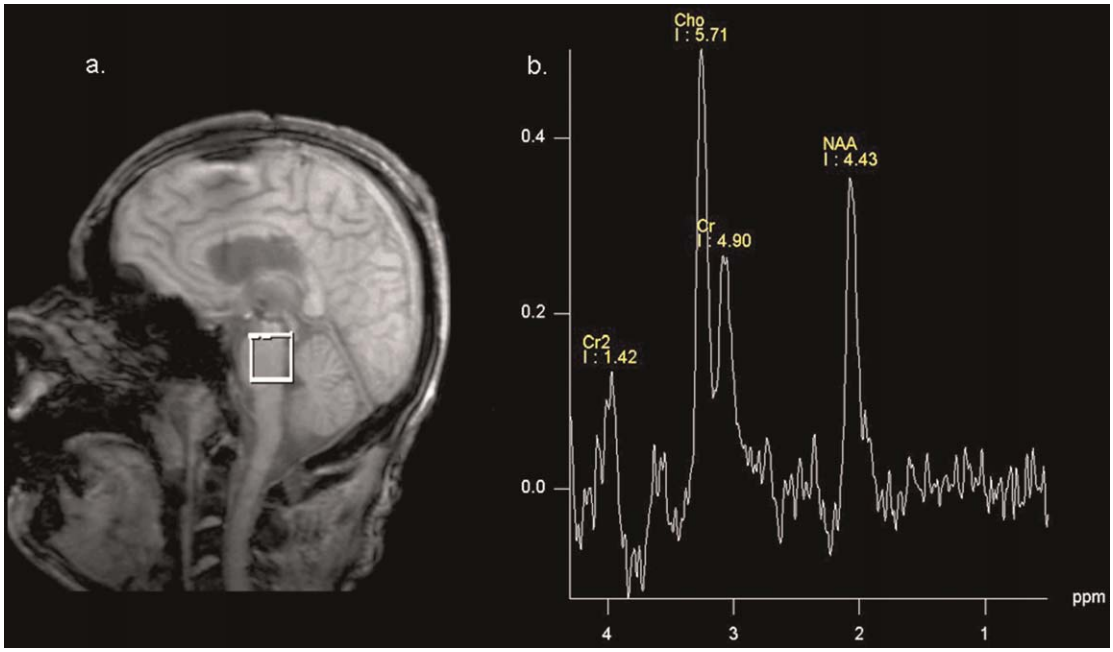


Fig. 3. Monovoxel spectroscopic (SVS) of the pons in a TBI patient. a: Location of the voxel on the sagittal T1-weighted acquisition. b: Decreased NAA spectrum (NAA/Cr = 0.90 and NAA/Cho+Cr+NAA = 0.29).

Comatose patients assessment

The timing of an optimal MRI assessment in comatose patients remains controversial (Table 1). An acute exploration may take into account reversible lesions such as edema or miss secondary lesions due to intracranial hypertension or systemic disorders. On the contrary, an examination performed late after the injury may only detect sequels such as global aspecific atrophy and has no impact on the initial medical management and on altered state of consciousness status prediction. With regard to time since TBI or stroke, MRS and DTI findings vary greatly and studies are heterogeneous as illustrated by last studies performed with MRS sequences. Four phases may be distinguished: an acute phase, which lasts 24 h after TBI; an early subacute phase, from the day 1 to 13; a late subacute phase, from days 14 to 20; and a chronic phase, which starts on day 21 (Weiss et al., 2007). Among these MRS studies, two included patients at the acute phase (Marino et al., 2007; Ross et al., 1998), two from the early subacute phase to the first month (Carpentier et al., 2006; Garnett et al., 2000), one at the late subacute phase up to 11 months (Choe et al., 1995), and four at the chronic phase from 3 weeks to 8 months after TBI (Friedman et al., 1999; Ricci et al., 1997; Sinson et al., 2001; Uzan et al., 2003). In a retrospective study using DTI, comatose patients were excluded if the time delay between trauma and MRI exceeded 7 days to avoid the various changes in anisotropic diffusion related to secondary tissue injury (Huisman et al., 2004). An early examination with precise quantification of the extent and degree of brain injury is essential for treatment decisions (i.e., to determine outcome, cognitive and behavioral deficits), and becomes a criterion of good practice in management of these patients. The late subacute phase seems to be the best moment to assess comatose patients taking into account the physiopathology and all issues (medical, ethical, legal, social) raised by the management of these patients.

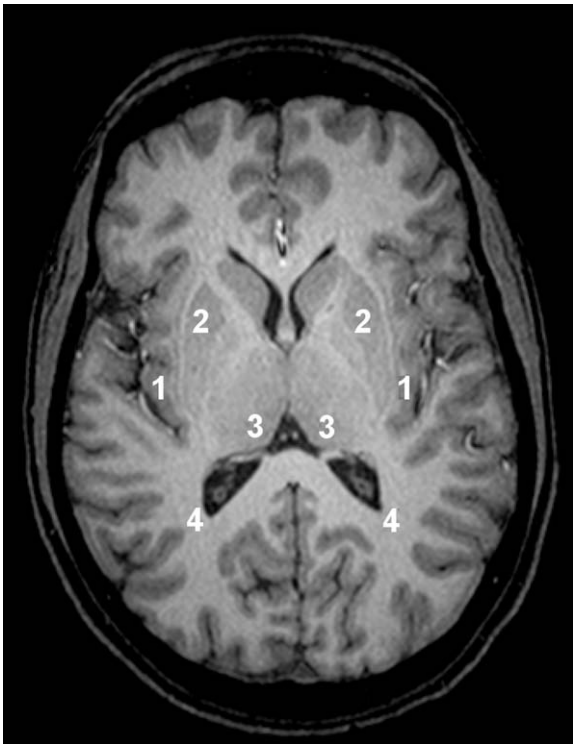


Fig. 4. Chemical shift imaging (CSI). Position of regions of interest: insula (1), lenticular nucleus (2), thalamus (3), and periventricular white matter (4).

Prediction of outcome with MRI

Although clinical examination and conventional imaging techniques provide useful information for TBI patient screening and acute care, none of them accurately predicts individual patient outcome. Developing a reliable MRI outcome-prediction tool is a major challenge for all physicians in charge of comatose patients. It would provide an objective basis for deciding to go on with prolonged aggressive care or to remove life-supporting therapy as well as for informing families and planning rehabilitation.

Conventional MRI

There is some evidence that MRI may have potential in terms of predicting outcome according to several studies performed with conventional MRI. Firsching and colleagues (1998) performed a prospective MRI study in 61 consecutive patients within 7 days after their injury. They found bilateral pontine lesions to be 100% fatal, whereas unilateral brainstem lesions were responsible of similar mortality rate as in patients with no brainstem injury and conclude that early MRI after head injury had a higher predictive value than CT scanning. Other studies have showed that MRI scans performed at acute and subacute phase after head injury provide several indicators for unfavorable outcome when there are lesions within the corpus callosum and dorsolateral brainstem (Kampfl et al.,1998), basal ganglia, hippocampus, midbrain, and pons (Wedekind et al., 1999). Presence of hemorrhage in DAI-type lesions and the association with traumatic space-occupying lesions was indicative of poor prognostic sign. Isolated non-hemorrhagic DAI-type lesions were not associated with poor clinical outcome (Paterakis et al., 2000). Hoelper

et al. (2000) observed that the number (>3) and volume (>1.5 mL) of brainstem lesions correlated with unfavorable outcome. There are also some evidences that the total lesion volume on FLAIR images correlates significantly with clinical outcome. The volume of lesions of the corpus callosum on the FLAIR sequence correlated significantly with scores on disability and cognition scales at the first clinical assessment. Volume of FLAIR lesions in the frontal lobes correlated significantly with outcome after 1 year (Pierallini et al., 2000). Moreover, the number of lesions detected by T2* was also shown as significantly greater than that detected by T2-FSE (Yanagawa et al., 2000). Lesions detected by T2* and FLAIR were inversely correlated with outcome of patient (Yanagawa et al., 2000; Carpentier et al., 2006).

In spite of these multiple morphological MRI studies and their encouraging results (Table 1), it remains difficult to explain why some patients in persistent vegetative state or with long-term marked cognitive impairments have no or minimal lesions on conventional MR examination performed with T2* and diffusion sequences. Therefore, morphological MRI alone cannot be considered as a reliable tool to assess coma severity, and to predict the comatose patient functional outcome.

Magnetic resonance spectroscopy

To our knowledge, Choe et al. (1995) performed the first assessment of patient with closed head injury using in vivo proton MRS to evaluate neuronal and axonal dysfunction. The main result in this case-control study was a significant decrease of NAA/Cr ratio compared with normal controls. The level of NAA/Cr ratio was significantly correlated with Glasgow Outcome Scale (GOS; Jennett and Bond, 1975) whereas no clear correlation of other metabolite ratios such as Cho/Cr was observed. Since then, several investigations that do appear in the literature were promising in terms of the role of proton MRS as an accurate tool to predict patient outcome. Ricci et al. (1997) examined 14 vegetative brain-injured patients with proton magnetic resonance single-volume spectroscopy performed 1–90 months after the injury. Cho/Cr was significantly higher, whereas NAA/Cho and NAA/Cr were markedly lower than in the control subjects. The NAA/Cho ratio was statistically significant in discriminating between the patients with a poor outcome (GOS score, 1–2) and those who regained awareness. Other studies have showed a reduced NAA/Cr level in gray and white matter of occipito-parietal regions in acute and subacute phase after injury, which correlated with bad outcome (Ross et al., 1998; Friedman et al., 1999). The frontal WM NAA/Cr acquired in the subacute phase significantly correlated with patient outcome, whereas Cho/Cr was increased at both the early and late phase compared with controls (Garnett et al., 2000). Decreased NAA/Cr ratio in the splenium of corpus callosum also correlated with the GOS score of acute and chronic patients (Sinson et al., 2001). The NAA/Cr ratio was reduced in the thalami of both persistent vegetative patients and patients who recovered 6–8 months after injury (Uzan et al., 2003). Moreover, NAA/Cr ratios were lower in persistent vegetative patient than in patients who regained awareness. Carpentier et al. (2006) observed three MRS profile of the pons after TBI: normal profile (the peak of NAA is higher than the peaks of Cho and Cr), neuronal loss profile (the NAA peak is decreased, nearly to the level of the Cr peak; the NAA/Cr ratio is <1.50 and NAA/Cho+Cr+NAA <0.40) (Fig. 3), and gliosis profile (increased Cho peak with no change in the Cr or NAA peak and Cho/Cr $>$ NAA/Cr or Cho/Cho+Cr+NAA >0.40).

The NAA/Cr ratio was correlated with the GOS score but not with lesions burden on T2* or FLAIR, whereas this lesions burden was correlated with the outcome score. Therefore, MRS and conventional MR seem to be complementary. The combination of these two techniques may be useful. Other people showed that NAA/Cr and NAA/all metabolites ratios to be significantly lower in the medial cortex of patients with TBI than in normal controls, whereas the La/Cr and La/all metabolites ratios were increased (Marino et al., 2007). Both NAA and La ratios correlated with GOS score. Data of MRS performed early after brain injury are clinically relevant. Increased La detected may be, at this stage, a reliable index

of injury severity and disease outcome in patients with TBI. Cohen et al. (2007) included 20 patients in a case-control study with the purpose to quantify the global decline of the neuronal marker NAA, as well as gray and white matter atrophy after mild traumatic brain injury (mTBI). Patients with mTBI exhibited, on average, a 12% whole-brain NAA deficit, which increased with age, as compared with the control subjects. Volumetric MRI in their patients showed decreased volume of gray matter, which, in combination with low whole-brain NAA, strongly suggests damage to the neurons and their axons. Tollard et al. (2009) observed NAA/Cr values at all measurement sites to be lowest in group of patients with unfavorable outcome (GOS, 1–3), intermediate in patients with favorable outcome (GOS, 4–5), and highest in control group. They did not find correlations between metabolic ratios and FA values; in particular, the NAA/Cr ratio of the pons was not correlated with the infratentorial FA value. Interestingly an unfavorable outcome after 1 year was predicted with up to 86% sensitivity and 97% specificity when taking into account both DTI and MRS values. Sensitivity was 79% and specificity 85% with FA only; corresponding values with MRS only were 75% and 75%.

In conclusion, proton MRS should be added to morphological MR examinations with minimal additional time. It is proved to be useful in assessing injury severity, guiding patient care, and predicting patient outcome (Table 1). We agree with Weiss et al. (2007) that MRS studies in TBI patients are heterogeneous in terms of patient selection, time from TBI to MRS, voxel location, method of outcome assessment, and timing of outcome assessment. MRS research suffers from disparate acquisition protocols across research teams. However, the normal NAA/Cr ratio in identical regions is similar across studies and its decrease appears to be a reliable index of unfavorable outcome. The NAA is shown to decrease within a few minutes after TBI and reach the trough value within 48 h. Its level remains stable within the first month after TBI, supporting the validity of MRS assessment during the second or third week (Holshouser et al., 2006; Signoretti et al., 2002). The later evolution of the NAA/Cr ratio between 6 weeks and 1 year after TBI is more heterogeneous, and NAA levels have been shown to decrease or increase. This possible variability in NAA levels is a potential limitation of this technique. In addition, the use of ratios may be problematic in TBI. Cr is assumed to be stable in normal brain tissue and used to standardize other brain metabolites. However, to the best of our knowledge, there is no evidence that Cr is invariable in TBI. Indeed, it could be affected similarly to the metabolite of interest as well (it is suggested to be reduced in hypermetabolic and raised in hypometabolic states; Castillo et al., 1996; Wood et al., 2003). This issue is important in particular as metabolism may be compromised in mTBI (Lewine et al., 1999). To minimize the potential negative impact of the NAA variability, repeated MRS examination during the subacute phase is probably needed and the whole-brain NAA estimation would improve the MRS yield. Studies have to be performed to prove the stability of Cr in TBI.

Diffusion tensor imaging

DTI may be a valuable biomarker for the severity of tissue injury and a predictor for outcome. It reveals changes in the WM that are correlated with both acute GCS and Rankin scores at discharge (Huisman et al., 2004). Significant early reduction of anisotropy was observed in WM structures, in particular in the internal capsule and the corpus callosum, which are the sites most commonly involved by DAI (Arfanakis et al., 2002). Moreover, several regions recovered normal values of anisotropy 1 month after the injury (Arfanakis et al., 2002). Xu et al. (2007) found significant differences in the corpus callosum, internal and external capsule, superior and inferior longitudinal fascicles, and the fornix in TBI patients. They showed that FA and ADC measurements offered superior sensitivity compared to conventional MRI diagnosis of DAI. Salmond et al. (2006) reported increased diffusivity in TBI patients at least 6 months after their injury in the cerebellum, frontal, insula, cingulate, parietal, temporal, and occipital lobes.

The anisotropy seems to be reduced both in the major WM tracts such as the corpus callosum and the internal and external capsule, and the associative fibers underlying the cortex. DTI has a number of advantages as an imaging biomarker of brain injury: first, it can be used to evaluate brain trauma in an unconscious or sedated patient; second, it could permit the evaluation of responses to treatment even when the clinical scores are inadequate for assessing the patient; third, quantitative DTI measurements are unlikely to be tainted by adverse central nervous system (CNS) effects of hypnotic drugs, unlike clinical scores; and fourth, DTI may be an important alternative marker, as low initial GCS scores are of limited value in predicting the prognosis (Huisman et al., 2004). Finally, Perlbarg et al. (2009) showed significant FA differences between favorable and unfavorable 1-year outcome groups around four FA tracks: in inferior longitudinal fasciculus, posterior limb of the internal capsule, cerebral peduncle, and posterior corpus callosum.

Conclusion

In the future, DTI and MRS may permit to evaluate response to therapeutic interventions in TBI even when the clinical scores are inadequate for assessing the patient. MRS and DTI detect abnormalities not demonstrated on conventional MRI or CT structural scans, which are generally correlated with clinical outcomes. It is becoming increasingly obvious that these techniques are complementary and that both could be required to explore comatose patients at subacute stage from TBI as part of a comprehensive multimodal MRI and clinical assessment. Their combination will also possibly allow the pathogenesis of brain impairment to be better understood and the outcome better predicted. However, it is important to keep in mind some pitfalls such as the variability of NAA values and the impact of brain swelling which can, respectively, diminish the reliability of NAA and early FA measurement for predicting outcome in individual brain-damaged patients.

Acknowledgments

This research was supported by the Fonds de la Recherche Scientifique (FRS), European Commission (DISCOS, Mindbridge & COST BM0605), McDonnell Foundation, Mind Science Foundation, Reine Elisabeth Medical Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340) and University and University Hospital of Liège. A. Vanhaudenhuyse was funded by ARC 06/11-340; M. Boly, and S. Laureys are, respectively, Research Fellow, Postdoctoral Researcher, and Senior Research Associate at FRS. The authors thank the technicians of the Department of Neuro-Radiology and the nurses of the Intensive Care Units of the Pitié-Salpêtrière Hospital, Paris and Centre Hospitalier Universitaire, Liège, for their active participation in the MRI studies in comatose patients.

References

Adams, J. H., Graham, D. I., Murray, L. S., & Scott, G. (1982). Diffuse axonal injury due to nonmissile head injury in humans: An analysis of 45 cases. *Annals of Neurology*, *12*, 557–563.

Anderson, C. V., Wood, D. M., Bigler, E. D., & Blatter, D. D. (1996). Lesion volume, injury severity, and thalamic integrity following head injury. *Journal of Neurotrauma*, *13*, 59–65.

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*(7048), 13–16.

Arfanakis, K., Haughton, V. M., Carew, J. D., Rogers, B. P., Dempsey, R. J., & Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. *American Journal of Neuroradiology*, *23*, 794–802.

Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. *Journal of Molecule Neuroscience*, *34*, 51–61.

Baslow, M. H., Hrabe, J., & Guilfoyle, D. N. (2007). Dynamic relationship between neurostimulation and N-acetylaspartate metabolism in the human visual cortex: Evidence that NAA functions as a molecular water pump during visual stimulation. *Journal of Molecule Neuroscience*, *32*, 235–245.

Baslow, M. H., Suckow, R. F., Gaynor, K., Bhakoo, K. K., Marks, N., Saito, M., et al. (2003). Brain damage results in down-regulation of N-acetylaspartate as a neuronal osmolyte. *Neuromolecular Medicine*, *3*, 95–104.

Beuthien-Baumann, B., Handrick, W., Schmidt, T., Burchert, W., Oehme, L., Kropp, J., et al. (2003). Persistent vegetative state: Evaluation of brain metabolism and brain perfusion with PET and SPECT. *Nuclear Medicine Communications*, *24*, 643–649.

Boly, M., Faymonville, M. E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., et al. (2008a). Perception of pain in the minimally conscious state with PET activation: An observational study. *Lancet Neurology*, *7*(11), 1013–1020.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T. T., et al. (2008b). Intrinsic brain activity in altered states of consciousness. How conscious is the default mode of brain function? *Annals of the New York Academy of Sciences*, *1129*, 119–129.

Carpentier, A., Galanaud, D., Puybasset, L., Muller, J. C., Lescot, T., Boch, A. L., et al. (2006). Early morphologic and spectroscopic magnetic resonance in severe traumatic brain injuries can detect "invisible brain stem damage" and predict "vegetative states". *Journal of Neurotrauma*, *23*, 674–685.

Castillo, M., Kwock, L., & Mukherji, S. K. (1996). Clinical applications of proton MR spectroscopy. *American Journal of Neuroradiology*, *17*, 1–15.

Cecil, K. M., Hills, E. C., Sandel, M. E., Smith, D. H., McIntosh, T. K., Mannon, L. J., et al. (1998). Proton magnetic resonance spectroscopy for detection of axonal injury in the splenium of the corpus callosum of brain-injured patients. *Journal of Neurosurgery*, *88*, 795–801.

Celesia, G. (1993). Persistent vegetative state. *Neurology*, *43*, 1457–1458.

Chan, Y. L., Chu, W. C., Wong, G. W., & Yeung, D. K. (2003). Diffusion-weighted MRI in shaken baby syndrome. *Pediatric Radiology*, *33*, 574–577.

Childs, N. L., & Mercer, W. N. (1996). Misdiagnosing the persistent vegetative state. Misdiagnosis certainly occurs. *British Medical Journal*, *313*(7062), 944.

Choe, B. Y., Suh, T. S., Choi, K. H., Shinn, K. S., Park, C. K., & Kang, J. K. (1995). Neuronal dysfunction in patients with closed head injury evaluated by in vivo 1H magnetic resonance spectroscopy. *Investigative Radiology*, *30*, 502–506.

Cohen, B. A., Inglese, M., Rusinek, H., Babb, J. S., Grossman, R. I., & Gonen, O. (2007). Proton MR spectroscopy and MRI-volumetry in mild traumatic brain injury. *American Journal of Neuroradiology*, *28*, 907–913.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, *130*, 2494–2507.

Cox, I. J. (1996). Development and applications of in vivo clinical magnetic resonance spectroscopy. *Progress in Biophysics and Molecular Biology*, *65*, 45–81.

Danielsen, E. R., & Ross, B. (1999). *Magnetic resonance spectroscopy diagnosis of neurological diseases* (1st ed.). New York: Marcel Dekker, Inc.

Ebisu, T., Rooney, W. D., Graham, S. H., Weiner, M. W., & Maudsley, A. A. (1994). N-acetylaspartate as an in vivo marker of neuronal viability in kainate-induced status epilepticus: 1H magnetic resonance spectroscopic imaging. *Journal of Cerebral Blood Flow & Metabolism*, *14*, 373–382.

Firsching, R., Woischneck, D., Diedrich, M., Klein, S., Ruckert, A., Wittig, H., et al. (1998). Early magnetic resonance imaging of brainstem lesions after severe head injury. *Journal of Neurosurgery*, *89*, 707–712.

Friedman, S., Brooks, W., Jung, R., Chiulli, S., Sloan, J., Montoya, B., et al. (1999). Quantitative proton MRS predicts outcome after traumatic brain injury. *Neurology*, *52*, 1384–1391.

Gale, S. D., Johnson, S. C., Bigler, E. D., & Blatter, D. D. (1995). Trauma-induced degenerative changes in brain injury: A morphometric analysis of three patients with preinjury and postinjury MR scans. *Journal of Neurotrauma*, *12*, 151–158.

Garnett, M. R., Blamire, A. M., Corkill, R. G., Cadoux-Hudson, T. A., Rajagopalan, B., & Styles, P. (2000). Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. *Brain*, *123*, 2046–2054.

Gean, A. D. (1994). *White matter shearing injury and brainstem injury*. New York: Raven.

Gentry, L. R., Godersky, J. C., Thompson, B., & Dunn, V. D. (1988). Prospective comparative study of intermediate-field MR and CT in the evaluation of closed head trauma. *American Journal of Roentgenology*, *150*, 673–682.

Gerber, D. J., Weintraub, A. H., Cusick, C. P., Ricci, P., & Whiteneck, G. G. (2004). Magnetic resonance imaging of traumatic brain injury: Relationship of T2*SE and T2GE to clinical severity and outcome. *Brain Injury*, *18*, 1083–1097.

Hoelper, B. M., Soldner, F., Chone, L., & Wallenfang, T. (2000). Effect of intracerebral lesions detected in early MRI on outcome after acute brain injury. *Acta Neurochirurgica. Supplement*, *76*, 265–267.

Holshouser, B. A., Tong, K. A., Ashwal, S., Oyoyo, U., Ghamsary, M., Saunders, D., et al. (2006). Prospective longitudinal proton magnetic resonance spectroscopic imaging in adult traumatic brain injury. *Journal of Magnetic Resonance Imaging*, *24*, 33–40.

Huisman, T., Sorensen, A., Hergan, K., Gonzalez, R., & Schaefer, P. (2003). Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. *Journal of Computer Assisted Tomography*, *27*, 5–11.

Huisman, T. A., Schwamm, L. H., Schaefer, P. W., Koroshetz, W. J., Shetty-Alva, N., Ozsunar, Y., et al. (2004). Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *American Journal of Neuroradiology*, *25*, 370–376.

Jennett, B. (2005). 30 years of the vegetative state: Clinical, ethical and legal problems. In S. Laureys (Ed.), *The boundaries of consciousness: Neurobiology and neuropathology* (Vol. 150, pp. 541–548). Amsterdam: Elsevier.

Jennett, B., & Bond, M. (1975). Assessment of outcome after severe brain damage. *Lancet*, *7905*, 480–484.

Kampfl, A., Schmutzhard, E., Franz, G., Pfausler, B., Haring, H. P., Ulmer, H., et al. (1998). Prediction of recovery from

post-traumatic vegetative state with cerebral magnetic-resonance imaging. *Lancet*, *351*, 1763–1767.

Katz, D. (1997). *Traumatic brain injury*. Malden: Blackwell Science.

Kelly, A. B., Zimmerman, R. D., Snow, R. B., Gandy, S. E., Heier, L. A., & Deck, M. D. F. (1988). Head trauma: Comparison of MR and CT-experience in 100 patients. *American Journal of Neuroradiology*, *9*, 699–708.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., et al. (1999). Impaired effective cortical connectivity in vegetative state. *Neuroimage*, *9*, 377–382.

Lewine, J. D., Davis, J. T., Sloan, J. H., Kodituwakku, P. W., & Orrison, W. W., Jr. (1999). Neuromagnetic assessment of pathophysiologic brain activity induced by minor head trauma. *American Journal of Neuroradiology*, *20*, 857–866.

Liu, A. Y., Maldjian, J. A., Bagley, L. J., Sinson, G. P., & Grossman, R. I. (1999). Traumatic brain injury: Diffusion-weighted MR imaging findings. *American Journal of Neuroradiology*, *20*, 1636–1641.

Marino, S., Zei, E., Battaglini, M., Vittori, C., Buscalferri, A., Bramanti, P., et al. (2007). Acute metabolic brain changes following traumatic brain injury and their relevance to clinical severity and outcome. *Jounral of Neurology, Neurosurgery and Psychiatry*, *78*, 501–507.

Melhem, E. R., Itoh, R., Jones, L., & Barker, P. B. (2000). Diffusion tensor MR imaging of the brain: Effect of diffusion weighting on trace and anisotropy measurements. *American Journal of Neuroradiology*, *21*, 1813–1820.

Moffett, J. R., Ross, B., Arun, P., Madhavarao, C. N., & Namboodiri, A. M. (2007). N-Acetylaspartate in the CNS: From neurodiagnostics to neurobiology. *Progress in Neurobiology*, *81*, 89–131.

Monti, M. M., Coleman, M. R., & Owen, A. M. (2009). Neuroimaging and the vegetative state: Resolving the behavioral assessment dilemma? *Annals of the New York Academy of Sciences*, *1157*(March), 81–89.

Murray, J. G., Gean, A. D., & Evans, S. J. (1996). Imaging of acute head injury. *Seminars in Ultrasound, CT and MRI*, *17*, 185–205.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *13*, 1402.

Parvizi, J., & Damasio, A. (2001). Consciousness and the brainstem. *Cognition*, *79*, 135–160.

Paterakis, K., Karantanas, A. H., Komnos, A., & Volikas, Z. (2000). Outcome of patients with diffuse axonal injury: The significance and prognostic value of MRI in the acute phase. *Journal of Trauma*, *49*, 1071–1075.

Payne, K., Taylor, R. M., Stocking, C., & Sachs, G. A. (1996). Physicians' attitudes about the care of patients in the persistent vegetative state: A national survey. *Annals of Internal Medicine*, *125*, 104–110.

Perlbarg, V., Puybasset, L., Tollard, E., Lehéricy, S., Benali, H., & Galanaud, D. (2009). Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: A diffusion tensor imaging study using voxel-based approaches. *Human Brain Mapping* (in press).

Pierallini, A., Pantano, P., Fantozzi, L. M., Bonamini, M., Vichi, R., Zylberman, R., et al. (2000). Correlation between MRI findings and long-term outcome in patients with severe brain trauma. *Neuroradiology*, *42*, 860–867.

Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology*, *201*, 637–648.

Plum, F., & Posner, J. (1980). *The diagnosis of stupor and coma* (3rd ed.). Oxford, UK: Oxford University Press.

Pouwels, P. J., & Frahm, J. (1998). Regional metabolite concentrations in human brain as determined by quantitative localized proton MRS. *Magnetic Resonance Medicine*, *39*, 53–60.

Ricci, R., Barbarella, G., Musi, P., Boldrini, P., Trevisan, C., & Basaglia, N. (1997). Localised proton MR spectroscopy of brain metabolism changes in vegetative patients. *Neuro radiology*, 313–319.

Ross, B., & Michaelis, T. (1994). Clinical applications of magnetic resonance spectroscopy. *Magnetic Resonance Quarterly*, *10*, 191–247.

Ross, B. D., Ernst, T., Kreis, R., Haseler, L. J., Bayer, S., Danielsen, E., et al. (1998). 1H MRS in acute traumatic brain injury. *Journal of Magnetic Resonance Imaging*, *8*, 829–840.

Salmond, C. H., Menon, D. K., Chatfield, D. A., Williams, G. B., Pena, A., Sahakian, B. J., et al. (2006). Diffusion tensor imaging in chronic head injury survivors: Correlations with learning and memory indices. *Neuroimage*, *29*, 117–124.

Schaefer, P. W., Huisman, T. A. G., Sorensen, A. G., Gonzalez, R. G., & Schwamm, L. H. (2004). Diffusion-weighted MR imaging in closed head injury: High correlation with initial Glasgow Coma Scale score and score on Modified Ranking Scale at Discharge. *Radiology*, *233*(1), 58–66.

Scheid, R., Preul, C., Gruber, O., Wiggins, C., & von Cramon, D. Y. (2003). Diffuse axonal injury associated with chronic traumatic brain injury: Evidence from $T2^*$-weighted gradient-echo imaging at 3 T. *American Journal of Neuroradiology*, *24*, 1049–1056.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., et al. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, *21*(9), 35.

Selden, N., Gitelman, D., Salamon-Murayama, N., Parrish, T., & Mesulam, M. (1998). Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. *Brain*, *121*, 2249–2257.

Shanmuganathan, K., Gullapalli, R. P., Mirvis, S. E., Roys, S., & Murthy, P. (2004). Whole-brain apparent diffusion coefficient in traumatic brain injury: Correlation with Glasgow Coma Scale. *American Jounral of Neuroradiogy*, *25*, 539–544.

Signoretti, S., Marmarou, A., Fatouros, P., Hoyle, R., Beaumont, A., Sawauchi, S., et al. (2002). Application of chemical shift

imaging for measurement of NAA in head injured patients. *Acta Neurochirurgica. Supplement*, *81*, 373–375.

Sinson, G., Bagley, L. J., Cecil, K. M., Torchia, M., McGowan, J. C., Lenkinski, R. E., et al. (2001). Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: Correlation with clinical outcome after traumatic brain injury. *American Journal Neuroradiology*, *22*, 143–151.

Strich, S. J. (1961). Shearing of nerve fibres as a cause of brain damage due to head injury: A pathological study of twenty cases. *Lancet*, *2*, 443–448.

Sullivan, E. V., Adalsteinsson, E., Spielman, D. M., Hurd, R. E., & Pfefferbaum, A. (2001). N-acetylaspartate — A marker of neuronal integrity. *Annals of Neurology*, *50*, 824–825.

Tollard, E., Galanaud, D., Perlbarg, V., Sanchez-Pena, P., Le Fur, Y., Abdennour, L., et al. (2009). Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. *Critical Care Medicine*, *37*, 1448–1455.

Trivedi, M. A., Ward, M. A., Hess, T. M., Gale, S. D., Dempsey, R. J., Rowley, H. A., et al. (2007). Longitudinal changes in global brain volume between 79 and 409 days after traumatic brain injury: Relationship with duration of coma. *Journal of Neurotrauma*, *24*(5), 766–771.

Uzan, M., Albayram, S., Dashti, S. G., Aydin, S., Hanci, M., & Kuday, C. (2003). Thalamic proton magnetic resonance spectroscopy in vegetative state induced by traumatic brain injury. *Journal of Neurolology, Neurosurgery and Psychiatry*, *74*, 33–38.

Voss, H. U., Uluç, A. M., Dyke, J. P., Watts, R., Kobylarz, E. J., McCandliss, B. D., et al. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *The Journal of Clinical Investigation*, *116*(7), 1823–1825.

Wedekind, C., Fischbach, R., Pakos, P., Terhaag, D., & Klug, N. (1999). Comparative use of magnetic resonance imaging and electrophysiologic investigation for the prognosis of head injury. *Journal of Trauma*, *47*, 44–49.

Weiss, N., Galanaud, D., Carpentier, A., Naccache, L., & Puybasset, L. (2007). Clinical review: Prognostic value of magnetic resonance imaging in acute brain injury and coma. *Critical Care*, *11*, 230.

Wood, S. J., Berger, G., Velakoulis, D., Phillips, L. J., McGorry, P. D., Yung, A. R., et al. (2003). Proton magnetic resonance spectroscopy in first episode psychosis and ultra high-risk individuals. *Schizophrenia Bulletin*, *29*, 831–843.

Xu, J., Rasmussen, I. A., Lagopoulos, J., & Haberg, A. (2007). Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. *Journal of Neurotrauma*, *24*, 753–765.

Yanagawa, Y., Tsushima, Y., Tokumaru, A., Un-no, Y., Sakamoto, T., Okada, Y., et al. (2000). A quantitative analysis of head injury using T2*-weighted gradient-echo imaging. *Journal of Trauma*, *49*, 272–277.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 16

A multimodal approach to the assessment of patients with disorders of consciousness

M.R. Coleman[1,3,*], T. Bekinschtein[1,2], M.M. Monti[1,2], A.M. Owen[1,2] and J.D. Pickard[1,3]

[1]*Impaired Consciousness Research Group, Wolfson Brain Imaging Centre, University of Cambridge, UK*
[2]*MRC Cognition and Brain Sciences Unit, Cambridge, UK*
[3]*Academic Neurosurgery Unit, University of Cambridge, UK*

Abstract: Unlike other neurological conditions, the heterogeneous pathology linked to disorders of consciousness currently excludes a distinction between the vegetative and minimally conscious states based upon pathological presentation. The clinical assessment is therefore made on the basis of the patient's clinical history and exhibited behaviour. This creates a particular challenge for the clinician who has to decide whether a certain behaviour, which might be inconsistent or incomplete, reflects a conscious or an unconscious process. In an alarmingly high number of cases, identified during clinical audit, this decision process has been shown to be particularly fallible. The behavioural assessment is not only highly subjective, but also dependent upon the ability of the patient to move or speak; it is the only way someone can demonstrate they are aware. To address this problem we propose a multimodal approach, which integrates objective tools, such as electrophysiology and functional brain imaging, with traditional behavioural scales. Together this approach informs the clinical decision process and resolves many of the dilemmas faced by clinicians interpreting solely behavioural indices. This approach not only provides objective information regarding the integrity of residual cognitive function, but also removes the dependency on the patient to move or speak by using specially designed paradigms that do not require a motor output in order to reveal awareness of self or environment. To demonstrate this approach we describe the case of BW, who sustained a traumatic brain injury seven months prior to investigation. BW was admitted to a five-day assessment programme, which implemented our multimodal approach. On behavioural assessment BW demonstrated evidence of orientation and visual pursuit. However, he showed no response to written or verbal command, despite holding command cards and scanning text. Electrophysiology confirmed that he retained a preserved neural axis supporting vision and hearing, and suggested some evidence that he was able to create a basic memory trace. A hierarchical fMRI auditory paradigm suggested he was able to perceive sound and speech, but revealed no evidence of speech comprehension or ability to respond to command. This was corroborated in the visual modality using a hierarchical paradigm demonstrating that he was able to perceive motion, objects and faces, but retained no evidence of being able to respond to command. We briefly review work by other teams advocating the use of brain imaging and electrophysiology and discuss the steps that are now

*Corresponding author.
Tel.: +44 1223 348135; Fax: +44 1223 274393;
E-mail: mrc30@cam.ac.uk

DOI: 10.1016/S0079-6123(09)17716-6

required in order to create an international standard for the assessment of persons with impaired consciousness after brain injury.

Keywords: vegetative state; minimally conscious state; functional magnetic resonance imaging; electrophysiology

Introduction

The assessment of persons with disorders of consciousness [vegetative state (VS), minimally conscious state (MCS)] is fraught with difficulties and challenges. Unlike other neurological conditions, disorders of consciousness are not distinguished by a particular pathology or quantifiable marker. Instead, the diagnostic decision-making process is informed by the clinical team's interpretation of the behaviours exhibited by a patient over a period of observation. Although specialist behavioural scales, such as the Sensory Modality Assessment and Rehabilitation Technique (SMART, Gill-Thwaites and Munday, 1999) and Coma Recovery Scale-Revised (CRS-R, Giacino et al., 2004), have been created to facilitate this process, the interpretation of exhibited behaviour remains highly subjective and heavily dependent upon the skills of the examiner. Whilst there is a growing consensus that the behavioural assessment should be conducted repeatedly over a number of weeks to quantify the incidence and context in which a response is made (Gill-Thwaites, 2006), the reliance upon the patient being able to move or speak, in order to demonstrate evidence of awareness, continues to be a central flaw. Indeed, the incidence of spasticity in long-term neurological conditions is widely recognised and occupies a large part of any neurorehabilitation programme (Elliott and Walker, 2005; Andrews, 2005). Hence, even if a patient were to retain some awareness of self and/or environment they may be unable to produce a motor output to signal that awareness to the examiner. The interpretation of exhibited behaviours is complicated further by the fact that we currently have an incomplete knowledge of consciousness and there remains considerable debate as to whether certain behaviours should be classified as conscious as opposed to unconscious processes. For instance, the American Multi-Society Task Force on PVS (1994), whom large parts of the world refer to for definition of the VS, assert that fixation and visual pursuit are conscious processes and mark the first signs of progression from the VS to an MCS (Giacino et al., 2002). In contrast, the Royal College of Physicians (2003), whom the United Kingdom and some parts of Europe refer to for a definition of VS, suggest these behavioural features are atypical for the VS, but not inconsistent. In the absence of a consensus, the clinical team's task is made no easier in those patients who do retain the ability to move or vocalise, since in the majority of such patients, behaviours are often inconsistent or incomplete and frequently constrained by factors, such as medication, nutrition, seating and posture.

The particular difficulties and challenges associated with the assessment of persons with disorders of consciousness have been further exposed in several clinical audits (Andrews et al., 1996; Childs et al., 1993). In a review of 40 patients referred to a specialist rehabilitation unit, Andrews and colleagues considered 17 (43%) of the patients as having been misdiagnosed. Notably most were found to have severe visual impairments and joint contractures, but when assessed by a specialist team, nearly all were able to communicate. Andrews postulated that a number of factors were likely to underlie this very high rate of misdiagnosis, including the rarity of the condition and the lack of experience and knowledge amongst non-specialist medical teams. The greatest potential for misdiagnosis thus occurs where patients are assessed in non-specialist units, by clinical teams who have not had the opportunity to accumulate knowledge or experience of these conditions. Moreover, due to the lack of a national/international protocol for the assessment of these patients, the level of assessment varies considerably from one centre to another. Thus,

one patient might undergo properly administered SMART or CRS assessments by a multidisciplinary team over several weeks, whereas another patient might be assessed on a single occasion with an inappropriate behavioural scale such as the Glasgow Coma Scale (GCS), which is unable to distinguish VS from MCS (see Gelling et al., 2004). In 2005 the UK government published the National Service Framework (NSF) for long-term conditions, in which it set out generic standard requirements for the care and treatment of persons with wide ranging neurological conditions. Although the NSF does not address individual conditions, there is clearly support for efforts to establish a basic level of assessment and treatment for persons with impaired consciousness. Hence, in this chapter we describe the assessment approach taken by the Cambridge Impaired Consciousness Research Group, and use a case example to demonstrate how the approach combines information from many sources to inform the diagnostic decision-making process, whilst making efforts to avoid the possibility of misdiagnosis.

Existing criteria

At present the Royal College of Physicians (2003) provides guidelines documenting the requirements for a diagnosis of VS. The guidelines define the terms 'wakefulness' and 'awareness' and explain how they define the condition of VS by outlining a series of clinical features that have been documented in people who are in a VS. The guidelines specify a number of preconditions that must be satisfied before a diagnosis can be made, including: establishing the cause of the condition as far as possible; excluding the possibility of persisting effects of sedative, anaesthetic or neuromuscular blocking drugs, which might mask behaviours; ascertaining that there are no treatable structural causes; and excluding the possibility that continuing metabolic disturbances may be responsible for the patient's behavioural presentation, but critically stop short of outlining a protocol for the subsequent assessment of patients or advocating any particular test. The guidelines do express an expectation that at least two doctors undertake the assessment and that they should take into account information from other staff including occupational therapists, but do not specify what training these people should have had. In hindsight the guidelines are a reflection of information available to the working party at that time — the SMART and CRS had not been validated, and empirical investigations using electrophysiology and functional brain imaging were in their infancy. However, in the six years that have passed, a large amount of research has been undertaken in this field and one might argue, particularly in light of the NSF, that there is good reason to reconvene a working party to address these shortfalls.

The need to establish tools to facilitate assessment

When Jennett and Plum first coined the term 'vegetative state', they based their terminology on the patient's behavioural features, largely because they wanted to be able to assess patients at the bedside, but also because quantifiable measures, such as blood flow and electrical function, had not proved helpful in distinguishing patients. However, by choosing the term 'vegetative state', they did not assume a particular pathological lesion or physio-anatomical abnormality, and openly stated they expected others to clarify the underlying pathophysiological mechanisms and develop more appropriate assessment tools. Unfortunately, perhaps due to the rarity of the condition, or historical nihilism that has existed in many parts of the medical community towards this patient group (Andrews, 1993), empirical studies, with the aim of addressing these issues, have only really gathered pace in the last two decades.

Behavioural assessment tools

A number of behavioural assessment tools have been created and validated, and there is now a general consensus that the behavioural assessment should explore each sensory modality in turn through a series of stimuli which scale in complexity. In each case the examiner must

determine whether, to the best of their experience, the patient retains purely reflexive responses or higher order, cortically mediated, purposeful responses to stimuli. Two behavioural assessment scales which embrace this hierarchical modular structure are SMART (Gill-Thwaites and Munday, 1999) and CRS-R (Giacino et al., 2004). In addition to the hierarchical structure embedded in both of these scales, the authors state that these assessments should be conducted repeatedly over a period of several weeks, where the Royal College of Physicians' preconditions have been met and where every effort has been made to optimise the environment and physiological factors, which Andrews (1996) and others have highlighted can seriously effect the assessment of a patient with impaired consciousness. There has also been evidence obtained, which encourages examiners to undertake the assessment of patients in different positions, including the standing position (Elliott et al., 2005) and numerous opinion papers encouraging a multidisciplinary approach, whereby the findings from formal behavioural assessments are combined with those of each allied health profession and those of family members (Gill-Thwaites, 2006). It is undoubtedly the view of some specialist centres that where longitudinal behavioural assessments have been conducted using SMART or CRS by experienced staff, the chances of misdiagnosis are likely to be greatly diminished (Giacino and Smart, 2007; Wilson et al., 2005). However, it is still apparent that the behavioural assessment of patients does fail to detect signs of awareness in a number of patients who retain islands of cerebral function (Eickoff et al., 2008; Coleman et al., 2007; Di et al., 2007; Owen et al., 2006, 2005, Staffen et al., 2006).

Electrophysiological assessment tools

Although early work using the electroencephalogram (EEG) proved unhelpful in informing the diagnostic decision-making process due to a lack of sensitivity (Young, 2000; Higashi et al., 1977), more recent work with sensory and cognitive evoked potentials has proved more beneficial (Neumann and Kotchoubey, 2004). Short-latency evoked potentials (several milliseconds to several tens of milliseconds after a stimulus) can tell the examiner whether a particular sensory pathway is functioning and whether there is any delay in propagation of sensory signals from receptors via ascending pathways to the cortex. Hence, where a conduction delay has been identified, the examiner can integrate this information into how they undertake the examination (i.e. leaving longer for the patient to respond in the case of a delay along the auditory pathway) and also in how they might interpret the patient's behavioural response to a particular stimulus. Nevertheless, despite the clear utility of short-latency sensory evoked potentials, and the widespread availability in most regional hospitals, these simple measures are rarely used. Another group of evoked potentials, referred to as event-related potentials (ERPs), are also rarely used clinically, but have growing empirical support. ERPs, which measure time-locked cortical function between 100 and 1000 ms after a stimulus, represent a non-invasive technique to obtain information about how the cortex processes signals and prepares actions. In short, ERPs are able to identify individual physiological components that contribute to a particular cognitive process, such as detecting an infrequent event in an auditory sequence. Empirical ERP studies with this patient group have expanded greatly since the Royal College of Physicians convened in 2003. Since that time ERP studies have identified aspects of preserved speech processing in patients considered to fulfil the clinical criteria defining VS and MCS (Schnakers et al., 2008; Kotchoubey et al., 2005). In a recent ERP study, Schnakers and colleagues presented patients with sequences of names containing the patients own name. In MCS patients, Schnakers found a larger P300 response to the patients own name in both a passive condition and an active condition in which she instructed the patient to count the number of times they heard their own name. Interestingly she found no P300 differences in the VS group in both the passive and active conditions. In a series of word meaning tasks, Kotchoubey has also identified cortical ERP responses to various semantic stimulus features, including related and unrelated word pairs and semantically

incongruent word endings to sentences. ERP studies have also shown some useful prognostic utility — identifying those patients who might go on to recover consciousness or progress to a VS following severe brain injury (Wijnen et al., 2007; Fischer and Luaute, 2005). In terms of informing the diagnostic decision-making process, ERPs would appear to represent an objective screening tool, which is capable of identifying those patients who might harbour covert cognitive function and thus would benefit from further investigation using brain imaging techniques.

Brain imaging assessment tools

When the Royal College of Physicians working party convened in 2003, there were a number of published brain imaging studies assessing the residual metabolic function of patients with disorders of consciousness (Rudolf et al., 1999; Tommasino et al., 1995; De Volder et al., 1990; Levy et al., 1987), but only two published studies that had sought to reveal residual cognitive function in disorder of consciousness patients. De Jong et al. (1997) had used $H_2^{15}O$ positron emission tomography (PET) to measure regional cerebral blood flow changes in response to a story told by the patient's mother. In comparison to non-word sounds, de Jong and colleagues found increased blood flow in the anterior cingulate and temporal cortices, possibly reflecting emotional processing of the contents, or tone, of the mothers speech. In another study, Menon and colleagues had used PET to study covert visual processing in response to familiar faces. When their patient was presented with pictures of the faces of family and close friends, robust activity was observed in the right fusiform gyrus, the so-called human 'face area'. Although both studies gave some indication of the utility of brain imaging to explore residual cognitive function, both studies only described single cases and it was unclear whether the utility of these tests would extend to groups of patients. Furthermore, although both provided interesting glimpses of retained function, neither task provided sufficient information to change the patient's diagnosis, since both could have occurred automatically without the patient necessarily being aware of the stimuli. The use of PET as a viable assessment tool to aid the assessment of this patient group was also limited by issues of radiation burden, precluding repeated investigation and follow-up. PET studies were also known to require group studies in order to satisfy standard statistical criteria and were therefore less applicable to the clinical evaluation of heterogeneous disorders of consciousness patients. Given these limitations the Royal College of Physicians working party had insufficient evidence to advocate any particular test, and work in this area rapidly switched emphasis from PET 'activation studies' to functional magnetic resonance imaging (fMRI). Not only is MRI more widely available than PET, it offers increased statistical power, improved spatial and temporal resolution, and has no associated radiation burden (Owen et al., 2001). fMRI has since been used to explore different aspects of cognitive function including speech comprehension and notably the ability of a patient to respond to command through mental imagery (Eickoff et al., 2008; Coleman et al., 2007; Di et al., 2007; Owen et al., 2006, 2005; Staffen et al., 2006; Bekinschtein et al., 2005). Ideally, fMRI studies should be designed to explore cognitive function in a hierarchal manner — starting with primary perceptual responses to sensory stimuli and following the chain of physiological events as information undergoes higher order levels of processing through to conscious interpretation and action. Although no single paradigm achieves all these goals, when combined they now, arguably, have the ability to provide clinically useful information which informs and may even change a patient's diagnosis. Indeed, when combined, the speech processing paradigm described by Coleman et al. (2007) and the volition task described by Owen et al. (2006) are capable of demonstrating aspects of speech comprehension and the ability to respond to command without requiring any form of motor output. Furthermore, when performed successfully, the volition paradigm described by Owen et al. (2006) provides unequivocal evidence that a patient retains awareness of themselves and/or their environment and thus has the

potential to inform the diagnostic decision-making process.

Additional brain imaging tools

In addition to functional brain imaging, diffusion tensor imaging (DTI) is also slowly emerging as a possible tool, with which to explore the pathophysiological basis of disorders of consciousness and monitor change. DTI relies on modified MRI techniques that render a sensitivity to microscopic, three-dimensional water motion within tissue. In cerebro-spinal fluid, water motion is isotropic, that is, roughly equivalent in all directions. In white matter, however, water diffuses in a highly directional or anisotropic manner. Due to the structure and insulation characteristics of myelinated fibres, water in these white matter bundles is largely restricted to diffusion along the axis of the bundle. DTI can thus be used to calculate two basic properties: the overall amount of diffusion and the anisotropy (Douaud et al., 2007; Benson et al., 2007; Kraus et al., 2007). To date there has only been one study using DTI to evaluate white matter integrity in patients with disorders of consciousness (Voss et al., 2006). In that study, two patients with traumatic brain injury were described: one who had remained in MCS for 6 years and one who had recovered expressive language after 19 years in MCS. Voss and colleagues quantified the amount of diffusion and anisotropy to discover widespread changes in white matter integrity for both of these patients. However, of particular significance they found increased anisotropy and directionality in the bilateral medial parieto-occipital regions in the second patient that reduced to normal values in a scan performed 18 months later. This coincided with increased metabolic activity, and the authors interpreted these findings as evidence of axonal regrowth. This study not only demonstrated the potential of DTI to quantify the amount of white matter loss in patients with disorders of consciousness, it also demonstrated the potential of this technique to monitor change — possibly induced in the future by pharmacological or surgical intervention.

The creation of a multimodal approach to the assessment of patients with impaired consciousness

Despite the existence of the above methods and empirical evidence supporting their ability to inform the diagnostic decision-making process, the Royal College of Physicians working party has not yet reconvened, nor has there been any consensus statement regarding the use of objective assessment tools such as ERPs or fMRI from other groups such as the American Neurological Association. Therefore, in the remainder of this chapter we will describe the multimodal assessment approach we have developed that combines the above methods to inform the diagnostic decision-making process. At each stage we will highlight how the additional information provided by these techniques informs the decision-making process and how it may reduce the rate of misdiagnosis.

The Cambridge assessment approach

Patients are recruited to a one-week programme of assessment ideally within six months of injury, where all preconditions set out by the Royal College of Physicians have been satisfied and the patient is medically stable. Patients referred to the study must be over 16 years of age and must be able to tolerate lying supine for a period of 2 h. Prior to recruitment all patients are reviewed in their normal care setting to determine whether they have any contra-indications preventing exposure to a strong magnetic field and whether they are able to tolerate lying supine, whilst not showing excessive spontaneous head movement — these criteria are essential in order to obtain useful functional imaging data and ensure their safety. All patients referred to the programme of assessment are admitted to a research ward, where they are cared for in an individual room by the in-house neurosurgical team. Due to the fact this is a one-week assessment approach rather than a longer term treatment and rehabilitation referral, no change to the patient's medication is made during the one-week programme, although

every effort is made to reduce medications, where possible, that might mask behaviours prior to referral. Patients are admitted on a Monday and discharged the same week on the Friday. Each patient undergoes daily behavioural assessments using the SMART and CRS-R (Gill-Thwaites and Munday, 1999; Giacino et al., 2004). These assessments are conducted alternately in the morning and afternoon each day, with the patient sitting in their wheel chair in a neutral environment free from distraction. During these assessments the examiner observes the patient at rest, without stimulation, for a minimum of 10 min during each session. The examiner then assesses the patient's response using stimuli of increasing complexity to systematically assess each sensory modality in turn. Hence, in the visual modality the examiner begins by assessing the patient's response to light and threat — proceeds to assess their response to pictures and objects — then assess whether they track a picture, object or mirror — followed by an assessment of whether they are able to discriminate colours or people and follow written commands. At each level the examiner is carefully documenting the response observed — even when a response is not seen at the lower level, they continue through each stage until they are satisfied there is no response. Indeed, particular caution is adopted over the first couple of sessions, since basic reflex responses are diminished in patients retaining higher order function. Hence, curtailing an examination because no response was observed to basic stimuli can miss important information unless the examiner is careful. This approach is also applied to the auditory, tactile, olfactory and gustatory modalities and the order of assessment is carefully rotated each day (i.e. commencing with the auditory modality during the second session) so as to avoid any order effect in the patient's response pattern. In addition to formal behavioural assessment sessions, the key to learning about patients is to also observe them spontaneously during physiotherapy and interaction with nursing staff and family members. A detailed family interview is also conducted to learn about the time course of change and behavioural pattern and responsiveness seen by members of the patient's family. During this interview great care is taken to determine the context in which behaviours were observed.

Electrophysiology

In addition to behavioural assessment, a battery of sensory evoked potentials and an EEG are undertaken on the second day of admission. Although published work regarding the use of the EEG with this patient group has been inconclusive with regard to its diagnostic and prognostic role (Young, 2000; Higashi et al., 1977), the Cambridge team feels the information obtained is useful to their overall assessment. The EEG provides a crude measure of consciousness; reveals evidence of sleep phenomena; and detects non-convulsive epileptiform activity, which may be influencing a patient's responsiveness. However, most importantly, it can give some early indications of residual cognitive function — for instance, if a patient is listening to a conversation in their environment, it is possible to detect a Mu rhythm (9–13 Hz) over the fronto-central regions of the cortex (Miner et al., 1998). Similarly through the use of standard activation procedures it is possible to assess whether the EEG is responsive to light, sound and noxious stimuli.

Following the EEG a series of sensory evoked potentials are undertaken, including a visual, auditory and somatosensory evoked potential (American Neurophysiology Society, 2006a, b, c). These measures provide crucial information about the integrity of the neural axis and inform the interpretation of behavioural assessments and the paradigms adopted for assessment with fMRI. Hence, an absent auditory evoked potential would instigate further clinical assessment, and the research team may decide to only pursue visual paradigms in the MRI scanner. In addition to a series of sensory evoked potentials, an upper limb motor evoked potential is also acquired from the biceps and abductor pollicis brevis muscle bilaterally in response to transcranial magnetic stimulation applied over the vertex using a circular coil (Ray et al., 2002). This test provides information about the integrity of descending

motor pathways and again greatly informs the behavioural assessment.

In addition to the battery of sensory electrophysiology, two ERP paradigms are undertaken. The first ERP assessment consists of two classic Pavlovian conditioning tasks. The first, a delayed conditioning exercise, records the eye blink and conditioned response to a repeated puff of air to the eye following an auditory tone. In volunteers, the air puff initially produces an eye blink, which can be measured by surface electrodes adjacent to the eye. However, with repeated presentation of the tone and air puff, a learned or conditioned response is observed, such that the closure of the eye (conditioned response) starts to occur before the eye blink and therefore serves as an adaptive or defensive response to the air puff. This conditioned response is thought to reflect a primitive, hardwired, subconscious neural system involving the cerebellum, but with no cortical component (Clark et al., 2001; Clark and Squire, 1998). The second eye blink conditioning paradigm involves the presentation of two tones: a target tone which always precedes the air puff, and a non-target tone which occurs without the air puff. This is called a trace conditioning exercise, and its name comes from the fact that some kind of trace must be left in the nervous system for an association to be learned between the target tone and the air puff. This response is again thought to reflect a hardwired neural system. However, in contrast to the delayed conditioning exercise, the hippocampus is thought to be involved in order for a declarative memory trace to be stored and used to recognise the association between the target tone and the air puff, which additionally occurs at a 500–1000 ms interval following the target tone. Interestingly, in healthy volunteers a conditioned response in the trace exercise only occurs in those persons who are able to identify an association between the target tone and the air puff at post-test recall, and is severely impaired in amnesic patients with damage that includes the hippocampus (Clark et al., 2002). Hence, in disorders of consciousness patients, this test has the potential to indicate those patients who might harbour the potential to consciously process information.

The second ERP assessment combines a classic mismatch negativity paradigm (MMN, Ulanovsky et al., 2003) with a higher order P300 auditory odd-ball paradigm (Squires et al., 1975). In this paradigm a patient hears a sequence of auditory tones with two embedded levels of auditory regularity. At the first level, referred to as local, or within trial, the patient hears four identical tones, which are followed by a fifth sound that can be identical (local standard) or different (local deviant) to the preceding tones. In this within trial violation, an ERP response to the deviant produces an MMN response, consistent with building a subconscious memory trace to identify the within trial auditory violation. At the second level, referred to as global, or between trial, the patient's detection of violation between the series of tones forming the local standard and the series of tones producing the local deviant is assessed. This global, between trial, ERP reflects a P300 auditory odd-ball P3b response and is thought to provide an index of working memory and conscious access (Bekinschtein et al., 2009). Together these two ERP paradigms are able to provide an objective, early indication that a patient may retain residual cognitive function, which may or may not be apparent during traditional behavioural assessment.

Brain imaging

Once basic sensory evoked potentials have been performed, all patients undergo a series of anatomical MRI scans, including axial T2, proton density, inversion recovery and haemosiderin-sensitive sequences using a 3T MRI Magnetom Trio Tim Scanner (Siemens Medical Systems, Germany). In addition to the anatomical series of scans, all patients undergo DTI using an axial diffusion weighted dataset with an echo planar imaging sequence and diffusion sensitising gradients applied along 12 non-collinear directions using five b values ranging from 340 to 1590 s/mm^2 and five $b = 0$ images. Then, over two sessions the patient is assessed with a series of auditory and visual fMRI paradigms.

Auditory fMRI paradigm

In the first instance all patients are assessed using the hierarchal speech processing task described by Coleman et al. (2007). This task consists of four conditions: two speech conditions (high-ambiguity sentences and low-ambiguity sentences), an unintelligible noise and a silence condition. Using these stimuli it is possible to assess three levels of auditory processing: (1) whether the patient retains a primary auditory cortex response to sound by comparing hearing conditions (sentences and signal correlated noise) versus silence, (2) whether the patient retains local processing to distinguish speech from non-speech by comparing speech conditions versus signal correlated noise and (3) whether the patient retains distributed cortical activity consistent with retrieving semantic information to interpret sentences, by comparing high-ambiguity sentences versus low-ambiguity sentences. Where patients are found to show high level 3 responses, indicating they may retain aspects of speech comprehension, they are then investigated using the volition paradigm described by Owen et al. (2006) to determine whether they are able to respond to command by manipulating their neural activity. In this paradigm, patients are asked to perform two mental imagery tasks. In the first task a patient is asked to imagine playing tennis every time they hear the command 'tennis' and to relax when they hear the command 'relax'. The task is presented in a classic box design (on–off), whereby the patient is instructed to imaging playing tennis (on) and to maintain this activity, before being asked to relax (off) for 30 s. In total a patient is asked to perform the 'on' and 'off' task five times over a 5-min scan period. In the second task the patient is asked to imagine moving around the rooms of their home every time they hear the command 'house' and to relax every time they hear the command 'relax' throughout the same block design. In healthy volunteers the motor imagery (tennis task) produces robust supplementary motor cortex activation, which can be seen in real-time whilst the patient is in the scanner (Boly et al., 2007). In contrast, the spatial navigation — house task — produces bilateral parahippocampal gyrus, posterior parietal-lobe and lateral premotor cortex activation, which can also be seen in real-time, where scanner facilities exist (Boly et al., 2007). Indeed, recently the real-time capabilities of the scanner have been adapted in order to assess a patient's response to a series of questions, where they have successfully demonstrated appropriate neural responses in the motor and spatial navigation task. In this later task, patients are asked to imagine playing tennis to indicate 'yes' and to imagine moving around the rooms of their home to indicate 'no'. Using this series of auditory paradigms the team is able to comprehensively determine whether a patient responds to sound, demonstrates activation consistent with speech comprehension, and whether ultimately they are able to respond to command and moreover express their thoughts, intentions, emotions and memories.

Visual fMRI paradigm

Although many disorders of consciousness patients demonstrate fluctuating periods of wakefulness, often exhibiting long periods of eye closure, there are still many opportunities for exploring retained cognitive function through visual stimulation, where an intact neural axis has been indicated by sensory evoked potentials. As with all fMRI paradigms created by the Cambridge team, the visual paradigm routinely employed consists of a series of scans, which scale in stimulus complexity — moving from basic perceptual responses to conscious volitional performance. At the first level a patient is presented with a pattern-reversal checkerboard in order to determine whether they maintain a preserved neural axis to the primary visual cortex. At the second level the patient's response to a static pattern of squares is compared to their response to the same pattern of squares scrolling in either the horizontal or vertical plane, in order to determine whether the patient retains motion perception. At the third level the patient is shown a series of congruent objects which are contrasted against a scrambled version of the same object in order to determine whether they are able to discriminate objects. At the fourth level the

patient is shown a series of faces and a series of houses in order to determine whether they retain aspects of face and object perception. If this is observed, a fifth and final level is undertaken, where a patient is shown a picture of a face superimposed on a picture of a house and asked, at 30-s intervals, to either attend to the picture of the face or to attend to the picture of house. If the patient is found to demonstrate the same pattern of activation he/she showed to individual pictures of faces and houses at level 4, in correspondence with the command to look and maintain fixation upon the face or house, there is every indication the patient is consciously following a command and is able to discriminate visual information. Hence, in both the visual and auditory modality a series of hierarchal paradigms are employed with each patient to explore the retention of cognitive function, which do not require the patient to move or speak in order to demonstrate that they retain an awareness of self or environment.

Diagnostic decision making and feedback to the referral team and family members

Once the above investigations have been performed, the findings of serial behavioural assessments, sensory and cognitive electrophysiology, together with anatomical and DTI, and not least functional brain imaging, are collated to form an impression of whether the investigated patient shows responses consistent with the VS or MCS or a conscious, severely disabled condition. The team's diagnostic impression is formed with full knowledge of the patient's medications, which might mask their ability to respond, and knowledge of whether they have any form of infection. This information is fed back to the referring team within one week of discharge, and it is expected that they will continue behavioural assessments together with necessary medical interventions, before making a diagnosis. In addition to feeding back to the referring medical team, great effort is made to provide comprehensive and prompt feedback to the patient's family, whom it should be noted have rarely received information about such conditions. Hence, within one week of discharge the family receives a detailed report of all the findings of the above tests, together with explanation and summary of what the findings mean and how that interpretation has been reached. In addition to receiving a report the family is also invited to a meeting where slides showing the results of each test are shown. Unless requested by the family, the patient's regular care team including therapists are invited to this meeting so that everyone has had chance to discuss the findings and discuss future courses of action. For the purposes of diagnosis, the more widely held opinion that fixation and visual pursuit are inconsistent with the VS, is adopted throughout the assessment process.

Application of the multimodal assessment approach to a single patient

To briefly illustrate the above assessment approach, the case of a 19-year-old male (BW) who sustained a traumatic brain injury following a road traffic accident in 2007 is described.

Clinical history

BW had sustained a depressed frontal skull fracture with underlying contusions and subarachnoid haemorrhage in August 2007 following a high-speed road traffic accident and had undergone a decompressive bifrontal craniotomy. Following a period of acute care, during which he had been weaned off sedation, but failed to recover consciousness, he was transferred to an interim brain injury assessment unit.

Behavioural assessment

Prior to referral seven months post ictus, BW had undergone repeated behavioural assessment using SMART. Over 10 sessions BW had demonstrated consistent evidence of orientation to visual and auditory stimuli, fixation and visual pursuit. BW focused on objects and people and tracked a mirror in the vertical and horizontal plane. BW also localised to upper limb tactile stimulation and intriguingly demonstrated accurate and quick pursuit of an object with his left and right

hand — holding his hand open in an appropriate shape to hold a ball, whilst a ball was moved in different directions just out of reach of his hand. BW showed no response to verbal command and curiously held instruction cards and appeared to scan written instructions, but showed no response.

The referring team had reached the impression that BW demonstrated behaviours consistent with the minimally conscious spectrum, but were unclear why BW failed to respond to written or verbal command, despite the fact he demonstrated clear indications of scanning written text. Similarly, without a response to command or behaviour indicating that BW was able to discriminate stimuli, they were at a loss in terms of where they could go with his rehabilitation. On admission to Cambridge, BW demonstrated the same intriguing pattern of behaviour, scoring 11 out of 23 on the CRS-R assessment (subscale scores = ~~a~~uditory startle 1; pursuit eye movements 3; object manipulation 4; oral reflexive movement 1; communication 0; eye opening without stimulation 2).

Sensory electrophysiology

BW demonstrated a slowed EEG background consisting of intermixed theta and delta frequencies with a breach rhythm over the bifrontal craniotomy wound. The EEG showed no evidence of epileptiform abnormalities or sleep phenomena and was unresponsive to eye opening. A brainstem auditory evoked potential revealed a preserved response from the eighth cranial nerve, pons and midbrain, bilaterally, with onset latencies within the normal range. A somatosensory and visual evoked potential also showed preserved primary sensory cortex responses bilaterally, with no evidence of conduction deficits.

Cognitive electrophysiology

BW demonstrated a conditioned response in the trace conditioning exercise, implying he was able to create a basic memory trace. BW also demonstrated an MMN equivalent response in the within-trial, local deviant, auditory violation task, consistent with the trace conditioning task, but showed no evidence of detecting the between-trial, global deviant thought to reflect conscious access of working memory.

Brain imaging

Axial T2, proton density, inversion recovery and haemosiderin-sensitive sequences revealed multiple areas of low intensity on T2 and gradient echo sequences near the grey–white matter junction of both cerebral hemispheres with more focal resolving haemorrhagic areas in both frontal lobes. There were also areas of low intensity surrounding the brainstem in keeping with haemosiderin deposition related to previous subarachnoid haemorrhage. Small focal areas of haemorrhage were also seen in both thalami, but there were no intrinsic brainstem lesions. The lateral and third ventricles were moderately prominent, including the temporal horn.

Speech processing

BW demonstrated bilateral superior temporal lobe activation to hearing sound versus silence (Fig. 1), and greater left superior temporal lobe activation to hearing speech versus signal correlated noise (Fig. 2). However, no evidence of distributed cortical activation consistent with volunteers retrieving semantic information was observed at level 3 — ambiguous versus unambiguous sentence contrast. A second speech processing task adopting the same design and structure as that described by Coleman et al. (2007), but replacing ambiguous sentences with anomalous sentences created by replacing content words to make them incoherent, whilst preserving phonological, lexical and syntactic structure, also showed an identical pattern of response — BW showed bilateral superior temporal activation to sound, left superior temporal activation to speech, but no evidence of distributed activation consistent with semantic retrieval.

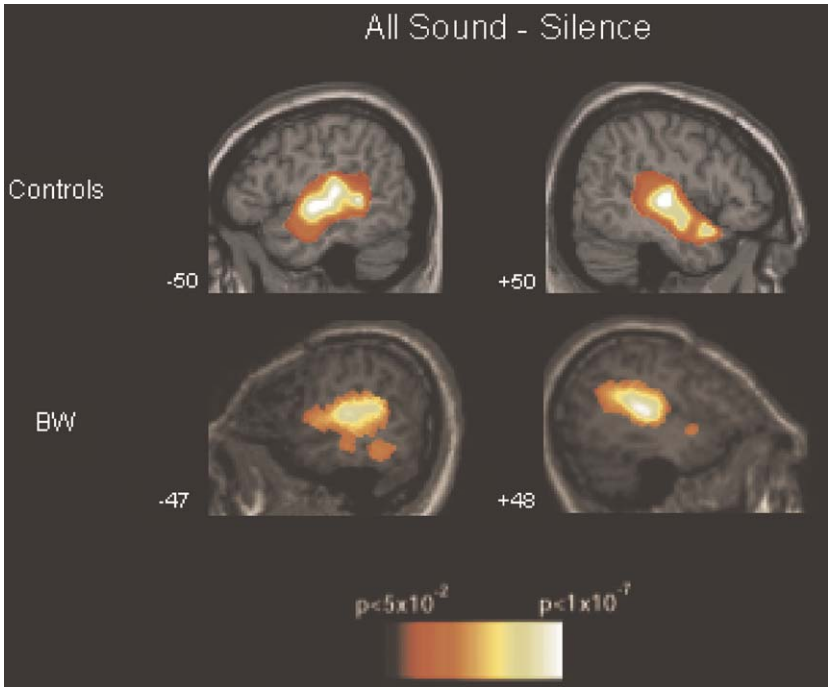


Fig. 1. fMRI speech processing paradigm — sound versus silence contrast results for BW. Bilateral superior temporal lobe activation can be seen consistent with healthy volunteers. Activations are thresholded at $p < 0.05$ false discovery rate corrected for multiple comparisons and shown on slices where the peak activation was observed.

Response to command

BW showed no appropriate areas of cortical activation in response to the commands 'imagine playing tennis' or 'imagine moving around the rooms of your home' over repeated trials.

Discrimination of visual information

BW demonstrated primary V1 activation to a reversing checkerboard, consistent with his visual evoked potential. BW also demonstrated V5/MT activation in response to a moving pattern, consistent with behavioural evidence of motion perception. BW also showed appropriate fusiform gyrus activation in response to pictures of faces and appropriate parahippocampal activation in response to pictures of houses. However, consistent with the auditory volition task, these same areas of activation were not seen time locked to the commands 'look at the house' or 'look at the face' during the visual volition task.

Diffusion tensor imaging

DTI revealed reduced (−38%) fractional anisotropy (FA; whole brain white matter 0.26) in comparison to healthy control subjects (mean 0.42), indicating widespread loss of white matter integrity (Fig. 3). Moreover, DTI revealed a significantly increased apparent diffusion coefficient (whole brain white matter 0.0008) in comparison to healthy volunteers (0.0006), suggesting loss of cortico-cortical connectivity. Indeed, a qualitative view of white matter paths using DTIquery (Sherbondy et al., 2005) revealed a loss of inferior temporal and inferior frontal pathways (Fig. 4), thought to mediate aspects of speech comprehension (Rodd et al., 2005; Davis and Johnsrude, 2003; Scott and Johnsrude, 2003; Scott et al., 2000).

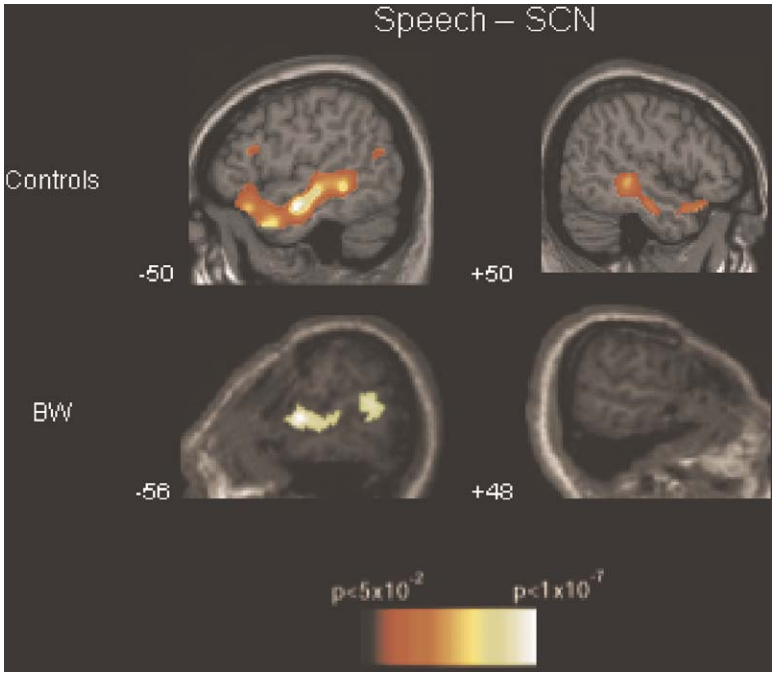


Fig. 2. fMRI speech processing paradigm — sentences (ambiguous and unambiguous) versus signal correlated noise (SCN) contrast results for BW. Left hemisphere superior temporal lobe activation can be seen consistent with healthy volunteers. Activations are thresholded at $p < 0.05$ false discovery rate corrected for multiple comparisons and shown on slices where the peak activation was observed.

Implications for the diagnostic decision-making process

The multimodal assessment approach undertaken in Cambridge corroborated earlier behavioural assessments of BW, but through the use of electrophysiology and brain imaging helped to resolve much of the assessment team's worry that they might be missing something. Electrophysiology and brain imaging confirmed that BW retained basic perceptual responses to visual and auditory information, but found no evidence of speech comprehension or ability to discriminate. Indeed, DTI provided strong visual information to suggest that the level of cortical integration required to support the higher level tasks, investigated during the SMART assessment, was no longer sufficient and thus BW retained some basic perceptual function, but was unable to comprehend or discriminate commands. Whilst this case illustrates how a multimodal assessment approach can help to resolve some of the dilemmas faced by the clinical team interpreting complex behavioural patterns, the assessment approach can also reveal evidence of covert function, where behavioural markers are absent and thus reduce the rate of misdiagnosis (see Owen et al., 2006).

Adoption of a standard assessment protocol

Since the Royal College of Physicians working party convened in 2003, there has been a considerable amount of empirical investigation with disorder of consciousness patients. As a result a number of electrophysiological and brain imaging paradigms have emerged as beneficial sources of information from which to inform the diagnostic decision-making process and thus work towards reducing the apparent high rates of misdiagnosis that exist for this patient population,

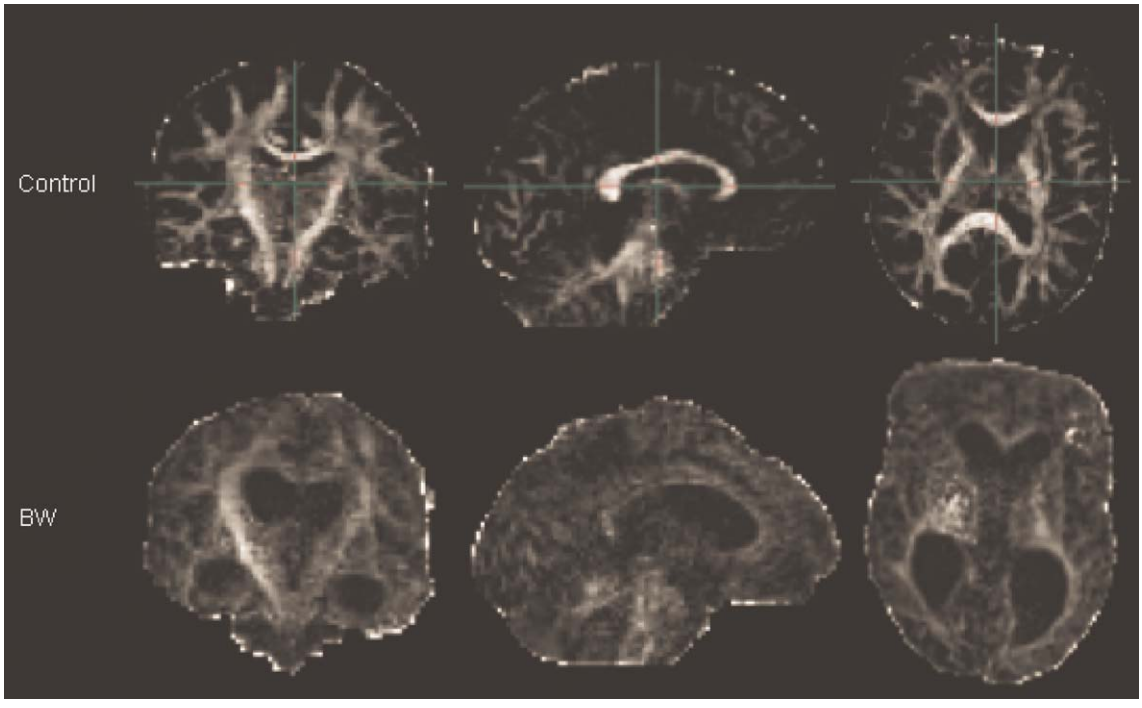


Fig. 3. Diffusion tensor imaging; fractional anisotropy maps showing widespread white matter loss for BW.

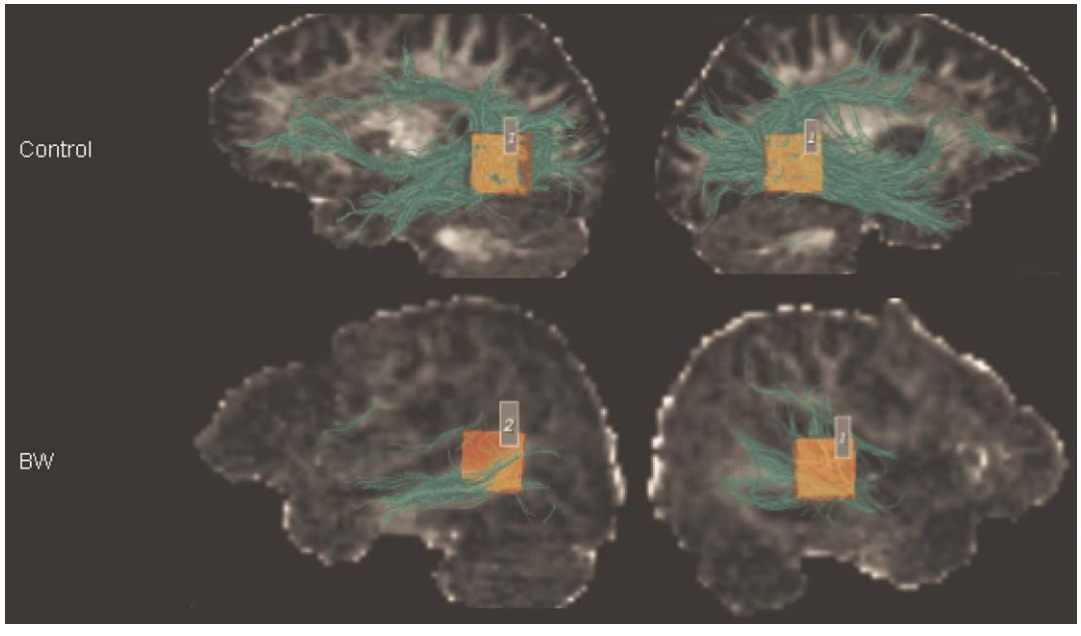


Fig. 4. Temporal lobe tractography maps showing loss of inferior temporal and inferior frontal pathways for BW.

where assessments rely solely on the exhibited behaviour of the patient. In the UK alone there are an estimated 12–15 persons per million thought to be in a VS, in any six-month period, with three times this figure thought to be in an MCS (Jennett, 2005). The vast majority of these patients are not assessed in specialist units, and primary care trusts are often reluctant to refer them to such units, where the period of stay may be many months at a cost in excess of 4000 pounds per week. Local resources are often limited, and due to the rarity of these conditions, clinicians rarely have opportunity to build up sufficient knowledge and experience (Andrews, 1993). One solution is to have a number of specialist units in the country offering a fixed-period, fixed-price referral service, who combine the technologies described above to provide a comprehensive screening process, which is repeated at least once within the first 12 months following a brain injury. Where this assessment process identifies patients who retain aspects of cognitive function, these patients are referred onto specialist rehabilitation centres for further rehabilitation, thus allocating additional funding to those who might benefit the most. Although this approach would significantly reduce the number of patients who are 'warehoused' in palliative care homes, without having been appropriately assessed in the first instance (see concerns raised by Fins et al., 2007, regarding current practice), the additional proviso that each patient is reviewed a second time within the first 12 months of injury would also safeguard against missing anyone who follows a slower course of recovery. Whilst some larger hospitals do have the appropriate knowledge and skills to assess patients with recognised behavioural scales, few have the resources to undertake electrophysiology or brain imaging. In these cases a referral could be made to acquire this data, which is then integrated into the referring unit's ongoing assessment programme — indeed, this is predominately the practice of those centres currently referring patients to Cambridge. In those centres, without the resources the former practice could be undertaken to reduce the rate of misdiagnosis. In all cases this approach would work to ensure the limited funds of primary care trusts are more efficiently managed and channelled to those who might benefit the most.

Information and support for families

It is often forgotten that the main victims of severe brain injury leading to impaired consciousness are the patient's family and friends. Although many hospitals offer general advice and counselling services, very little printed information exists specifically relating to disorders of consciousness. In a survey of patients' families attending the Cambridge assessment programme, none of the families had received any information about disorders of consciousness during their stay in acute or chronic care facilities. Similarly, none of the families had had anybody sit down with them and explain what the different conditions were and how they were diagnosed. Nearly every family had had some contact with the charity Headway (www.headway.org.uk), either accessing their website for general information or speaking to one of their advisors via their telephone helpline. However, all noted that they did not specifically offer an information booklet describing disorders of consciousness. Every family questioned said the Internet had been their main or only source of information, and most described searching endlessly for some sort of information about the condition. Indeed, many had subsequently contacted the authors of research publications to ask for advice. In all cases the families recounted stories of struggling to obtain clear answers about their relatives' condition, of a constant air of confusion, the regular occurrence of health care workers talking over their relative, and a common nihilism towards such conditions by medical personnel. One family, whose youngest son had suffered an intra-cerebral bleed, were asked if they had any other sons and were told to concentrate on them. Many had received blunt and negative comments, which had not helped them to adjust to the distressing situation they found themselves in. In each case, the family felt having the opportunity to see the damage underlying their relatives' condition via brain imaging, and to a lesser extent

electrophysiology, had helped them to understand what had happened. The need to educate and inform families cannot therefore be understated, and any assessment process must ensure that central to its aims are the families and their care. In a large number of cases there is very little that can be done to help the patient, but there is a considerable amount that can be done for the family, whose lives change and who suffer enormous grief, depression, anxiety and often financial hardship as a result of the injury.

Conclusion

In this chapter we have called for the adoption of a standard protocol to assess patients with impaired consciousness after brain injury that not only addresses the limitations of the current behavioural assessment of patients, but also attempts to address the unacceptably high rate of misdiagnosis indicated by clinical audits. In this chapter we have reviewed some of the accumulated empirical evidence supporting the use of electrophysiology and brain imaging with this patient group and have outlined a multimodal assessment approach that informs the diagnostic decision-making process. In our opinion there is now sufficient evidence supporting the use of objective tests — and impetus — (see Department of Health, 2005)to warrant reconvening the Royal College of Physicians working party on VS and/or other governing bodies in order to establish a standard protocol.

Information for families

An information booklet written for families and carers, which describes disorders of consciousness, can be found at www.coma-science.com.

Acknowledgments

The authors are grateful to the staff of the Wolfson Brain Imaging Centre and Wellcome Trust Clinical Research Facility at Addenbrookes Hospital, Cambridge. The Cambridge Impaired Consciousness Research Programme is supported by the National Institute for Health Research Biomedical Research Centre at Cambridge, the UK Department of Health Technology Platform, in addition to funding from the Medical Research Council and the McDonnell Foundation.

References

American Neurophysiology Society. (2006a). Guideline 9B: Guidelines on visual evoked potentials. *American Journal of Electroneurodiagnostic Technology*, *46*(3), 254–274.

American Neurophysiology Society. (2006b). Guideline 9C: Guidelines on short-latency auditory evoked potentials. *American Journal of Electroneurodiagnostic Technology*, *46*(3), 275–286.

American Neurophysiology Society. (2006c). Guideline 9D: Guidelines on short-latency somatosensory evoked potentials. *American Journal of Electroneurodiagnostic Technology*, *46*(3), 287–300.

Andrews, K. (1993). Should PVS patients be treated? *Neuropsychological Rehabilitation*, *3*(2), 109–119.

Andrews, K. (2005). Rehabilitation practice following profound brain damage. *Neuropsychological Rehabilitation*, *15*(3/4), 461–472.

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*, 13–16.

Bekinschtein, T., Tiberti, C., Niklison, J., Tamashiro, M., Ron, M., Carpintiero, S., et al. (2005). Assessing level of consciousness and cognitive changes from vegetative state to full recovery. *Neuropsychological Rehabilitation*, *15*(3/4), 307–322.

Bekinschtein, T. A., Dehaene, S., Rohaut, B., Tadel, F., Cohen, L., & Naccache, L. (2009). Neural signature of the conscious processing of auditory regularities. *Proceedings of the National Academy of Sciences*, *106*(5), 1672–1677.

Benson, R., Meda, S., Vasudevan, S., Kou, Z., Govindarajan, K., Hanks, R., et al. (2007). Global white matter analysis of diffusion tensor images is predictive of injury severity in traumatic brain injury. *Journal of Neurotrauma*, *24*, 446–459.

Boly, M., Coleman, M. R., Davis, M. H., Hampshire, A., Bor, D., Moonen, G., et al. (2007). When thoughts become action: An fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage*, *36*, 979–992.

Childs, N. L., Mercer, W. N., & Childs, H. W. (1993). Accuracy of diagnosis of persistent vegetative state. *Neurology*, *43*, 1465–1467.

Clark, R. E., Manns, J. R., & Squire, L. R. (2001). Trace and delay eyeblink conditioning: Contrasting phenomena of declarative and nondeclarative memory. *Psychological Science*, *12*, 304–308.

Clark, R. E., Manns, J. R., & Squire, L. R. (2002). Classical conditioning, awareness and brain systems. *Trends in Cognitive Sciences*, *6*(12), 524–531.

Clark, R. E., & Squire, L. R. (1998). Classical conditioning and brain systems: The role of awareness. *Science*, *280*, 77–81.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, *130*, 2494–2507.

Davis, M. H., & Johnsrude, I. S. (2003). Hierarchical processing in spoken language comprehension. *Journal of Neuroscience*, *23*, 3423–3431.

de Jong, B., Willemsen, A. T., & Paans, A. M. (1997). Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. *Clinical Neurology and Neurosurgery*, *99*(3), 213–216.

Department of Health. (2005). *National Service Framework (NSF) for long-term conditions*. London, UK.

de Volder, A. G., Goffinet, A. M., Bol, A., Michel, C., de, B. T., & Laterre, C. (1990). Brain glucose metabolism in postanoxic syndrome. Positron emission tomographic study. *Archives of Neurology*, *47*(2), 197–204.

Di, H. B., Yu, S. M., Weng, X. C., Laureys, S., Yu, D., Li, J. Q., et al. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology*, *68*, 895–899.

Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., et al. (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain*, *130*, 2375–2386.

Eickoff, S. B., Dafotakis, M., Grefkes, C., Stocker, T., Shah, N. J., Schnitzler, A., et al. (2008). fMRI reveals cognitive and emotional processing in a long-term comatose patient. *Experimental Neurology*, *214*, 240–246.

Elliott, L., Coleman, M. R., Shiel, A., Wilson, B. A., Badwan, D., Menon, D. K., et al. (2005). The effect of posture on levels of arousal and awareness in vegetative and minimally conscious state patients: A preliminary investigation. *Journal of Neurology, Neurosurgery and Psychiatry*, *76*(2), 298–299.

Elliott, L., & Walker, L. (2005). Rehabilitation interventions for vegetative and minimally conscious patients. *Neuropsychological Rehabilitation*, *15*(3/4), 480–493.

Fins, J. J., Schiff, N. D., & Foley, K. M. (2007). Late recovery from the minimally conscious state: Ethical and policy implications. *Neurology*, *68*, 304–307.

Fischer, C., & Luaute, J. (2005). Evoked potentials for the prediction of vegetative state in the acute stage of coma. *Neuropsychological Rehabilitation*, *15*(3/4), 372–380.

Gelling, L., Shiel, A., Elliott, L., Owen, A., Wilson, B., Menon, D., et al. (2004). Commentary on ''Oh H. and Seo W. (2003) Sensory stimulation programme to improve recovery in comatose patients''. *Journal of Clinical Nursing*, *12*, 394–404.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*(3), 349–353.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation*, *85*, 2020–2029.

Giacino, J. T., & Smart, C. M. (2007). Recent advances in behavioural assessment of individuals with disorders of consciousness. *Current Opinion in Neurology*, *20*(6), 614–619.

Gill-Thwaites, H. (2006). Lotteries, loopholes and luck: Misdiagnosis in the vegetative state patient. *Brain Injury*, *20*(13–14), 1321–1328.

Gill-Thwaites, H., & Munday, R. (1999). The Sensory Modality Assessment and Rehabilitation Technique (SMART): A comprehensive and integrated assessment and treatment protocol for the vegetative state and minimally responsive patient. *Neuropsychological Rehabilitation*, *9*, 305–320.

Higashi, K., Sakata, Y., & Hatano, M.etal. (1977). Epidemiological studies on patients with a persistent vegetative state. *Journal of Neurology Neurosurgery and Psychiatry*, *40*, 870–878.

Jennett, B. (2005). Thirty years of the vegetative state: Clinical, ethical and legal problems. In S. Laureys (Ed.), *Progress in Brain Research: The boundaries of consciousness* (Vol. 150, pp. 537–543). Oxford, UK: Elsevier.

Kotchoubey, B., Lang, S., Mezger, G., Schmalohr, D., Schneck, M., Semmler, A., et al. (2005). Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. *Clinical Neurophysiology*, *116*, 2441–2453.

Kraus, M. F., Susmaras, T., Caughlin, B. P., Walker, C. J., Sweeney, J. A., & Little, D. M. (2007). White matter integrity and cognition in chronic traumatic brain injury: A diffusion tensor imaging study. *Brain*, *130*, 2508–2519.

Levy, D. E., Sidtis, J. J., Rottenberg, D. A., Jarden, J. O., Strother, S. C., Dhawan, V., et al. (1987). Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Annals of Neurology*, *22*(6), 673–682.

Miner, L. A., McFarland, D. J., & Wolpaw, J. R. (1998). Answering questions with an electroencephalogram-based brain–computer interface. *Archives of Physical Medicine and Rehabilitation*, *79*, 1029–1033.

Multi-Society Task Force on the Persistent Vegetative State. (1994). Medical aspects of a persistent vegetative state. *New England Journal of Medicine*, *330*, 499–508. 572–579.

Neumann, N., & Kotchoubey, B. (2004). Assessment of cognitive functions in severely paralysed and severely brain-damaged patients: Neuropsychological and electrophysiological methods. *Brain Research Protocols*, *14*, 25–36.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Owen, A. M., Coleman, M. R., Menon, D. K., Johnsrude, I. S., Rodd, J. M., Davis, M. H., et al. (2005). Residual auditory function in persistent vegetative state: A combined PET and fMRI study. *Neuropsychological Rehabilitation*, *15*(3/4), 290–306.

Owen, A. M., Epstein, R., & Johnsrude, I. S. (2001). fMRI: Applications to cognitive neuroscience. In P. Jezzard, P. M. Mathews, & S. M. Smith (Eds.), *Functional magnetic resonance imaging: An introduction to methods*. Oxford, UK: Oxford University Press.

Ray, J. L., McNamara, B., Priest, A., & Boniface, S. J. (2002). Measuring TMS stimulus/response characteristics from both hemispheres simultaneously for proximal and distal upper limb muscles. *Journal of Clinical Neurophysiology*, *19*(4), 371–375.

Rodd, J. M., Davis, M. H., & Johnsrude, I. S. (2005). The neural mechanisms of speech comprehension: fMRI studies of semantic ambiguity. *Cerebal Cortex*, *15*, 1261–1269.

Royal College of Physicians. (1996). *The permanent vegetative state*. Report of a Working Party. Royal College of Physicians, London.

Royal College of Physicians. (2003). *The vegetative state: Guidance on diagnosis and management*. Report of a Working Party. Royal College of Physicians, London.

Rudolf, J., Ghaemi, M., Haupt, W. F., Szelies, B., & Heiss, W. D. (1999). Cerebral glucose metabolism in acute and persistent vegetative state. *Journal of Neurosurgery and Anesthesiology*, *11*(1), 17–24.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., et al. (2008). Voluntary brain processing in disorders of consciousness. *Neurology*, *71*, 1614–1620.

Scott, S. K., Blank, C. C., Rosen, S., & Wise, R. J. (2000). Identification of a pathway for intelligible speech in the left temporal lobe. *Brain*, *123*, 2400–2406.

Scott, S. K., & Johnsrude, I. S. (2003). The neuroanatomical and functional organization of speech perception. *Trends in Neuroscience*, *26*, 100–107.

Sherbondy, A., Akers, D., Mackenzie, R., Dougherty, R., & Wandell, B. (2005). Exploring connectivity of the brain's white matter with dynamic queries. *IEEE Transactions on Visualisation and Computer Graphics*, *11*(4), 419–430.

Squires, N. K., Squires, K. C., & Hillyard, S. A. (1975). Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalography Clinical Neurophysiology*, *38*, 387–401.

Staffen, W., Kronbichler, M., Aichhorn, M., Mair, A., & Ladurner, G. (2006). Selective brain activity in response to ones's own name in the persistent vegetative state. *Journal of Neurology, Neurosurgery and Psychiatry*, *77*, 1383–1384.

Tommasino, C., Grana, C., Lucignani, G., Torri, G., & Fazio, F. (1995). Regional cerebral metabolism of glucose in comatose and vegetative state patients. *Journal of Neurosurgery and Anesthesiology*, *7*(2), 109–116.

Ulanovsky, N., Las, L., & Nelken, I. (2003). Processing of low-probability sounds by cortical neurons. *Nature Neuroscience*, *6*, 391–398.

Voss, H. U., Uluc, A. M., Dyke, J. P., Watts, R., Kobylarz, E. J., McCandliss, B. D., et al. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *Journal of Clinical Investigation*, *116*, 2005–2011.

Wijnen, V. J. M., van Boxtel, G. J. M., Eilander, H. J., & de Gelder, B. (2007). Mismatch negativity predicts recovery from the vegetative state. *Clinical Neurophysiology*, *118*, 597–605.

Wilson, F. C., Graham, L. E., & Watson, T. (2005). Vegetative and minimally conscious states: Serial assessment approaches in diagnosis and management. *Neuropsychological Rehabilitation*, *15*(3/4), 431–441.

Young, G. B. (2000). The EEG in coma. *Journal of Clinical Neurophysiology*, *17*(5), 473–485.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 17

Executive functions in the absence of behavior: functional imaging of the minimally conscious state

Martin M. Monti[1,2,*], Martin R. Coleman[2] and Adrian M. Owen[1,2]

[1]*MRC Cognition and Brain Sciences Unit, Cambridge, UK*
[2]*Impaired Consciousness Research Group, Wolfson Brain Imaging Centre, University of Cambridge, UK*

Abstract: One of the major challenges in the clinical evaluation of brain injury survivors is to comprehensively assess the level of preserved cognitive function in order to inform diagnostic decisions and suggest appropriate rehabilitation strategies. However, the limited (if any) capacity for producing behavior in some of these patients often limits the extent to which cognitive functions can be explored via standard bedside methods. We present a novel neuroimaging paradigm that allows the assessment of residual executive functions without requiring the patient to produce any behavioral output. In particular, we target processes such as active maintenance of information through time and willful adoption of ''mind-sets'' that have been proposed to require conscious awareness. Employing an fMRI block design paradigm, healthy volunteers were presented with a series of neutral (i.e., not emotionally salient) words, and alternatively instructed to listen to all the words, or to count the number of times a given target is repeated. Importantly, the perceptual stimulation in the passive listening and the counting tasks was carefully matched. Contrasted with passive listening, the counting task revealed a fronto-parietal network previously associated with target detection and working memory. Remarkably, when tested on this same procedure, a minimally conscious patient presented a highly similar pattern of activation. Furthermore, the activity in these regions appeared highly synchronous to the onset and offset of the counting blocks. Considering the close matching of sensory stimulation across the two tasks, these findings strongly suggest that the patient could willfully adopt differential ''mind-sets'' as a function of condition, and could actively maintain information across time. Neither cognitive function was apparent when the patient was (behaviorally) tested at the bedside. This paradigm thus exemplifies the potential for fMRI to explore high-level cognitive functions, and awareness, in the absence of any behavioral response.

Keywords: functional magnetic resonance imaging; consciousness; disorders of consciousness; vegetative state; minimally conscious state; executive functions; target detection; working memory

One of the most ubiquitous and least understood concepts in the study of the human brain is ''consciousness'' (Laureys et al., 2007). In the absence of an agreed definition or measure (Seth et al., 2008), the only means we currently have to ascertain whether someone is conscious is if they

*Corresponding author.
Tel.: +44(0) 1223 273646; Fax: +44(0) 1223 359062;
E-mail: Martin.Monti@mrc-cbu.cam.ac.uk

DOI: 10.1016/S0079-6123(09)17717-8

directly tell us so. Assessing another individual's state of consciousness then essentially relies on them revealing, either via direct report or via some voluntary behavior, that they are both awake and aware. Generally, people experience little difficulty in recognizing a state of conscious wakefulness from states such as general anesthesia, deep sleep, or coma. Indeed, in the latter three cases, permanently closed eyes indicate low levels of arousal, and, more importantly, the absence of any goal-directed behavior seems to imply the lack of awareness (of the self and the environment). Conversely, a state of conscious wakefulness is recognizable by high levels of arousal, and especially by the presence of purposeful (i.e., non-reflexive) behavior, which requires — and thereby reveals the presence of — conscious awareness (see Laureys, 2005).

Recent advances in intensive care have greatly increased the number of patients that survive severe brain injury. Some patients thus go on to make a full recovery. Other brain injury survivors, however, regain high levels of arousal, but fail to demonstrate any sign of awareness, only exhibiting reflexive behavior. These patients are said to be in a vegetative state (VS; Jennett, 2002; Jennett and Plum, 1972). While this latter state can be permanent, some patients do regain a (fluctuating) level of awareness, thus progressing to a minimally conscious state (MCS; Giacino et al., 2002) either permanently or on the way to durable recovery of consciousness. A central challenge in the care of patients with disorders of consciousness is the assessment of their residual cognitive abilities. In particular, detection of any evidence of voluntary behavior that may signal a state of awareness is fundamental to disentangling VS from MCS. However, brain injury often constrains the ability to produce motoric output, restricting the possibility that a patient might demonstrate purposeful behavior, and thereby awareness. Consequently, use of motor behavior to assess residual cognition and awareness might, under such circumstances, underestimate residual brain function and misidentify conscious patients as unconscious (Monti et al., 2009; Owen and Coleman, 2008). Indeed, according to recent estimates, the misdiagnosis rate by which MCS patients are ''mistaken'' for VS is around 40% (Andrews et al., 1996; Childs et al., 1993). In the face of the important medical (Elliott and Walker, 2005), legal, and ethical ramifications (Fins et al., 2008) of such mistakes, correct diagnosis is essential. Many factors are known to have an impact on diagnostic error, including sensory impairments of the patient (e.g., blindness), and variable knowledge and expertise in administering clinical tests (see Andrews et al., 1996; Majerus et al., 2005). It appears increasingly clear, however, that use of motor behavior as an index of conscious awareness and residual cognition is also an important source of diagnostic error. In fact, this approach exposes a central conundrum in our understanding of consciousness. Our ability to detect whether someone is conscious depends crucially on his or her capacity for communicating that fact. Therefore, if someone were to be entirely aware but unable to produce any behavioral sign to indicate so, logically, there would be no way to determine that they were actually conscious (Monti et al., 2009; Owen and Coleman, 2008). Indeed, one recent study employing noninvasive neuroimaging has reported the case of a patient who, despite appearing vegetative by internationally agreed criteria and standard procedures, was, in fact, consciously aware (Owen et al., 2006).

In what follows, we present a novel neuroimaging approach aimed at exploring how deep the hiatus between cognition and behavior can run in patients with disorders of consciousness. Employing functional magnetic resonance imaging (fMRI), we develop a test of executive function that, without requiring any behavioral expression on the part of the patient, can reveal the integrity of high-level cognitive processes that are thought to be crucial to consciousness (Dehaene and Naccache, 2001). In particular, the procedure is designed to assess the residual ability to maintain information through time, and willfully allocate attention toward a stimulus. We first describe the results from a ''proof of concept'' study in a set of healthy participants, and then employ the same paradigm in a minimally conscious patient who could successfully complete the task.

Methods and materials

Participants

Twenty healthy volunteers (12 female) with no history of neurological disorder and one MCS patient participated in the experiment. Healthy volunteers signed informed consent prior to the experimental session. For the patient, assent was obtained from the next of kin. This study was approved by the Cambridge Local Research Ethics Committee.

Patient history

The patient was first hospitalized on October 28, 2007 after suffering a cardio-respiratory arrest, and was resuscitated in ITU (defibrillated/intubated and ventilated). A computed tomography scan (CT) on admission revealed no evidence of intracranial hemorrhage. However, it did reveal widespread loss of grey-white matter differentiation, consistent with an anoxic brain injury. The ventricles, basal cisterns, and other cerebrospinal fluid spaces were preserved and there was no evidence of severe swelling.

Patient behavioral assessment

The patient was behaviorally assessed multiple times throughout his stay at the Addenbrooke's Hospital (Cambridge, UK). When tested with the JFK Coma Recovery Scale (CRS; Giacino et al., 2004), the patient demonstrated a portfolio of behaviors consistent with the MCS, achieving a score of 13. In particular, command following and nonfunctional communication could be observed, behaviors that confirm the MCS diagnosis.

Task

Participants (i.e., healthy volunteers and the patient) were required to perform two tasks in alternating fashion. In both tasks, they were aurally presented with a sequence of 26 words, at 1 Hz. In the ''passive listening'' baseline task, participants were instructed to listen to the words that were presented. In the ''target detection'' task (or ''counting'' task, interchangeably), they were instructed to count the number of times they heard a given target word (different for every block). Two aural cues were used to distinguish baseline from counting blocks. Both cues started with a 250 ms tone followed by the words ''Listen All'' to signal a passive listening block, and the words ''Count *[target word]*'' to signal a target detection block (and to reveal the target word). Each cue lasted 4 s. Full instructions were delivered prior to the functional session.

Stimuli

A total of 120 monosyllabic words, recorded in a female voice, were available for each session. Out of these, 50 were randomly selected, uniquely for every participant, and randomly distributed in groups of 5 to each of 10 blocks (5 baseline, 5 target detection). Within each block, words that were randomly assigned to each be repeated 7, 6, 5, or 4 times (with 2 words being repeated 4 times), generating a total of 26 words per block. The 26 words were then randomly distributed across each block, under the sole constrain that no word appeared twice in a row. For the five counting blocks, the target was twice assigned to be the 7- and the 6-repetition word, and once the 5-repetition word. Which block featured the 7-, 6-, or 5-repetition targets was randomly varied for each participant. In this design, baseline and target detection blocks are thus perfectly matched in terms of perceptual stimulation, including repetition frequencies, while prompting (via the cue) for differing mental sets.

Experimental design

Volunteers and patients underwent one structural and one functional scan (as part of a longer fMRI experiment). In the functional session, participants performed five target detection blocks and five passive listening blocks, in an ABAB alternating fashion, always starting with passive listening (see Fig. 1). Each block started with a 4 s aural cue indicating the nature of the block (and a target word, for the counting blocks), followed by the 26 words.

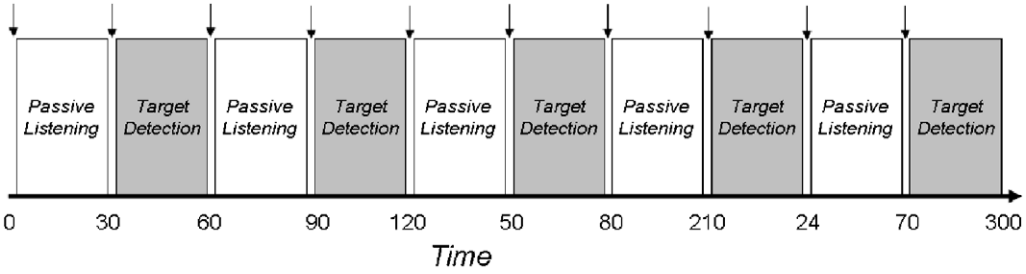


Fig. 1. Experimental design. Arrows depict cue delivery, while shaded and unshaded blocks represent stimulus delivery periods in the target detection and passive listening blocks, respectively.

fMRI data acquisition

Healthy volunteer data were acquired on a Siemens 3T Tim Trio at the MRC Cognition and Brain Sciences Unit, Cambridge (UK), while the patient data were acquired at the Wolfson Brain Imaging Centre at Addenbrooke's Hospital, Cambridge (UK). At both sites, T1 sensitive images were acquired with an MP-RAGE sequence at 1 mm isovoxel resolution. T2* sensitive images were acquired using the Siemens echo planar sequence for real-time scanning (32 descending slices, 3 mm^2 in-plane resolution, TR = ~~2~~ s, TE = ~~30~~ ms, FA = ~~78~~°).

fMRI data analysis

Analysis methods were performed using FSL 5.91 (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Prior to functional analyses, each individual Echo Planar Imaging (EPI) time series was motion corrected to the middle time point using a six-parameter, rigid-body method (as implemented in MCFLIRT; Jenkinson et al., 2002). Data were smoothed with a Gaussian kernel of 8 mm FWHM, and signal from extraneous non-brain tissue was removed using Brain Extraction Tool (BET; Smith, 2002). The 4D data was normalized to the grand-mean intensity by a single multiplicative factor and high-pass filtered (Gaussian-weighted least-squares straight line fitting, with sigma = ~~30~~.0 s). Finally, functional data was co-registered to structural images using a seven-parameter optimization method (Jenkinson and Smith, 2001).

Statistical analyses were performed using a general linear model approach, as implemented in FEAT (fMRI Expert Analysis Tool; Woolrich et al., 2001), including pre-whitening correction for autocorrelation. The model included one regressor of interest, representing the working memory blocks (and thus, implicitly, the baseline blocks), and seven regressors of noninterest. The latter included the cue period (for both working memory and baseline blocks) and six motion parameters. For each dataset (i.e., healthy volunteers and patient), we compared blood oxygenation level dependent (BOLD) signal observed in the target detection blocks to that observed in the baseline blocks. Z (Gaussianised T) statistic images were thresholded using clusters determined by $Z > 2.7$ and a (corrected) cluster significance threshold of $p = ~~0.~~001$ (Worsley et al., 1992).

For healthy volunteers, group average statistics were also computed. Prior to multi-subject analyses, each individual dataset was co-registered to the MNI152 standard template brain using a 12-parameter optimization method (Jenkinson and Smith, 2001). Group mean statistics for each contrast were generated with a mixed-effects model resulting from the use of within-session variance (i.e., fixed effects) at the single subject level and between-session variance (i.e., random effects) at the group level (Friston et al., 2005). Statistical parametric maps were computed in FLAME (Beckmann et al., 2003; Woolrich et al., 2004) and thresholded at $p < 0.05$ full-brain voxel-wise corrected.

Results

Healthy volunteers

Averaging across all healthy volunteers, the target detection versus passive listening contrast revealed activations spanning frontal, temporal, and parietal cortex, along with regions of the cerebellum (see Table 1 and Fig. 2). Frontal cortex was activated bilaterally in the sub-lobar sections of the inferior frontal gyrus (BA 47), and in the middle frontal gyrus (BA 10). Activation was also observed in the right superior frontal (BA 10) and cingulate gyri (BA 32), left precentral gyrus (BA 6), along with the medial frontal gyrus (in BA 6 and 32). Activation in posterior parietal cortex was focused in the left supramarginal gyrus (BA 40) and the right inferior parietal lobule (BA 40). Temporal cortex was activated in the right inferior gyrus (BA 20). Finally, activations were also detected bilaterally in various subregions of the posterior cerebellum, including the pyramis, uvula, inferior semilunar lobule, and vermis. This pattern of activation replicates previous studies of target detection in healthy volunteers (see Naghavi and Nyberg, 2005). Furthermore, this same general pattern is also robustly observed at the single subject level (cf. Fig. 4).

MCS patient

The target detection minus passive listening contrast revealed, in the MCS patient, a pattern of activation similar to that observed in healthy volunteers (see Figs. 3 and 4). Extensive

Table 1. Group average healthy volunteer data for the target detection versus passive listening blocks

MNI coordinates			*Z*	Hem.	Region (Brodmann area)
x	*y*	*z*			
Frontal					
10	18	36	5.89	R	Cingulate gyrus (32)
−30	24	0	5.69	L	Inferior frontal gyrus (47)
−6	8	48	5.61	L	Medial frontal gyrus (32)
30	26	2	5.45	R	Inferior frontal gyrus (47)
−46	−2	52	5.32	L	Precentral gyrus (6)
−10	−2	64	5.16	L	Medial frontal gyrus (6)
36	48	26	4.98	R	Superior frontal gyrus (10)
−32	48	6	4.70	L	Middle frontal gyrus (10)
32	50	8	4.59	R	Middle frontal gyrus (10)
Temporal					
56	−24	−22	4.33	R	Inferior temporal gyrus (20)
52	−28	−20	4.32	R	Inferior temporal gyrus (20)
Parietal					
48	−42	42	5.43	R	Inferior parietal lobule (40)
−32	−48	36	4.75	L	Supramarginal gyrus (40)
66	−36	30	4.66	R	Inferior parietal lobule (40)
−44	−42	36	4.47	L	Supramarginal gyrus (40)
Cerebellum					
−6	−76	−40	4.61	L	Cerebellum (pyramis)
6	−80	−44	4.58	R	Cerebellum (uvula)
8	−76	−46	4.49	R	Cerebellum (inferior semilunar lobule)
−30	−74	−46	4.36	L	Cerebellum (inferior semilunar lobule)
−36	−68	−42	4.36	L	Cerebellum (pyramis)
−2	−76	−40	4.29	L	Cerebellum (pyramis of vermis)

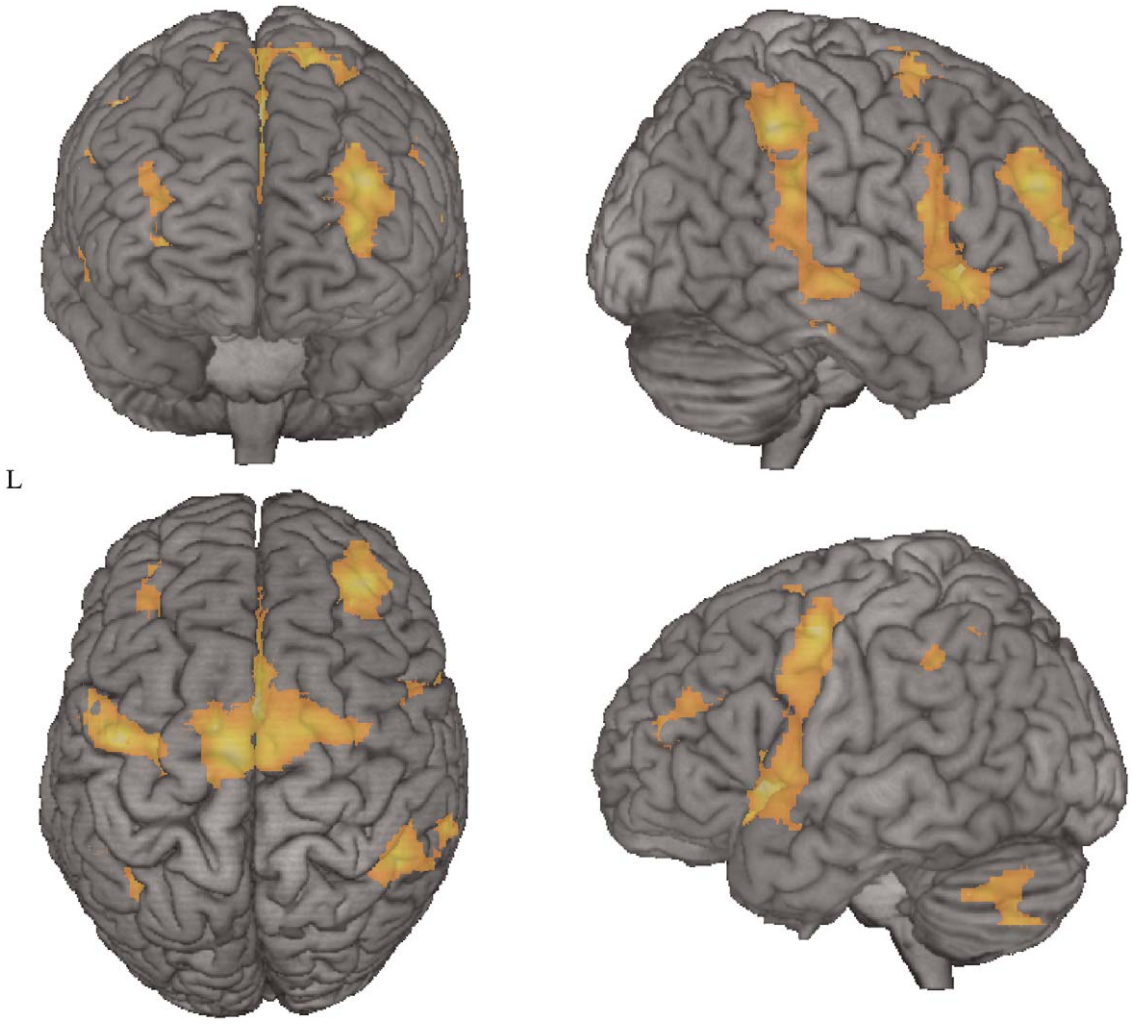


Fig. 2. Group data (healthy volunteers only). Group activation for the target detection versus passive listening contrast ($p<0.05$ voxel-wise corrected).

activation was detected in frontal cortex, especially left lateralized, spanning the superior and middle frontal gyri, the sub-lobar section of the inferior frontal gyrus, and the post central gyrus. A large focus was localized in the medial wall of frontal cortex, spanning cingulate and medial frontal gyri. Extensive parietal activation was also detected in right supramarginal gyri (posterior section) and bilateral inferior parietal lobuli, extending dorsally into the superior parietal lobule (in the right hemisphere only). Temporal activation was revealed bilaterally in the planum temporale, medial temporal gyrus, and, although to a much lesser extent, in the inferior temporal gyri. Finally, subcortical activations were revealed in the cerebellum and posterior section of thalamus.

To compare the activations observed in the MCS patient with the normal variability seen in healthy volunteers, we report, in Fig. 4, all regions activated by at least three healthy participants (in blue–green–red) and those observed in the patient (in red–yellow, masked with the healthy volunteer group result). With the exception of the

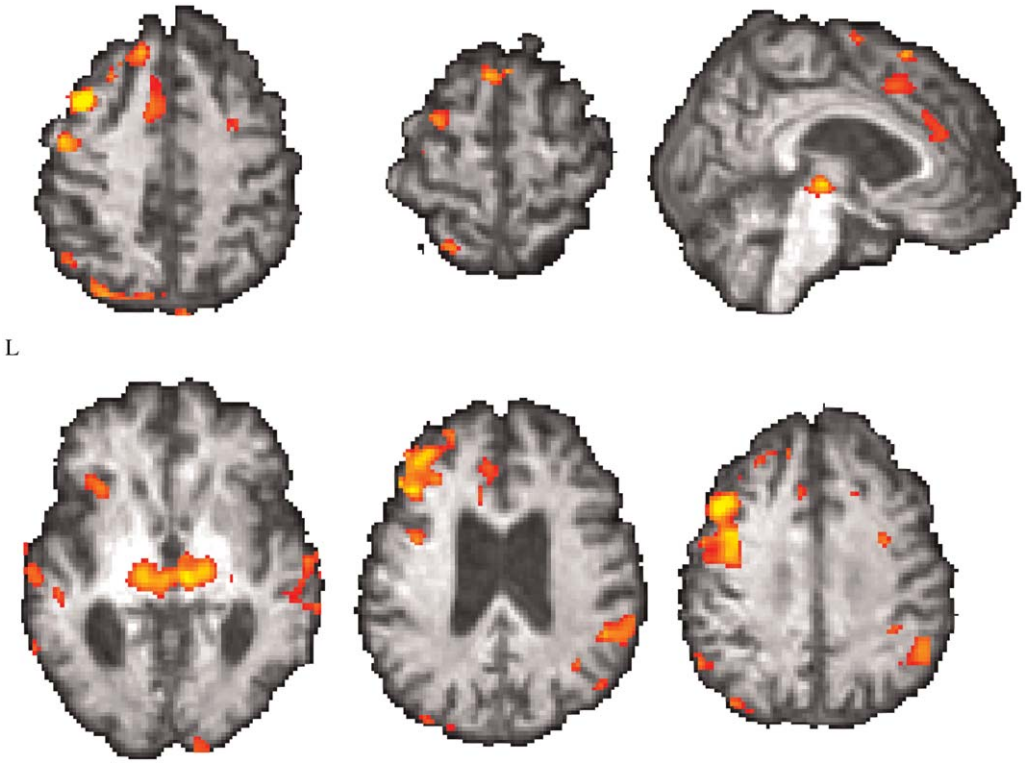


Fig. 3. Patient data. Brain results for the target detection versus passive listening contrast ($Z > 2.7$, $p = 0.001$ corrected).

left parietal cluster, the patient data falls well within what is seen in healthy volunteers performing the same task. Moreover, as exemplified by the time course of the medial frontal cluster (Fig. 4), the observed activations were protracted along the 30 s counting blocks. In addition, Fig. 5 shows that the activations were repetitively and consistently time locked to the counting task, peaking and falling in synchrony with its onset and offset. It is noteworthy, however, that passive listening and counting blocks were perfectly matched for perceptual stimulation.

Discussion

Compared to simple listening, the counting task elicited, in all healthy volunteers, a pattern of activation similar to that reported in previous studies of executive function, including target detection and working memory (see Naghavi and Nyberg, 2005). The very fact that the two (perceptually identical) tasks elicited different patterns of activation confirms that our paradigm does elicit the expected cognitive processes including maintenance of information through time and willful adoption of ''mind-sets'' (as well as language comprehension). When tested on the same task, the MCS patient exhibited an extremely similar set of activations. While it is not possible to infer which of these cognitive processes such activations reflect exactly (Henson, 2005), it is difficult to interpret these results without accepting that the patient retained several types of cognitive ability. In particular, the patient must have retained sufficient linguistic processing to comprehend the instructions, the ability to maintain information through time, and the ability to monitor incoming stimuli. The difference in activation across periods of identical stimulation also indicates that the patient could willfully adopt, on command, different ''mind-sets'' as a

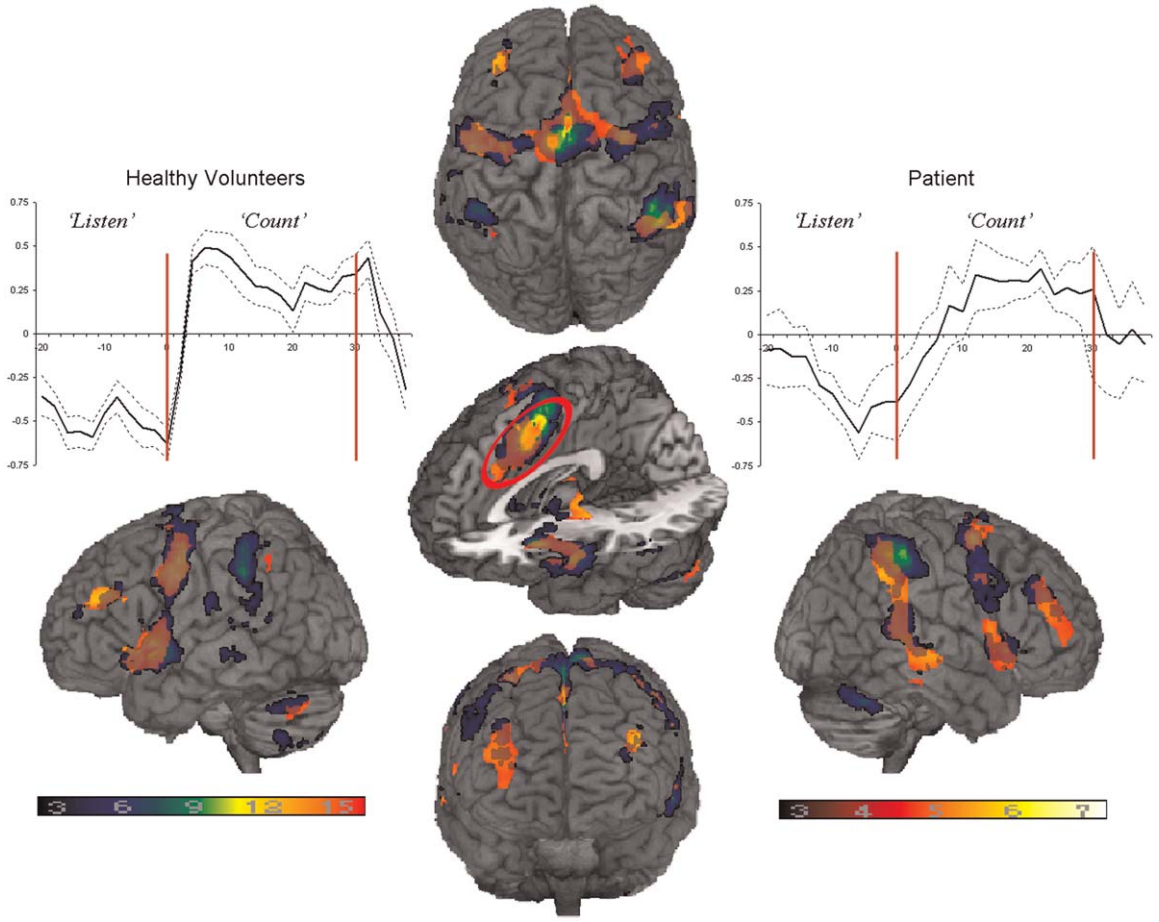


Fig. 4. Single subject and patient data. Overlay of the single subjects (dark shades; blue-green-red in the web version) and patient (light shades; orange-yellow in the web version) results for the target detection minus passive listening contrast. Graphs depict the average peristimulus activation profile of a representative ROI in medial cortex (highlighted in white; red in the web version) for the group of healthy volunteers and the patient (dashed lines indicate the standard error).

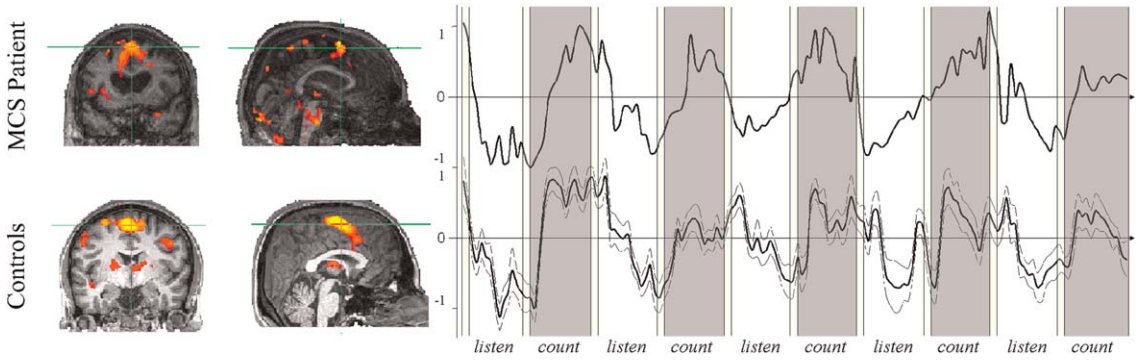


Fig. 5. ROI time course. Activation time course of the medial frontal cluster for the patient and healthy volunteers (dashed lines indicate the standard error).

function of condition. Furthermore, he must have been capable of voluntarily assigning, in a top-down fashion, saliency to words (i.e., the targets) that would otherwise be ''neutral'' and logically incapable of eliciting such activation automatically. Remarkably, none of these cognitive abilities was apparent when the patient was tested at the bedside. While behavioral signs of awareness were apparent, including some level of command following, the information provided by the fMRI assessment far exceeded what could be learned with the standard clinical tools.

Previous studies have used electroencephalography (EEG) and event-related potentials (ERPs) to investigate the ability of patients to detect and recognize targets among distracters (Di et al., 2007; Perrin et al., 2006; Qin et al., 2008). These studies, however, have used the patient's own name as the target word; that is, an intrinsically salient and over-learned stimulus. Under these circumstances, differential brain response to the target stimulus, compared to nontargets, is very informative in terms of residual linguistic processing, but is not a good indicator of whether such a response is voluntary or purely automatic. In one notable exception, however, the own name paradigm was adapted to include, as targets, both the patient's own name and other ''non-salient'' names (e.g., similarly frequent names that had no relation to the patient or his/her family; Schnakers et al., 2008). In that study, all the tested MCS patients exhibited a significant response when passively listening to their own name, as in the above mentioned studies. In addition, however, five out of fourteen patients showed greater activity for hearing their own name when instructed to count its occurrences as opposed to when they passively heard it. Remarkably, a similar effect was found, in a different subset of four patients, for neutral targets (i.e., not the patient's own name).

The study reported here takes this same idea one step further, making exclusive use of neutral words as targets and nontargets. In both approaches, differential activity across tasks for neutral words is difficult to explain without assuming a conscious decision on the part of the patient to actively maintain in working memory a target word and to monitor incoming stimuli. In addition, while Schnakers and colleagues focus on the detection of targets, our study focuses on the more general notion of executive functions, including willful adoption of ''mind-sets,'' maintenance of information in working memory, and monitoring of incoming stimuli. Crucially, our task addresses the process of ''holding in mind'' information through time, which is considered to require conscious awareness (Dehaene and Naccache, 2001). Furthermore, our fMRI approach is also able to reveal that this particular task elicits activation in regions that are thought to be a crucial component of the neural basis of consciousness (Baars, 2002; Baars et al., 2003; Dehaene et al., 2003; Rees et al., 2002).

Conclusions

Detecting consciousness in brain injury survivors is critical for appropriate diagnosis and patient management (Bernat, 2006). Objective assessment on the basis of observed and elicited behavior, however, can be extremely challenging in patients with little ability for behavioral output. Use of noninvasive neuroimaging techniques to detect residual cognitive abilities and awareness may thus be crucial to reducing diagnostic error (Owen and Coleman, 2008). While there is at present limited information on the prognostic value of ''activation'' paradigms, the increasing number of studies reporting the integrity of cognitive functions that are not detectable at the bedside (Coleman et al., 2007; Laureys et al., 2002; Owen et al., 2006; Schnakers et al., 2008) does warrant the use of such tools to supplement standard diagnostic assessments.

Experimental approaches such as the one we present here directly address processes that are thought to require consciousness (Dehaene and Naccache, 2001). First, successful completion of our target detection task requires durable and explicit maintenance of information through time including task instructions and the target word. Such processes, as pointed out by Dehaene and Naccache (2001), are not possible in the absence of awareness. For example, while much

information processing can occur automatically (e.g., Dehaene et al., 1998), the neural response to nonconscious stimuli is typically short lived, and access to such information tends to decay very quickly (Dehaene et al., 2006). Beyond active maintenance of information, our paradigm also requires intentional behavior, which also implies consciousness (Dehaene and Naccache, 2001). In the absence of a conscious decision to keep in mind the target word and monitor incoming stimuli, the careful matching of perceptual stimulation in the two conditions should yield identical neural activity.

Overall, these findings further confirm the potential for neuroimaging to define both the extent and the precise nature of cognitive processing that is available to patients with disorders of consciousness, without the need for any behavioral (i.e., physical) response (Laureys et al., 2004; Owen and Coleman, 2008; Owen et al., 2007). Indeed, in the MCS case report here, fMRI provided novel information about the patient's working memory abilities that far exceeded expectations based on the standard behavioral assessment. It is important to keep in mind, however, that application of this technology to such patient groups requires careful consideration of many issues (see Giacino et al., 2006; Owen and Coleman, 2007). First, not all patients will benefit from undergoing neuroimaging testing. Where sufficient levels of behavior are preserved, simple motor responses may suffice to assess residual cognition and awareness. Second, neuroimaging tools often impose constraints on the ability of patients to enter their environment (e.g., compatibility with the magnetic field in MRI) and require a level of cooperation throughout the experimental session (e.g., limited motion) that may not always be possible. Third, differences in the coupling of hemodynamic response and neuronal firing (Gsell et al., 2000; Rossini et al., 2004), as well as the pathological anatomy and functional neuroanatomy in this patient group, may affect the interpretability of neuroimaging data.

Several studies have shown that brain responses to stimuli can be detected in the absence of conscious processing (e.g., Dehaene et al., 1998; Vuilleumier et al., 2002a, 2002b). Classifying brain activity as conscious thus requires careful neuroimaging methodology with different conditions being closely matched for perceptual stimulation, and only differing with respect to the required mind-set. Under such circumstances, differential activations across conditions cannot be explained in terms of automatic brain response and hence reveal conscious processing. Finally, it should also be noted that, as for behavioral testing, negative results in neuroimaging experiments cannot be taken as evidence of lack of awareness or cognition. Indeed, lack of brain response may simply result from the patient being asleep throughout the session, or unwilling to cooperate. Nonetheless, when careful methodology is employed, activation studies may be used in patients with disorders of consciousness as ''neural markers'' of residual cognitive abilities and awareness, thus providing information that may well exceed bedside assessments and valuably inform the diagnostic process.

References

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*, 13–16.

Baars, B. J. (2002). The conscious access hypothesis: Origins and recent evidence. *Trends in Cognitive Sciences*, *6*, 47–52.

Baars, B. J., Ramsoy, T. Z., & Laureys, S. (2003). Brain, conscious experience and the observing self. *Trends in Neurosciences*, *26*, 671–675.

Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2003). General multilevel linear modeling for group analysis in FMRI. *NeuroImage*, *20*, 1052–1063.

Bernat, J. L. (2006). Chronic disorders of consciousness. *Lancet*, *367*, 1181–1192.

Childs, N. L., Mercer, W. N., & Childs, H. W. (1993). Accuracy of diagnosis of persistent vegetative state. *Neurology*, *43*, 1465–1467.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, *130*, 2494–2507.

Dehaene, S., Changeux, J. P., Naccache, L., Sackur, J., & Sergent, C. (2006). Conscious, preconscious, and subliminal processing: A testable taxonomy. *Trends in Cognitive Sciences*, *10*, 204–211.

Dehaene, S., & Naccache, L. (2001). Towards a cognitive neuroscience of consciousness: Basic evidence and a workspace framework. *Cognition*, *79*, 1–37.

Dehaene, S., Naccache, L., Le Clec, H. G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., et al. (1998). Imaging unconscious semantic priming. *Nature*, *395*, 597–600.

Dehaene, S., Sergent, C., & Changeux, J. P. (2003). A neuronal network model linking subjective reports and objective physiological data during conscious perception. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 8520–8525.

Di, H. B., Yu, S. M., Weng, X. C., Laureys, S., Yu, D., Li, J. Q., et al. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology*, *68*, 895–899.

Elliott, L., & Walker, L. (2005). Rehabilitation interventions for vegetative and minimally conscious patients. *Neuropsychological Rehabilitation*, *15*, 480–493.

Fins, J. J., Illes, J., Bernat, J. L., Hirsch, J., Laureys, S., & Murphy, E. (2008). Neuroimaging and disorders of consciousness: Envisioning an ethical research agenda. *The American Journal of Bioethics*, *8*, 3–12.

Friston, K. J., Stephan, K. E., Lund, T. E., Morcom, A., & Kiebel, S. (2005). Mixed-effects and fMRI studies. *NeuroImage*, *24*, 244–252.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*, 349–353.

Giacino, J. T., Hirsch, J., Schiff, N., & Laureys, S. (2006). Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Archives of Physical Medicine and Rehabilitation*, *87*, S67–S76.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK coma recovery scale-revised: Measurement, characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation*, *85*, 2020–2029.

Gsell, W., De Sadeleer, C., Marchalant, Y., MacKenzie, E. T., Schumann, P., & Dauphin, F. (2000). The use of cerebral blood flow as an index of neuronal activity in functional neuroimaging: Experimental and pathophysiological considerations. *Journal of Chemical Neuroanatomy*, *20*, 215–224.

Henson, R. (2005). What can functional imaging tell the experimental psychologist? *Quarterly Journal of Experimental Psychology*, *58*, 193–233.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*, 825–841.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, *5*, 143–156.

Jennett, B. (2002). The vegetative state. *Journal of Neurology, Neurosurgery, and Psychiatry*, *73*, 355–357.

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage. *RN*, *35*, ICU1–ICU4.

Laureys, S. (2005). The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences*, *9*, 556–559.

Laureys, S., Faymonville, M. E., Peigneux, P., Damas, P., Lambermont, B., Del Fiore, G., et al. (2002). Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *NeuroImage*, *17*, 732–741.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*, 537–546.

Laureys, S., Perrin, F., & Bredart, S. (2007). Self-consciousness in non-communicative patients. *Consciousness and Cognition*, *16*, 722–741. discussion 742–5

Majerus, S., Gill-Thwaites, H., Andrews, K., & Laureys, S. (2005). Behavioral evaluation of consciousness in severe brain damage. *Progress in Brain Research*, *150*, 397–413.

Monti, M. M., Coleman, M. R., & Owen, A. M. (2009). Neuroimaging and the vegetative state: Resolving the behavioural assessment dilemma? *Disorders of Consciousness: Annals of the New York Academy of Sciences*, *1157*, 81–89.

Naghavi, H. R., & Nyberg, L. (2005). Common fronto-parietal activity in attention, memory, and consciousness: Shared demands on integration?. *Consciousness and Cognition*, *14*, 390–425.

Owen, A. M., & Coleman, M. R. (2007). Functional MRI in disorders of consciousness: Advantages and limitations. *Current Opinion in Neurology*, *20*, 632–637.

Owen, A. M., & Coleman, M. R. (2008). Functional neuroimaging of the vegetative state. *Nature Reviews. Neuroscience*, *9*, 235–243.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2007). Using functional magnetic resonance imaging to detect covert awareness in the vegetative state. *Archives of Neurology*, *64*, 1098–1102.

Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Bredart, S., et al. (2006). Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Archives of Neurology*, *63*, 562–569.

Qin, P., Di, H., Yan, X., Yu, S., Yu, D., Laureys, S., et al. (2008). Mismatch negativity to the patient's own name in chronic disorders of consciousness. *Neuroscience Letters*, *448*, 24–28.

Rees, G., Kreiman, G., & Koch, C. (2002). Neural correlates of consciousness in humans. *Nature Reviews. Neuroscience*, *3*, 261–270.

Rossini, P. M., Altamura, C., Ferretti, A., Vernieri, F., Zappasodi, F., Caulo, M., et al. (2004). Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? *Brain*, *127*, 99–110.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., et al. (2008). Voluntary brain processing in disorders of consciousness. *Neurology*, *71*, 1614–1620.

Seth, A. K., Dienes, Z., Cleeremans, A., Overgaard, M., & Pessoa, L. (2008). Measuring consciousness: Relating behavioural and neurophysiological approaches. *Trends in Cognitive Sciences*, *12*, 314–321.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*, 143–155.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(Suppl. 1), S208–S219.

Vuilleumier, P., Armony, J. L., Clarke, K., Husain, M., Driver, J., & Dolan, R. J. (2002a). Neural response to emotional faces with and without awareness: Event-related fMRI in a parietal patient with visual extinction and spatial neglect. *Neuropsychologia*, *40*, 2156–2166.

Vuilleumier, P., Schwartz, S., Clarke, K., Husain, M., & Driver, J. (2002b). Testing memory for unseen visual stimuli in patients with extinction and spatial neglect. *Journal of Cognitive Neuroscience*, *14*, 875–886.

Woolrich, M. W., Behrens, T. E., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. *NeuroImage*, *21*, 1732–1747.

Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *NeuroImage*, *14*, 1370–1386.

Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism*, *12*, 900–918.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 18

Reaching across the abyss: recent advances in functional magnetic resonance imaging and their potential relevance to disorders of consciousness

Andrea Soddu[1,4,*], Melanie Boly[1,2], Yuval Nir[5], Quentin Noirhomme[1], Audrey Vanhaudenhuyse[1], Athena Demertzi[1], Anat Arzi[3], Smadar Ovadia[3], Mario Stanziano[4], Michele Papa[4], Steven Laureys[1,2] and Rafael Malach[3]

[1]*Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium*
[2]*Neurology Department, CHU Sart Tilman Hospital, University of Liège, Belgium*
[3]*Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel*
[4]*Medicina Pubblica Clinica e Preventiva, Second University of Naples, Naples, Italy*
[5]*Department of Psychiatry, University of Wisconsin, Madison, WI, USA*

Abstract: Disorders of consciousness (DOC) raise profound scientific, clinical, ethical, and philosophical issues. Growing knowledge on fundamental principles of brain organization in healthy individuals offers new opportunities for a better understanding of residual brain function in DOCs. We here discuss new perspectives derived from a recently proposed scheme of brain organization underlying consciousness in healthy individuals. In this scheme, thalamo-cortical networks can be divided into two, often antagonistic, global systems: (i) a system of externally oriented, sensory-motor networks (the ''extrinsic'' system); and (ii) a system of inward-oriented networks (the ''intrinsic'' or default system). According to this framework, four distinct mental states would be possible that could be relevant for understanding DOCs. In normal healthy volunteers and locked-in syndrome patients, a state of high functionality of both the extrinsic and intrinsic or default systems is expected — associated with full awareness of environment and self. In this case, mental imagery tasks combined with fMRI can be used to detect covert awareness in patients that are unable to communicate. According to the framework, two complementary states of system imbalance are also possible, in which one system is in a hyperfunctional state, while the other is hypoactive. Extrinsic system hyperfunction is expected to lead to a state of total sensory-motor ''absorption'' or ''lost self.'' In contrast, intrinsic or default system hyperfunction is expected to lead to a state of complete detachment from the external world. A state where both extrinsic and intrinsic systems are hypofunctional is predicted to lead to markedly impaired consciousness as seen in DOCs. Finally, we review the potential use of ultra-slow fluctuations in BOLD signal as a tool for assessing the functional integrity of extrinsic and intrinsic systems during ''resting state'' fMRI acquisitions. In particular, we

*Corresponding author.
Tel.: +32 4 366 23 35; Fax: +32 4 366 29 46;
E-mail: Andrea.Soddu@ulg.ac.be

DOI: 10.1016/S0079-6123(09)17718-X

discuss the potential provided by assessment of these slow spontaneous BOLD fluctuations as a novel tool in assessing the cognitive state and chances of recovery from brain pathologies underlying DOCs.

Keywords: coma; consciousness; resting state; spontaneous activity; imagery; functional magnetic resonance imaging; default network

Introduction

Disorders of consciousness (DOC) are a devastating spectrum of clinical conditions involving profound disruption in global conscious states due to massive brain lesions (Bernat, 2006; Giacino et al., 2002; Laureys et al., 2004; Plum and Posner, 1972; Schiff, 2006b). Clinical characterization of the different DOCs is based on two main distinct components of human consciousness: arousal and awareness (Plum and Posner, 1972). If arousal refers to the behavioral alternation of sleep and wakefulness, awareness refers to the collective thoughts and feelings of an individual (Laureys, 2005). Coma is characterized by the absence of arousal and hence of awareness. Vegetative-state patients are aroused but unaware of environment and self (Jennett and Plum, 1972). Minimally conscious state patients are unable to reliably communicate but show reproducible behavioral evidence of awareness of environment or self (Giacino et al., 2002, 2004; Majerus et al., 2005). Locked-in syndrome patients (Plum and Posner, 1972) are fully conscious but have no means of producing speech, limb, or facial movements, except for small movements of the eyes or eyelids.

While progress has been made in describing DOCs from the clinical perspective (Giacino et al., 2004), we focus in the present review on examining DOCs from the point of view of recent developments and understandings derived from the healthy human brain. We argue that recent insights obtained through functional magnetic resonance imaging (fMRI) are relevant to a better understanding of DOCs and have the potential of allowing a better diagnosis and treatment (Giacino et al., 2006; Laureys et al., 2006; Schiff, 2006a, b). Specifically, we will focus on assessing brain function in a set of areas, termed the ''default'' network (Raichle et al., 2001; Raichle and Snyder, 2007), characterized by higher activity at rest than during externally oriented sensory-motor or cognitive tasks. This network appears to show antagonistic behavior to sensory-motor areas, which show increased fMRI signal under such tasks. Importantly, areas belonging to the default network also show a tendency for coherent fluctuations both during rest (Greicius et al., 2003; Nir et al., 2006) and during visual activation (Hasson et al., 2004) further supporting their association within a common functional system.

Based on the functional antagonistic profile of the sensory-motor cortex on the one hand and the default system on the other, as well as their complementary neuroanatomical organization (Boly et al., 2007a; Fox et al., 2005, 2009; Golland et al., 2007, 2008; Tian et al., 2007; see Fig. 1) we have proposed (Boly et al., 2008a, b; Golland et al., 2008) a fundamental ''dual'' subdivision of the human cortex into two basic — ''extrinsic'' versus ''intrinsic'' — functionalities. More specifically, we hypothesize that the cerebral cortex can be subdivided according to two basic functional orientations — an ''extrinsic'' orientation, which engages sensory-motor cortices, and an ''intrinsic'' orientation, which engages the default system. Sensory-motor cortices are involved in the processing of information immediately incoming from the external world, while the complementary ''intrinsic'' or default system appears to be involved in self-representations, episodic memory, mind wandering, and stimulus-independent thoughts (e.g., see Goldberg et al., 2006; Mason et al., 2007; D'Argembeau et al., 2005; Laureys et al., 2007).

We here will address the study of residual brain function in DOCs from the perspective of this ''extrinsic'' versus ''intrinsic'' functional subdivision and propose a conceptual framework around which to organize our knowledge and hypotheses concerning DOCs. Specifically we will consider

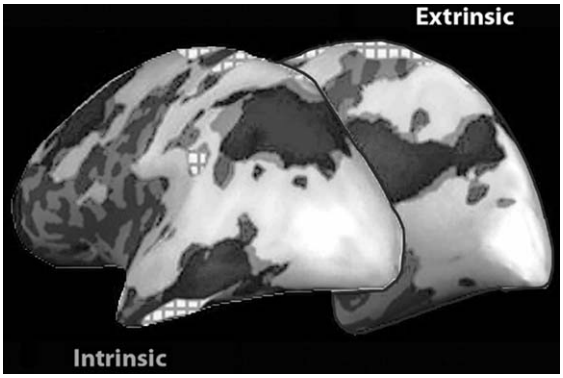


Fig. 1. An illustration of the proposed fundamental specialization of the human cortex showing the ''extrinsic'' sensory motor system and the ''intrinsic'' or default networks. It is hypothesized that the extrinsic system specializes in processing incoming information from the external environment, while the more enigmatic intrinsic or default system is specialized in internally oriented functions. Note the complementary nature of the ''extrinsic'' and ''intrinsic'' or default networks. Adapted from Golland et al. (2007).

four different mental states associated with different extrinsic–intrinsic organizations, as predicted by our framework.

High extrinsic and intrinsic functionality: the "locked-in" syndrome

The first case to consider is the situation in which both the extrinsic and intrinsic systems are highly functional yet the patient is unable to communicate or report in an effective manner about her or his mental state. In the case of locked-in syndrome this situation of disconnection between internal states and verbal or nonverbal report is due to quadriplegia and anarthria, classically caused by a ventral pontine lesion, disrupting the corticospinal and corticobulbar pathways (Plum and Posner, 1972; Smart et al., 2008). In the case of fully conscious but completely paralyzed patients (i.e., complete locked-in syndrome; Schnakers et al., 2009), fMRI may be able to detect response to command using brain activation in the absence of any overt motor response. fMRI activation paradigms offer the opportunity to directly communicate with locked-in syndrome patients by assessing responses from their brains without dependence on motor output (Birbaumer et al., 2008, 2006; Sorger et al., 2009). A demonstration that this method could effectively work was provided in recent years by the successful use of mental imagery tasks and fMRI imaging to uncover awareness in a patient clinically assessed as vegetative (Boly et al., 2007b; Owen et al., 2006). Two important methodological considerations have to be taken into account while developing fMRI activation paradigms. First, we need to find tasks that produce the most reliable and robust activation pattern in a single subject. Second, we need to be cautious in designing the fMRI paradigms, in order to avoid brain activations which could occur passively, in the absence of any willful mental effort. To address these two issues, we conducted two fMRI experiments in healthy individuals.

In the first experiment, six healthy subjects were scanned in a 3 T MRI scanner during: (i) passive listening to verbal commands and (ii) active mental imagery in response to the same instructions. Mental imagery tasks included: (1) imagining opening and closing the left hand, (2) mental calculation (counting down), (3) imaging preparing luggage, (4) imaging walking from home to work, (5) covertly describing a face, (6) imaging filling in a check, and (7) covertly describing ones own thoughts. An eighth condition of rest (eyes closed) was used as a baseline. In the second experiment, we compared visual mental imagery (eyes closed) with passive visual stimulation (Farah, 1989; Ganis et al., 2004). Here, eight healthy subjects were

scanned in four different conditions: (i) visual, (ii) imagery, (iii) visual and verbal description (covert), and (iv) imagery and verbal description (covert). The tasks (lasting 12 s) included viewing or imaging: (a) walking from home to work, (b) filling a check, (c) observing the own face, and (d) preparing a luggage. A fifth condition of rest (blank screen for visual and keeping the eyes closed for imagery) was used as reference "baseline" activity. A common finding for all active tasks in the first experiment (Fig. 2) was a widespread activation encompassing bilateral intraparietal sulcus, primary sensory-motor areas, supplementary motor area, parahippocampal gyrus, inferior and middle temporal gyri, language-related and inferior frontal areas. Together with the activation pattern, there was also a consistent activity reduction in the intrinsic or default network during performance of the tasks. In Fig. 2, the superimposed contour map show the intrinsic or default network (identified using independent component analysis from a group of seven healthy volunteers scanned during 10 min "eyes-closed resting state") encompassing precuneus and adjacent posterior cingulate cortex, mesiofrontal cortex and adjacent anterior cingulate cortex, and bilateral temporoparietal junctions areas. The combined increased activation of the extrinsic network and the deactivation of the intrinsic system suggest that mental imagery tasks have a preferentially extrinsic component, likely due to a process of "replay" of extrinsic sensory-motor activations (Gelbard-Sagiv et al., 2008). These activations were consistent across individual subjects. Table 1 shows identified areas for the seven different mental imagery tasks. In line with previous studies (e.g., Boly et al., 2007b), the spatial navigation task (imagining walking from home to work) was among the tasks showing the most consistent activity across subjects (together with imagery tasks of writing a check and preparing a luggage). Figure 3 shows the activation patterns during two different sessions for the active mental imagery task (spatial navigation) compared to activation induced by passive listening to the same task instructions. While passive listening did not elicit activation, both active imagery tasks elicited activation of parahippocampal areas, well known to be involved in spatial navigation tasks (Epstein et al., 1999; Epstein and Kanwisher, 1998). This differential activation in active

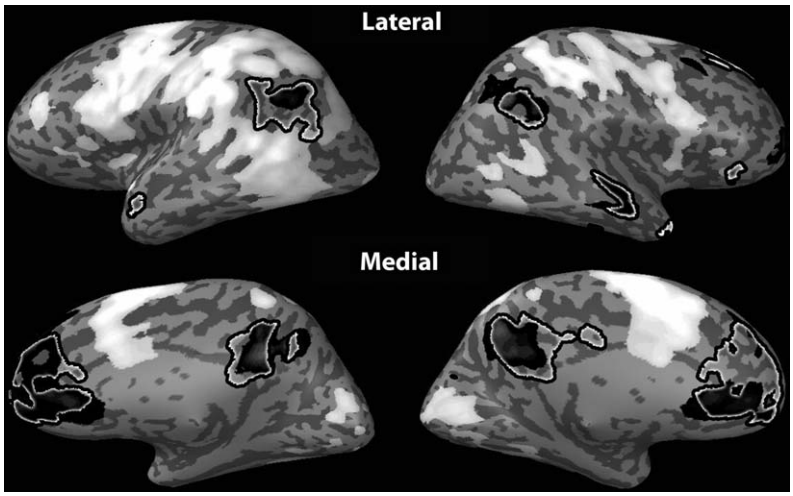


Fig. 2. Common activation and deactivation patterns (as compared to eyes-closed resting) observed during seven mental imagery tasks (i.e., imagining opening and closing the left hand; mental calculation; imaging preparing luggage; imaging walking from home to work; covertly describing ones own face; imaging filling in a check and covertly describing ones own thoughts). Fixed effects group analysis thresholded at false discovery rate corrected $p < 0.05$. The contours of the independently identified default mode network are contoured in black. Note the robust imagery-related activation overlapping with regions associated with the extrinsic system (see text for details).

Table 1. Random effect group analyses identifying areas activating during the seven mental imagery tasks as compared to eyes-closed resting state

Imagery task	Region	*X*	*Y*	*Z*	*T*-value	*p*-value
Imagining opening and closing the left hand	Superior parietal lobe	−36	−35	40	9.3	<0.001
	Supplementary motor area	2	7	50	6.5	<0.001
	Middle temporal gyrus	−50	−52	3	6.4	<0.001
Counting down	Superior parietal lobe	−42	−33	40	5.7	<0.001
	Precentral gyrus	−53	2	23	5.5	<0.001
	Supplementary motor area	−1	4	51	5.2	<0.001
Imaging preparing luggage	Superior parietal lobe	−35	−34	42	6.2	<0.001
	Parieto-occipital sulcus	−18	−59	44	5.4	<0.001
	Supplementary motor area	−5	5	48	5.3	<0.001
Imaging walking from home to work	Parahippocampal gyrus	−13	−56	10	7.1	<0.001
	Superior parietal lobe	−35	−34	38	6.6	<0.001
	Medial occipitotemporal gyrus	−24	−36	−7	5.7	<0.001
Describing a face	Superior parietal lobe	−44	−30	38	7.9	<0.001
	Supplementary motor area	−5	5	50	5.9	<0.001
	Lateral occipitotemporal gyrus	−40	−54	−14	5.3	<0.001
Imaging filling a check	Superior parietal lobe	−48	−29	42	6.7	<0.001
	Superior parietal lobe	−33	−35	40	6.4	<0.001
	Middle temporal gyrus	−44	−45	−4	6.2	<0.001
Describing own thoughts	Middle frontal gyrus	−44	−1	51	4.9	<0.001
	Superior parietal lobe	−46	−33	41	4.6	<0.001
	Superior temporal gyrus	−61	−39	10	4.3	<0.001

compared to passive conditions strengthens the hypothesis that observed brain responses are indeed associated with intentional mental effort and are not merely induced by passive listening to the task instructions. Finally, Fig. 4 illustrates brain activation patterns when one sees a video of oneself walking (visual) compared to imagining oneself walking, and when the visual imagery process is accompanied by a covert description. The activation of Broca's area both in the ''imagining'' and ''imagining and verbal description'' conditions suggests that even when subjects were asked to perform the mental imagery tasks using only visualization strategies they could not avoid adding a verbal component to the visual imagery aspect.

Overall, three conclusions can be drawn from these results. First, robust brain activations can be elicited and measured with fMRI without the subjects performing any overt responses. This brain activation seems particularly robust in tasks involving action planning, while recognition tasks such as imagining faces seemed less effective. Second, the obtained activations could be differentiated in a reproducible manner from the passive conditions in which subjects did not engage in any active mental imagery. Finally, requiring a verbal description of the cognitive action while performing mental imaging tasks increases the neural activation intensity and extent. These results are encouraging in showing that a consistently detected increase in fMRI signal can be obtained when subjects are engaged in active mental imagery, and that this activation pattern can be reliably differentiated from the more automatic neural responses to presentation of the task instructions. On the other hand, for communication purposes, it appears that relying only on the patterns of activations associated with different mental imagery tasks may not be an effective solution as in the above-reported study many patterns of activations were rather similar between tasks. In this context, it is useful to also collect information on the timing of the fMRI response to a given task (i.e., starting time and latency of the subject's BOLD response) in order to better segregate the activation patterns elicited by different mental imagery tasks (see Sorger et al., 2009).

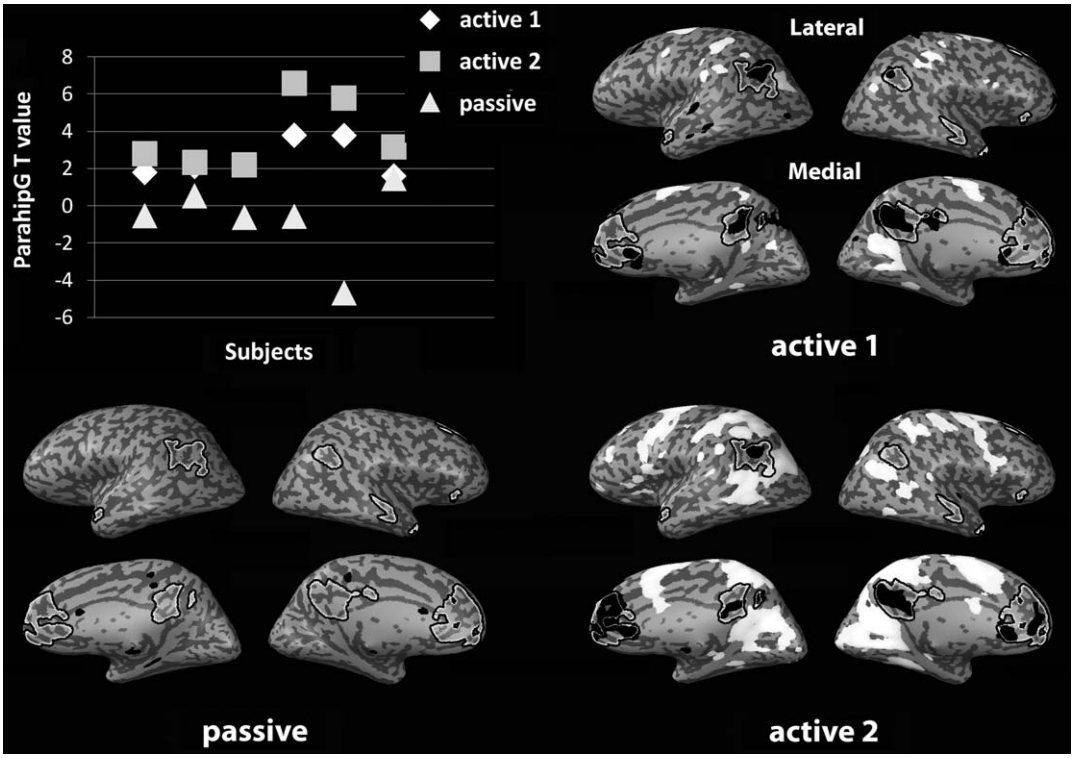


Fig. 3. Activation patterns observed during two different sessions of active mental imagery (spatial navigation) compared to activation induced by passive listening to the same task instructions. Fixed effects group analysis thresholded at false discovery rate corrected $p<0.05$. Superimposed are the contours of the default mode network as in Fig. 2. Parahippocampal gyrus activity (Talairach coordinates $X=-13$, $Y=-15$, $Z=10$ mm) is shown for each of the six healthy volunteers for the three acquisitions. Note the consistently higher activation during active imagery compared to passive listening.

We described here the first condition predicted by the framework, that is, full consciousness with preserved functionality of both extrinsic and intrinsic networks, and the use of mental imagery tasks to detect this condition in brain-damaged patients. We will now consider two hypothetical situations in which there is an imbalance between the extrinsic and intrinsic systems.

"Losing the self": hypoactivity of the intrinsic system

Perhaps the most robust fMRI finding which concerns the functionality of the intrinsic or default system is the consistent reduction of activity in this network during performance of cognitively demanding externally oriented tasks such as visual recognition and motor planning (Gusnard et al., 2001). In contrast, the intrinsic system shows increased fMRI activity during no-task "resting" conditions, leading to the notion that this network might be a "task-negative" system (Fox et al., 2005, 2009) or be engaged in a "default" function during resting conditions (Raichle et al., 2001; Raichle and Snyder, 2007). It has been proposed that this reduced activity may be attributed to the fact that during an intense externally oriented task, the performing subject is fully attentive to the external world, and metaphorically speaking "loses itself" in the act (Goldberg et al., 2006; Golland et al., 2007). What then could be the outcome of a permanent reduction in the intrinsic system activity due to brain abnormality? Since no direct data are available, yet from DOCs one can only

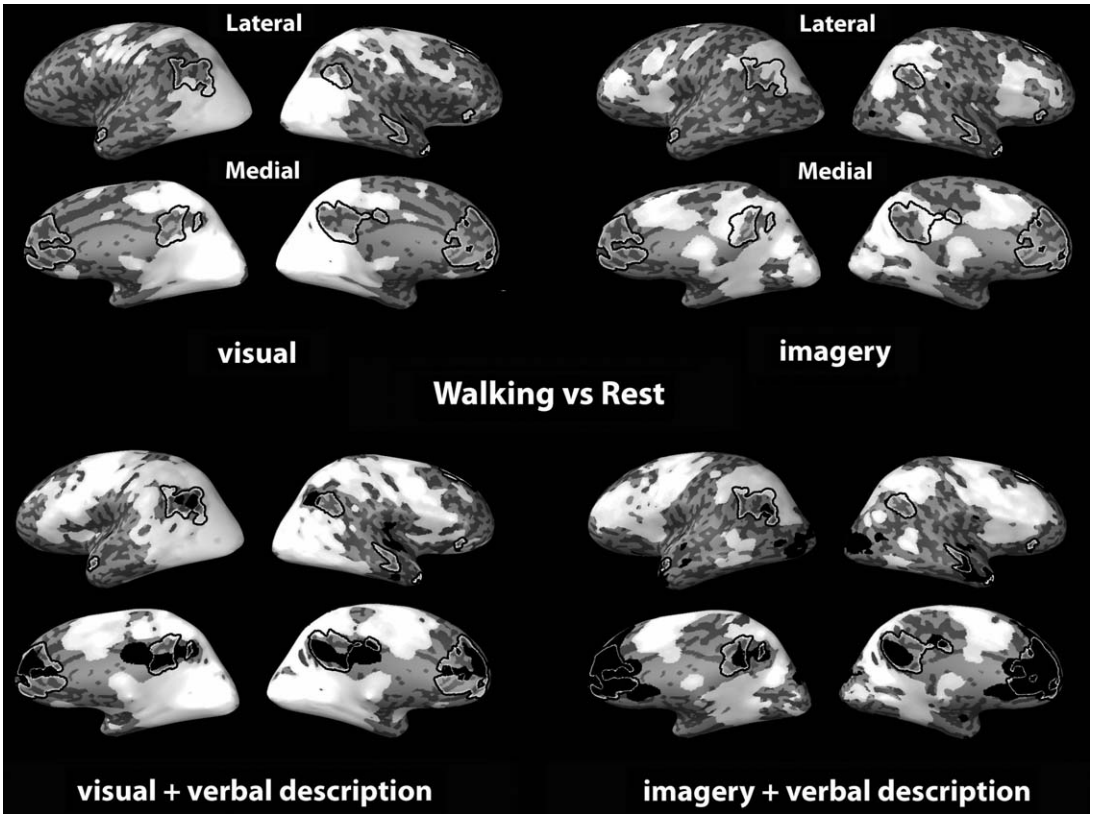


Fig. 4. Activation patterns induced by passively seeing a video of oneself walking (visual); imagining oneself walking (imagery), covert verbal description during the visual stimulation, and covert verbal description during the mental visual imagery task. Fixed effects group analysis thresholded at false discovery rate corrected $p<0.01$. Superimposed are the contours of the default mode network. Note the substantial overlap of activity patterns between all four conditions, and the enhancement in neural activation associated with verbal descriptions.

extrapolate from studies in healthy individuals. It appears that some aspect of the intrinsic system function may be associated with voluntary decisions and action initiation (Goldberg et al., 2008). Extrapolating from such findings leads to the conjecture that a possible consequence of a pathological damage to this system might be a condition akin to catatonic or akinetic mutism (Naccache et al., 2004) in which the patient is unable to voluntarily initiate a motor action — in De Tiege et al. (2003) akinetic mutism was indeed linked to medial prefrontal dysfunction. Note that such a condition, associated with lack of movement, could in principle masquerade as a DOC since the patient may not initiate any response or communication.

"Self-centered absorption"

The third condition predicted by the framework, in which the extrinsic system is hypofunctional, would be reflected by the disengagement of the subjects from the external environment. Few hints associate such conditions with "mind wandering," where typically high default network activity is observed (Christoff et al., 2009; Gilbert et al., 2007; Mason et al., 2007; Wang et al., 2009). While these notions fit the conceptual framework of an antagonistic relationship between the extrinsic and intrinsic networks — that is, an enhancement in intrinsic activity comes at the expense of processing of the extrinsic information, the relevant data are too scant as yet. Nevertheless,

it is tempting to speculate how a pathological imbalance in which the extrinsic system is largely inactive should be reflected in the mental state of DOCs. From our conceptual framework we anticipate that such an imbalance would manifest itself again in a severe motor inaction, but also in a reduced sensory responsivity (since the patient is detached and self-absorbed and is incapable of orienting to the external world) either in terms of receiving sensory signals, or emitting motor actions. Behaviorally, then, the two conditions (''lost self'' and ''self-centered absorption'') could paradoxically lead to similar behavioral manifestations. Again, brain imaging, and particularly the study of spontaneous cerebral BOLD fluctuations by means of fMRI, might provide useful clues in diagnosing these hypothetical conditions — as will be discussed later. Finally, we consider the possibility that both systems are abnormally hypofunctional. In this case, we predict a deep DOC in which the patient does not respond and is also incapable of initiating any voluntary communication. In such severe and widespread brain abnormalities we expect a greatly reduced brain metabolism and a general reduction in neuronal activity.

Spontaneous fMRI activity patterns as a diagnostic tool in DOCs

Although the above discussions of possible abnormalities associated with the new framework of brain organization are largely hypothetical and speculative, they do illustrate the complexity of brain abnormalities that could produce behavioral symptoms which may deceptively appear identical at the behavioral level. Here, the potentially powerful approach of functional brain imaging (Hirsch, 2005; Laureys et al., 2000, 1999a, b; Schiff et al., 2005) and particularly of fMRI may come as a useful and incisive tool. It may be argued that functional neuroimaging, if using active paradigms (Boly et al., 2007b; Owen et al., 2006, 2007) will be useful only in those limited ''pseudo locked-in'' cases where the patient behaviorally looks unconscious but in reality is fully aware and can initiate complex voluntary mental activity. Recent progress in studying spontaneous brain activity (Biswal et al., 1995; Cordes et al., 2000; Damoiseaux et al., 2006; Fox and Raichle, 2007; Fox et al., 2005; Greicius et al., 2003; Lowe et al., 1998; Mitra et al., 1997; Nir et al., 2006; Vincent et al., 2007; Xiong et al., 1999) demonstrating activity patterns that emerge without any task or sensory stimulation, promise for studying higher-order associative network functionality and revealing their potential abnormalities in the absence of the patients' collaboration (Boly et al., 2009b; Greicius et al., 2004; Rombouts et al., 2009).

The functional significance of low-frequency fMRI activity fluctuations remains yet poorly understood. A demonstration that such spontaneous activity occurs in primary sensory systems is of particular importance in this context. Indeed, the spontaneous nature of brain activity can be ascertained in such systems, if the sensory stimuli are completely blocked, and careful controls for imagery and attention are used (Nir et al., 2006, 2008). Recent research using intracranial recordings have revealed a putative electrophysiological correlate of such fMRI spontaneous activity in the neuronal responses of human cortex (He et al., 2008; Nir et al., 2008). More specifically, during resting-state conditions the human cortex manifests ultra-slow modulations of neuronal activity reflected both in firing rate modulations of individually isolated cortical neurons, as well as in modulation of high-frequency gamma power of local field potentials. These ultra-slow fluctuations show a remarkable coherence across functionally similar sites, and interestingly, are greatly accentuated during different sleep stages. Figure 5 depicts an example of such spontaneous activity recorded bilaterally from human auditory cortex during quiet rest (stage II sleep), showing a remarkable coherence of the activity in auditory cortices of both hemispheres. Although these activity patterns have a much slower dynamics than task-related activations (Nir et al., 2008), their widespread nature and remarkable reproducibility among subjects (Damoiseaux et al., 2006) makes them a potential tool for assessing the viability and functionality of cortical networks.

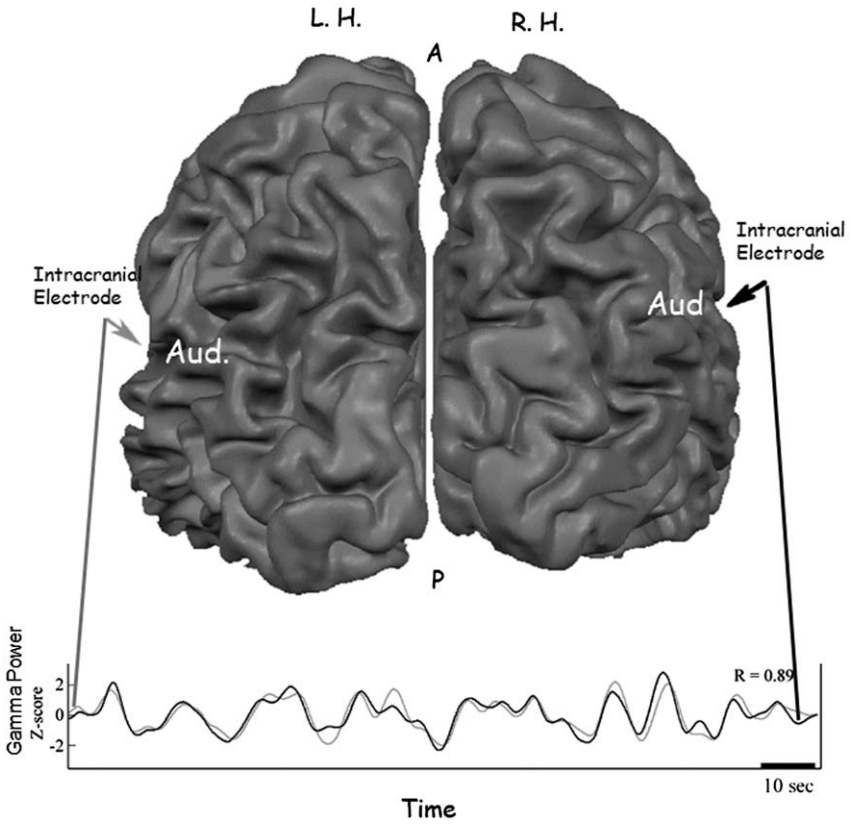


Fig. 5. Intracranial recordings obtained from bilateral auditory cortex depicting gamma power modulations in the local field potentials. Note the ultra-slow, spontaneous fluctuations and their remarkable correlation across the two hemispheres. Adapted from Nir et al. (2008).

Data-driven approaches such as independent component analysis (Hyvärinen, 1999) or *k*-clustering (Golland et al., 2008) applied to spontaneous activity, could reveal a full set of independent networks with a particular spatial distribution and a characteristic frequency power spectrum (Beckmann et al., 2005; De Luca et al., 2006; Esposito et al., 2008, 2006, 2005; Mantini et al., 2007; McKeown et al., 1998; Perlbarg and Marrelec, 2008). The advantage of studying these activity patterns is that they nicely correspond to the functional organization of global brain systems (Bullmore and Sporns, 2009; Hagmann et al., 2008; Honey et al., 2009). Thus, cortical systems, which are functionally coupled during task performance, also show a similar coupling of spontaneous activity. Consequently, these spontaneous activations offer a tool in assessing cortical functional abnormalities in patients that cannot cooperate. Indeed, a recent report has presented important evidence that such spontaneous activity can provide a sensitive marker for detecting cortical abnormalities in neurodegenerative disorders (Seeley et al., 2009). More specific to DOCs, we have recently demonstrated that default network connectivity was decreased in severely brain-damaged patients in proportion to their degree of consciousness impairment Boly et al., (2009); Vanhaudenhuyse et al. (submitted), Boly et al., (2009), demonstrated absent cortico-thalamic BOLD functional connectivity (i.e., cross-correlation between precuneal areas and medial thalamus) but partially preserved cortico-cortical connectivity within the default network in a vegetative-state patient studied 2.5 years following cardio-respiratory arrest (see Fig. 6). In a more comprehensive

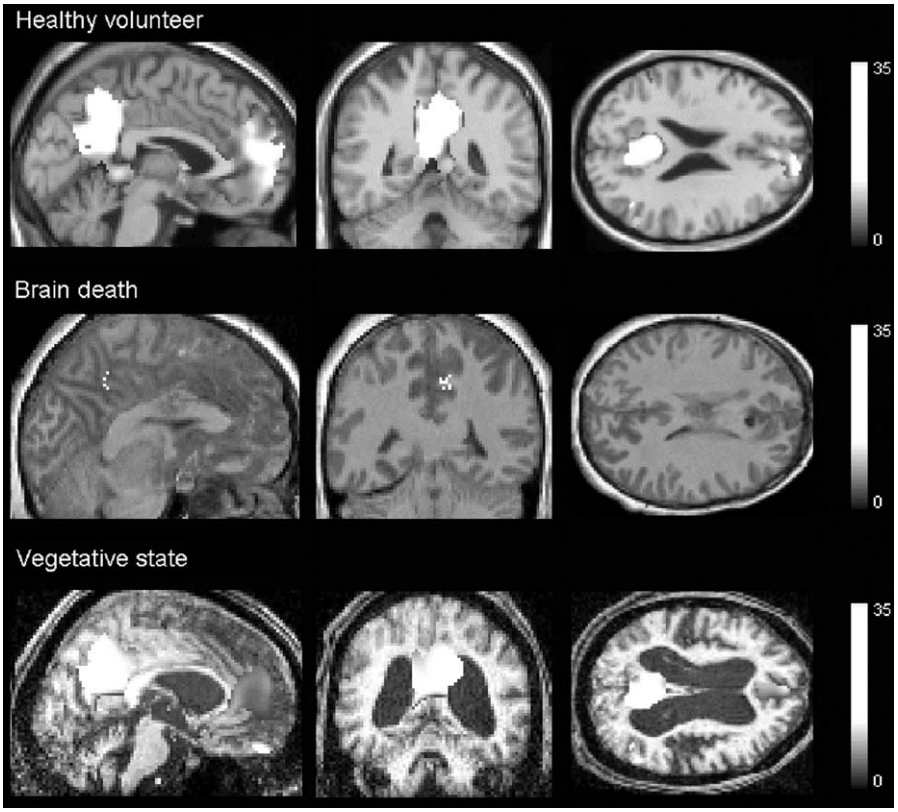


Fig. 6. Positive correlations with precuneal and posterior cingulate activity in a healthy volunteer, a patient in brain death and a patient in a vegetative state. Results are thresholded at false discovery rate corrected $p<0.001$. Note that there is no residual long-range functional connectivity in brain death. In the vegetative state, despite the presence of residual functional connectivity within the default network, the observed activity is reduced compared to healthy controls. Adapted from Boly et al. (2009).

study (Vanhaudenhuyse et al. (submitted)) 14 noncommunicative brain-damaged patients and 14 healthy controls participated in a resting-state fMRI protocol. Connectivity was investigated using probabilistic-independent component analysis and an automated template-matching component selection approach. Connectivity in all default network areas was found to be linearly correlated with the degree of consciousness, ranging from healthy volunteers and locked-in syndrome to minimally conscious, vegetative, and comatose patients. Furthermore, precuneus connectivity was found to be significantly stronger in minimally conscious patients compared to vegetative-state patients. Locked-in syndrome patients' default network connectivity was shown not to be significantly different from healthy control subjects.

A remaining issue in the study of spontaneous BOLD signal fluctuations, especially for patients that show a significantly reduced neuronal activity, is the possible contamination by noise sources (Birn et al., 2006; Chuang and Chen, 2001; Cordes et al., 2000). Different strategies have been adopted based on two major defining characteristics of spontaneous brain activity as reported also by fMRI studies: (i) their tendency to be correlated across hemispheres (Biswal et al., 1995; Cordes et al., 2000; Damoiseaux et al., 2006; Fox and Raichle, 2007; Fox et al., 2005; Golland et al., 2007; Greicius et al., 2003; Lowe et al., 1998; Nir et al., 2006; Vincent et al., 2007; Xiong et al., 1999) and (ii) their neuroanatomical selectivity, that is, such fluctuations are not global, and distinct functional systems are often decorrelated (Biswal

et al., 1995; Cordes et al., 2000; Damoiseaux et al., 2006; Fox and Raichle, 2007; Fox et al., 2005; Golland et al., 2007; Greicius et al., 2003; Lowe et al., 1998; Nir et al., 2006; Vincent et al., 2007; Xiong et al., 1999). Data-driven approaches like independent component analysis offer the advantage to better isolate physiological artifacts from the neuronal components and are now being commonly adopted in this field (Beall and Lowe, 2007; Birn et al., 2008; Perlbarg et al., 2007).

In conclusion, the integration and cross-referencing from recent advances in studying the healthy human brain provide new conceptual frameworks and methodological approaches that could help better diagnosing and understanding DOC. We here emphasized two perspectives for such integration: (i) from a neuroanatomical point of view (i.e., the subdivision of the human cortex according to a fundamental extrinsic versus intrinsic specialization reflected in two global and complementary cortico-thalamic systems); and (ii) from a functional point of view (i.e., the discovery of spontaneous ultra-slow and coherent activity patterns). Both perspectives are likely to provide important advances in our attempts to reach across the abyss and gain further insight in the neural correlates of human consciousness.

Acknowledgments

This work was supported by ISF 160/07 and Minerva grants (RM), MIUR-Progetto FIRB Internazionalizzazione-RBIN04KW43 (AS), the European Commission (DISCOS, Mindbridge and COST), the McDonnell Foundation, the Mind Science Foundation, the Reine Elisabeth Medical Foundation, and University of Liège. M. Boly and S. Laureys are, respectively, Research Fellow and Senior Research Associate at the Belgian National Fund for Scientific Research.

References

Beall, E. B., & Lowe, M. J. (2007). Isolating physiologic noise sources with independently determined spatial measures. *Neuroimage*, *37*, 1286–1300.

Beckmann, C. F., DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *360*, 1001–1013.

Bernat, J. L. (2006). Chronic disorders of consciousness. *Lancet*, *367*, 1181–1192.

Birbaumer, N., Murguialday, A. R., & Cohen, L. (2008). Brain-computer interface in paralysis. *Current Opinion in Neurology*, *21*, 634–638.

Birbaumer, N., Weber, C., Neuper, C., Buch, E., Haapen, K., & Cohen, L. (2006). Physiological regulation of thinking: Brain–computer interface (BCI) research. *Progress in Brain Research*, *159*, 369–391.

Birn, R. M., Diamond, J. B., Smith, M. A., & Bandettini, P. A. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *Neuroimage*, *31*, 1536–1548.

Birn, R. M., Murphy, K., & Bandettini, P. A. (2008). The effect of respiration variations on independent component analysis results of resting state functional connectivity. *Human Brain Mapping*, *29*, 740–750.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*, 537–541.

Boly, M., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., et al. (2007a). Baseline brain activity fluctuations predict somatosensory perception in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 12187–12192.

Boly, M., Coleman, M. R., Davis, M. H., Hampshire, A., Bor, D., Moonen, G., et al. (2007b). When thoughts become action: An fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *Neuroimage*, *36*, 979–992.

Boly, M., Phillips, C., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., et al. (2008a). Consciousness and cerebral baseline activity fluctuations. *Human Brain Mapping*, *29*, 868–874.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T. T., et al. (2008b). Intrinsic brain activity in altered stated of consciousness—How conscious is the default mode of brain function? *Annals of the New York Academy of Sciences*, *1129*, 119–129.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., et al. (2009). Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping 30*(8), 2393–2400.

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews. Neuroscience*, *10*, 186–198.

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of*

Sciences of the United States of America. doi:10.1073/pnas.0900234106.

Chuang, K. H., & Chen, J. H. (2001). IMPACT: Image-based physiological artifacts estimation and correction technique for functional MRI. *Magnetic Resonance in Medicine*, *46*, 344–353.

Cordes, D., Haughton, V. M., Arfanakis, K., Wendt, G. J., Turski, P. A., Moritz, C. H., et al. (2000). Mapping functionally related regions of brain with functional connectivity MR imaging. *American Journal of Neuroradiology*, *21*, 1636–1644.

Damoiseaux, J. S., Rombouts, S. A., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., et al. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*, *103*, 13848–13853.

D'Argembeau, A., Collette, F., Van der Linden, M., Laureys, S., Del Fiore, G., Degueldre, C., et al. (2005). Self-referential reflective activity and its relationship with rest: A PET study. *Neuroimage*, *25*, 616–624.

De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage*, *29*, 1359–1367.

De Tiege, X., Bier, J. C., Massat, I., Laureys, S., Lotstra, F., Berre, J., et al. (2003). Regional cerebral glucose metabolism in akinetic catatonia and after remission. *Journal of Neurology, Neurosurgery, and Psychiatry*, *74*, 1003–1004.

Epstein, R., Harris, A., Stanley, D., & Kanwisher, N. (1999). The parahippocampal place area: Recognition, navigation, or encoding? *Neuron*, *23*, 115–125.

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature*, *392*, 598–601.

Esposito, F., Aragri, A., Pesaresi, I., Cirillo, S., Tedeschi, G., Marciano, E., et al. (2008). Independent component model of the default-mode brain function: Combining individual-level and population-level analyses in resting-state fMRI. *Journal of Magnetic Resonance Imaging*, *26*, 905–913.

Esposito, F., Bertolino, A., Scarabino, T., Latorre, V., Blasi, G., Popolizio, T., et al. (2006). Independent component model of the default-mode brain function: Assessing the impact of active thinking. *Brain Research Bulletin*, *70*, 263–269.

Esposito, F., Scarabino, T., Hyvarinen, A., Himberg, J., Formisano, E., Comani, S., et al. (2005). Independent component analysis of fMRI group studies by self-organizing clustering. *Neuroimage*, *25*, 193–205.

Farah, M. J. (1989). The neural basis of mental imagery. *Trends in Neurosciences*, *12*, 395–399.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*, 700–711.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 9673–9678.

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The Global Signal and Observed Anticorrelated Resting State Brain Networks. *Journal of Neurophysiology*, *101*, 3270–3283.

Ganis, G., Thompson, W. L., & Kosslyn, S. M. (2004). Brain areas underlying visual mental imagery and visual perception: An fMRI study. *Brain Research. Cognitive Brain Research*, *20*, 226–241.

Gelbard-Sagiv, H., Mukamel, R., Harel, M., Malach, R., & Fried, I. (2008). Internally generated reactivation of single neurons in human hippocampus during free recall. *Science*, *322*, 96–101.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*, 349–353.

Giacino, J. T., Hirsch, J., Schiff, N., & Laureys, S. (2006). Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Archives of Physical Medicine and Rehabilitation*, *87*, S67–S76.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK coma recovery scale-revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation*, *85*, 2020–2029.

Gilbert, S. J., Dumontheil, I., Simons, J. S., Frith, C. D., & Burgess, P. W. (2007). Comment on ''Wandering minds: The default network and stimulus-independent thought''. *Science*, *317*, 43. author reply 43.

Goldberg, I., Ullman, S., & Malach, R. (2008). Neuronal correlates of ''free will'' are associated with regional specialization in the human intrinsic/default network. *Consciousness and Cognition*, *17*, 587–601.

Goldberg, I. I., Harel, M., & Malach, R. (2006). When the brain loses its self: Prefrontal inactivation during sensorimotor processing. *Neuron*, *50*, 329–339.

Golland, Y., Bentin, S., Gelbard, H., Benjamini, Y., Heller, R., Nir, Y., et al. (2007). Extrinsic and intrinsic systems in the posterior cortex of the human brain revealed during natural sensory stimulation. *Cerebral Cortex*, *17*, 766–777.

Golland, Y., Golland, P., Bentin, S., & Malach, R. (2008). Data-driven clustering reveals a fundamental subdivision of the human cortex into two global systems. *Neuropsychologia*, *46*, 540–553.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 253–258.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: Evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 4637–4642.

Gusnard, D. A., Raichle, M. E., & Raichle, M. E. (2001). Searching for a baseline: Functional imaging and the resting human brain. *Nature reviews. Neuroscience*, *2*, 685–694.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., et al. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biology*, *6*, e159.

Hasson, U., Nir, Y., Levy, I., Fuhrmann, G., & Malach, R. (2004). Intersubject synchronization of cortical activity during natural vision. *Science*, *303*, 1634–1640.

He, B. J., Snyder, A. Z., Zempel, J. M., Smyth, M. D., & Raichle, M. E. (2008). Electrophysiological correlates of the brain's intrinsic large-scale functional architecture. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 16039–16044.

Hirsch, J. (2005). Functional neuroimaging during altered states of consciousness: How and what do we measure? *Progress in Brain Research*, *150*, 25–43.

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., et al. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 2035–2040.

Hyvärinen, A. (1999). Fast and robust fixed-point algorithms for independent component analysis. *IEEE Transactions on Neural Networks*, *10*(3), 626–634.

Jennett, B., & Plum, F. (1972). Persistent vegetative after brain damage. *Lancet*, *1*, 4.

Laureys, S. (2005). The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences*, *9*, 556–559.

Laureys, S., Faymonville, M. E., Degueldre, C., Fiore, G. D., Damas, P., Lambermont, B., et al. (2000). Auditory processing in the vegetative state. *Brain*, *123*(Pt 8), 1589–1601.

Laureys, S., Giacino, J. T., Schiff, N. D., Schabus, M., & Owen, A. M. (2006). How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs? *Current Opinion in Neurology*, *19*, 520–527.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., et al. (1999a). Impaired effective cortical connectivity in vegetative state: Preliminary investigation using PET. *Neuroimage*, *9*, 377–382.

Laureys, S., Lemaire, C., Maquet, P., Phillips, C., & Franck, G. (1999b). Cerebral metabolism during vegetative state and after recovery to consciousness. *Journal of Neurology, Neurosurgery, and Psychiatry*, *67*, 121.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*, 537–546.

Laureys, S., Perrin, F., & Brédart, S. (2007). Self-consciousness in non-communicative patients. *Consciousness & Cognition*, *16*, 722–741.

Lowe, M. J., Mock, B. J., & Sorenson, J. A. (1998). Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage*, *7*, 119–132.

Majerus, S., Gill-Thwaites, H., Andrews, K., & Laureys, S. (2005). Behavioral evaluation of consciousness in severe brain damage. *Progress in Brain Research*, *150*, 397–413.

Mantini, D., Perrucci, M. G., Del Gratta, C., Romani, G. L., & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 13170–13175.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: The default network and stimulus-independent thought. *Science*, *315*, 393–395.

McKeown, M. J., Makeig, S., Brown, G. G., Jung, T. P., Kindermann, S. S., Bell, A. J., et al. (1998). Analysis of fMRI data by blind separation into independent spatial components. *Human Brain Mapping*, *6*, 160–188.

Mitra, P. P., Ogawa, S., Hu, X. P., & Ugurbil, K. (1997). The nature of spatiotemporal changes in cerebral hemodynamics as manifested in functional magnetic resonance imaging. *Magnetic Resonance in Medicine*, *37*(4), 511–518.

Naccache, L., Obadia, M., Crozier, S., Detante, O., Guillerm, C., Bonneville, F., et al. (2004). Preserved auditory cognitive ERPs in severe akinetic mutism: A case report. *Brain Research. Cognitive Brain Research*, *19*, 202–205.

Nir, Y., Hasson, U., Levy, I., Yeshurun, Y., & Malach, R. (2006). Widespread functional connectivity and fMRI fluctuations in human visual cortex in the absence of visual stimulation. *Neuroimage*, *30*, 1313–1324.

Nir, Y., Mukamel, R., Dinstein, I., Privman, E., Harel, M., Fisch, L., et al. (2008). Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. *Nature Neuroscience*, *11*, 1100–1108.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2007). Using functional magnetic resonance imaging to detect covert awareness in the vegetative state. *Archives of Neurology*, *64*, 1098–1102.

Perlbarg, V., Bellec, P., Anton, J. L., Pelegrini-Issac, M., Doyon, J., & Benali, H. (2007). CORSICA: Correction of structured noise in fMRI by automatic identification of ICA components. *Magnetic Resonance Imaging*, *25*, 35–46.

Perlbarg, V., & Marrelec, G. (2008). Contribution of exploratory methods to the investigation of extended large-scale brain networks in functional MRI: Methodologies, results, and challenges. *International Journal of Biomedical Imaging*, *2008*, 218519. doi:10.1155/2008/218519.

Plum, F., & Posner, J. B. (1972). The diagnosis of stupor and coma. *Contemporary Neurology Series*, *10*, 1–286.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 676–682.

Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: A brief history of an evolving idea. *Neuroimage*, *37*, 1083–1090. Discussion 1097-9.

Rombouts, S. A., Damoiseaux, J. S., Goekoop, R., Barkhof, F., Scheltens, P., Smith, S. M., et al. (2009). Model-free group analysis shows altered BOLD FMRI networks in dementia. *Human Brain Mapping*, *30*, 256–266.

Schiff, N. D. (2006a). Measurements and models of cerebral function in the severely injured brain. *Journal of Neurotrauma*, *23*, 1436–1449.

Schiff, N. D. (2006b). Multimodal neuroimaging approaches to disorders of consciousness. *The Journal of Head Trauma Rehabilitation*, *21*, 388–397.

Schiff, N. D., Rodriguez-Moreno, D., Kamal, A., Kim, K. H., Giacino, J. T., Plum, F., et al. (2005). fMRI reveals large-scale network activation in minimally conscious patients. *Neurology*, *64*, 514–523.

Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., et al. (2009). Detecting consciousness in a total locked-in syndrome: An active event related paradigm. *Neurocase*, *25*, 1–7.

Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron*, *62*, 42–52.

Smart, C. M., Giacino, J. T., Cullen, T., Moreno, D. R., Hirsch, J., Schiff, N. D., et al. (2008). A case of locked-in syndrome complicated by central deafness. *Nature Clinical Practice. Neurology*, *4*, 448–453.

Sorger, B., Dahmen, B., Reithler, J., Gosseries, O., Maudoux, A., Laureys, S., Goebel, R. (2009). Another kind of 'BOLD response': Answering multiple-choice questions via online decoded single-trial brain signals, *Progress in Brain Research* (this volume).

Tian, L., Jiang, T., Liu, Y., Yu, C., Wang, K., Zhou, Y., et al. (2007). The relationship within and between the extrinsic and intrinsic systems indicated by resting state correlational patterns of sensory cortices. *Neuroimage*, *36*, 684–690.

Vanhaudenhuyse, A., Noirhomme, Q., Tshibanda, J.-F. L., Bruno, M.-A., Boveroux, P., Schnakers, C., et al. (Submitted). Default network connectivity reflects the level of consciousness in non-communicative brain damaged patients. *Brain*.

Vincent, J. L., Patel, G. H., Fox, M. D., Snyder, A. Z., Baker, J. T., Van Essen, D. C., et al. (2007). Intrinsic functional architecture in the anaesthetized monkey brain. *Nature*, *447*, 83–86.

Wang, K., Yu, C., Xu, L., Qin, W., Li, K., Xu, L., et al. (2009). Offline memory reprocessing: Involvement of the brain's default network in spontaneous thought processes. *PLoS ONE*, *4*, e4867.

Xiong, J., Parsons, L. M., Gao, J. H., & Fox, P. T. (1999). Interregional connectivity to primary motor cortex revealed using MRI resting state images. *Human Brain Mapping*, *8*, 151–156.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 19

Another kind of 'BOLD Response': answering multiple-choice questions via online decoded single-trial brain signals

Bettina Sorger[1,2,3,*], Brigitte Dahmen[3], Joel Reithler[1,2], Olivia Gosseries[3], Audrey Maudoux[3], Steven Laureys[3] and Rainer Goebel[1,2]

[1]*Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands*
[2]*Maastricht Brain Imaging Centre (M-BIC), Maastricht, The Netherlands*
[3]*Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium*

Abstract: The term '*locked-in*' *syndrome* (LIS) describes a medical condition in which persons concerned are severely paralyzed and at the same time fully conscious and awake. The resulting anarthria makes it impossible for these patients to naturally communicate, which results in diagnostic as well as serious practical and ethical problems. Therefore, developing alternative, muscle-independent communication means is of prime importance. Such communication means can be realized via brain–computer interfaces (BCIs) circumventing the muscular system by using brain signals associated with preserved cognitive, sensory, and emotional brain functions. Primarily, BCIs based on electrophysiological measures have been developed and applied with remarkable success. Recently, also blood flow–based neuroimaging methods, such as functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS), have been explored in this context.

After reviewing recent literature on the development of especially hemodynamically based BCIs, we introduce a highly reliable and easy-to-apply communication procedure that enables untrained participants to motor-independently and relatively effortlessly answer multiple-choice questions based on intentionally generated single-trial fMRI signals that can be decoded online. Our technique takes advantage of the participants' capability to voluntarily influence certain spatio-temporal aspects of the blood oxygenation level–dependent (BOLD) signal: source location (by using different mental tasks), signal onset and offset. We show that healthy participants are capable of hemodynamically encoding at least four distinct information units on a single-trial level without extensive pretraining and with little effort. Moreover, real-time data analysis based on simple multi-filter correlations allows for automated answer decoding with a high accuracy (94.9%) demonstrating the robustness of the presented method. Following our 'proof of concept', the next step will involve clinical trials with LIS patients, undertaken in close collaboration with their relatives and caretakers in order to elaborate individually tailored communication protocols.

*Corresponding author.
Tel.: +31 (0) 43 388 2177; Fax: +31 (0) 43 388 4125;
E-mail: b.sorger@maastrichtuniversity.nl

DOI: 10.1016/S0079-6123(09)17719-1

As our procedure can be easily transferred to MRI-equipped clinical sites, it may constitute a simple and effective possibility for online detection of residual consciousness and for LIS patients to communicate basic thoughts and needs in case no other alternative communication means are available (yet) — especially in the acute phase of the LIS. Future research may focus on further increasing the efficiency and accuracy of fMRI-based BCIs by implementing sophisticated data analysis methods (e.g., multivariate and independent component analysis) and neurofeedback training techniques. Finally, the presented BCI approach could be transferred to portable fNIRS systems as only this would enable hemodynamically based communication in daily life situations.

Keywords: 'locked-in' syndrome; motor disability; communication; consciousness; neurorehabilitation; clinical neuroscience; brain–computer interface; real-time functional magnetic resonance imaging; online data analysis; mental imagery

Introduction

The 'locked-in' syndrome (LIS) constitutes a medical condition in which patients suffer from an almost complete motor de-efferentiation leading to quadriparesis or quadriplegia and anarthria (Plum and Posner, 1966). However, cognitive, sensory, and emotional functions can be widely preserved (e.g., Schnakers et al., 2008). Consequently and most characteristically, LIS patients are unable to communicate naturally but are fully awake and conscious.

The acute LIS is most commonly caused by stroke, more precisely by small circumscribed bilateral ventro-pontine lesions in the brainstem. Other potential causes are various neurological diseases, such as infections (e.g., encephalitis), central pontine myelinolysis, or dysequilibrated states like hypo- or hyperglycemia (Gosseries et al., 2008; Leon-Carrion et al., 2002). A slowly developing LIS is found in the context of progressive motor neuron diseases, such as amyotrophic lateral sclerosis (ALS) (Birbaumer et al., 1999; Bruno et al., 2008).

The prevalence of the LIS is difficult to establish considering the probably high number of unregistered cases caused by the challenging diagnostics. However, the prevalence is estimated to lie around 0.7 or 0.8 per 100,000 inhabitants in Western countries. In 2008, the *French Association for the* '*Locked-in*' *Syndrome* (ALIS) counted about 490 LIS patients in France since its foundation in 1997 (La lettre d'ALIS, August 2008). In Western countries, the yearly incidence of ALS cases is about two persons out of 100,000 (Wijesekera and Leigh, 2009).

Three LIS subtypes have been defined (Bauer et al., 1979): (1) the so-called *incomplete* LIS, in which voluntary movements are still possible to a small extent, (2) the *classical* LIS, in which the whole body is immobile except for eye blinking and small vertical eye movements, and finally, (3) the *complete* (or *total*) LIS, in which patients are completely unable to voluntarily move any part of their body. The patient's inability to communicate naturally poses serious problems, especially in terms of diagnostics and treatment as detailed below.

Diagnostic of the LIS

Misdiagnosis of the LIS as vegetative state or as minimally conscious state occurs frequently, especially during the first months after brain injury onset (Leon-Carrion et al., 2002). Studies report percentages of up to 40% of erroneous diagnoses (Majerus et al., 2005). Interestingly, in most cases (55%) the first signs of consciousness in LIS patients are detected by family members and not by treating physicians (Leon-Carrion et al., 2002). Therefore, it remains a great challenge to reliably assess the patient's residual state of consciousness and therewith to diagnose a LIS immediately following acute stroke or traumatic brain injury. Functional neuroimaging can provide information on the presence, degree, and location of residual brain function in patients with severe brain damage (Laureys et al., 2004) and may thus play

a key role in detecting consciousness. Recently, Owen and colleagues successfully used functional magnetic resonance imaging (fMRI) to assess residual brain activation associated with preserved cognitive function. Through letting the patient — initially diagnosed with vegetative state — perform mental imagery tasks (e.g., imagining playing tennis), preserved conscious awareness could be demonstrated by revealing brain activation that unmistakably resulted from the patient's cooperation (Owen et al., 2006).

Patient care and treatment

In patients with *incomplete* or *classical* LIS, residual control over small (mostly eye) movements can enable social interactions (Laureys et al., 2005). Of course, these remaining capabilities are very limited but at least they allow for basic communication. However, the *complete* LIS prevents even this rudimentary form of communication. A complete inability to communicate can result in serious psychological, practical, and ethical problems. For example, as communication is a basic human need, the unavoidable social isolation associated with the *complete* LIS can reduce the quality of life to an unacceptable degree and result in depression. Note that for the patient's relatives and caretakers, the situation can constitute a tremendous burden as well. The inability to express thoughts, feelings, and desires also impedes individualized patient care and treatment, and can leave ethical issues unresolved. The development of alternative muscle-independent communication means constitutes a possibility to cope with these two main problems and is thus of great importance. Such devices can be realized via brain–computer interfaces (BCIs). A BCI is a system that 'translates' an individual's thoughts via brain signals into commands to control or communicate via computer or electromechanical hardware. It therewith establishes a direct connection between thoughts and the external world in the absence of motor output (Kubler and Neumann, 2005).

In this article, we first review recent BCI research relevant for the development of alternative communication devices under particular consideration of techniques based on hemodynamic brain signals. Moreover, we present a novel method for answering multiple-choice questions that exploits intentionally generated single-trial blood oxygenation level–dependent (BOLD) responses and real-time fMRI. Finally, we indicate potential clinical applications for the diagnosis and treatment of noncommunicative patients and promising paths for future research in the field of hemodynamically based BCI development.

Brain–computer interfaces for severely motor-disabled patients

BCI techniques rely on either electrophysiologic (neuroelectric) or hemodynamic brain signals. Figure 1 provides an overview of currently available and potential techniques. Effective BCI-based communication or device control in severely motor-disabled patients has been demonstrated using:

1. electroencephalography (EEG) employing slow cortical potentials (Birbaumer et al., 1999; Karim et al., 2006; Kubler et al., 1999), brain oscillations (Pfurtscheller et al., 2000), or event-related potentials (Nijboer et al., 2008),
2. intracortical recordings (ICoR) using ensemble spiking activity (Hochberg et al., 2006), and
3. magnetoencephalography (MEG) through volitional modulation of micro-rhythm amplitudes (Buch et al., 2008).

Other functional brain imaging techniques, namely electrocorticography (ECoG) (Felton et al., 2007; Leuthardt et al., 2006; Ramsey et al., 2006; Scherer et al., 2003) and blood flow-based methods, such as fMRI (Lee et al., 2009b; Weiskopf et al., 2003; Yoo et al., 2004) and functional near-infrared spectroscopy (fNIRS) (Coyle et al., 2004; Naito et al., 2007; Sitaram et al., 2007b), also show potential for communication and device control in motor-disabled patients.

In the following, we will focus our review on hemodynamically based BCI research [for electrophysiological BCI techniques see other reviews

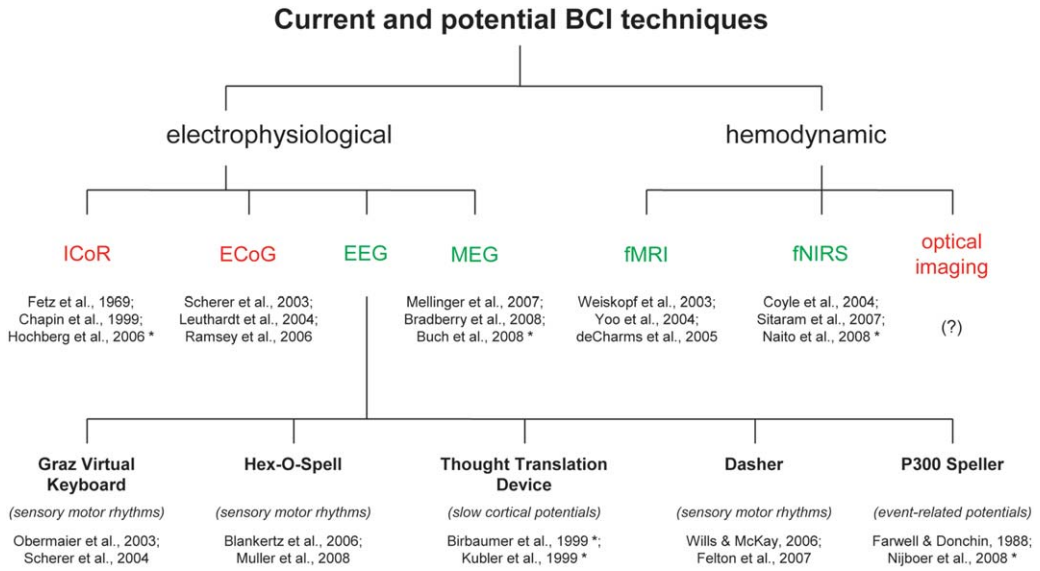


Fig. 1. Classification of current and potential BCI techniques. The figure provides an overview of both already available and currently explored BCI techniques classified according to the specific nature of the signal they are based on. Moreover, relevant references of pioneering research are quoted. Since EEG-based communication devices have played a prominent role so far, the most commonly known speller interfaces and the particular brain measure they rely on are shown at the lowest branch. Remarks: References marked with "*" indicate clinical studies in motor-disabled patients. Non-invasive methods are underlined (green in the web version) and invasive methods are not underlined (red in the web version).

(Allison et al., 2007; Birbaumer and Cohen, 2007; Birbaumer et al., 2008; Lebedev and Nicolelis, 2006; Schwartz et al., 2006)]. Hemodynamically based brain imaging modalities (fMRI, fNIRS or invasive optical imaging) exploit the physiological fact that neural activity in a certain brain region results in an increased local blood flow and metabolic changes (hemodynamics). Therefore, these methods provide relatively indirect measures of brain activation.

To our knowledge, invasive optical imaging has not been explored in the context of BCI research yet, but this might be promising given its high spatio-temporal resolution in the order of a few microns and milliseconds (Vanzetta, 2006). Most hemodynamic BCI studies have actually used fMRI. This imaging technique has developed at a breathtaking pace, especially during the last ten years. Recent advances, e.g., in computational power, data acquisition and analysis techniques, gave rise to a variety of potential real-time fMRI applications for research and clinical use (Bagarinao et al., 2006).

fMRI-based BCI research

Besides research that has explicitly dealt with the development of fMRI-based BCI techniques for communication and control purposes (see below), there is another stream of BCI research — focusing on neurofeedback training effects and exploiting fMRI-based BCI as a tool for neuroscientific research and treatment (deCharms, 2007, 2008; Sitaram et al., 2007a; Weiskopf et al., 2004b, 2007), e.g., to learn more about and enhance cognitive functioning in healthy humans (e.g., Rota et al., 2009; Scharnowski et al., 2004). Moreover, fMRI-based neurofeedback training may help to understand and ultimately treat certain pathological conditions as recently shown by deCharms et al. (2005): Chronic pain patients were trained to control BOLD activation in the rostral anterior cingulate cortex — a region putatively involved in pain perception and regulation — and reported accordant decreases in the ongoing level of chronic pain. Further clinical applications are conceivable (see e.g., Birbaumer et al., 2006).

One major goal in BCI research focusing on the development of alternative communication and control means is to increase the number of different commands that can be generated by the BCI user (e.g., a LIS patient), measured by the applied brain imaging method, and 'interpreted' (decoded) by the BCI system as this would increase communication efficiency. Since human brain functions can be spatially localized and fMRI provides relatively high spatial resolution (i.e., the source location of the measured signal can be determined quite well), this method provides a great opportunity to increase the degrees of freedom in BCI applications: Separate commands can be encoded by employing different cognitive brain functions. Since different cognitive states evoke spatially different brain activation patterns and fMRI techniques can disentangle these, the original intention of the encoder can be derived.

This possibility was tested by Yoo et al. (2004) in a pioneering study: They asked participants to perform four different mental tasks ('right hand motor imagery', 'left hand motor imagery', 'mental calculation', and 'inner speech') that evoke differential brain activation in four distinct brain locations and were interpreted as predetermined BCI commands (''right,'' ''left,'' ''up,'' and ''down''). This allowed the participants to navigate through a simple two-dimensional (2D) maze by solely using their thoughts. Each movement command (e.g., ''up'') was based on the average of three separate (e.g., 'mental calculation') trials and took 2 min and 15 s. Only recently, this research group demonstrated that it is also possible to control 2D movements of a robotic arm by using the same principles (Lee et al., 2009b). A similar approach was followed by another research group (Monti et al., 2008): Participants were asked autobiographical questions that they answered with ''yes'' or ''no'' by generating two different mental states ('motor imagery' and 'spatial navigation'). Based on multiple trials, the experimenters were able to infer the answers of 16 participants with 100% accuracy by the end of each 5 min-run.

Our research group has tested another approach, namely utilizing the fMRI signal amplitude to encode discrete information units. By using real-time fMRI-based neurofeedback, participants were able to differentially adjust regional brain activation to three different target levels (''low,'' ''middle,'' and ''high'') within one fMRI session (Sorger et al., 2004). In a later study, extending the training to four fMRI sessions, a differentiation of four levels was possible when averaging across all sessions (Dahmen et al., 2008). Finally, we could show that participants can play an analog of the computer game 'pong' just by using their differentially generated brain signal level (Goebel et al., 2004, 2005). Note that this approach relied on single-trial responses for coding one command which is of course much more desirable for BCI applications. During the last years, our research group has further focused on the possibility to increase the degrees of freedom that can be coded by a single cognitive event. In a later section, we will propose a new fMRI-based BCI communication technique that works on the single-trial level.

fNIRS-based BCI research

fNIRS offers a noninvasive, safe, potentially portable, and relatively inexpensive possibility to indirectly measure brain activity (Irani et al., 2007; Villringer and Chance, 1997). Its suitability for BCI applications has been demonstrated by several studies using multi-channel systems (Luu and Chau, 2009; Sitaram et al., 2007b). However, the results of the study by Naito et al. (2007) using a single-channel fNIRS system are of particular importance — showing that for about 40% of the 17 tested patients in a *complete* LIS state, voluntary control via performing different mental tasks was possible (coding ''yes'' and ''no'' answers with 80% accuracy). Before that, no other kind of BCI had been successfully applied to this patient group.

Answering multiple-choice questions based on single-trial BOLD responses

Based on previous research reviewed above, we have developed a novel information encoding

technique that allows to further increase the number of distinct information units transmitted. Next to the advantageous high spatial resolution of fMRI, we exploited the fact that the signal-to-noise ratio in fMRI time courses is sufficiently high to reliably detect BOLD signal onsets and offsets on a single-trial level. This led us to the hypothesis that a systematic variation of temporal aspects of executing a mental task would result in differentiable dynamic BOLD activation patterns, which might be exploited to encode distinctive BCI commands — even using only one mental task. To test our hypothesis, we performed a real-time fMRI communication experiment in which participants motor-independently answered multiple-choice questions based on intentionally generated single-trial BOLD responses. Figure 2 shows the encoding parameters that we used for generating differential BOLD responses necessary to answer multiple-choice questions with four response options in a reasonable timeframe (1 min). The parameters were chosen in such a way that each of the expected BOLD responses differed with respect to at least two of three influenceable BOLD signal aspects (*source location*, *onset*, *offset*). Furthermore, given the sluggishness and

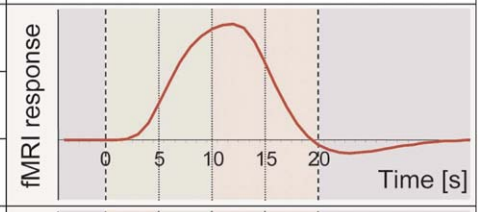
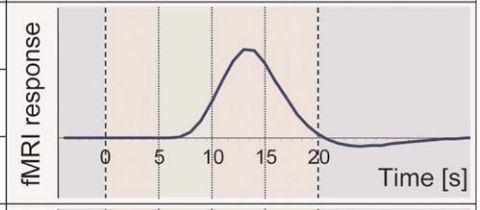
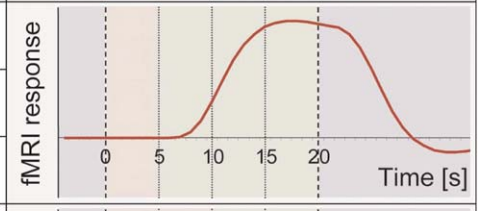
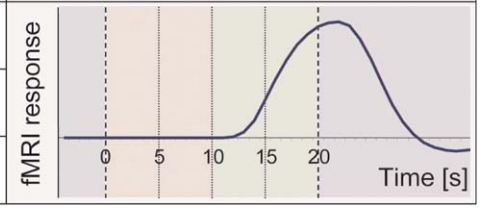
response option	encoding parameters		expected single-trial time courses
A	mental task	motor imagery	
	onset	0s	
	offset	10s	
B	mental task	mental calculation	
	onset	5s	
	offset	10s	
C	mental task	motor imagery	
	onset	5s	
	offset	20s	
D	mental task	mental calculation	
	onset	10s	
	offset	20s	

Fig. 2. Answer coding scheme. The figure displays the particular parameters (columns 2/3) assigned for coding the four different answer options (column 1) used by participant 7. Schematic single-trial time courses for coding the four different answer options are shown in order to illustrate their expected temporal differences (curves in column 4). Remarks: Gray-shaded areas (red-shaded in web version) in column 4 represent phases in which the participant does not perform any mental task; brighter areas (green-shaded in web version) respectively represent active encoding phases within the general answer encoding period (0–20 s).

therewith the temporal limits of the BOLD response (Menon and Kim, 1999), we expected that varying the temporal encoding parameters in steps of 5 s would still result in clearly distinguishable fMRI responses (see Fig. 2).

Materials and methods

General procedure of the study

At first, a 'localizer experiment' was performed in order to determine brain regions (regions-of-interest; ROIs) that were differentially engaged in the performance of three mental tasks ('motor imagery', 'mental calculation', and 'inner speech') and showed clear and consistent task-related BOLD signal changes. Later, fMRI activation time courses derived from two of these three ROIs were used for deciphering the participants' answers (see section *Real-time data analysis*). Then, questions (that could be generally answered by all participants and of which the answer was unknown to the experimenters) and possible multiple-choice answers were visually presented to the volunteers (see Table 1 and Fig. 3).

Participants were asked to select a response option and encode the corresponding letter (A, B, C, or D) by performing a certain mental task in a specific time window (see Fig. 2). The encoding process was facilitated by a convenient dynamic display that fully guided the answer encoding. To encode a particular answer option, participants only had to visually attend to the corresponding letter and perform the designated mental task as long as the letter was highlighted in the display (see Fig. 4).

Immediately after answer encoding, an automated decoding procedure deciphered the answer by analyzing the generated single-trial BOLD responses online (see below).

Table 1. Questions and multiple-choice answers provided to the participants (selection)

Question	A	B	C	D
Which color do you like most?	Red	Blue	Green	Black
Which animal do you like best?	Cat	Dog	Bird	Horse
Which fruit do you like most?	Pear	Apple	Orange	Banana
Do you have children?	None	A son	A daughter	More children
How did you get to work today?	Walk	Car	Public transport	(motor-) Bike
What music style do you like?	Punk	Jazz	Classical music	Pop/rock
Which TV genre do you prefer?	News	Sport	Movies	Documentary
What do you prefer to drink?	Tea	Coffee	Milk	Soft drink

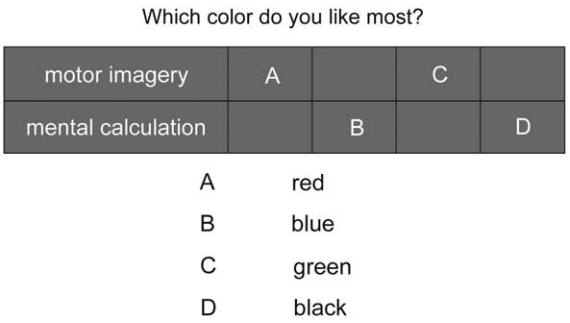


Fig. 3. Multiple-choice question and appropriate answer options. This figure demonstrates an example display presented to the participant immediately before scanning to initiate answer encoding. A multiple-choice question and four appropriate answer possibilities were visually presented.

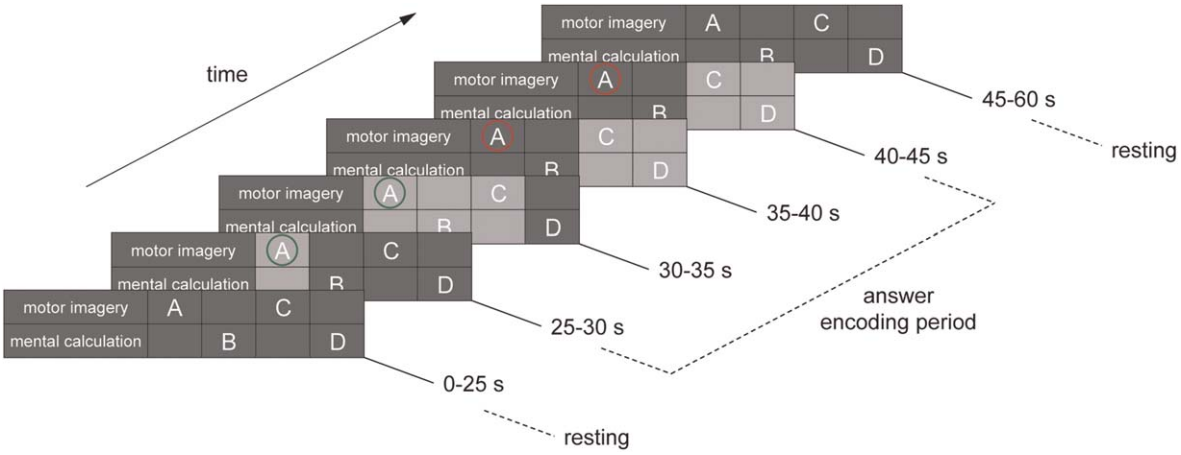


Fig. 4. Answer encoding display with time-line. The dynamic display consists of a sequence of monochrome images. Participants are asked to attend to the letter corresponding with their selected answer and to perform the particular mental task assigned to the respective row (indicated in the first column of each window) as long as the accordant letter cell is highlighted by the moving light gray bar. In order to encode, e.g., answer ''A'', the participant focuses on letter ''A''. During the initial resting period (25 s), no mental task has to be performed. When the ''A'' cell gets highlighted, the participant immediately starts performing 'motor imagery' and stops as soon as the letter cell is no longer highlighted (after 10 s in this example). Finally, the participant keeps focusing on letter ''A'' for 25 s until the whole functional mini-run has ended. Remark: Circles were not visible for participants; they are additionally inserted in order to emphasize active (white; green in web version) and passive (gray; red in web version) answer encoding phases within the general answer encoding period when encoding answer ''A''.

Participants

Eight healthy volunteers (age: 28.4 ± 7.2 years [mean ± 1 s.d.]; two males) with normal or corrected-to-normal vision participated in the fMRI study. Table 2 documents relevant participants' characteristics. All participants were right-handed as evaluated by the *Edinburgh Handedness Inventory* (Oldfield, 1971). Note that five volunteers had no or very little fMRI experience. The participants gave their written informed consent prior to the fMRI experiment that was conducted in conformity to the Declaration of Helsinki and approved by the local Ethics Committee of the Faculty of Psychology and Neuroscience at Maastricht University.

Preparation

Before starting the fMRI experiment, the participants were introduced to the general procedure and logic of the study. Moreover, the experimenters shortly explained how to perform the different mental tasks and the use of the answer encoding display. The participants practiced the mental tasks performance and answer encoding for about 10 min. Participants were instructed to suppress any movements (including lip and tongue movements) while being scanned.

fMRI experiments

'Localizer experiment'. The 'localizer experiment' consisted of one functional run. Participants were instructed to perform the three mental tasks via visually presented gray letter strings on black background (e.g., ''motor imagery''). Each mental task had to be performed nine times (three times for 5, 10, and 15 s). The experimental blocks appeared in pseudorandom order separated by baseline periods of 20 s (indicated by ''resting''). Participants were asked to pay attention to the instructions and to perform the respective mental task as long as it was indicated.

Table 2. Participants' characteristics and ROI specifications

Participant	Age (years)	Previous fMRI sessions	Mental task selected	Regions selected	Talairach coordinates		
					x	*y*	*z*
1	31	0	Motor imagery	IPS	−37	−39	32
			Inner speech	PreCG/preCS (ventrPM)	−52	−7	41
2	22	1	Motor imagery	PreCG/preCS (dorsPM)	−20	−9	65
			Inner speech	STS	−58	−29	1
3	24	0	Motor imagery	PreCG/preCS (dorsPM)	−28	−7	50
			Inner speech	STS	−56	−24	5
4	21	1	Motor imagery	SPL	−34	−55	57
			Inner speech	PreCG/preCS (ventrPM)	−50	−8	42
5	39	0	Motor imagery	IPS	−27	−56	50
			Inner speech	PostSTG/SMG	−53	−27	12
6	25	5	Motor imagery	SPL	−37	−47	54
			Inner speech	STS/STG	−55	−33	7
7	26	5	Motor imagery	PreCG/preCS	−26	−18	45
			Mental calculation	MFG/IFS	−45	19	26
8	39	10	Motor imagery	PreCG/preCS (dorsPM)	−31	−11	51
			Inner speech	Med-post SFG (SMA)	−1	−7	62

Remarks/abbreviations: participants 5 and 8, males; CG, central gyrus; CS, central sulcus; dors, dorsal; IFS, inferior frontal sulcus; inf, inferior; IPS, intraparietal sulcus; med-post, medio-posterior; MFG, middle frontal gyrus; post, posterior; PM, premotor area; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; STS, superior temporal sulcus; ventr, ventral.

Pretraining during the acquisition of the anatomical data set. During acquisition of the three-dimensional (3D) anatomical data set, participants were provided with the answer encoding display and asked to further practice answer encoding. In the meantime, experimenters analyzed the data of the 'localizer experiment' using Turbo-BrainVoyager (Version 2.6; Brain Innovation, Maastricht, The Netherlands) that was employed for online data analysis throughout the whole fMRI session.

'Communication experiment'. After the anatomical scan had been obtained, a question and four appropriate answer possibilities (A–D) were visually presented to the participant (see Fig. 3 for an example trial). Participants were asked to encode their answers using the encoding display while functional images were collected. Each communication trial took 60 s. During answer encoding, the functional data were analyzed in real time (see below). Following automated answer decoding, an experimenter auditorily informed the participant via the intercom system about the decoding result (supposed answer). Participants performed at least four different answer encoding trials. Some participants volunteered to run more (up to seven) cycles. Each MRI session lasted approximately 45 min. Following scanning, the participants filled in a questionnaire to verify the encoded answers.

Stimulus presentation in the scanner

Visual stimuli were generated by a personal computer and were projected onto a frosted screen located at the end of the scanner bore (at the side of the participant's head) with a liquid crystal display projector (PLC-XT11, Sanyo North America Corporation, San Diego, USA) and

presented in the center of the visual field. Participants viewed the screen via a mirror mounted onto the head coil at an angle of $\sim 45^{\circ}$.

MRI data acquisition

Images were acquired using a commercial head scanner with a magnetic field strength of 3 T (Siemens Allegra, Siemens AG, Erlangen, Germany) and equipped with a standard quadrature birdcage head coil. The participants were placed comfortably in the scanner and their head was fixated with foam padding to minimize spontaneous or task-related motion.

Functional measurements. Repeated single-shot echo-planar imaging (EPI) was performed using the BOLD effect as an indirect marker of local neuronal activity (Ogawa et al., 1990). Except for the number of acquisitions ('localizer experiment': 835 volumes; 'communication experiment': 60 volumes) identical scanning parameters were used during both experimental steps resulting in almost whole brain coverage (repetition time [TR] = 1000 ms, echo time [TE] = 30 ms, flip angle [FA] = 90°, field of view [FOV] = 224 × 224 mm^2, matrix size = 64 × 64, number of slices = 34, slice thickness = 3.5 mm, no gap, slice order = ascending/interleaved). Functional images were reconstructed and written to the scanner console's hard disk in real time using a custom-made image export running on the image reconstruction computer (Weiskopf et al., 2004a, 2005) (implemented in Siemens ICE VA30). The real-time data analysis software (see below) running on a separate PC retrieved the image files via a local area network and a Windows drive map as soon as they were created by the image reconstruction system.

Anatomical measurements. For each participant, a 3D T1-weighted data set encompassing the whole brain was acquired following the 'localizer experiment' (scan parameters: TR = 2250 ms, TE = 2.6 ms, FA = 9°, FOV = 256 × 256 mm^2, matrix size = 256 × 256, number of slices = 192, slice thickness = 1 mm, no gap, total scan time = 8 min and 26 s). Parameters of this anatomical MRI sequence were based on the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Real-time data analysis

Online analysis of the 'localizer experiment'. The first five volumes of each functional run were skipped to account for their stronger T1 saturation. Then, the functional time series were preprocessed (online intra-session motion correction, linear trend removal, temporal high-pass filtering [cut-off: seven cycles/time course]).

Three ROIs (one for each mental task) were functionally determined (see Table 2) for each participant by performing regression analysis based on a general linear model and using predictors corresponding to the particular mental task conditions. More precisely, potential regions were initially identified by comparing the hemodynamic responses during the different mental task conditions (separately) to the activation in the resting condition (e.g., 'motor imagery' vs. 'resting'). Although not mandatory in the current context, all applied contrasts were significant at $p < 0.05$ (one-tailed, Bonferroni-corrected).

During ROI selection, the following ROI definition criteria were applied:

1. The ROI should show a clear mental task 'preference'[1] for the particular task it is selected for (i.e., pronounced BOLD signal level differences between the three mental task conditions).
2. The ROI time courses should demonstrate a reliable, robust, and typical hemodynamic response shape (low noise level, high signal-to-noise ratio, high onset and offset

[1] Usage of the expression mental task-'preference' instead of mental task-'specificity' was intended to indicate that in most cases the selected ROIs also showed a clear BOLD response during the performance of the other two mental tasks. Therefore, the ROIs did not exclusively respond to any of the mental tasks. Moreover, the expression mental task-'sensitivity' seems to be inappropriate also as this would not stress that ROI selection was focused on regions ideally demonstrating a stronger response for the particular mental task compared to the other two mental tasks.

sensitivity) and a high % BOLD signal amplitude relative to baseline.
3. The ROI should comprise four contiguous voxels within a single fMRI slice.

The two ROIs that fulfilled these criteria the most were chosen as regions for feeding the automated answer decoder (see below).

Online analysis of the 'communication experiment' data. The answer coding procedure was based on the combination of two mental tasks and certain temporal aspects of their execution. In order to describe the temporal parameters of the different BOLD response shapes expected, four (two for each ROI) standard reference time courses (RTCs) derived from the two gamma response function (Friston et al., 1998) were generated (see Fig. 2). Each of the four RTCs consisted of 40 time points encompassing five data points before the general encoding onset, the 20 data points of the whole answer encoding period, and 15 data points following the general encoding offset (see Figs. 2 and 5).

The automated answer decoding procedure was applied to online motion-corrected time series. As soon as the sequential measurements were available, the respective time courses of the two selected ROIs were extracted and normalized to % BOLD signal change values using as baseline the mean of the five last data point values of the preceding resting period. In order to decode the participants' answers, the two extracted ROI time courses were separately correlated with the four modeled RTCs that were relevant for the particular ROI (see above) resulting in four correlation values representing the goodness of fit between the empirical data and the used model responses. These and the corresponding answer choices were displayed to the experimenters in ranked order.

Offline data analysis

Post hoc analysis of the individual anatomical and functional data sets was performed using BrainVoyager QX (Version 1.10; Brain Innovation, Maastricht, The Netherlands). This additional analysis primarily served for determining the Talairach coordinates of the selected ROIs, thus enabling the comparison between participants and to previous fMRI studies. All anatomical and functional volumes as well as the ROIs were spatially transferred to Talairach space (Talairach and Tournoux, 1988).

Results

'Localizer experiment' (ROI selection)

The individually selected ROIs considerably differed across participants in terms of location (see Table 2). Except for participant 7, 'motor imagery' and 'inner speech' were chosen as mental tasks to be used in the 'communication experiment' as the corresponding ROIs had proven to be most promising with respect to the above-mentioned ROI definition criteria. The anatomical descriptions of the selected regions and their Talairach coordinates are provided in Table 2.

'Communication experiment' (online answer decoding accuracy)

Participants' answers were correctly decoded in 37 out of 39 answer encoding trials resulting in a mean accuracy of 94.9% (see Table 3). Thus, for six participants (75%) the decoding accuracy was 100% and also for the two remaining participants, the decoding accuracy was clearly above chance level (85.7 and 75%; chance level: 25%). Figure 5 shows answer encoding data for a representative trial demonstrating the robustness of the extracted single-trial fMRI time courses.

Results of the post hoc analysis

In order to disclose potential reasons for the two decoding errors that occurred, we explored all obtained data related to these two trials (online motion correction parameters, ROI time courses, and answer decoding values). The decoding error of participant 6 was very likely caused by severe

Table 3. Online answer decoding results

Participant	Trial	Encoded answer	Answer decoding choices (correlation coefficients in brackets)					Accuracy (%)
			1st	2nd	3rd	4th	1st–2nd	
1	1	A	A (0.84)	C (0.30)	B (−0.09)	D (−0.52)	0.54	100
	2	D	D (0.70)	C (0.22)	A (0.15)	B (−0.03)	0.48	
	3	C	C (0.72)	A (0.63)	D (0.50)	B (0.41)	0.11	
	4	A	A (0.69)	B (0.25)	C (0.03)	D (−0.56)	0.44	
2	1	C	C (0.68)	A (0.37)	D (0.01)	B (−0.17)	0.31	100
	2	B	B (0.45)	D (0.24)	A (0.17)	C (−0.10)	0.21	
	3	A	A (0.81)	C (0.20)	D (−0.05)	B (−0.17)	0.61	
	4	D	D (0.62)	B (−0.02)	C (−0.15)	A (−0.32)	0.64	
3	1	C	C (0.83)	A (0.30)	D (0.18)	B (0.11)	0.53	100
	2	D	D (0.63)	B (0.25)	C (0.18)	A (0.17)	0.38	
	3	A	A (0.46)	C (0.11)	D (0.00)	B (−0.02)	0.35	
	4	C	C (0.67)	D (0.52)	B (0.05)	A (0.23)	0.15	
	5	D	D (0.60)	B (0.50)	C (0.35)	A (0.26)	0.10	
4	1	C	C (0.71)	A (0.38)	D (0.36)	B (−0.06)	0.33	100
	2	D	D (0.82)	C (0.37)	B (0.22)	A (0.18)	0.45	
	3	C	C (0.72)	D (0.49)	A (0.43)	B (−0.32)	0.23	
	4	D	D (0.81)	C (0.31)	A (0.14)	B (0.10)	0.50	
	5	B	B (0.71)	C (0.36)	A (−0.03)	D (−0.08)	0.35	
5	1	D	D (0.78)	C (0.51)	A (0.19)	B (0.06)	0.27	85.7
	2	D	D (0.76)	A (0.74)	C (0.49)	B (0.21)	0.02	
	3	A[a]	D (0.06)	B (−0.04)	A (−0.06)	C (−0.15)	0.10	
	4	C	C (0.59)	D (0.38)	A (0.28)	B (0.19)	0.21	
	5	B	B (0.82)	A (0.81)	C (0.39)	D (−0.13)	0.01	
	6	D	D (0.83)	A (0.72)	C (0.37)	B (0.24)	0.11	
	7	B	B (0.79)	A (0.72)	C (0.17)	D (−0.09)	0.07	
6	1	C	C (0.81)	B (0.24)	A (0.23)	D (0.11)	0.57	75
	2	B	B (0.20)	D (−0.15)	A (−0.31)	C (−0.44)	0.35	
	3	D	D (0.56)	A (0.21)	B (0.14)	C (0.06)	0.35	
	4	A[a]	C (0.18)	B (0.11)	D (0.00)	A (−0.15)	0.07	
7	1	A	A (0.89)	B (0.52)	C (0.06)	D (−0.20)	0.37	100
	2	A	A (0.81)	C (0.05)	D (−0.02)	B (−0.08)	0.76	
	3	B	B (0.59)	A (0.20)	D (−0.17)	C (−0.24)	0.39	
	4	C	C (0.82)	A (0.43)	D (0.41)	B (0.15)	0.39	
	5	B	B (0.58)	A (0.40)	C (0.09)	D (0.48)	0.18	
8	1	B	B (0.66)	A (0.60)	C (−0.07)	D (−0.21)	0.06	100
	2	C	C (0.89)	D (0.82)	B (0.37)	A (0.26)	0.07	
	3	D	D (0.74)	A (0.45)	B (0.23)	C (−0.13)	0.29	
	4	A	A (0.69)	B (0.63)	C (0.18)	D (0.11)	0.06	
	5	D	D (0.81)	A (0.62)	B (0.13)	C (0.12)	0.19	
Group								94.9

[a]Misclassified answer trials.

head motion that could not be corrected successfully by the online motion correction procedure. Using BrainVoyager QX post hoc, a more advanced motion correction procedure successfully coped with the head motion, in the end leading to the correct decoding of the given answer. When looking at the answer decoding value of the third trial of participant 5 ($r = 0.06$), it becomes clear that this value is extremely small (especially compared to the corresponding values of all other trials of this participant; $r = 0.76 \pm 0.09$ [mean ± 1 s.d.]) — and in this sense constitutes an outlier that led to a misclassification. Thus, we assume that in this case the participant made an encoding error.

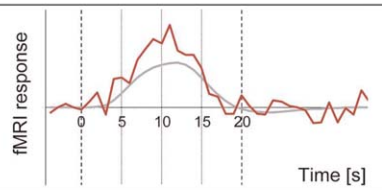
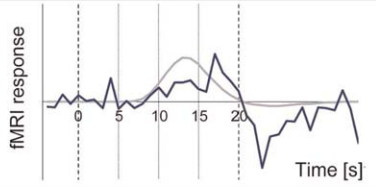
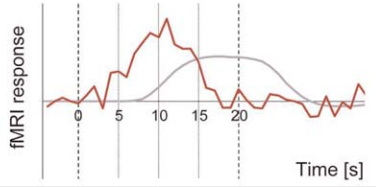
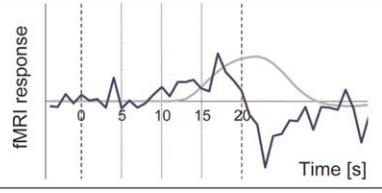
response option	encoding parameters		single-trial time courses and RTCs	ranking (correlation)
A	brain location	'motor imagery' ROI		1st (0.89)
	onset	0s		
	offset	10s		
B	brain location	'mental calculation' ROI		2nd (0.52)
	onset	5s		
	offset	10s		
C	brain location	'motor imagery' ROI		3rd (0.06)
	onset	5s		
	offset	15s		
D	brain location	'mental calculation' ROI		4th (-0.20)
	onset	10s		
	offset	20s		

Fig. 5. Single-trial ROI time courses and corresponding RTCs. The figure provides the particular parameters used for coding the four different answer options. Moreover, single-trial time courses (black curves; red and blue curves in web version) generated by participant 7 during encoding of the answer option "A" are shown separately for the 'motor imagery' (rows 1 and 3) and the 'mental calculation' ROI (rows 2 and 4). Additionally, the RTCs corresponding to each answer option are displayed within the time course plots (gray curves) to demonstrate the close match of the data encoding the answer "A" with the particular RTC. The final column indicates the resulting correlation values and the automated ranking of the answer options according to their probability. Remarks: dashed vertical lines signify onsets and offsets of the general encoding periods; only time course segments relevant for decoding are shown (first 20 volumes skipped).

Discussion

The present research shows that by using appropriate experimental designs, participants are able to reliably generate differentiable fMRI brain signals that can be used to encode at least four distinct information units on a single-trial basis and in a reasonable amount of time, e.g., in order to motor-independently answer multiple-choice questions. The participants' answers were successfully extracted in 94.9% of the cases (chance level: 25%). Note that this high decoding accuracy was achieved in untrained volunteers of whom three had not participated in any fMRI study beforehand, i.e., prior fMRI experience was not mandatory for successful participation. All these facts argue for the robustness of the suggested procedure.

In our study, real-time fMRI data analysis allowed for online decoding of a chosen answer, opening the possibility for back-and-forth communication within a single fMRI session. Note, however, that our encoding technique can be beneficial even when real-time facilities (in terms of data throughput and analysis) are not (yet) available. Offline decoded answers might still be

of great importance. Moreover, a post hoc data analysis could result in additional gains in accuracy and might be advisable anyway, especially when the patient's answers would have a substantial impact on decisions, e.g., with respect to patient care. Another advantage of our method is that it requires very little effort and preparation time. Note also that the 'localizer experiment' needs to be conducted only once: The ROIs of the first fMRI session can be simply imported and used for communication experiments in later sessions.

Our study constitutes a 'proof of concept' working with nonclinical participants who mimicked the LIS patients' limited behavioral capabilities by exclusively using thought processes for communication. Next, clinical trials in LIS patients are needed.

Potential clinical applications for patients with severe motor disabilities

By reviewing the relevant literature and presenting a novel effective encoding technique we could show that using fMRI-based BCIs constitutes a promising approach for the development of alternative communication and control tools for motor-disabled patients. Therewith, this direction considerably enriches the spectrum of already available non-fMRI-based BCI techniques (Birbaumer et al., 2008). Since each brain imaging method has its strengths and weaknesses, patients may differently benefit from one or the other technique. Thus, providing a method exploiting a complementary, namely *hemodynamic* (vs. electrophysiological) brain signal can have considerable merits. In the following, we will shortly discuss potential clinical applications.

Online detection of consciousness

It is conceivable that the available real-time fMRI methods are also suited for online detection of consciousness in nonresponsive patients following acute brain damage. This would further extend the approach developed by Owen et al. (2006) that relied on offline analyses. A short real-time fMRI experiment to assess consciousness might be performed in the context of standard (anatomical) MRI diagnostics and — if successful — could be followed by a back-and-forth communication procedure. Additionally, the proposed procedures could be exploited for a further refinement of the diagnostics, e.g., by adaptive testing of cognitive functions (Iversen et al., 2008).

Communication and control

The suggested method for answering multiple-choice questions based on fMRI signals might offer a simple and effective possibility for LIS patients to communicate basic thoughts and needs in case no other alternative communication means are available (yet). Thus, especially patients in the acute phase of the LIS may benefit: Since the introduced method is grounded on relatively basic experimental and statistical principles and MRI scanners constitute standard clinical equipment, the techniques are easy to apply and can be readily transferred to clinical sites. Basic communication in an early stage of the LIS could give patients confidence and may therefore prevent the development of depression and loss of general communication or cognitive abilities. In this context, an immediately usable communication approach as shown here to be feasible with real-time fMRI could serve as 'first-aid' intervention.

Promising paths for future hemodynamically based BCI developments

One principle goal in BCI research is to increase the number of correctly decoded information units within a certain time interval, thus improving the *efficiency* and *accuracy* of the BCI method. Moreover, a BCI system should be *patient-friendly*, *easy-to-handle*, and *flexible*. The current developmental state of BCIs exploiting hemodynamic brain signals leaves room for improvements in any of these respects. Therefore, we will, in the following sections, propose possible promising paths for future research in this field.

Increasing efficiency

Although gains in the efficiency and the accuracy of information transfer are more closely linked to, respectively, the encoding and decoding aspect of the discussed techniques, multiple interdependencies exist as, e.g., more sophisticated decoding methods can open up advanced possibilities for more efficient information encoding.

We think that the currently achieved degree of freedom in generating differential single-trial brain signals — that can be decoded online — can be significantly increased. For instance, more mental tasks and temporal variations of their execution can be included in the design, e.g., in order to encode single letters (Sorger et al., 2007). However, more sensitive decoding procedures have to be developed or implemented (see below) to reliably disentangle very similar but still distinctive brain activation patterns online. These more sophisticated methods in turn may contribute to the decrease of necessary encoding time. Another possibility to increase the communication efficacy is the implementation of adaptive procedures, like automatic word completion or the use of 'communication trees'.

Increasing accuracy

In order to improve decoding accuracy, it might be beneficial to follow a (coarse) multivariate approach by, e.g., selecting more than one region per mental task as this would most probably increase the robustness of the classification. However, this could result in a time-consuming ROI selection process that would need to be overcome by implementing automated ROI selection procedures. Additionally, it might be advantageous to use individually determined (vs. standard) reference time courses (Handwerker et al., 2004), especially in brain-damaged patients for whom the BOLD signal might differ from that of healthy humans. Moreover, the following more sophisticated data analysis techniques might be implemented:

1. real-time independent component analysis (Esposito et al., 2003), e.g., to automatically detect artifacts (caused by motion or undesired thought processes during encoding) and
2. real-time multivariate analysis techniques, such as real-time multi-voxel pattern analysis (LaConte et al., 2007), e.g., support vector machines (Lee et al., 2009a), that might help to increase the sensitivity to detect more subtle spatial differences of brain activation patterns.

Customizing

One important aspect in further developing fMRI-based BCI methods for communication and control would be the design of more patient-friendly procedures. This implicates that the particular communication procedures should be individually tailored for each participant and might involve the following aspects:

1. elaborating the individual degrees of freedom in generating differentiable brain signals for each participant resulting in patient-tailored communication protocols (ranging from two-class BCI based on multiple trials up to multi-class BCI based on a single-trial level),
2. improving BOLD signal quality, e.g., through training of general mental imagery abilities, meditation (Eskandari and Erfanian, 2008) or neurofeedback training (Hwang et al., 2009),
3. developing encoding aids based on nonvisual, e.g., auditory (Kubler et al., 2009; Nijboer et al., 2008) or tactile sensory modalities to allow for communication in case of impaired vision,
4. considering individual preferences and particular abilities of the patient (e.g., when choosing the mental tasks).

Mobility

Finally and maybe most importantly, the developed real-time fMRI-based methods should be transferred to portable high-density fNIRS systems allowing extending the use of hemodynamic brain signals for communication and control beyond clinical settings.

After overcoming the current challenges, hemodynamic BCI techniques might become beneficial even for patients in the *incomplete* and *classical* LIS state. Although these patient groups still do have some form of residual muscle control, BCIs based on the hemodynamic response (or any other BCI type) could constitute an alternative means of interaction, e.g., in situations of muscular fatigue. Moreover, it is conceivable that the suggested techniques may provide considerably more degrees of freedom and would therewith allow for more effective communication compared to other non-BCI-based solutions.

Abbreviations

BCI(s)	brain–computer interface(s)
BOLD	blood oxygenation level–dependent
ECoG	electrocorticography
EEG	electroencephalography
(f)MRI	(functional) magnetic resonance imaging
(f)NIRS	(functional) near-infrared spectroscopy
ICoR	intracortical recordings
LIS	'locked-in' syndrome
MEG	magnetoencephalography
ROI(s)	region(s)-of-interest
RTC(s)	reference time course(s)
2D	two-dimensional
3D	three-dimensional

Acknowledgements

The authors gratefully acknowledge the support of the BrainGain Smart Mix Programme of the Netherlands Ministry of Economic Affairs and the Netherlands Ministry of Education, Culture and Science. This research was also supported by the Fonds de la Recherche Scientifique (FRS), European Commission (DECODER, DISCOS, Mindbridge and COST), McDonnell Foundation and Mind Science Foundation. OG and AM are Research Fellow at FRS and SL is Senior Research Associate at FRS. Further, we would like to thank Lars Riecke for comments on the manuscript.

References

Allison, B. Z., Wolpaw, E. W., & Wolpaw, J. R. (2007). Brain-computer interface systems: Progress and prospects. *Expert Review of Medical Devices*, *4*, 463–474.

Bagarinao, E., Nakai, T., & Tanaka, Y. (2006). Real-time functional MRI: Development and emerging applications. *Magnetic Resonance in Medical Sciences*, *5*, 157–165.

Bauer, G., Gerstenbrand, F., & Rumpl, E. (1979). Varieties of the locked-in syndrome. *Journal of Neurology*, *221*, 77–91.

Birbaumer, N., & Cohen, L. G. (2007). Brain-computer interfaces: Communication and restoration of movement in paralysis. *The Journal of Physiology*, *579*, 621–636.

Birbaumer, N., Ghanayim, N., Hinterberger, T., Iversen, I., Kotchoubey, B., Kubler, A., et al. (1999). A spelling device for the paralysed. *Nature*, *398*, 297–298.

Birbaumer, N., Murguialday, A. R., & Cohen, L. (2008). Brain-computer interface in paralysis. *Current Opinion in Neurology*, *21*, 634–638.

Birbaumer, N., Weiskopf, N., Weber, C., Kubler, A., Goebel, R., Caria, A., et al. (2006). An fMRI–Brain–computer-interface for the conditioning of the fear circuit in psychopaths. *12th Annual Meeting of the Organization for Human Brain Mapping*. Florence, Italy.

Bruno, M., Bernheim, J. L., Schnakers, C., & Laureys, S. (2008). Locked-in: Don't judge a book by its cover. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*, 2.

Buch, E., Weber, C., Cohen, L. G., Braun, C., Dimyan, M. A., Ard, T., et al. (2008). Think to move: A neuromagnetic brain-computer interface (BCI) system for chronic stroke. *Stroke*, *39*, 910–917.

Coyle, S., Ward, T., Markham, C., & McDarby, G. (2004). On the suitability of near-infrared (NIR) systems for next-generation brain-computer interfaces. *Physiological Measurement*, *25*, 815–822.

Dahmen, B., Sorger, B., Sinke, C. B. A., & Goebel, R. (2008). When the brain takes BOLD 'steps': Controlling differential brain activation levels via real-time fMRI-based neurofeedback training. *14th Annual Meeting of the Organization for Human Brain Mapping* (Vol. 41, p. 43). Melbourne: Elsevier.

deCharms, R. C. (2007). Reading and controlling human brain activation using real-time functional magnetic resonance imaging. *Trends in Cognitive Sciences*, *11*, 473–481.

deCharms, R. C. (2008). Applications of real-time fMRI. *Nature Reviews Neuroscience*, *9*, 720–729.

deCharms, R. C., Maeda, F., Glover, G. H., Ludlow, D., Pauly, J. M., Soneji, D., et al. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 18626–18631.

Eskandari, P., & Erfanian, A. (2008). Improving the performance of brain-computer interface through meditation practicing. *Conference of the IEEE Engineering in Medicine and Biology Society*, 662–665.

Esposito, F., Seifritz, E., Formisano, E., Morrone, R., Scarabino, T., Tedeschi, G., et al. (2003). Real-time

independent component analysis of fMRI time-series. *Neuroimage*, *20*, 2209–2224.

Felton, E. A., Wilson, J. A., Williams, J. C., & Garell, P. C. (2007). Electrocorticographically controlled brain-computer interfaces using motor and sensory imagery in patients with temporary subdural electrode implants. Report of four cases. *Journal of Neurosurgery*, *106*, 495–500.

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., & Turner, R. (1998). Event-related fMRI: Characterizing differential responses. *Neuroimage*, *7*, 30–40.

Goebel, R., Sorger, B., Birbaumer, N., & Weiskopf, N. (2005). Learning to play BOLD Brain Pong: From individual neurofeedback training to brain-brain interactions. *11th Annual Meeting of the Organization for Human Brain Mapping*. Toronto.

Goebel, R., Sorger, B., Kaiser, J., Birbaumer, N., & Weiskopf, N. (2004). BOLD brain pong: Self regulation of local brain activity during synchronously scanned, interacting subjects. *34th Annual Meeting of the Society for Neuroscience*. San Diego.

Gosseries, O., Demertzi, A., Noirhomme, Q., Tshibanda, J., Boly, M., de Beeck, M. O., et al. (2008). Functional neuroimaging (fMRI, PET and MEG): What do we measure? *Revue Medicale de Liege*, *63*, 231–237.

Handwerker, D. A., Ollinger, J. M., & D'Esposito, M. (2004). Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. *Neuroimage*, *21*, 1639–1651.

Hochberg, L. R., Serruya, M. D., Friehs, G. M., Mukand, J. A., Saleh, M., Caplan, A. H., et al. (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature*, *442*, 164–171.

Hwang, H. J., Kwon, K., & Im, C. H. (2009). Neurofeedback-based motor imagery training for brain-computer interface (BCI). *Journal of Neuroscience Methods*, *179*, 150–156.

Irani, F., Platek, S. M., Bunce, S., Ruocco, A. C., & Chute, D. (2007). Functional near infrared spectroscopy (fNIRS): An emerging neuroimaging technology with important applications for the study of brain disorders. *The Clinical Neuropsychologist*, *21*, 9–37.

Iversen, I. H., Ghanayim, N., Kubler, A., Neumann, N., Birbaumer, N., & Kaiser, J. (2008). A brain-computer interface tool to assess cognitive functions in completely paralyzed patients with amyotrophic lateral sclerosis. *The Clinical Neuropsychologist*, *119*, 2214–2223.

Karim, A. A., Hinterberger, T., Richter, J., Mellinger, J., Neumann, N., Flor, H., et al. (2006). Neural internet: Web surfing with brain potentials for the completely paralyzed. *Neurorehabilitation and Neural Repair*, *20*, 508–515.

Kubler, A., Furdea, A., Halder, S., Hammer, E. M., Nijboer, F., & Kotchoubey, B. (2009). A brain-computer interface controlled auditory event-related potential (p300) spelling system for locked-in patients. *Annals of the New York Academy of Sciences*, *1157*, 90–100.

Kubler, A., Kotchoubey, B., Hinterberger, T., Ghanayim, N., Perelmouter, J., Schauer, M., et al. (1999). The thought translation device: A neurophysiological approach to communication in total motor paralysis. *Experimental Brain Research*, *124*, 223–232.

Kubler, A., & Neumann, N. (2005). Brain-computer interfaces — The key for the conscious brain locked into a paralyzed body. *Progress in Brain Research*, *150*, 513–525.

LaConte, S. M., Peltier, S. J., & Hu, X. P. (2007). Real-time fMRI using brain-state classification. *Human Brain Mapping*, *28*, 1033–1044.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*, 537–546.

Laureys, S., Pellas, F., Van Eeckhout, P., Ghorbel, S., Schnakers, C., Perrin, F., et al. (2005). The locked-in syndrome: What is it like to be conscious but paralyzed and voiceless? *Progress in Brain Research*, *150*, 495–511.

Lebedev, M. A., & Nicolelis, M. A. (2006). Brain-machine interfaces: Past, present and future. *Trends in Neurosciences*, *29*, 536–546.

Lee, J. H., Marzelli, M., Jolesz, F. A., & Yoo, S. S. (2009a). Automated classification of fMRI data employing trial-based imagery tasks. *Medical Image Analysis*, *13*, 392–404.

Lee, J. H., Ryu, J., Jolesz, F. A., Cho, Z. H., & Yoo, S. S. (2009b). Brain-machine interface via real-time fMRI: Preliminary study on thought-controlled robotic arm. *Neuroscience Letters*, *450*, 1–6.

Leon-Carrion, J., van Eeckhout, P., & Dominguez-Morales Mdel, R. (2002). The locked-in syndrome: A syndrome looking for a therapy. *Brain Injury*, *16*, 555–569.

Leuthardt, E. C., Miller, K. J., Schalk, G., Rao, R. P., & Ojemann, J. G. (2006). Electrocorticography-based brain computer interface — The Seattle experience. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *14*, 194–198.

Luu, S., & Chau, T. (2009). Decoding subjective preference from single-trial near-infrared spectroscopy signals. *Journal of Neural Engineering*, *6*, 016003.

Majerus, S., Gill-Thwaites, H., Andrews, K., & Laureys, S. (2005). Behavioral evaluation of consciousness in severe brain damage. *Progress in Brain Research*, *150*, 397–413.

Menon, R. S., & Kim, S. G. (1999). Spatial and temporal limits in cognitive neuroimaging with fMRI. *Trends in Cognitive Sciences*, *3*, 207–216.

Monti, M. M., Coleman, M. R., & Owen, A. M. (2008). 'Brain Reading' with real-time fMRI: Communication via detection of brain states in the absence of motor response. *14th Annual Meeting of the Organization for Human Brain Mapping*, (Vol. 1, p. 133). Melbourne: Elsevier.

Naito, M., Michioka, Y., Ozawa, K., Ito, Y., Kiguchi, M., & Kanazawa, T. (2007). A communication means for totally locked-in ALS patients based on changes in cerebral blood volume measured with near-infrared light. *IEICE Transactions on Information and Systems*, *E90-D*, 1028–1037.

Nijboer, F., Sellers, E. W., Mellinger, J., Jordan, M. A., Matuz, T., Furdea, A., et al. (2008). A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. *Journal of Clinical Neurophysiology*, *119*, 1909–1916.

Ogawa, S., Lee, T. M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*, *87*, 9868–9872.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*, 97–113.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Pfurtscheller, G., Guger, C., Muller, G., Krausz, G., & Neuper, C. (2000). Brain oscillations control hand orthosis in a tetraplegic. *Neuroscience Letters*, *292*, 211–214.

Plum, F., & Posner, J. B. (1966). *The Diagnosis of stupor and coma: Edited book title*. Philadelphia, PA: Davis, F.A.

Ramsey, N. F., van de Heuvel, M. P., Kho, K. H., & Leijten, F. S. (2006). Towards human BCI applications based on cognitive brain systems: An investigation of neural signals recorded from the dorsolateral prefrontal cortex. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *14*, 214–217.

Rota, G., Sitaram, R., Veit, R., Erb, M., Weiskopf, N., Dogil, G., et al. (2009). Self-regulation of regional cortical activity using real-time fMRI: The right inferior frontal gyrus and linguistic processing. *Human Brain Mappings*, *30*, 1605–1614.

Scharnowski, F., Weiskopf, N., Mathiak, K., Zopf, R., Studer, P., Bock, S. W., et al. (2004). Self-regulation of the BOLD signal of supplementary motor area (SMA) and parahippocampal place area (PPA): fMRI-neurofeedback and its behavioural consequences. *10th Annual Meeting of the Organization for Human Brain Mapping*. Budapest, Hungary.

Scherer, R., Graimann, B., Huggins, J. E., Levine, S. P., & Pfurtscheller, G. (2003). Frequency component selection for an ECoG-based brain-computer interface. *Biomedizinische Technik (Berlin)*, *48*, 31–36.

Schnakers, C., Majerus, S., Goldman, S., Boly, M., Van Eeckhout, P., Gay, S., et al. (2008). Cognitive function in the locked-in syndrome. *Journal of Neurology*, *255*, 323–330.

Schwartz, A. B., Cui, X. T., Weber, D. J., & Moran, D. W. (2006). Brain-controlled interfaces: Movement restoration with neural prosthetics. *Neuron*, *52*, 205–220.

Sitaram, R., Caria, A., Veit, R., Gaber, T., Rota, G., Kuebler, A., et al. (2007a). FMRI brain-computer interface: A tool for neuroscientific research and treatment. *Computational Intelligence and Neuroscience*, 25487.

Sitaram, R., Zhang, H., Guan, C., Thulasidas, M., Hoshi, Y., Ishikawa, A., et al. (2007b). Temporal classification of multichannel near-infrared spectroscopy signals of motor imagery for developing a brain-computer interface. *Neuroimage*, *34*, 1416–1427.

Sorger, B., Bareither, I., Weiskopf, N., Rodriguez, E. F., Birbaumer, N., & Goebel, R. (2004). Voluntary modulation of regional brain activity to different target levels based on real-time fMRI neurofeedback. *34th Annual Meeting of the Society for Neuroscience*. San Diego.

Sorger, B., Dahmen, B., Reithler, J., & Goebel, R. (2007). BOLD communication: When the brain speaks for itself. *13th Annual Meeting of the Organization for Human Brain Mapping* (Vol. 36, p. 37). Chicago: Elsevier.

Talairach, G., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.

Vanzetta, I. (2006). Hemodynamic responses in cortex investigated with optical imaging methods. Implications for functional brain mapping. *Journal of Physiology (Paris)*, *100*, 201–211.

Villringer, A., & Chance, B. (1997). Non-invasive optical spectroscopy and imaging of human brain function. *Trends in Neurosciences*, *20*, 435–442.

Weiskopf, N., Klose, U., Birbaumer, N., & Mathiak, K. (2005). Single-shot compensation of image distortions and BOLD contrast optimization using multi-echo EPI for real-time fMRI. *Neuroimage*, *24*, 1068–1079.

Weiskopf, N., Mathiak, K., Bock, S. W., Scharnowski, F., Veit, R., Grodd, W., et al. (2004a). Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). *IEEE Transactions on Bio-Medical Engineering*, *51*, 966–970.

Weiskopf, N., Scharnowski, F., Veit, R., Goebel, R., Birbaumer, N., & Mathiak, K. (2004b). Self-regulation of local brain activity using real-time functional magnetic resonance imaging (fMRI). *Journal of Physiology (Paris)*, *98*, 357–373.

Weiskopf, N., Sitaram, R., Josephs, O., Veit, R., Scharnowski, F., Goebel, R., et al. (2007). Real-time functional magnetic resonance imaging: methods and applications. *Magnetic Resonance Imaging*, *25*, 989–1003.

Weiskopf, N., Veit, R., Erb, M., Mathiak, K., Grodd, W., Goebel, R., et al. (2003). Physiological self-regulation of regional brain activity using real-time functional magnetic resonance imaging (fMRI): Methodology and exemplary data. *Neuroimage*, *19*, 577–586.

Wijesekera, L. C., & Leigh, P. N. (2009). Amyotrophic lateral sclerosis. *Orphanet Journal of Rare Diseases*, *4*, 3.

Yoo, S. S., Fairneny, T., Chen, N. K., Choo, S. E., Panych, L. P., & Park, H. (2004). Brain-computer interface using fMRI: Spatial navigation by thoughts. *Neuroreport*, *15*, 1591–1595.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 20

Pharmacotherapy to enhance arousal: what is known and what is not

Ross Zafonte[1,*], Flora Hammond[2], Andrew Dennison[2] and Effie Chew[1]

[1]*Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Network, Boston, MA*
[2]*Charlotte Institute for Rehabilitation, Carolinas Medical Center, Charlotte, NC*

Abstract: Severe brain injury results in a disturbance among a wide range of critical neurotransmitter systems. Each neurotransmitter system places its own functional role while being interconnected to a multitude of other systems and functions. This chapter seeks to review the major neurotransmitter systems involved after severe acquired brain injury. While limited in their construct, animal models of brain injury have demonstrated agents that may assist in the recovery process and those that may further slow recovery. We review further the issue of laboratory evidence and what is transferable to the clinic. Lastly, this chapter reviews published clinical pharmacotherapy studies or trials in the arena of arousal for those with clinical severe brain injury. We discuss limitations as well as findings and present the available evidence in a table-based format. While no clear evidence exists to suggest a defined and rigid pharmacotherapeutic approach, interesting data does suggest that several medications have been associated with enhanced arousal. Several studies are underway or about to begin that will shed more light on the utility of such agents in improving function after severe brain injury. For now, clinicians must employ their own judgment and what has been learned from the limited literature to the care of a challenging group of persons.

Keywords: brain injury; arousal; pharmacotherapy; neurotransmitter; clinical trial

Introduction

This chapter will seek to describe the neurotransmitters and systems involved in arousal and subsequently review the clinical studies that have been employed so far to enhance arousal after brain injury.

Arousal may be seen as a starting point for consciousness. It is the general activation of the mind upon which more directed aspects of consciousness including awareness and attention may be superimposed (Pop-Jordanov and Pop-Jordanova, 2009). Some definitions have linked arousal and consciousness, including ''the general operation of consciousness'' (Thacher and John, 1977) and the ''background state of consciousness'' (Chalmers, 2000). Arousal is distinguished from both the content of consciousness (''the present moment'') and the focused operation of consciousness (attention). A foundation of

*Corresponding author:
Tel.: +617 573 2754; Fax: 617 573 2759;
E-mail: rzafonte@partners.org

DOI: 10.1016/S0079-6123(09)17720-8

arousal is necessary for the emergence of these higher level functions. From the neurophysical perspective, continued progress is being made in developing an explanation of the substrates of consciousness through the use of quantum mechanics (Pop-Jordanov and Pop-Jordanova, 2009). Much has been learned about the neuroanatomical structures important for arousal and the redundant widely-projecting neurotransmitter systems important for arousal. The influence of the widespread neurotransmitter systems on arousal provides the clinician with the opportunity to influence arousal through the use of pharmacological treatments. An understanding of these processes is important to learning how to best apply this information clinically while weighing the considerations of benefit versus potential harm.

In the first section, we outline important anatomical structures involved in arousal and look at how several different neurotransmitter systems may influence arousal. Second, we summarize what has been learned about brain injury and these neuroanatomic functions. Lastly, the authors seek to review prior clinical studies, discuss limitations, and briefly touch on trials that are underway.

Neuroanatomy of arousal

Reticular formation

The reticular formation (RF) stretches from the pons to the midbrain and is in the position to incorporate multiple modalities of bottom-up afferent and top-down inputs and cause an appropriate arousing response. The RF was identified by Moruzzi and Magoun in 1949 when stimulation of the region in a cat model resulted in the replacement of slow, high-voltage, synchronized EEG activity with low-voltage, fast desynchronized EEG activity consistent with waking (Moruzzi et al., 1995). Ascending projections predominately from the mesencephalic and oral pontine RF connect the RF with the forebrain via two pathways: a dorsal pathway connecting to the thalamus and a ventral pathway connecting to the hypothalamus and basal forebrain (Jones and Jones, 2003). Descending projections arising predominately from the caudal pontine and medullary RF project to both the dorsal and ventral horns and the intermediate zone of the spinal cord. It has been postulated that glutamate is the primary neurotransmitter in the RF (Jones, 1995). In one study using in situ hybridization, the murine vesicular glutamate transporter DNPI/VGLUT2 has been detected to be present in analogous regions to the RF (Stornetta et al., 2002). In a study using a labeled antibody, regions of the RF were presumed to have the ability to produce glutamate due to the presence of glutaminase, a major synthetic enzyme for the production of glutamate (Kaneko et al., 1989). However, in both of these examples, these markers were also found in nearby regions of the brainstem outside the RF proper.

GABAergic neurons are also present both within the RF as well as in nearby diffusely projecting nuclei including the dopaminergic ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), the serotonergic dorsal raphe, and the cholinergic laterodorsal and pedunculopontine tegmental nuclei (LDT and PPT) (Ford et al., 1995). While many of these GABAergic neurons project within the reticular core where they exert local inhibition on output from the diffusely projecting systems, a subset of GABAergic neurons projects more diffusely alongside presumed glutaminergic, monoaminergic, and cholinergic neurons to exert a more direct influence on distant regions (Jones and Jones, 2003).

Cholinergic pontine tegmentum

The cholinergic LDT and PPT are located adjacent to the rostral aspect of the RF at the junction of oral pons and caudal mesencephalon. These nuclei appear to communicate with the RF and send projections along a parallel path to the thalamus, though they also project to the lateral hypothalamus and basal forebrain through the ventral pathway (Jones and Jones, 2008). Stimulation of the PPT nuclei in a cat model resulted in increased 20–40 Hz EEG activity consistent with a waking state. This was independent of cholinergic inputs from the basal forebrain and disrupted by administration of scopolamine, a muscarinic antagonist (Steriade et al., 1991). These nuclei

appear to be important not only for generation of a waking state, but also for rapid eye movement (REM) sleep, causing increased cortical activation and eliciting a descending atonia through spinal projections at the onset of REM sleep. Increased activity of the PPT and LDT nuclei during waking and REM sleep likely exerts an inhibitory influence on the thalamic system that generates synchronized spindle oscillations seen in non-REM sleep (Steriade et al., 1990).

Noradrenergic locus ceruleus

The noradrenergic locus ceruleus is located close to the LDT and PPT nuclei in the periventricular gray at the midpons. Projections may be excitatory or inhibitory depending on the receptor type, with alpha-1 and beta receptors generally being excitatory and alpha-2 receptors generally being inhibitory. Excitatory projections may increase arousal through connections to the dorsal thalamo-cortical system (McCormick and McCormick, 1992) or through the ventral cholinergic basalo-cortical network (Fort et al., 1995). The medial preoptic area and the median septal areas in the basal forebrain have been particularly recognized as being wake-promoting (Berridge, 2008). Projections from noradrenergic nuclei may also directly excite the cortex and inhibit sleep-promoting regions. The prefornical region of the lateral hypothalamus has been shown to have noradrenergic afferent input in a rat model (Baldo et al., 2003), suggesting a vital role for norepinephrine in the release of orexin. This suggests a further mechanism for norepinephrine to influence arousal and wakefulness. There is evidence that REM sleep is inhibited by the presence of adrenergic activity (Hobson et al., 1975). This system is particularly active in facilitating cortical activation during times of stress and is dependent on local release of corticotrophin releasing factor in a mouse model (Valentino et al., 1991). Norepinephrine also appears to be important for the arousal effect of amphetamine medications, with one experiment showing that halothane anesthetized rates show no EEG evidence of arousal with the administration of amphetamine if pretreated with a beta antagonist (Lin et al., 1992).

Dopaminergic ventral mesencephalon

Dopaminergic neurons can be found in both the substantia nigra (SN) and the VTA within the ventral mesencephalon. The nigrostriatal pathway projects from the SN through the median forebrain bundle to the dorsal striatum. The mesolimbo-cortical pathways project primarily from the VTA diffusely to the basal forebrain, ventral striatum (including the nucleus accumbens), and the cortex. Though no changes in dopamine have been found related to sleep patterns (Miller et al., 1983), dopamine can have an effect in the promotion of arousal in tasks involving reward and positive stimulation through the nucleus accumbens. Resulting deficits in dopamine therefore can cause profound behavioral deficits such as anhedonia superimposed on an intact basal substrate of arousal (Wise et al., 1978).

Serotonergic raphe nuclei

Several raphe nuclei can be found throughout the brainstem, with the midbrain dorsal raphe nucleus being notable for ascending projections to the forebrain and cortex. Generally, the release of serotonin has been thought to be associated with satiety, with lesions to serotonergic regions causing increased eating and sexual activity (Dement and Henriksen, 1973). Stimulation of the dorsal raphe nucleus in cats resulted in mild increase of arousal along with suppression of feeding in an animal deprived of food for three days (Jacogs et al., 1973). Lesions to the central superior raphe nucleus in cats have been shown to cause a disinhibition of wakefulness that secondarily may cause a decrease in sleep (Arpa and De Andres, 1993). Another study monitoring raphe activity on freely moving cats showed a relationship between levels of arousal and activity in the raphe nuclei. In comparison to waking levels, extracellular serotonin levels are decreased in non-REMs and yet lower, but still present in REMs (Portas et al., 1998). On the contrary, however, a depletion of serotonin may lead to insomnia and increased arousal due to increased sexual and eating behaviors (Jones and Jones, 2003).

Dorsal pathway: thalamo-cortical activating system

Projections from the RF, LDT, PPT, locus ceruleus, and raphe nuclei project through a dorsal pathway to the midline and intralaminar thalamic nuclei. These ''nonspecific'' thalamic nuclei are differentiated from classic thalamic ''specific'' relay nuclei due to a higher proportion of diffusely projecting ''matrix'' cells in place of modality-specific ''core'' cells (Benarroch, 2008). From these thalamic relays, a ''nonspecific'' thalamo-cortical system emerges with multiple reciprocal connections. This system creates two major firing patterns: a rhythmic burst firing associated with non-REM sleep with a high amplitude, slow EEG pattern, and a tonic firing pattern associated with wakefulness and REM sleep with a high-frequency, low-amplitude EEG pattern. While thalamo-cortical projections seem to use primarily glutamate as a neurotransmitter, the thin reticular nucleus surrounds the thalamus and influences thalamic activity through GABAergic projections within the thalamus. The reticular nucleus of the thalamus also receives inputs from the brainstem nuclei. The reticular nucleus becomes hyperpolarized when the inputs from the brainstem decrease with the onset of sleep, leading to the creation of spindles and delta waves during slow-wave sleep (Jones and Jones, 2003). Thalamocortical projections are posited to be critical for the content of consciousness due to their ability to synchronize cortical activity, but are thought not to be entirely necessary for basic arousal, as a crude awake state may be maintained with only input from the ventral pathway. The thalamic projections are key and have been posited to be a major concern in disorders of consciousness.

Ventral pathway: hypothalamic arousal systems

Several areas within the hypothalamus are important in the generation and maintenance of arousal: the posterior hypothalamus, the tuberomammillary neurons, and the prefornical neurons. Inhibition with muscimol (a GABA agonist) of the preoptic and anterior hypothalamus causes increased vigilance and arousal, while inhibition of the middle and anterior portions of the posterior hypothalamus with muscimol causes decreased arousal with loss of REM sleep. Additionally, inhibition of the ventrolateral portion of the hypothalamus causes an increase in both non-REM and REM sleep (Lin et al., 1989). Similarly to the RF, there is evidence of both glutamate (Ziegler et al., 2002) and GABA (Decavel et al., 1990; Vincent et al., 1983) activity in the hypothalamus.

Located in the ventrolateral aspect of the posterior hypothalamus, the tuberomamillary nucleus sends histaminergic projections diffusely to multiple areas of the brain. Histamine-immunoreactive nerve fibers were found to be most dense in the hypothalamus itself, followed by dense projections in the medial septum, nucleus of the diagonal band, and the VTA. Less dense regions included the cortex, the olfactory bulb and tubercle, the bed nucleus of the stria terminalis, the amygdale, basal parts of the hippocampus, inferior and superior colliculi, SN, lateral and medial parabrachial nucleus, and the nucleus of the solitary tract. Finally, small amounts of projections were found in the caudate, putamen, thalamic nuclei, and pontine and ventral medullary nuclei (Panula et al., 1989). Knockout rats unable to produce histamine have shown decreased arousal to novel environments though the basal amount of waking is unaffected. Presumably, histamine is an important component in maintaining arousal when faced with behavioral challenges (Parmentier et al., 2002).

A more recently identified neuropeptide orexin (or hypocretin) is produced in the prefornical region of the hypothalamus. This region of the hypothalamus has diffuse projections in addition to projections to multiple regions: the hypothalamus itself, the locus coeruleus, the septal nuclei, the bed nucleus of the stria terminalis, the paraventricular and reunions nuclei of the thalamus, the zona incerta, the subthalamic nucleus, the central gray, the SN, the raphe nuclei, the parabrachial area, the medullary reticular area, and the nucleus of the solitary tract (Peyron et al., 1998). Notably, orexin projections lead to the basal forebrain acetylcholine regions, but not to

the PPT and LDT nuclei in the pontine tegmentum. Orexin appears to have a critical role in sleep and sleep dysfunction (Dugovic et al., 2009). While the densest extrahypothalamic projections were found in the locus ceruleus, there is also evidence that noradrenergic input is important for the activation of orexin neurons in the prefornical areas (Baldo et al., 2003), suggesting a close interplay between these two neurotransmitter systems in the maintenance of arousal. A defect in the function of orexin has been implicated in the etiology of narcolepsy with subsequent cataplexy and decreased latency to REM sleep. This would be consistent with the theory that orexin is an important factor in preventing descending inhibition of spinal pathways by brainstem cholinergic activity in the waking state. Cells within the pontine tegmentum have been found to possess both orexin 2 receptors and muscarinic 2 receptors that presumably have opposite effects (Jones and Jones, 2008), with orexin leading to continued muscle tone and acetylcholine leading to loss of descending muscle tone as seen in REM sleep or cataplexy.

Ventral pathway: basal forebrain

Cholinergic, glutamatergic, and GABAergic neurons are found in the medial septum-diagonal band, magnocellular preoptic nucleus, substantia innominata, and globus pallidus. These nuclei receive inputs from multiple brainstem and hypothalamic neurons including cholinergic, serotonergic, monoaminergic (Jones et al., 1989), and histaminergic (Panula et al., 1989) inputs. The cholinergic basal forebrain projections have been shown to be activated by glutamatergic (Khateb et al., 1995b), noradrenergic (Fort et al., 1995), and histaminergic (Khateb et al., 1995a) inputs, but there is evidence of decreased tonic firing from serotonin inputs (Khateb et al., 1993).

Basal forebrain projections that are 35–45% cholinergic extend to the hippocampus from the medial septal nucleus and the vertical limb of the diagonal band. Basal forebrain projections that are 80–90% cholinergic extend to the cortex from the horizontal and vertical limbs of the diagonal band and the substantia innominata-nucleus basalis (Rye et al., 1984). Similar to the cholinergic projections from the LDT and PPT, cholinergic projections from the basal forebrain show increased activity in the waking state and during REM sleep, with a bursting discharge synchronous with theta waves (Lee et al., 2005). On the other hand, basal forebrain GABAergic activity has been shown to be associated slow-wave activity consistent with non-REM sleep, while a general decrease in activity is seen with increased cortical activity (Manns et al., 2000). Therefore, the presence of both a thalamo-cortical system and a basal forebrain-cortical system may be another example of the redundant nature of arousal-promoting mechanism in the brain (Table 1).

Neuroanatomic and neurotransmitter function following brain injury

Traumatic brain injury

Alterations in neurotransmitter function have been recognized after traumatic brain injury (TBI). An important component of the pathophysiology of TBI is diffuse axonal injury (DAI) due to stretch or shear of neurons. DAI has been categorized using three progressively more severe grades by Adams et al. (1989): Grade 1 DAI shows scattered axonal bulbs throughout the white matter; Grade 2 DAI shows a focal lesion in the corpus callosum in addition to white matter changes; and Grade 3 DAI has a focal lesion in the dorsolateral aspect of the brainstem in addition to white matter damage. Damage to the dorsolateral aspect of the brainstem does not occur without other lesions being seen in the cerebral hemispheres and the brainstem (Meythaler et al., 2001b).

In one swine model of experimental DAI, greater strain was observed along cortical margins than within the deep white matter (Meaney et al., 1995), suggesting that the higher centripetal forces at a greater distance from the center of rotation contribute to greater strain. As the rotational forces become greater, the noted damage may occur more and more central to the axis of rotation, as seen with the progressive stages of DAI suggested by Adams. It is possible that the

Table 1. Summary of diffusely projecting neurotransmitter systems important in arousal

Neurotransmitter	Origin	Projections	Function
Glutamate	(1) Mesencephalic and oral pontine RFp; (2) Thalamocortical projections. (3) basalocortical systems: MS-DB, magnocellular preoptic nucleus, SI, and GP	Pathways from the mesencephalic and oral pontine RF: (1) dorsal pathway: projects to thalamic nuclei; (2) ventral pathway: projects to the hypothalamus and basal forebrain	Primary excitatory neurotransmitter. A key neurotransmitter in thalamocortical system and basalocortical system, whose activities form basic substrates of arousal
GABA	Widely distributed throughout all systems: RF, VTA, SNc, dorsal raphe nucleus, LDT, PDT, basal forebrain, and reticular nucleus of the thalamus	Locally as an interneuron and diffusely with glutamatergic, serotonergic, and monoaminergic projections	Exerts both locally and diffusely projecting inhibition. Hyperpolarization of the reticular nucleus of the thalamus leads to loss of GABA input and subsequent disinhibition of production of spindles and delta waves consistent with slow-wave sleep
Acetylcholine	(1) Brainstem tegmentum: PPT, LDT	(1) Dorsal: thalamus (thalamocortical system); (2) ventral pathway: basal forebrain and lateral hypothalamus	Important for generation of EEG activity consistent with both the awake state and with REM sleep
	(2) Basal forebrain: SI-nucleus basalis, MS-DB, GP, magno-cellular preoptic nucleus	(1) The MS-DB projects to the hippocampus; (2) horizontal and vertical limbs of the DB and the SI-nucleus basalis project to the cortex	May function as a redundant system to the thalamocortical system to maintain a state of arousal
Norepinephrine	LC (supplies >50%) and scattered nuclei within the lateral tegmentum	(1) Dorsal: thalamo-cortical system; (2) ventral: medial preoptic area, median septal area, prefornical area of the lateral hypothalamus; (3) cortical: direct connections to multiple regions	Important for increased arousal during times of stress, norepinephrine influences arousal through multiple pathways. Postulated to be responsible for the arousing effects of amphetamine medications
Dopamine	VTA and SNc	(1) Mesolimbic projections to the nucleus accumbens, basal forebrain, amygdale, hippocampus, and limbic cortex; (2) mesocortical projections to the prefrontal cortex; (3) nigrostriatal projections to the dorsal striatum	Postulated effect on arousal in tasks involving reward and positive stimulation through the nucleus accumbens. Deficiencies in dopamine may cause severe anhedonia or abulia that may appear similar to a disorder of arousal
Serotonin	Raphe nuclei – particularly the dorsal raphe nucleus	Diffuse projections, both excitatory and inhibitory to the cortex, thalamus (thalamo-cortical system), basal ganglia, brainstem, cerebellum and spinal cord	Appears to modulate satiety. Deficiencies lead to insomnia and increased arousal due to increased sexual and eating behaviors

Table 1. (*Continued*)

Neurotransmitter	Origin	Projections	Function
Histamine	TMN in the posterior hypothalamus	Highest in the hypothalamus, MD-DB, and VTA. Moderate levels in the olfactory bulb, BN-ST, amygdala, hippocampus, inferior and superior colliculi, SN, lateral and medial parabrachial nucleus, and nucleus of the solitary tract. Lower levels still seen in the caudate, putamen, thalamic nuclei, and pontine and ventral medullary nuclei	Shown to be important for increasing arousal when confronted with novel environments/behavioral challenges in a rat model
Orexin	Prefornical region of the lateral hypothalamus	Hypothalamus (most dense), locus coeruleus (most dense outside the hypothalamus), septal nuclei, BN-ST, paraventricular and reunions nuclei of the thalamus, zona incerta, subthalamic nucleus, central gray, SN, raphe nuclei, parabrachial area, medullary reticular area, nucleus of the solitary tract	Loss of orexin activity leads to narcolepsy with daytime lethargy, decreased latency to REM sleep and cataplexy. Likely plays an important role in the normal transition through stages of sleep, activated by norepinephrine to prevent premature transition from non-REM sleep to REM sleep

BN-ST, bed nucleus of the stria terminalis; GP, globus pallidus; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; MCPO, magnocellular preoptic nucleus; MS-DB, medial septum diagonal band; PPT, pedunculopontine tegmental nucleus; RF, reticular formation; SI, substantia innominata; SNc, substantia nigra pars compacta; TMN, tuberomamillary nucleus; VTA, ventral tegmental area.

more profound effects on arousal seen in the severe injuries that involve greater shear forces may be due to a disruption of the more centrally located pathways of the widely distributed neurotransmitter systems mentioned above, particularly norepinephrine (Morrison et al., 1979) and acetylcholine. Supporting this concept is the observation by Smith et al. (2003) that axonal injury in the brainstem seems to be a primary factor in coma after TBI.

A two-phase model of brain injury has been developed that describes an initial hyperglycolytic stage associated with a ''neurotransmitter storm'' that is notable for elevated levels of most of the excitatory neurotransmitters and associated excitotoxicity. Subsequently, a chronic state develops characterized by a global reduction in metabolic activity and associated with alterations in neurotransmitter levels (Arciniegas and Silver, 2006; Povlishock and Katz, 2005). This conceptualization brings into focus the relevance of appropriate timing of medication administration to address impairments in arousal, attention, and other cognitive processes.

Levels of excitatory amino acids increase dramatically immediately after TBI and appear to be related to severity of injury. In one study using rat models, levels of both aspartate and glutamate measured by microdialysis increased significantly after fluid percussion injury. Levels reached a peak value at 10 min and continued to be elevated over an hour. Additionally, antagonism of NMDA receptors in an animal model appeared to decrease subsequent signs of damage, suggesting that elevated levels of glutamate mediate excitotoxicity through the activation of NMDA receptors (Faden et al., 1989). Human studies of cerebrospinal fluid (CSF) samples after TBI also confirm a positive relationship between severity of injury and elevation of glutamate (Baker et al., 1993) and aspartate levels up over one week out (Zhang et al., 2001).

Catecholamine levels have also generally been found to be altered following TBI. Elevated levels of dopamine, norepinephrine, and epinephrine exist that may further contribute to the excitotoxic phenomenon. In a rat model TBI study, an acute decrease in cortical dopamine levels was seen within 1 h of injury that persisted at the last measurement at two weeks. In the same study, striatal dopamine concentrations were slightly elevated at 6 h and quickly resolved to normal levels, and hypothalamic concentrations of both dopamine and norepinephrine were increased at 1 h and stayed elevated up to 24 h for dopamine and one week for norepinephrine (McIntosh et al., 1994). This uneven distribution of changes in dopamine concentrations would seem to indicate a loss of the ability to transport the neurotransmitters from their origin to their appropriate destination, though other explanations could certainly be given. Chronic deficits have been established in the ipsilateral frontal cortex of an injured rodent model, and upregulation of tyrosine hydroxylase — a critical step in the synthesis of dopamine — is also observed (Massucci et al., 2004; Yan et al., 2007). Dopamine transporter plays a key role in the uptake of dopamine and is noted to undergo downregulation in chronic TBI models (Yan et al., 2002). It has been found the dopamine transporter genotype and sex may alter the degree of dopamine-mediated damage (Wagner et al., 2007). Human studies have found increased blood levels of norepinephrine, epinephrine, and dopamine within 48 h that are correlated with severity of injury after TBI (Clifton et al., 1981; Hamill et al., 1987). On the other hand, another rat study using a cortical impact method of low-grade severity showed a decrease in norepinephrine levels in the region of focal damage as soon as 30 min (Prasad et al., 1994), suggesting that a focal cortical lesion may respond differently than DAI in terms of norepinephrine. Accordingly, one must be careful not to generalize about neurotransmitter fluctuations throughout the whole range of pathology in acquired brain injury. Metabolites of norepinephrine and dopamine have been shown to be increased and directly correlated with severity acutely in TBI, and a subsequent decrease in metabolite levels closer to control levels was associated with clinical improvement (Markianos et al., 1992; Markianos et al., 1996). Chronically, children with TBI have been shown to have a chronic systemic tonic increase in both norepinephrine and epinephrine given elevated resting excretion levels of the corresponding metabolites normetanephrine and metanephrine, though the effects of this on the central nervous system are uncertain (Konrad et al., 2003).

The rate of serotonin synthesis has been found to be increased after 72 h in a rat model of brain injury using a freezing technique (Tsuiki et al., 1995b). In this study, elevated levels of serotonin were found to mediate a decrease in glucose utilization. In human subjects, two studies showed an increase in the concentration of CSF serotonin metabolites (Markianos et al., 1992; Markianos et al., 1996) and another showed decreased CSF levels of serotonin within 24 h after injury (Karakucuk et al., 1997). This apparent discrepancy may be due to an increase in neurotransmitter turnover after TBI that generally improves along with an improvement in the clinical state.

Though usually absent in the CSF (Bakay et al., 1986), acetylcholine has been found to be present in the CSF in both experimental TBI models (Bornstein, 1946) and in human TBI (Tower and McEachern, 1949). Fluid percussion injury in a rat model of TBI has shown a loss of basal forebrain cholinergic neurons but maintained pontomesencephalic cholinergic neurons (Schmidt et al., 1995). A study in rats showed an increase over weeks in hippocampal levels of vesicular acetylcholine transferase and a decrease in M2 presynaptic receptors that serve as an inhibitory feedback mechanism, suggesting a compensatory cellular response to decreased acetylcholine levels after TBI (Ciallella et al., 1998). Finally, low levels of hypocretin-1 (orexin A) in the CSF have been identified during the acute phase after brain injury and were seen to be present in 30 of 31 human subjects after severe TBI (Baumann et al., 2005).

Ischemia and anoxia

Similarly to TBI, anoxia and ischemia within the brain have been shown to alter neurotransmitter levels. A review of the literature found the most common regions affected by anoxia to be the watershed cerebral cortex and basal ganglia, followed by the hippocampus (Caine and Watson, 2000). Within the striatum, ischemia is associated with a 500-fold increase in dopamine, a 7-fold increase in glutamate and a 5-fold increase in GABA. When the dopamine increase is blocked by a lesion to the SN, there is an attenuation of glutamate release, suggesting that dopamine plays a role in mediating cytotoxic damage (Globus et al., 1988). Within the hippocampus, norepinephrine levels are found to be acutely elevated after transient ischemia (Globus et al., 1989). Cell death within the hippocampus CA1 region in particular has been postulated to be mediated through serotonin release (Globus et al., 1992). On the other hand, serotonin has been shown to attenuate glutamate efflux after cortical ischemia in human subjects and is thought to possibly be protective against glutamate-mediated excitotoxicity (Marcoli et al., 2004). In a human sample of ischemia cerebral tissue in the temporal lobe, a marked increase in glutamate was seen along with a milder but more significant increase in serotonin and no increase in norepinephrine (Kanthan et al., 1996). In a study involving bilateral common carotid artery occlusion (a technique to cause chronic mild hypoperfusion in rats), an initial decrease of acetylcholine in the striatum was seen at one month and a subsequent decrease of acetylcholine in the cortex, striatum, and hypothalamus was evident at four months, suggesting two phases of injury and subsequent memory impairment (Ni et al., 1995). This was accompanied by two corresponding types of damage: acute initial damage to the cortex and striatum stable at one month and presumed to be due to the initial ischemia, and progressive damage to the hippocampus and white matter not yet visible at one month, but visible at four months. Chronic decreases in the turnover rates of norepinephrine in the hippocampus and dopamine in the caudate-putamen have been seen in rats six months out of anoxic injury (Speiser et al., 1990).

Challenges

One of the significant challenges in translating the basic science data to the clinic is the limitation that exists in severe TBI models. Few, if any, adequate animal models of disorders of consciousness exist. Such injuries are challenging to reproduce, and it remains difficult to avoid injury so severe as to cause animal death. Thus, few animal-based trials have focused on pharmacotherapy to enhance arousal and responses.

Enhancement of dopaminergic pathways with methylphenidate (Kline et al., 2000), amantadine (Dixon et al., 1999), and bromocriptine (Kline et al., 2002) has been shown to improve cognitive performance in experimental models of TBI. Experimental models of TBI have further shown that the action of methylphenidate on dopamine function is likely to be through alteration of dopamine transporter (DAT) expression and transcriptional changes. Wagner et al. (2005) found that controlled cortical impact (CCI) in rats resulted in a decrease in total tissue striatal DAT expression 2–4 weeks after CCI, and reduced evoked dopamine neurotransmission and clearance. Furthermore, daily injections of methylphenidate 5 mg/kg for 14 days following CCI resulted in robust increases in evoked striatal dopamine neurotransmission and transcription factor *c-fos* expression (Wagner et al., 2009). Total DAT expression was unchanged by treatment. Bromocriptine treatment is also associated with increased survival of hippocampal neurons (Kline et al., 2002), although the same effect was not seen with amantadine (Dixon et al., 1999). Rat studies also suggest that bromocriptine attenuates the effect of oxidative stress, in particular lipid peroxidation, following TBI (Kline et al., 2004b). This was associated with better spatial learning on the water maze performance.

Noradrenergic augmentation in the form of amphetamine administration, when combined with physical therapy, was shown to augment plasticity, significantly increase axonal growth in the deafferented basilar pontine nuclei in rats that had

sustained a unilateral sensorimotor cortical lesion (Ramic et al., 2006). Low-dose atomoxetine (1 mg/kg) is also shown to improve cognitive ability in rat TBI model (Reid and Hamm, 2008). Higher doses of atomoxetine did not further improve cognitive deficits. No cognitive improvement was observed when treatment was delayed for 11 days.

There is some evidence from experimental models of TBI to suggest the efficacy of the 5-HT(1A) receptor agonist 8-Hydroxy-N,N-dipropyl-2-aminotetralin (8-OH-DPAT) in enhancing cognitive recovery after TBI. When administered early as a single dose (Kline et al., 2004a; Kline et al., 2007b), 8-OH-DPAT is reported to improve performance at the water maze task, decrease cortical lesion volume, and improve hippocampal neuronal survival (Kline et al., 2004a). When given in a delayed and chronic fashion (Cheng et al., 2008) at a lower dose (0.1 mg/kg), it was associated with enhanced spatial learning and memory retention. Higher doses (0.5 mg/kg) did not confer benefit and, in fact, worsened performance. The mechanism is proposed to be through restoration of dopamine neurotransmission.

Trials of a number of other drugs have been carried out in animal models of TBI to enhance cognitive recovery, including the nootropic aniracetam (Baranova et al., 2006), which conferred benefit when given acutely, or in a delayed, chronic manner. Ker et al. (2009) recently reviewed the literature on the effects of beta-2 receptor antagonists in animal models of TBI. Although methodological quality was poor, the evidence suggested that beta-2 antagonists are associated with improved functional outcomes and reduced cerebral edema. The proposed mechanism is through the blockade of the kinin-kallikrein system, preventing the production of bradykinin, which is implicated in the breakdown of the endothelial junctions that comprise the blood–brain barrier, contributing to increased intracranial pressure.

Pharmacotherapy that may impair arousal

Over the past two decades an increasing body of literature has begun to focus on medications that may slow or impair recovery. In a landmark article published in *Science* in 1982, Feeney et al. (1982) demonstrated slowed recovery in animals who received the dopaminergic blocking drug haloperidol. Since that time, investigators have suggested that dopamainergic and alpha adenergic blocking medications appear to have a negative impact on the recovery process in the animal model (Kline et al., 2007a). However, the clarity within the human literature is as yet lacking. Recent evidence suggest that some but not all atypical antipsychotic agents may have a similar negative profile, specifically when administered on a more chronic basis (Goldstein and Bullman, 2002; Kline et al., 2008; Wilson et al., 2003). Thus, at least in the chronic setting, catecholimergic blocking agents remain a concern. Animal evidence notes later acetylcholine neurotransmission after TBI, and clinical suspicion exists that anticholinergic agents may slow the recovery process (Arciniegas, 2003; Dixon et al., 1995).

Pharmacotherapy of arousal

Review of clinical research in arousal and awareness

The purpose of this section is to review the present clinical data and findings involving studies aimed at enhancing arousal and improving awareness.

Review of clinical literature on drugs

Neurostimulants

Amphetamines and methylphenidate increase dopamine and norepinephrine availability at the synaptic cleft by (1) increasing their release, (2) blocking reuptake, and (3) inhibiting monoamine oxidase-mediated degradation of dopamine, (4) binding to and reversing the action of dopamine reuptake transporter, resulting in greater dopamine activity in the striatum and large areas of the cerebral cortex in animal models, particularly in dopamine-rich areas of the

caudate nucleus and mediofrontal cortex. Amphetamines appear to promote the release of newly synthesized dopamine more selectively.

The dose of methylphenidate used in most studies is 0.15–0.3 mg/kg/dose twice daily, to a maximum of 20 mg/dose; and the dose of dextroamphetamine is 5–30 mg/day. The onset of action is within 0.5–1 h after administration.

There are few studies on the use of neurostimulants to enhance emergence from states of impaired consciousness. The evidence is inconclusive. A recent meta-analysis of 22 single-subject repeated crossover trials in patients with altered consciousness found no clinically meaningful effect of methylphenidate on responsiveness or command-following (Martin and Whyte, 2007). Seventeen of these subjects had sustained a TBI. Another randomized, placebo-controlled study suggests that early use of methylphenidate in the ICU is associated with shorter hospital lengths of stay, with a trend toward shorter ICU length of stay following severe injury (Moein et al., 2006).

Some clinicians are reluctant to use methylphenidate in brain-injured patients due to the risk of lowering seizure threshold, particularly in susceptible patients with more severe injury. A retrospective study of seizure frequency before and after methylphenidate initiation in 30 consecutive patients with active seizure disorders with brain injury showed a trend toward less frequent seizures while on methylphenidate (Wroblewski et al., 1992). Four patients had greater seizure frequency while on methylphenidate, three of whom received concomitant tricyclic antidepressants. Small open-label trials of methylphenidate in adult epilepsy patients with concomitant attention deficit hyperactivity disorder (ADHD) have not demonstrated increased seizure activity (Moore et al., 2002; van der Feltz-Cornelis and Aldenkamp, 2006). In the pediatric ADHD population, no controlled studies have shown convincing evidence of increased development, or increased frequency of seizures in children with concomitant active seizure or those with electroencephalographic abnormalities (Gucuyener et al., 2003; Hemmer et al., 2001). Children with well-controlled epilepsy have been treated safely with methylphenidate (Hemmer et al., 2001). In addition, several trials have been conducted using the combination of methylphenidate and serotonin reuptake inhibitors such as fluoxetine, without demonstrating an increase in the incidence of seizures (Lavretsky et al., 2006; Patkar et al., 2006).

With regard to the adverse effects of methylphenidate on blood pressure and heart rate, one randomized placebo-controlled crossover study found modest increases in mean pulse rate and blood pressure with methylphenidate therapy, 0.3 mg/kg/dose, twice daily (Alban et al., 2004). The mean pulse increase was 7 beats/min. The average increase in mean arterial pressure was 2.5 mmHg ($p = 0.046$). Average systolic pressure rise was 3.67 ($p = 0.024$). There was no correlation between baseline blood pressure and pulse rate, and their subsequent increase with treatment. The authors concluded that pretreatment hypertension was not an indication for withholding methylphenidate. Nevertheless, monitoring of vital signs is important upon initiation of methylphenidate therapy.

Dopaminergic agents

Amantadine was originally developed as an antiviral for influenza A. It is also an antiparkinsonion that increases presynaptic dopamine release, inhibits dopamine reuptake, and increases the density of postsynaptic dopamine receptors, increasing the availability of dopamine in the striatum. It is also an uncompetitive antagonist at NMDA receptors. The role of NMDA antagonism in the action of amantadine in promoting arousal is yet unclear. It may act via prevention of glutamate-mediated neurotoxicity, and also indirectly through stimulation of striatal acetylcholine release. There is also interesting evidence that this class of medications may enhance brain neurotrophic factors and thus improve the repairative process (Meisner et al., 2008).

There is a small body of evidence supporting the use of amantadine in impairment of consciousness due to TBI. A double-blind, placebo-controlled, crossover study evaluated the effect of

early and later use of amantadine in subjects 4–6 weeks postinjury. A trend toward significant improvement in Mini Mental State Examination (MMSE), Glasgow Outcome Scale (GOS), and Disability Rating Scale (DRS) was demonstrated with six weeks of amantadine, compared to placebo, whichever drug was administered first (Meythaler et al., 2002). Baseline differences in DRS between the treatment and control groups, and spontaneous recovery in the acute phase made comparison between the two groups difficult in a crossover design. In another case report, Zafonte et al. (2001) reported a dose-dependent effect of amantadine on emergence from MCS in a single subject. The effect on arousal was reversed upon withdrawal of amantadine, and improved again on reinitiation of the drug. Amantadine has also been reported to improve survival and GCS at the time of discharge, when given intravenously for three days, from the third day of acute admission (Saniova et al., 2004). Gualtieri et al. (1989) reported benefits in arousal, fatigue, distractibility, and assaultiveness in 30 TBI patients with amantadine treatment.

Negative studies include a retrospective cohort study of 123 medically stable subjects with severe TBI in coma for more than one week, 28 of whom had received amantadine 100–200 mg twice daily (Hughes et al., 2005). No difference was found in the rate of coma emergence between those who had received amantadine and those who had not.

In the pediatric population, both amantadine and pramipexole, another dopamine agonist, were associated with improved responses in patients in low-response states following TBI, in a randomized, double-blind study (Patrick et al., 2006). Significant improvement was found on the Coma Near Coma (CNC) Scale, Western NeuroSensory Stimulation Profile (WNSSP), and DRS in 10 children and adolescents in low-response states while on amantadine or pramipexole compared to off medication. No difference was found between the two treatment groups.

The starting dose of amantadine is 50 mg twice daily. Effective dose is generally 100 mg twice daily. Doses beyond 400 mg/day result in the emergence of adverse effects with minimal added benefit. Gastrointestinal side effects, confusion, and psychosis may occur at high doses. Amantadine is renally excreted and dose adjustment is required in the presence of renal impairment. Neuroleptic malignant syndrome has been reported with rapid withdrawal of amantadine (Ito et al., 2001). Amantadine has also been reported to lower seizure threshold. Case reports of amantadine-induced generalized seizure exist (Ohta et al., 2000), although amantadine is also reported to be used as an adjunct anticonvulsant agent in select populations (Drake, et al., 1991; Shields et al., 1985). In overdose, amantadine has been reported to induce status epilepticus (Claudet and Marechal, 2009), besides arrhythmia, cardiac arrest (Pimentel and Hughes, 1991), and anticholinergic side effects.

Bromocriptine is another dopamine-enhancing agent that has been examined less extensively. It is a predominantly postsynaptic D2 dopamine receptor agonist, which has been reported to effect a greater rate of transition from persistent VS to MCS in a retrospective chart review (Passler and Riggs, 2001). Levodopa, another dopamine agent, has been credited with the remarkable recovery of a 24-year-old man in a VS six months postinjury who became conversant within days of levodopa initiation (Haig and Ruess, 1990), as well as greater responsiveness in chronic TBI patients in PVS and MCS for whom levodopa was initiated for the treatment of rigidity (Matsuda et al., 2005). Krimchansky et al. (2004) described the clinical pattern of recovery of consciousness in eight patients in VS who were treated with incremental doses of levodopa. All patients could follow commands within two weeks of initiating medication; seven achieved ability for reciprocal interaction, including two who were more than nine months postinjury. Another retrospective review of 10 children and adolescents in VS or MCS who were on various dopamine-enhancing medications (amantadine, methylphenidate, pramipexole, bromocriptine, levodopa) demonstrated significant improvement in responses to structured stimuli, in a double baseline serial measure AABBB design (Patrick et al., 2003). Seven of the 10 subjects had sustained a TBI.

Apomorphine is among the most powerful of dopaminergic medications and has been employed in resistant cases of Parkinson's disease. Employing a unique pump-based delivery system, Fridman et al. (2009) reported on a case of fast awakening after continuous administration of apomorphine. These investigators have also recently completed an open-label series of eight subjects with severe TBI who were difficult to arouse. The results of this study have been presented as positive and await publication.

Antidepressants

Serotonergic projections to frontal, limbic, and hippocampal areas are susceptible to biomechanical injury in TBI. Acute injury appears to be associated with an increase in hemispheric serotonin levels, and a decrease in cerebral glucose utilization in areas of high serotonin synthesis (Tsuiki et al., 1995a). Increase in levels of serotonin is postulated to cause neuronal cell death. However, some studies have documented a decrease in serotonin levels, suggesting a chronic downregulation of the serotonin system (Mobayed and Dinan, 1990). Chronic supplementation with serotonin agents has been associated with neurogenesis in the animal model (Duan et al., 2008). Sertraline, a selective serotonin reuptake inhibitor (SSRI), did not result in improvement in arousal after a two-week course in a small, randomized, prospective, placebo-controlled trial with 11 subjects with severe TBI (Meythaler et al., 2001a).

Amitriptyline and desipramine are tricyclic antidepressants that are postulated to exert their action by blocking reuptake of serotonin and norepinephrine. Reinhard et al. (1996) reported three patients with severe injury who demonstrated significant improvement in arousal and initiation following administration of amitriptyline or desipramine. Two of these experienced deterioration of symptoms when the medications were discontinued and improvement again when reinitiated. The third patient began verbalizing after being mute for more than a year following TBI.

Modafinil

Modafinil is a wakefulness-promoting agent approved for treatment of excessive daytime sleepiness associated with narcolepsy. Its mechanism of action is unclear. It has little effect on the catecholamine, serotonin, histamine, adenosine, and monamine oxidase B systems. There is evidence that it causes inhibition of the posterior hypothalamus and medial preoptic area and also an increase in the level of glutamate in these regions. Animal models have demonstrated increased activation in the anterior hypothalamus, hippocampus, and amygdala. In the narcolepsy population, it resulted in improved energy level, overall social functioning, improved psychological well-being, increased productivity, attention, and self-esteem when compared to controls. In sleep-deprived military personnel, modafinil improved performance in cognitive tasks (Elovic, 2000). In one open-label series of 10 patients with closed head injury not otherwise characterized, modafinil was reported to decrease daytime sleepiness (Teitelman, 2001). However, a recent, randomized, placebo-controlled, crossover study of chronic TBI subjects with disabling fatigue and/or excessive daytime sleepiness showed no significant difference in measures of fatigue and daytime sleepiness between treatment and control groups (Jha et al., 2008). A substantial placebo effect in fatigue symptoms was noted. No studies to date have investigated the use of modafinil to improve emergence from impaired conscious states following severe TBI, although its use is being clinically employed.

Zolpidem

Zolpidem belongs to the drug class imidazopiridines. It acts as an agonist on the $\alpha 1$ subtype of gamma-aminobutyric acid (GABA)-A receptors, while benzodiazepines act on all GABA-A receptor subtypes. The postulated mechanism of zolpidem in ''awakening'' is through reversing GABA-mediated diaschisis in the brain. Single photon emission computed tomography (SPECT) studies have shown improved blood flow in areas

of hypoperfusion after zolpidem administration (Clauss and Nel, 2006; Clauss et al., 2000).

Its use as an ''awakening'' agent has been reported by several authors (Clauss and Nel, 2006; Clauss et al., 2000; Clauss et al., 2001; Cohen and Duong, 2008; Shames and Ring, 2008) in PVS following traumatic and anoxic brain injury to dramatic effect. Its effect on consciousness was reversed 2–4 h after drug administration and recurred with zolpidem readministration. However, an assessor-blinded, single case study of a man in MCS following TBI documented no improvement in ability to follow instructions with zolpidem. There was slight worsening in performance at some tasks. Assessments in this study were performed daily for one week while on zolpidem and for another week off zolpidem (Singh et al., 2008). A recent study of 15 subjects by Whyte and Myers (2009) suggest that a few patients made a clear and discernable improvement associated with the drug; however, most failed to respond. Further controlled studies are required to determine the role of zolpidem in disorders of consciousness following TBI.

Naltrexone

Naltrexone is a competitive pure opioid antagonist. It is commonly used as an opioid antidote and for the treatment of alcohol dependence. Endogenous opioids have been implicated in pathophysiological processes contributing to neuronal damage following brain injury, through impairing NMDA-mediated cerebrovasodilation in the pial arteries (Armstead, 1997). Selective activation of kappa receptors has been shown to exacerbate, while selective blockade of kappa receptors provided protection in animal models of TBI (McIntosh et al., 1987b; McIntosh et al., 1987a; McIntosh, 1993). Immunoreactivity to dynorphin, an endogenous opioid, is also increased in regions of histopathologic damage and decreased blood flow in rat brain following fluid percussion TBI (McIntosh et al., 1987b). However, other studies suggest the protective effect of mu-selective agonist and the deleterious effect of mu-selective antagonists in rat models of TBI (Hayes et al., 1990; Lyeth et al., 1995). Clinical data is currently limited to case reports, in which naltrexone resulted in overall improvement in functional status in TBI patients in low-arousal states, and in cases of abulia and akinesia (Calvanio et al., 2000; Seliger et al., 1998). It is also reported to improve symptoms of postconcussional syndrome (Tennant and Wild, 1987) (Table 2).

Nonpharmacologic

Deep brain stimulation

Deep brain stimulation (DBS) involves the continuous application of electrical stimulation pulses at high frequency to specific brain regions via implanted electrodes. Stimulation to different structures in the basal ganglia is used in the treatment of movement disorders including Parkinson's disease, dystonia, and tremors. It has also been used in major depression and chronic pain. The role of this technique is covered by another chapter.

Noninvasive brain stimulation

Noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct stimulation (tDCS) have demonstrated efficacy in a number of rehabilitation settings. rTMS and tDCS have been shown to augment motor recovery following stroke (Boggio et al., 2007; Hummel et al., 2005). Preliminary data also suggests that tDCS has a role in motor recovery following TBI. rTMS and tDCS have also been reported to improve functional performance in Parkinson's disease subjects.

With rTMS, repeated magnetic pulses are delivered over the scalp using a coil, inducing weak eddy currents in the underlying cortex. The depth and focality of the stimulation varies with the shape of the magnetic coil. In tDCS, a constant current of 1–2 mA is delivered through surface electrodes over the scalp.

Table 2. Psychopharmacologic treatments for slow to recover states

Reference	Population	Study design	Regimen	Results
Neurostimulants				
Methylphenidate: Martin and Whyte (2007)	$N =$ 22, MCS or VS (17 traumatic)	Meta-analysis of single-subject crossover studies	Methylphenidate 7.5–25 mg/day	No significant difference in responsiveness or accuracy in command-following
Methylphenidate: Moein et al. (2006)	$N = 80$, ICU patients with moderate (40) to severe (40) TBI	Randomized placebo-controlled study	Methylphenidate 0.3 mg/kg/dose twice daily to max of 20 mg/dose	23% decrease in ICU LOS (9.85 vs. 12.95; $p = 0.06$) and hospital LOS (14.1 vs. 18.35; $p = 0.029$) in severe TBI patients. 26% decrease in ICU LOS (4.09 vs. 5.58; $p = 0.05$), no significant difference in hospital LOS in moderate TBI patients (11.12 vs. 13.72; $p = 0.043$)
Dopaminergic agents				
Amantadine: Zafonte et al. (2001)	$N = 1$, MCS 5 months postinjury	ABAB	Amantadine 100–400 mg/day	Dose-dependent emergence from MCS, measured by CNCS
Amantadine: Gualtieri et al. (1989)	$N = 30$	Case series		Improved arousal, decreased fatigue, decreased distractibility and assaultiveness
Amantadine: Meythaler et al. (2002)	$N = 35$, severe TBI, 4 days to 6 weeks postinjury	Randomized double-blind placebo-controlled crossover study	Amantadine 200 mg/day for 6 weeks	Significant improvement in MMSE, GOS, DRS and FIM-cog, regardless of when amantadine therapy was initiated during the recovery period. Group 2 (active drug second 6 weeks) demonstrated significant spontaneous recovery while on placebo. Group 1 (active drug first 6 weeks) showed no significant additional improvement on placebo
Amantadine: Hughes et al. (2005)	$N = 123$, severe TBI who remained in coma for more than 1 week despite being medically stable	Retrospective cohort study	Amantadine 100–200 mg twice daily	28 of the 123 subjects received amantadine. No significant difference in the rate of emergence from coma with and without amantadine
Amantadine: Saniova et al. (2004)	$N = 74$, severe TBI in ICU 3 days post-trauma	Retrospective review	IV amantadine 200 mg twice daily for 3 days	33 subjects received standard therapy, 41 received IV amantadine from day 3 of admission. Survival and GCS on discharge was significantly better in those treated with amantadine (9.76 vs., 5.73; $p < 0.001$)

Table 2. (*Continued*)

Reference	Population	Study design	Regimen	Results
Various dopamine agonists: Patrick et al. (2003)	$N = 10$ Children and adolescents in MCS/VS at least 30 days postinjury	Retrospective chart review (AABBB)	Amantadine, methylphenidate, pramipexole, bromocriptine, or levodopa	Rate of improvement of WNSSP was significantly better with dopamine agonist treatment than before treatment ($p = 0.03$)
Amantadine: Nickels et al. (1994)	$N = 12$, heterogeneous brain injury treated with amantadine for cognitive deficits	Retrospective chart review	Amantadine 100–200 mg twice daily	8 of 9 low-arousal subjects had increased level of responsiveness
Pramipexole: Patrick et al. (2006)	$N = 10$ children and adolescents in MCS or VS at least 1 month postinjury	Randomized double-blind trial	Amantadine up to 100 mg twice daily; pramipexole dosed according to age, up to 0.25 mg twice daily. Medication increased over 4 weeks, weaned over 2, then discontinued	No difference in efficacy between amantadine and pramipexole. Higher rate of change of CNCS, WNSSP, and DRS while on medication than off medication ($p < 0.05$)
Bromocriptine: Passler and Riggs (2001)	$N = 5$, consecutive VS patients 33–50 days postinjury	Retrospective chart review	Bromocriptine 2.5 mg twice daily	Greater than normally reported rate of transition from persistent VS to MCS on bromocriptine, on DRS, over 12 months, compared to reported literature
Levodopa: Haig and Ruess (1990)	$N = 1$, PVS patient	Case report	Levodopa/carbidopa 100/10 mg twice daily	Became responsive and conversant within days of initiation of levodopa/carbidopa
Levodopa: Krimchansky et al. (2004)	$N = 8$, VS >1 month postinjury (2 patients >9 months postinjury)	Prospective series	Carbidopa/levodopa 25/250 mg 1/4 tab 5 times a day to 1 tab TID	All followed commands within 2 weeks of drug initiation. 7 had reciprocal interaction in a mean time of 31 days (including the 2 patients >9 months postinjury); 1 remained in MCS
Apomorphine: Fridman et al. (2009)	$N = 1$, MCS. 104 days postinjury	Case report	Continuous apomorphine subcutaneous 12 hours/day up to 8 mg/h for 179 days	Able to follow commands within the first day. CNCS, DRS, and GOS improved. Deterioration in cognitive and motor function upon trials of drug withdrawal
Antidepressants				
Sertraline: Meythaler et al. (2001a)	$N = 11$, within 2 weeks of severe TBI	Randomized prospective placebo-controlled trial	Sertraline 100 mg/day for 2 weeks	No significant difference in the rate of cognitive recovery measured by the O-log, GOAT, and ABS with sertraline
Amitriptyline & desipramine: Reinhard et al. (1996)	$N = 3$, 5–19 months post severe injury	Case series	Amitriptyline 50 mg/day initiated for treatment of complex regional pain syndrome. Desipramine 50 mg/day and 75 mg/day	Significant improvement in arousal and initiation which was reversed in 2 subjects on drug withdrawal

Table 2. (*Continued*)

Reference	Population	Study design	Regimen	Results
Modafinil				
Modafinil: Teitelman (2001)	$N = 10$, closed head injury	Open-label case series	Modafinil 100–400 mg/day	Subjective decreased daytime sleepiness
Modafinil: Jha et al. (2008)	$N = 51$, chronic TBI without neurological deficits	Randomized, blinded, placebo-controlled crossover study	Modafinil 400 mg/day for 4 weeks.	No significant differences in measures of fatigue and daytime sleepiness
Zolpidem				
Zolpidem: Clauss et al. (2000)	$N = 1$, PVS 3 years post-TBI	Case report	Zolpidem 10 mg/day was administered initially to treat restlessness	Verbal responsiveness improved 15 min after first administration. Increased blood flow was seen through areas of hypoactivity on brain SPECT
Zolpidem: Clauss and Nel (2006)	$N = 3$, PVS at least 3 years post-TBI (2) or anoxic injury	Case reports	Zolpidem 10 mg/day	GCS improved from 6–9 to 10–15. RLAS improved from I–II to V–VII
Zolpidem: Singh et al. (2008)	$N = 1$, MCS, 4 years post-TBI	Assessor blinded single case study	Zolpidem 10 mg/day for 1 week	No benefit in tests of following instructions of increasing complexity, compared to placebo
Naltrexone				
Naltrexone: Calvanio et al. (2000)	$N = 1$, Rancho Los Amigos Level II, 14 weeks post-TBI	Case report	Naltrexone 50 mg/day increased to 100 mg/day after 1 week	FIM score improved 16 points in 6 weeks vs. 5 points in 12 weeks before medication. Improved accuracy in answering nonverbal questions, initiation, and attention
Naltrexone: Seliger et al. (1998)	$N = 1$, severe abulia and akinesia following TBI	Case report		Improvement in FIM scores with naltrexone after unsuccessful trials of other pharmacotherapy

CNCS, coma/near coma scale; DRS, disability rating scale; FIM, functional independence measure; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; LOS, length of stay; MCS, minimally conscious state; MMSE, mini mental state examination; RLAS, Rancho Los Amigos Scale; VS, vegetative state; WNSSP, Western NeuroSensory Stimulation Profile.

The nature of neuromodulation achieved by these techniques depends on the frequency of rTMS and the polarity of tDCS. Cortical excitability is an indicator of neuromodulation and is defined as the responsiveness of the brain region to stimulation. Low-frequency rTMS (1 Hz and below) and cathodal tDCS inhibit cortical excitability (Nitsche et al., 2003). High-frequency rTMS (>5 Hz) and anodal tDCS are facilitatory (Nitsche and Paulus, 2000; Nitsche and Paulus, 2001), resulting in heightened cortical excitability. The after-effects of stimulation last beyond the period of stimulation and are associated with synaptic strengthening (Liebetanz et al., 2002; Nitsche et al., 2003). The after-effects depend on the duration of stimulation, the number and intensity of rTMS pulses delivered, and the intensity of tDCS current.

No studies thus far have examined the ability of noninvasive brain stimulation to augment arousal following brain injury. However, rTMS to the primary motor cortex has been shown to induce release of striatal dopamine in healthy subjects (Strafella, 2001; Strafella et al., 2003). In fact, prefrontal rTMS has also been shown to increase striatal dopamine activity to a similar degree as that induced by 0.3 mg/kg of intravenous dextroamphetamine administration. In view of the postulated role of disrupted dopaminergic pathways in hypoarousal post-TBI, a possible role exists for noninvasive cortical stimulation in augmenting arousal.

The modulation of cortical excitability may have a role in enhancing arousal. Functional imaging studies indicate the preservation of cerebral networks, which are underactive in certain subjects in MCS (Boly et al., 2004). Cortical brain stimulation may be used to activate these networks, similar to the postulated mechanism of DBS. Furthermore, a combination of noninvasive stimulation and pharmacological augmentation may be more effective.

Recent studies have begun to shed light on the interaction between medications acting on neurotransmitter pathways, and the neuroplasticity induced by noninvasive brain stimulation. There is an observation that dopamine prolongs the inhibitory or facilitatory effect on neuroplasticity in the motor cortex. It has been shown to modulate tDCS-induced excitability changes, possibly contributing to NMDA-dependent neuroplasticity (Nitsche et al., 2006). Furthermore, D2 receptor blockade with sulpiride has been shown to abolish tDCS-induced excitability changes. tDCS appears to have dose-dependent effects upon dopamine receptor activation thus impacting plasticity in humans (Monte-Silva et al., 2009). Conversely, it enhances the paired associative stimulation (PAS)-induced synapse-specific excitability, indicating that dopamine enhances the synaptic strength of learning-related neuronal connections represented by focal plasticity, but inhibits nonfocal plasticity induced by tDCS. This is in contrast to the finding that amphetamines prolong the anodal tDCS-generated excitability enhancement, but do not influence the cathodal tDCS-induced inhibition (Nitsche et al., 2004).

Further studies are required to ascertain the effect of noninvasive brain stimulation on the neural networks impacting arousal, and the interaction between stimulation sites and spatial release of neurotransmitters.

Conclusion

The field of pharmacologic intervention for those in low-level states has been limited by limited animal models, small studies, and challenging metrics. However, optimism is justified as improvements have been observed and novel interventions are being tried. Further studies are required also to elucidate the role of pharmacotherapy in the recovery of consciousness and function.

References

Adams, J. H., Doyle, D., Ford, I., Gennarelli, T. A., Graham, D. I., & McLellan, D. R. (1989). Diffuse axonal injury in head injury: Definition, diagnosis and grading. *Histopathology*, *15*, 49–59.

Alban, J. P., Hopson, M. M., Ly, V., & Whyte, J. (2004). Effect of methylphenidate on vital signs and adverse effects in adults with traumatic brain injury. *American Journal of Physical Medicine and Rehabilitation*, *83*, 131–137.

Arciniegas, D. B. (2003). The cholinergic hypothesis of cognitive impairment caused by traumatic brain injury. *Current Psychiatry Reports*, *5*, 391–399.

Arciniegas, D. B., & Silver, J. M. (2006). Pharmacotherapy of posttraumatic cognitive impairments. *Behavioural Neurology*, *17*, 25–42.

Armstead, W. M. (1997). Role of opioids in the physiologic and pathophysiologic control of the cerebral circulation. *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine*, *214*,
210–221.

Arpa, J., & De Andres, I. (1993). Re-examination of the effects of raphe lesions on the sleep/wakefulness cycle states of cats. *Journal of Sleep Research*, *2*, 96–102.

Bakay, R. A., Sweeney, K. M., & Wood, J. H. (1986). Pathophysiology of cerebrospinal fluid in head injury: Part 1. Pathological changes in cerebrospinal fluid solute composition after traumatic injury. *Neurosurgery*, *18*, 234–243.

Baker, A. J., Moulton, R. J., MacMillan, V. H., & Shedden, P. M. (1993). Excitatory amino acids in cerebrospinal fluid following traumatic brain injury in humans. *Journal of Neurosurgery*, *79*, 369–372.

Baldo, B. A., Daniel, R. A., Berridge, C. W., & Kelley, A. E. (2003). Overlapping distributions of orexin/hypocretin- and dopamine-beta-hydroxylase immunoreactive fibers in rat brain regions mediating arousal, motivation, and stress. *The Journal of Comparative Neurology*, *464*, 220–237.

Baranova, A. I., Whiting, M. D., & Hamm, R. J. (2006). Delayed, post-injury treatment with aniracetam improves cognitive performance after traumatic brain injury in rats. *Journal of Neurotrauma*, *23*, 1233–1240.

Baumann, C. R., Stocker, R., Imhof, H. G., Trentz, O., Hersberger, M., Mignot, E., et al. (2005). Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. *Neurology*, *65*, 147–149.

Benarroch, E. E. (2008). The midline and intralaminar thalamic nuclei: Anatomic and functional specificity and implications in neurologic disease. *Neurology*, *71*, 944–949.

Berridge, C. W. (2008). Noradrenergic modulation of arousal. *Brain Research Reviews*, *58*, 1–17.

Boggio, P. S., Nunes, A., Rigonatti, S. P., Nitsche, M. A., Pascual-Leone, A., & Fregni, F. (2007). Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restorative Neurology and Neuroscience*, *25*, 123–129.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, P., Del, F. G., et al. (2004). Auditory processing in severely brain injured patients: Differences between the minimally conscious state and the persistent vegetative state. *Archives of Neurology*, *61*, 233–238.

Bornstein, MB. (1946). Presence and action of acetylcholine in experimental brain injury. *Journal of Neurophysiology*, *9*, 349–366.

Caine, D., & Watson, J. D. (2000). Neuropsychological and neuropathological sequelae of cerebral anoxia: A critical review. *Journal of the International Neuropsychological Society*, *6*, 86–99.

Calvanio, R., Burke, D. T., Kim, H. J., Cheng, J., Lepak, P., Leonard, J., et al. (2000). Naltrexone: Effects on motor function, speech, and activities of daily living in a patient with traumatic brain injury. *Brain Injury*, *14*, 933–942.

Chalmers, D. (2000). What is a neural correlate of consciousness? In: T. Metzinger (Ed.), Neural correlates of consciousness: Empirical and conceptual questions (pp. 17–40), Cambridge, MA: MIT Press.

Cheng, J. P., Hoffman, A. N., Zafonte, R. D., & Kline, A. E. (2008). A delayed and chronic treatment regimen with the 5-HT1A receptor agonist 8-OH-DPAT after cortical impact injury facilitates motor recovery and acquisition of spatial learning. *Behavioural Brain Research*, *194*, 79–85.

Ciallella, J. R., Yan, H. Q., Ma, X., Wolfson, B. M., Marion, D. W., DeKosky, S. T., et al. (1998). Chronic effects of traumatic brain injury on hippocampal vesicular acetylcholine transporter and M2 muscarinic receptor protein in rats. *Experimental Neurology*, *152*, 11–19.

Claudet, I., & Marechal, C. (2009). Status epilepticus in a pediatric patient with amantadine overdose. *Pediatric Neurology*, *40*, 120–122.

Clauss, R., & Nel, W. (2006). Drug induced arousal from the permanent vegetative state. *NeuroRehabilitation*, *21*, 23–28.

Clauss, R. P., Guldenpfennig, W. M., Nel, H. W., Sathekge, M. M., & Venkannagari, R. R. (2000). Extraordinary arousal from semi-comatose state on zolpidem. A case report. *South African Medical Journal*, *90*, 68–72.

Clauss, R. P., van der Merwe, C. E., & Nel, H. W. (2001). Arousal from a semi-comatose state on zolpidem. *South African Medical Journal*, *91*, 788–789.

Clifton, G. L., Ziegler, M. G., Grossman, R. G., Clifton, G. L., Ziegler, M. G., & Grossman, R. G. (1981). Circulating catecholamines and sympathetic activity after head injury. *Neurosurgery*, *8*, 10–14.

Cohen, S. I., & Duong, T. T. (2008). Increased arousal in a patient with anoxic brain injury after administration of zolpidem. *American Journal of Physical Medicine and Rehabilitation*, *87*, 229–231.

Decavel, C., Van den Pol, A. N., Decavel, C., & Van den Pol, A. N. (1990). GABA: A dominant neurotransmitter in the hypothalamus. *The Journal of Comparative Neurology*, *302*, 1019–1037.

Dement, W., & Henriksen, S. (1973). Biogenic amines, phasic events, and behavior. *Pharmacology and the Future of Man*, 74–89.

Dixon, C. E., Kraus, M. F., Kline, A. E., Ma, X., Yan, H. Q., Griffith, R. G., et al. (1999). Amantadine improves water maze performance without affecting motor behavior following traumatic brain injury in rats. *Restorative Neurology and Neuroscience*, *14*, 285–294.

Dixon, C. E., Liu, S. J., Jenkins, L. W., Bhattachargee, M., Whitson, J. S., Yang, K., et al. (1995). Time course of increased vulnerability of cholinergic neurotransmission following traumatic brain injury in the rat. *Behavioural Brain Research*, *70*, 125–131.

Drake, M. E., Jr., Pakalnis, A., Denio, L. S., & Phillips, B. (1991). Amantadine hydrochloride for refractory generalized epilepsy in adults. *Acta Neurologica Belgica*, *91*, 159–164.

Duan, W., Peng, Q., Masuda, N., Ford, E., Tryggestad, E., Ladenheim, B., et al. (2008). Sertraline slows disease progression and increases neurogenesis in N171-82Q mouse model of Huntington's disease. *Neurobiology of Disease*, *30*, 312–322.

Dugovic, C., Shelton, J. E., Aluisio, L. E., Fraser, I. C., Jiang, X., Sutton, S. W. et al. (2009). Blockade of orexin-1 receptors attenuates orexin-2 receptor antagonism-induced sleep promotion in the rat. The *Journal of Pharmacology and Experimental Therapeutics*, *330*(1), 142–151.

Elovic, E. (2000). Use of provigil for underarousal following TBI. *The Journal of Head Trauma Rehabilitation*, *15*, 1068–1071.

Faden, A. I., Demediuk, P., Panter, S. S., Vink, R., Faden, A. I., Demediuk, P., et al. (1989). The role of excitatory amino acids and NMDA receptors in traumatic brain injury. *Science*, *244*, 798–800.

Feeney, D. M., Gonzalez, A., & Law, W. A. (1982). Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science*, *217*, 855–857.

Ford, B., Holmes, C. J., Mainville, L., Jones, B. E., Ford, B., Holmes, C. J., et al. (1995). GABAergic neurons in the rat pontomesencephalic tegmentum: Codistribution with cholinergic and other tegmental neurons projecting to the posterior lateral hypothalamus. *The Journal of Comparative Neurology*, *363*, 177–196.

Fort, P., Khateb, A., Pegna, A., Muhlethaler, M., Jones, B. E., Fort, P., et al. (1995). Noradrenergic modulation of cholinergic nucleus basalis neurons demonstrated by in vitro pharmacological and immunohistochemical evidence in the guinea-pig brain. *The European Journal of Neuroscience*, *7*, 1502–1511.

Fridman, E. A., Calvar, J., Bonetto, M., Gamzu, E., Krimchansky, B. Z., Meli, F., et al. (2009). Fast awakening from minimally conscious state with apomorphine. *Brain Injury*, *23*, 172–177.

Globus, M. Y., Busto, R., Dietrich, W. D., Martinez, E., Valdes, I., Ginsberg, M. D., et al. (1988). Effect of ischemia on the in vivo release of striatal dopamine, glutamate, and gamma-aminobutyric acid studied by intracerebral microdialysis. *Journal of Neurochemistry*, *51*, 1455–1464.

Globus, M. Y., Busto, R., Dietrich, W. D., Martinez, E., Valdes, I., Ginsberg, M. D., et al. (1989). Direct evidence for acute and massive norepinephrine release in the hippocampus during transient ischemia. *Journal of Cerebral Blood Flow and Metabolism*, *9*, 892–896.

Globus, M. Y., Wester, P., Busto, R., Dietrich, W. D., Globus, M. Y., Wester, P., et al. (1992). Ischemia-induced extracellular release of serotonin plays a role in CA1 neuronal cell death in rats. *Stroke*, *23*, 1595–1601.

Goldstein, L. B., & Bullman, S. (2002). Differential effects of haloperidol and clozapine on motor recovery after sensorimotor cortex injury in rats. *Neurorehabilitation and Neural Repair*, *16*, 321–325.

Gualtieri, T., Chandler, M., Coons, T. B., & Brown, L. T. (1989). Amantadine: A new clinical profile for traumatic brain injury. *Clinical Neuropharmacology*, *12*, 258–270.

Gucuyener, K., Erdemoglu, A. K., Senol, S., Serdaroglu, A., Soysal, S., & Kockar, A. I. (2003). Use of methylphenidate for attention-deficit hyperactivity disorder in patients with epilepsy or electroencephalographic abnormalities. *Journal of Child Neurology*, *18*, 109–112.

Haig, A. J., & Ruess, J. M. (1990). Recovery from vegetative state of six months' duration associated with Sinemet (levodopa/carbidopa). *Archives of Physical Medicine and Rehabilitation*, *71*, 1081–1083.

Hamill, R. W., Woolf, P. D., McDonald, J. V., Lee, L. A., Kelly, M., Hamill, R. W., et al. (1987). Catecholamines predict outcome in traumatic brain injury. *Annals of Neurology*, *21*, 438–443.

Hayes, R. L., Lyeth, B. G., Jenkins, L. W., Zimmerman, R., McIntosh, T. K., Clifton, G. L., et al. (1990). Possible protective effect of endogenous opioids in traumatic brain injury. *Journal of Neurosurgery*, *72*, 252–261.

Hemmer, S. A., Pasternak, J. F., Zecker, S. G., & Trommer, B. L. (2001). Stimulant therapy and seizure risk in children with ADHD. *Pediatric Neurology*, *24*, 99–102.

Hobson, J. A., McCarley, R. W., Wyzinski, P. W., Hobson, J. A., McCarley, R. W., & Wyzinski, P. W. (1975). Sleep cycle oscillation: Reciprocal discharge by two brainstem neuronal groups. *Science*, *189*, 55–58.

Hughes, S., Colantonio, A., Santaguida, P. L., & Paton, T. (2005). Amantadine to enhance readiness for rehabilitation following severe traumatic brain injury. *Brain Injury*, *19*, 1197–1206.

Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W. H., Gerloff, C., et al. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*, *128*, 490–499.

Ito, T., Shibata, K., Watanabe, A., & Akabane, J. (2001). Neuroleptic malignant syndrome following withdrawal of amantadine in a patient with influenza A encephalopathy. *European Journal of Pediatric Surgery*, *160*, 401.

Jacogs, B. L., Asher, R., Dement, W. C., Jacogs, B. L., Asher, R., & Dement, W. C. (1973). Electrophysiological and behavioral effects of electrical stimulation of the raphe nuclei in cats. *Physiology and Behavior*, *11*, 489–495.

Jha, A., Weintraub, A., Allshouse, A., Morey, C., Cusick, C., Kittelson, J., et al. (2008). A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *23*, 52–63.

Jones, B. E. (1995). Reticular formation. Cytoarchitecture transmitters and projections. In: *The rat nervous system* (pp. 155–171). New South Wales, Australia: Academic Press.

Jones, B. E., Cuello, A. C., Jones, B. E., & Cuello, A. C. (1989). Afferents to the basal forebrain cholinergic cell area from pontomesencephalic — catecholamine, serotonin, and acetylcholine — neurons. *Neuroscience*, *31*, 37–61.

Jones, B. E., & Jones, B. E. (2003). Arousal systems. *Frontiers in bioscience*, *8*, s438–s451.

Jones, B. E., & Jones, B. E. (2008). Modulation of cortical activation and behavioral arousal by cholinergic and orexinergic systems. *Annals of the New York Academy of Sciences*, *1129*, 26–34.

Kaneko, T., Itoh, K., Shigemoto, R., Mizuno, N., Kaneko, T., Itoh, K., et al. (1989). Glutaminase-like immunoreactivity in the lower brainstem and cerebellum of the adult rat. *Neuroscience*, *32*, 79–98.

Kanthan, R., Shuaib, A., Griebel, R., el Alazounni, H., Miyashita, H., Kalra, J., et al. (1996). Evaluation of monoaminergic neurotransmitters in the acute focal ischemic human brain model by intracerebral in vivo microdialysis. *Neurochemical Research*, *21*, 563–566.

Karakucuk, E. I., Pasaoglu, H., Pasaoglu, A., Oktem, S., Karakucuk, E. I., Pasaoglu, H., et al. (1997). Endogenous neuropeptides in patients with acute traumatic head injury. II: Changes in the levels of cerebrospinal fluid substance P, serotonin and lipid peroxidation products in patients with head trauma. *Neuropeptides*, *31*, 259–263.

Ker, K., Perel, P., & Blackhall, K. (2009). Beta-2 receptor antagonists for traumatic brain injury: A systematic review of controlled trials in animal models. *CNS Neuroscience and Therapeutics*, *15*, 52–64.

Khateb, A., Fort, P., Alonso, A., Jones, B. E., Muhlethaler, M., Khateb, A., et al. (1993). Pharmacological and immunohistochemical evidence for serotonergic modulation of cholinergic nucleus basalis neurons. *The European Journal of Neuroscience*, *5*, 541–547.

Khateb, A., Fort, P., Pegna, A., Jones, B. E., Muhlethaler, M., Khateb, A., et al. (1995a). Cholinergic nucleus basalis neurons are excited by histamine in vitro. *Neuroscience*, *69*, 495–506.

Khateb, A., Fort, P., Serafin, M., Jones, B. E., Muhlethaler, M., Khateb, A., et al. (1995b). Rhythmical bursts induced by NMDA in guinea-pig cholinergic nucleus basalis neurones in vitro. *The Journal of Physiology (London)*, *487*, 623–638.

Kline, A. E., Hoffman, A. N., Cheng, J. P., Zafonte, R. D., & Massucci, J. L. (2008). Chronic administration of antipsychotics impede behavioral recovery after experimental traumatic brain injury. *Neuroscience Letters*, *448*, 263–267.

Kline, A. E., Massucci, J. L., Dixon, C. E., Zafonte, R. D., & Bolinger, B. D. (2004a). The therapeutic efficacy conferred by the 5-HT(1A) receptor agonist 8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) after experimental traumatic brain injury is not mediated by concomitant hypothermia. *Journal of Neurotrauma*, *21*, 175–185.

Kline, A. E., Massucci, J. L., Ma, X., Zafonte, R. D., & Dixon, C. E. (2004b). Bromocriptine reduces lipid peroxidation and enhances spatial learning and hippocampal neuron survival in a rodent model of focal brain trauma. *Journal of Neurotrauma*, *21*, 1712–1722.

Kline, A. E., Massucci, J. L., Marion, D. W., & Dixon, C. E. (2002). Attenuation of working memory and spatial acquisition deficits after a delayed and chronic bromocriptine treatment regimen in rats subjected to traumatic brain injury by controlled cortical impact. *Journal of Neurotrauma*, *19*, 415–425.

Kline, A. E., Massucci, J. L., Zafonte, R. D., Dixon, C. E., DeFeo, J. R., & Rogers, E. H. (2007a). Differential effects of single versus multiple administrations of haloperidol and risperidone on functional outcome after experimental brain trauma. *Critical Care Medicine*, *35*, 919–924.

Kline, A. E., Wagner, A. K., Westergom, B. P., Malena, R. R., Zafonte, R. D., Olsen, A. S., et al. (2007b). Acute treatment with the 5-HT(1A) receptor agonist 8-OH-DPAT and chronic environmental enrichment confer neurobehavioral benefit after experimental brain trauma. *Behavioural Brain Research*, *177*, 186–194.

Kline, A. E., Yan, H. Q., Bao, J., Marion, D. W., & Dixon, C. E. (2000). Chronic methylphenidate treatment enhances water maze performance following traumatic brain injury in rats. *Neuroscience Letters*, *280*, 163–166.

Konrad, K., Gauggel, S., Schurek, J., Konrad, K., Gauggel, S., & Schurek, J. (2003). Catecholamine functioning in children with traumatic brain injuries and children with attention-deficit/hyperactivity disorder. *Cognitive Brain Research*, *16*, 425–433.

Krimchansky, B. Z., Keren, O., Sazbon, L., & Groswasser, Z. (2004). Differential time and related appearance of signs, indicating improvement in the state of consciousness in vegetative state traumatic brain injury (VS-TBI) patients after initiation of dopamine treatment. *Brain Injury*, *18*, 1099–1105.

Lavretsky, H., Park, S., Siddarth, P., Kumar, A., & Reynolds, C. F., III (2006). Methylphenidate-enhanced antidepressant response to citalopram in the elderly: A double-blind, placebo-controlled pilot trial. *The American Journal of Geriatric Psychiatry*, *14*, 181–185.

Lee, M. G., Hassani, O. K., Alonso, A., Jones, B. E., Lee, M. G., Hassani, O. K., et al. (2005). Cholinergic basal forebrain neurons burst with theta during waking and paradoxical sleep. *Journal of Neuroscience*, *25*, 4365–4369.

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, *125*, 2238–2247.

Lin, J. S., Roussel, B., Akaoka, H., Fort, P., Debilly, G., Jouvet, M., et al. (1992). Role of catecholamines in the modafinil and amphetamine induced wakefulness: A comparative pharmacological study in the cat. *Brain Research*, *591*, 319–326.

Lin, J. S., Sakai, K., Vanni-Mercier, G., Jouvet, M., Lin, J. S., Sakai, K., et al. (1989). A critical role of the posterior hypothalamus in the mechanisms of wakefulness determined by microinjection of muscimol in freely moving cats. *Brain Research*, *479*, 225–240.

Lyeth, B. G., Jiang, J. Y., Gong, Q. Z., Hamm, R. J., & Young, H. F. (1995). Effects of mu opioid agonist and antagonist on neurological outcome following traumatic brain injury in the rat. *Neuropeptides*, *29*, 11–19.

Manns, I. D., Alonso, A., Jones, B. E., Manns, I. D., Alonso, A., & Jones, B. E. (2000). Discharge profiles of juxtacellularly labeled and immunohistochemically identified GABAergic basal forebrain neurons recorded in association with the electroencephalogram in anesthetized rats. *Journal of Neuroscience*, *20*, 9252–9263.

Marcoli, M., Cervetto, C., Castagnetta, M., Sbaffi, P., Maura, G., Marcoli, M., et al. (2004). 5-HT control of ischemia-evoked glutamate efflux from human cerebrocortical slices. *Neurochemistry International*, *45*, 687–691.

Markianos, M., Seretis, A., Kotsou, A., Christopoulos, M., Markianos, M., Seretis, A., et al. (1996). CSF neurotransmitter metabolites in comatose head injury patients during changes in their clinical state. *Acta Neurochirurgica (Wien)*, *138*, 57–59.

Markianos, M., Seretis, A., Kotsou, S., Baltas, I., Sacharogiannis, H., Markianos, M., et al. (1992). CSF neurotransmitter metabolites and short-term outcome of patients in coma after head injury. *Acta Neurologica Scandinavica*, *86*, 190–193.

Martin, R. T., & Whyte, J. (2007). The effects of methylphenidate on command following and yes/no communication in

persons with severe disorders of consciousness: A meta-analysis of n-of-1 studies. *American Journal of Physical Medicine and Rehabilitation*, *86*, 613–620.

Massucci, J. L., Kline, A. E., Ma, X., Zafonte, R. D., & Dixon, C. E. (2004). Time dependent alterations in dopamine tissue levels and metabolism after experimental traumatic brain injury in rats. *Neuroscience Letters*, *372*, 127–131.

Matsuda, W., Komatsu, Y., Yanaka, K., & Matsumura, A. (2005). Levodopa treatment for patients in persistent vegetative or minimally conscious states. *Neuropsychological Rehabilitation*, *15*, 414–427.

McCormick, D. A., & McCormick, D. A. (1992). Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Progress in Neurobiology*, *39*, 337–388.

McIntosh, T. K. (1993). Novel pharmacologic therapies in the treatment of experimental traumatic brain injury: A review. *Journal of Neurotrauma*, *10*, 215–261.

McIntosh, T. K., Hayes, R. L., DeWitt, D. S., Agura, V., & Faden, A. I. (1987a). Endogenous opioids may mediate secondary damage after experimental brain injury. *The American Journal of Physiology*, *253*, E565–E574.

McIntosh, T. K., Head, V. A., & Faden, A. I. (1987b). Alterations in regional concentrations of endogenous opioids following traumatic brain injury in the cat. *Brain Research*, *425*, 225–233.

McIntosh, T. K., Yu, T., Gennarelli, T. A., McIntosh, T. K., Yu, T., & Gennarelli, T. A. (1994). Alterations in regional brain catecholamine concentrations after experimental brain injury in the rat. *Journal of Neurochemistry*, *63*, 1426–1433.

Meaney, D. F., Smith, D. H., Shreiber, D. I., Bain, A. C., Miller, R. T., Ross, D. T., et al. (1995). Biomechanical analysis of experimental diffuse axonal injury. *Journal of Neurotrauma*, *12*, 689–694.

Meisner, F., Scheller, C., Kneitz, S., Sopper, S., Neuen-Jacob, E., Riederer, P., et al. (2008). Memantine upregulates BDNF and prevents dopamine deficits in SIV-infected macaques: A novel pharmacological action of memantine. *Neuropsychopharmacology*, *33*, 2228–2236.

Meythaler, J. M., Brunner, R. C., Johnson, A., & Novack, T. A. (2002). Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: A pilot double-blind randomized trial. *The Journal of Head Trauma Rehabilitation*, *17*, 300–313.

Meythaler, J. M., Depalma, L., Devivo, M. J., Guin-Renfroe, S., & Novack, T. A. (2001a). Sertraline to improve arousal and alertness in severe traumatic brain injury secondary to motor vehicle crashes. *Brain Injury*, *15*, 321–331.

Meythaler, J. M., Peduzzi, J. D., Eleftheriou, E., & Novack, T. A. (2001b). Current concepts: Diffuse axonal injury-associated traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *82*, 1461–1471.

Miller, J. D., Farber, J., Gatz, P., Roffwarg, H., German, D. C., Miller, J. D., et al. (1983). Activity of mesencephalic dopamine and non-dopamine neurons across stages of sleep and walking in the rat. *Brain Research*, *273*, 133–141.

Mobayed, M., & Dinan, T. G. (1990). Buspirone/prolactin response in post head injury depression. *Journal of Affective Disorders*, *19*, 237–241.

Moein, H., Khalili, H. A., & Keramatian, K. (2006). Effect of methylphenidate on ICU and hospital length of stay in patients with severe and moderate traumatic brain injury. *Clinical Neurology and Neurosurgery*, *108*, 539–542.

Monte-Silva, K., Kuo, M. F., Thirugnanasambandam, N., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2009). Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans. *Journal of Neuroscience*, *29*, 6124–6131.

Moore, J. L., McAuley, J. W., Long, L., & Bornstein, R. (2002). An evaluation of the effects of methylphenidate on outcomes in adult epilepsy patients. *Epilepsy and Behavior*, *3*, 92–95.

Morrison, J. H., Molliver, M. E., Grzanna, R., Morrison, J. H., Molliver, M. E., & Grzanna, R. (1979). Noradrenergic innervation of cerebral cortex: Widespread effects of local cortical lesions. *Science*, *205*, 313–316.

Moruzzi, G., Magoun, H. W., Moruzzi, G., & Magoun, H. W. (1995). Brain stem reticular formation and activation of the EEG 1949. *Journal of Neuropsychiatry and Clinical Neurosciences*, *7*, 251–267.

Ni, J. W., Matsumoto, K., Li, H. B., Murakami, Y., Watanabe, H., Ni, J. W., et al. (1995). Neuronal damage and decrease of central acetylcholine level following permanent occlusion of bilateral common carotid arteries in rat. *Brain Research*, *673*, 290–296.

Nickels, J. L., Schneider, W. N., Dombovy, M. L., & Wong, T. M. (1994). Clinical use of amantadine in brain injury rehabilitation. *Brain Injury*, *8*, 709–718.

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., et al. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology*, *553*, 293–301.

Nitsche, M. A., Grundey, J., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2004). Catecholaminergic consolidation of motor cortical neuroplasticity in humans. *Cerebral Cortex*, *14*, 1240–1245.

Nitsche, M. A., Lampe, C., Antal, A., Liebetanz, D., Lang, N., Tergau, F., et al. (2006). Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. *The European Journal of Neuroscience*, *23*, 1651–1657.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527* (Pt 3), 633–639.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*, 1899–1901.

Ohta, K., Matsushima, E., Matsuura, M., Toru, M., & Kojima, T. (2000). Amantadine-induced multiple spike waves on an electroencephalogram of a schizophrenic patient. *The World Journal of Biological Psychiatry*, *1*, 59–64.

Panula, P., Pirvola, U., Auvinen, S., Airaksinen, M. S., Panula, P., Pirvola, U., et al. (1989). Histamine-immunoreactive nerve fibers in the rat brain. *Neuroscience*, *28*, 585–610.

Parmentier, R., Ohtsu, H., Djebbara-Hannas, Z., Valatx, J. L., Watanabe, T., Lin, J. S., et al. (2002). Anatomical, physiological, and pharmacological characteristics of histidine decarboxylase knock-out mice: Evidence for the role of brain histamine in behavioral and sleep–wake control. *Journal of Neuroscience*, *22*, 7695–7711.

Passler, M. A., & Riggs, R. V. (2001). Positive outcomes in traumatic brain injury-vegetative state: Patients treated with bromocriptine. *Archives of Physical Medicine and Rehabilitation*, *82*, 311–315.

Patkar, A. A., Masand, P. S., Pae, C. U., Peindl, K., Hooper-Wood, C., Mannelli, P., et al. (2006). A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in out-patients with treatment-resistant depression. *Journal of Clinical Psychopharmacology*, *26*, 653–656.

Patrick, P. D., Blackman, J. A., Mabry, J. L., Buck, M. L., Gurka, M. J., & Conaway, M. R. (2006). Dopamine agonist therapy in low-response children following traumatic brain injury. *Journal of Child Neurology*, *21*, 879–885.

Patrick, P. D., Buck, M. L., Conaway, M. R., & Blackman, J. A. (2003). The use of dopamine enhancing medications with children in low response states following brain injury. *Brain Injury*, *17*, 497–506.

Peyron, C., Tighe, D. K., Van den Pol, A. N., de Lecea, L., Heller, H. C., Sutcliffe, J. G., et al. (1998). Neurons containing hypocretin (orexin) project to multiple neuronal systems. *Journal of Neuroscience*, *18*, 9996–10015.

Pimentel, L., & Hughes, B. (1991). Amantadine toxicity presenting with complex ventricular ectopy and hallucinations. *Pediatric Emergency Care*, *7*, 89–92.

Pop-Jordanov, J., & Pop-Jordanova, N. (2009). Neurophysical substrates of arousal and attention. *Cognitive Processing*, *10*, S71–S79.

Portas, C. M., Bjorvatn, B., Fagerland, S., Gronli, J., Mundal, V., Sorensen, E., et al. (1998). On-line detection of extracellular levels of serotonin in dorsal raphe nucleus and frontal cortex over the sleep/wake cycle in the freely moving rat. *Neuroscience*, *83*, 807–814.

Povlishock, J. T., & Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *20*, 76–94.

Prasad, M. R., Ramaiah, C., McIntosh, T. K., Dempsey, R. J., Hipkens, S., Yurek, D., et al. (1994). Regional levels of lactate and norepinephrine after experimental brain injury. *Journal of Neurochemistry*, *63*, 1086–1094.

Ramic, M., Emerick, A. J., Bollnow, M. R., O'Brien, T. E., Tsai, S. Y., & Kartje, G. L. (2006). Axonal plasticity is associated with motor recovery following amphetamine treatment combined with rehabilitation after brain injury in the adult rat. *Brain Research*, *1111*, 176–186.

Reid, W. M., & Hamm, R. J. (2008). Post-injury atomoxetine treatment improves cognition following experimental traumatic brain injury. *Journal of Neurotrauma*, *25*, 248–256.

Reinhard, D. L., Whyte, J., & Sandel, M. E. (1996). Improved arousal and initiation following tricyclic antidepressant use in severe brain injury. *Archives of Physical Medicine and Rehabilitation*, *77*, 80–83.

Rye, D. B., Wainer, B. H., Mesulam, M. M., Mufson, E. J., Saper, C. B., Rye, D. B., et al. (1984). Cortical projections arising from the basal forebrain: A study of cholinergic and noncholinergic components employing combined retrograde tracing and immunohistochemical localization of choline acetyltransferase. *Neuroscience*, *13*, 627–643.

Saniova, B., Drobny, M., Kneslova, L., & Minarik, M. (2004). The outcome of patients with severe head injuries treated with amantadine sulphate. *Journal of Neural Transmission*, *111*, 511–514.

Schmidt, R. H., Grady, M. S., Schmidt, R. H., & Grady, M. S. (1995). Loss of forebrain cholinergic neurons following fluid-percussion injury: Implications for cognitive impairment in closed head injury. *Journal of Neurosurgery*, *83*, 496–502.

Seliger, G. M., Lichtman, S. W., & Hornstein, A. (1998). Naltrexone improves severe posttraumatic abulia. *Neurorehabilitation and Neural Repair*, *12*, 29–31.

Shames, J. L., & Ring, H. (2008). Transient reversal of anoxic brain injury-related minimally conscious state after zolpidem administration: A case report. *Archives of Physical Medicine and Rehabilitation*, *89*, 386–388.

Shields, W. D., Lake, J. L., & Chugani, H. T. (1985). Amantadine in the treatment of refractory epilepsy in childhood: An open trial in 10 patients. *Neurology*, *35*, 579–581.

Singh, R., McDonald, C., Dawson, K., Lewis, S., Pringle, A. M., Smith, S., et al. (2008). Zolpidem in a minimally conscious state. *Brain Injury*, *22*, 103–106.

Smith, D. H., Meaney, D. F., & Shull, W. H. (2003). Diffuse axonal injury in head trauma. *The Journal of Head Trauma Rehabilitation*, *18*, 307–316.

Speiser, Z., Amitzi-Zonder, J., Ashkenazi, R., Gitter, S., Cohen, S., Speiser, Z., et al. (1990). Central catecholaminergic dysfunction and behavioural disorders following hypoxia in adult rats. *Behavioural Brain Research*, *37*, 19–27.

Steriade, M., Datta, S., Pare, D., Oakson, G., Curro Dossi, R. C., Steriade, M., et al. (1990). Neuronal activities in brainstem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *Journal of Neuroscience*, *10*, 2541–2559.

Steriade, M., Dossi, R. C., Pare, D., Oakson, G., Steriade, M., Dossi, R. C., et al. (1991). Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proceedings of the National Academy of Sciences of the United States of America*, *88*, 4396–4400.

Stornetta, R. L., Sevigny, C. P., Schreihofer, A. M., Rosin, D. L., Guyenet, P. G., Stornetta, R. L., et al. (2002). Vesicular glutamate transporter DNPI/VGLUT2 is expressed by both C1 adrenergic and nonaminergic presympathetic vasomotor neurons of the rat medulla. *The Journal of Comparative Neurology*, *444*, 207–220.

Strafella, A., Paus, T., Barrett, J., & Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *The Journal of Neuroscience*, *21*, RC157.

Strafella, A. P., 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.

Teitelman, E. (2001). Off-label uses of modafinil. *The American Journal of Psychiatry*, *158*, 1341.

Tennant, F. S., Jr., & Wild, J. (1987). Naltrexone treatment for postconcussional syndrome. *The American journal of Psychiatry*, *144*, 813–814.

Thatcher, R. W., & John, E. R. (1977). Functional neuroscience: Foundations of cognitive processes. In: E. R. John & R. W. Thatcher (Eds), (Vol. 1). NJ: L. Erlbaum Assoc.

Tower, D. B., & McEachern, D. (1949). Acetylcholine and neuronal activity: Cholinesterase patterns and acetylcholine in cerebrospinal fluids of patients with craniocerebral trauma. *Canadian Journal of Research (Section E: Medical Sciences)*, 105–119.

Tsuiki, K., Takada, A., Nagahiro, S., Grdisa, M., Diksic, M., & Pappius, H. M. (1995a). Synthesis of serotonin in traumatized rat brain. *Journal of Neurochemistry*, *64*, 1319–1325.

Tsuiki, K., Takada, A., Nagahiro, S., Grdisa, M., Diksic, M., Pappius, H. M., et al. (1995b). Synthesis of serotonin in traumatized rat brain. *Journal of Neurochemistry*, *64*, 1319–1325.

Valentino, R. J., Page, M. E., Curtis, A. L., Valentino, R. J., Page, M. E., & Curtis, A. L. (1991). Activation of noradrenergic locus coeruleus neurons by hemodynamic stress is due to local release of corticotropin-releasing factor. *Brain Research*, *555*, 25–34.

van der Feltz-Cornelis, C. M., & Aldenkamp, A. P. (2006). Effectiveness and safety of methylphenidate in adult attention deficit hyperactivity disorder in patients with epilepsy: An open treatment trial. *Epilepsy Behavior*, *8*, 659–662.

Vincent, S. R., Hokfelt, T., Skirboll, L. R., Wu, J. Y., Vincent, S. R., Hokfelt, T., et al. (1983). Hypothalamic gamma-aminobutyric acid neurons project to the neocortex. *Science*, *220*, 1309–1311.

Wagner, A. K., Drewencki, L. L., Chen, X., Santos, F. R., Khan, A. S., Harun, R., et al. (2009). Chronic methylphenidate treatment enhances striatal dopamine neurotransmission after experimental traumatic brain injury. *Journal of Neurochemistry*, *108*, 986–997.

Wagner, A. K., Ren, D., Conley, Y. P., Ma, X., Kerr, M. E., Zafonte, R. D., et al. (2007). Sex and genetic associations with cerebrospinal fluid dopamine and metabolite production after severe traumatic brain injury. *Journal of Neurosurgery*, *106*, 538–547.

Wagner, A. K., Sokoloski, J. E., Ren, D., Chen, X., Khan, A. S., Zafonte, R. D., et al. (2005). Controlled cortical impact injury affects dopaminergic transmission in the rat striatum. *Journal of Neurochemistry*, *95*, 457–465.

Whyte, J., & Myers, R. (2009). Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: A preliminary placebo controlled trial. *American Journal of Physical Medicine and Rehabilitation 88*, 410–418.

Wilson, M. S., Gibson, C. J., & Hamm, R. J. (2003). Haloperidol, but not olanzapine, impairs cognitive performance after traumatic brain injury in rats. *American Journal of Physical Medicine and Rehabilitation*, *82*, 871–879.

Wise, R. A., Spindler, J., deWit, H., & Gerberg, G. J. (1978). Neuroleptic-induced ''anhedonia'' in rats: Pimozide blocks reward quality of food. *Science*, *201*, 262–264.

Wroblewski, B. A., Leary, J. M., Phelan, A. M., Whyte, J., & Manning, K. (1992). Methylphenidate and seizure frequency in brain injured patients with seizure disorders. *The Journal of Clinical Psychiatry*, *53*, 86–89.

Yan, H. Q., Kline, A. E., Ma, X., Li, Y., & Dixon, C. E. (2002). Traumatic brain injury reduces dopamine transporter protein expression in the rat frontal cortex. *Neuroreport*, *13*, 1899–1901.

Yan, H. Q., Ma, X., Chen, X., Li, Y., Shao, L., & Dixon, C. E. (2007). Delayed increase of tyrosine hydroxylase expression in rat nigrostriatal system after traumatic brain injury. *Brain Research*, *1134*, 171–179.

Zafonte, R. D., Lexell, J., & Cullen, N. (2001). Possible applications for dopaminergic agents following traumatic brain injury: Part 2. *The Journal of Head Trauma Rehabilitation*, *16*, 112–116.

Zhang, H., Zhang, X., Zhang, T., Chen, L., Zhang, H., Zhang, X., et al. (2001). Excitatory amino acids in cerebrospinal fluid of patients with acute head injuries. *Clinical Chemistry*, *47*, 1458–1462.

Ziegler, D. R., Cullinan, W. E., Herman, J. P., Ziegler, D. R., Cullinan, W. E., & Herman, J. P. (2002). Distribution of vesicular glutamate transporter mRNA in rat hypothalamus. *The Journal of Comparative Neurology*, *448*, 217–229.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 21

Intrathecal administration of GABA agonists in the vegetative state

Takaomi Taira*

Department of Neurosurgery, Tokyo Women's Medical University, Shinjuku, Tokyo, Japan

Abstract: Gamma aminobutylic acid (GABA) is an inhibitor neurotransmitter that plays many important roles in the central nervous system. Because the half-life time of GABA is very short in vivo, GABA itself is not used for clinical practice. An analogue of GABA, baclofen, is an agonist of GABA-B receptor, and has very strong antispastic effect by acting to the posterior horn of the spinal cord. However, baclofen poorly crosses through the blood brain barrier, and the antispastic effect is modest when administered orally. Therefore, direct continuous infusion of small doses of baclofen into the cerebrospinal fluid (intrathecal baclofen therapy, ITB) has become an established treatment for control of otherwise intractable severe spasticity. Spasticity is clinically defined as hypertonic state of the muscles with increased tendon reflexes, muscles spasm, spasm pain, abnormal posture, and limitation of involuntary movements. Spasticity is a common symptom after damage mainly to the pyramidal tract system in the brain or the spinal cord. Such damage is caused by traumatic brain injury, stroke, spinal cord injury, multiple sclerosis, and so on. Patients in persistent vegetative state (PVS) usually have diffuse and widespread damage to the brain, spasticity is generally seen in such patients. Control of spasticity may become important in the management of PVS patients in terms of nursing care, pain relief, and hygiene, and ITB may be indicated. Among PVS patients who had ITB to control spasticity, sporadic cases of dramatic recovery from PVS after ITB have been reported worldwide. The mechanism of such recovery of consciousness is poorly understood, and it may simply be a coincidence. On the other hand, electrical spinal cord stimulation (SCS) has been tried for many years in many patients in PVS, and some positive effects on recovery of consciousness have been reported. SCS is usually indicated for control of neuropathic pain, but it has also antispastic effect. The mechanism of SCS on pain is known to be mediated through the spinal GABA neuronal system. Thus, ITB and SCS have a common background, spinal GABA neuronal mechanism. The effect of GABA agonists on recovery of consciousness is not yet established, but review of such case studies becomes a clue to solve problems in PVS, and there may be hidden serendipity.

Keywords: GABA; vegetative state; spasticity; intrathecal baclofen; spinal cord stimulation; consciousness recovery

*Corresponding author.
Tel.: +813 3353 8112 (ext. 28634); Fax: +813 5269 7599;
E-mail: ttaira@nij.twmu.ac.jp

DOI: 10.1016/S0079-6123(09)17721-X

Introduction

Patients in either minimally conscious state (MCS) or persistent vegetative state (PVS) have diffuse brain damage due to cerebral stroke, traumatic brain injury, anoxic insult, and other neurological disorders. In such diffusely damaged brain, the neural structures for motor control are generally involved, and patients have a various types of motor dysfunctions such as paresis, spasticity, involuntary movements, and dystonia. In clinical settings of management of MCS or PVS patients, control of spasticity is an important issue. Spasticity is caused by hyperexcitation of motor neurons anterior horn of the spinal cord due to decreased inhibitory control from the higher canters. Spasticity is defined as ''a movement disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyperexcitability of stretch reflex, as one component of the upper motor neuron syndrome'' (Lance, 1980, 1990; Lance and Burke, 1974). This is basically neurophysiological definition. In clinical situations, abnormal postures like abnormally flexed fingers, wrists, elbow joints, or abnormal extension of the lower extremities with decreased passive motion may become a problem in rehabilitation or nursing care. Of course, if the spasticity is mild, it helps paralyzed limbs to maintain good posture or to support standing and gait. However, severe spasticity restricts voluntary movements, induces organic contractures, and may induce pain due to muscle spasms. Such severe spasticity is regarded as harmful, and active control of spasticity should be considered. There are both medical (Young, 1994; Young and Delwaide, 1981a, b) and surgical treatment of spasticity (Dones et al., 2006; Kan et al., 2008; Sgouros, 2007; Steinbok, 2006). Medical treatment with benzodiazepine drugs, baclofen, and dantrolene is useful when spasticity is mild, but not satisfactory for most severe cases. If high doses are given to relieve spasticity, side effects such as sleepiness become a problem. There are three major surgical treatments: selective peripheral neurotomy (Berard et al., 1998; Sindou et al., 1985; Sindou and Mertens, 1988), selective dorsal rhizotomy (Fasano et al., 1978; Gul et al., 1999; McLaughlin et al., 1998; Park and Johnston, 2006; Peacock and Arens, 1982; Peacock and Staudt, 1991; Steinbok, 2007), and intrathecal baclofen therapy (ITB). Indication of each surgical treatment is mainly decided with the patient's age and distribution of spasticity. For example, selective peripheral neurotomy is indicated for focal spasticity in adults like post-stroke ankle equinus posture. Selective dorsal rhizotomy is mainly for paraplegic spasticity in cerebral palsy children. In patients with diffuse spasticity involving in both extremities and even in cervical and trunk muscles, continuous infusion of baclofen into the spinal subarachnoid space is a good choice, and majority of MCS or PVS patients have such kind of diffuse spasticity.

Intrathecal baclofen therapy

Baclofen is a derivative of gamma aminobutyric acid (GABA) and an agonist of GABA-B receptor (Fig. 1). Baclofen has been known for many years to be a useful drug in the treatment of spasticity. However, when the spasticity is severe, the systemic administration has to be increased, often without therapeutic effects but frequently with central side effects. Baclofen

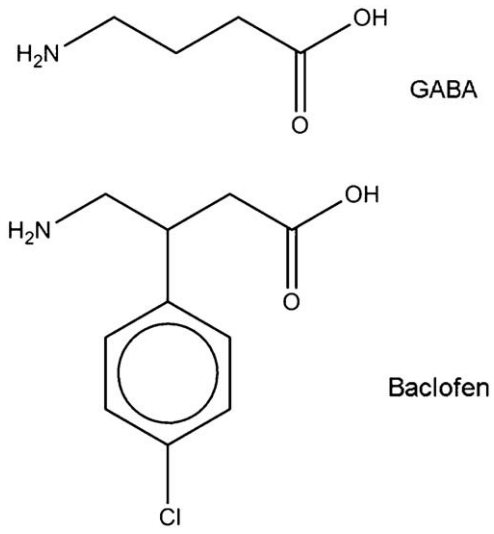


Fig. 1. Chemical structures of GABA and baclofen.

given intrathecally, however, in microgram doses has been reported to be effective and safe. After some preliminary studies (Kroin et al., 1984), Penn, a neurosurgeon in Chicago, introduced and established ITB treatment for severe spasticity (Penn and Kroin, 1984, 1985, 1987; Penn et al., 1989), and more than 50,000 patients have been treated so far.

As baclofen is poorly permeable through the blood brain barrier, and the effect of bolus injection lasts only for 24 h, we have to use an implantable infusion pump that is connected to a spinal subarachnoid catheter. The pump is about 8 cm in diameter and the infusion rates are controlled with a programmer. This is usually implanted under the abdominal skin. The volume of the drug reservoir is 20 ml, and it is refilled through percutaneous puncture about every 3 months in outpatient clinic. The battery longevity of the pump is about 7 years and once the battery is depleted, the pump itself is replaced. The surgical procedure is straightforward, but we have to pay very careful attention for catheter trouble or unexpected overdose that may lead serious complications (Albright et al., 2006). Sudden cessation of baclofen infusion may induce serious withdrawal syndrome such as excessive hypertonus, fever, and malignant syndrome (Alden et al., 2002; Coffey et al., 2002; Salazar and Eiland, 2008; Shirley et al., 2006). Overdose may induce deep comatose state that is usually reversible with appropriate respiratory and circulation management (Anderson et al., 2002; Romijn et al., 1986; Tunali et al., 2006). Although such complications may occur, ITB is accepted as the most reliable and adjustable treatment for diffuse severe spasticity of both spinal and cerebral origin such as spinal cord injury (Elovic and Kirshblum, 2003; Lewis and Mueller, 1993; Loubser et al., 1991), multiple sclerosis (Dario and Tomei, 2007; Ridley, 2006), cerebral palsy (Albright et al., 2003; Hoving et al., 2007; Kolaski and Logan, 2007; Motta et al., 2008), traumatic and anoxic brain damage (Becker et al., 1997; Francisco et al., 2007; Francois et al., 2001; Rifici et al., 1994), and stroke (Francisco, 2001; Francisco et al., 2006; Meythaler et al., 2001). Thus, ITB is a choice of treatment of otherwise uncontrollable spasticity in patients in MCS or PVS to improve hygiene and daily care, to reduce spasm related pain, and to calm down respiratory distress. Patients in PVS, MCS, or in acute stage of severe brain damage may have attack-wise or persistent autonomic dysfunction or so-called hypothalamic storm characterized with tachycardia, tachypnea, high fever, and harsh respiration. Such abnormal autonomic reaction is also controlled effectively with ITB (Becker et al., 1999, 2000; Francois et al., 2001; Turner, 2003). ITB may be indicated for other rare conditions such as stiff-person syndrome and tetanus (Bardutzky et al., 2003; Boots et al., 2000; Engrand et al., 1999; Penn and Mangieri, 1993; Santos et al., 2004; Silbert et al., 1995).

Recovery from unconscious state after ITB

There are sporadic case reports on unexpected recovery from unconscious state after intrathecal administration of baclofen (ITB) (Kawecki et al., 2007; Sarà et al., 2007; Taira and Hori, 2003, 2007; Taira et al., 2006). Most patients were treated with ITB for control of intractable spasticity without hoping recovery of consciousness. For example, Kawecki et al. (2007) reported on an 11-year-old girl with diffuse axonal injury after car accident. On admission, she was unconscious (GCS 4) and presented with brain contusion, pulmonary contusion, severe tetraparesis, spasticity, and seizures. Eighteen days after admission, she received 100 μg of baclofen, and her spasticity decreased and motor and sensor aphasia resolved. Because the duration of consciousness disturbance is too short for PVS or MCS, we cannot conclude whether this was really the effect of ITB or a coincidence. However, Sarà et al. (2007) reported a case of dramatic recovery of consciousness with ITB after 19-month unconscious state. This was a 44-year-old man who had recovery of consciousness with persistent severe disability 19 months after a non-traumatic brain injury at least in part triggered and maintained by ITB administration.

Sarà et al. (2009) and Sarà and Pistoia (2009) described more detailed evaluation using a rating scale. They summarized findings on five patients with PVS treated with ITB. They were judged

eligible for ITB therapy for spasticity: 2 weeks after pump implantation, patients began to show a clinical improvement in terms of consciousness, that, at the end of a follow-up 6-month period, was stable in all but one patients, ranging from a mere increased alertness to a full recovery of consciousness, as revealed by changes of the Coma Recovery Scale-Revised (CRS-R) score (Giacino et al., 2004; Kalmar and Giacino, 2005). Before the ITB, the CRS-R was 5+1.5 in average, and it became 15.2+6.3.

The author's personal experience of unexpected recovery from persistent unconscious state after intrathecal administration of baclofen (Taira et al., 1997) is described as follows.

Case reports

Case 1

An 8-year-old boy suffered severe head injury due to traffic accident. On admission to an emergency hospital, he was deeply comatose (Glasgow Coma Scale: GCS, E1MlV1). He underwent cardiopulmonary resuscitation. A computed tomography (CT) scan showed spotty hemorrhages in the thalamus and basal ganglia (Fig. 2). Two and half months after the accident, he was transferred to our hospital for further possible treatment. At this point, his consciousness level was E2V2M3 (GCS). Although minimal involuntary eye

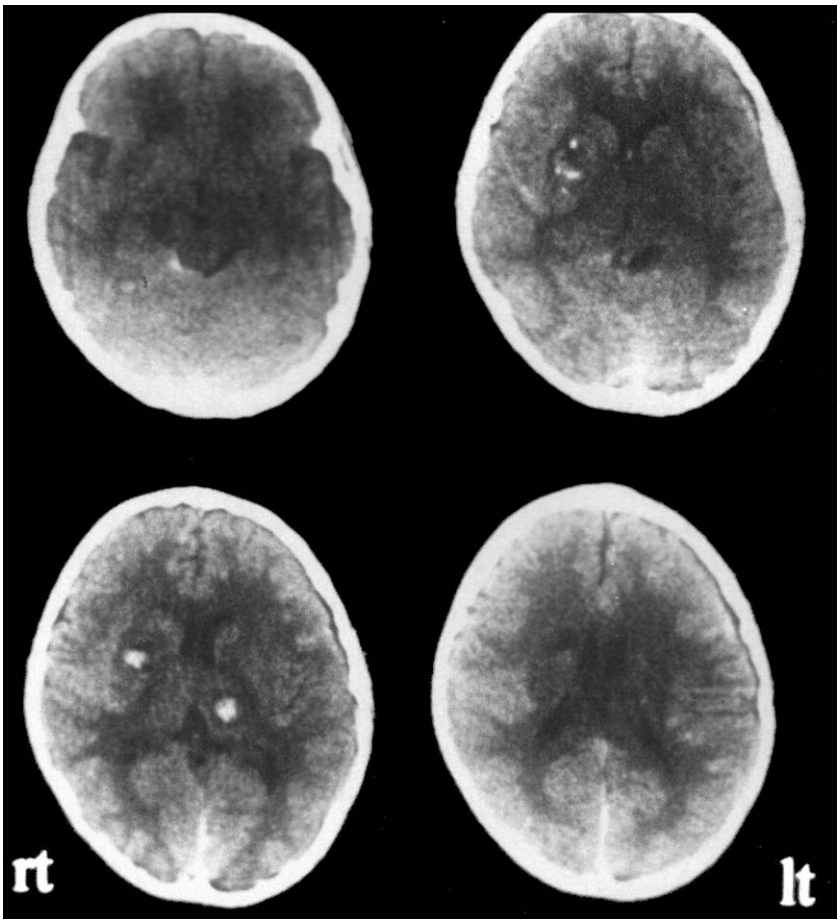


Fig. 2. A computed tomographic scan of case 1.

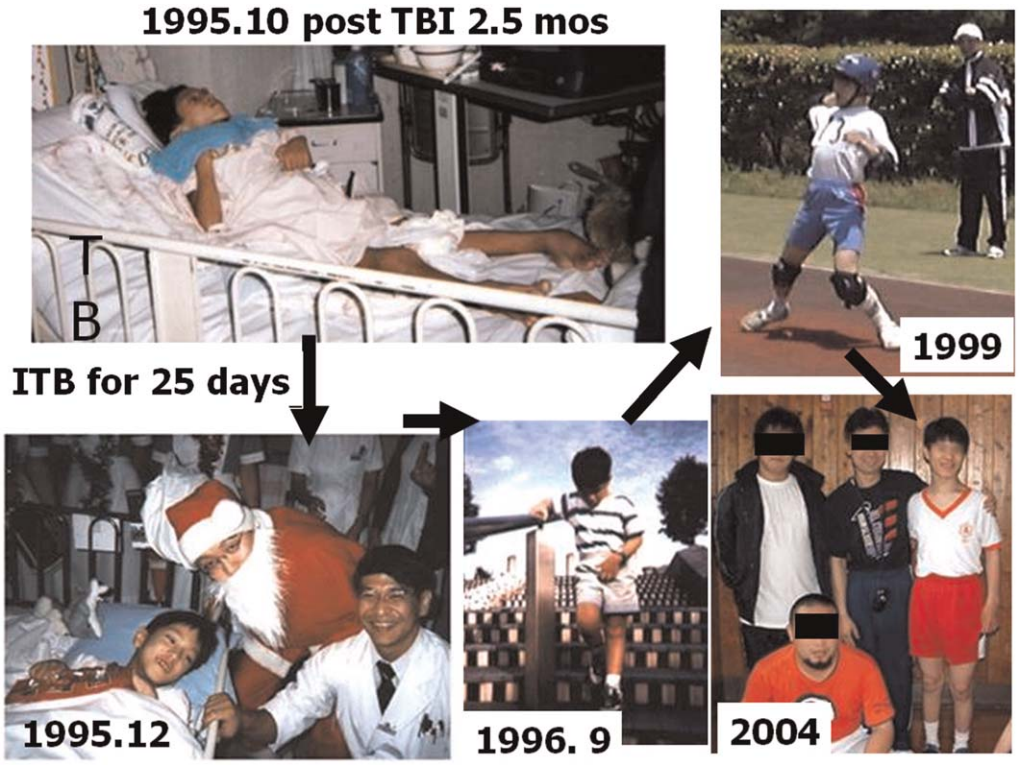


Fig. 3. Clinical course of case 1 after intrathecal baclofen treatment (ITB).

movements were noted to verbal stimulation, there was no spontaneous eye opening or verbal communication. Bilateral upper extremities were markedly in flexed position and the lower extremities showed marked extension posture. He showed opisthotonus to painful stimuli. Ashworth scale of the extremities was 4–5. Electroencephalography showed diffuse slow waves without epileptic discharges. The left upper photo of Fig. 3 shows the patient 2.5 months after the injury. ITB was started to relieve his spasticity. Because an implantable pump for chronic administration was not available, we administered baclofen though a lumbar puncture. We gave 50 μg/day for the initial 3 days, and subsequently 75 μg/day for l0 day and 100 μg/day for l0 days. To our surprise, he began to open his eyes spontaneously 3 days after starting baclofen injection, to speak some words from the fifth day, and to put out his fingers responding to verbal commands from the eighth day. He became able to sit up on the 14th day. Figure 4 summarizes the clinical course. There was no information of the patient's IQ or cognitive function before the accident, but he was an ordinary schoolboy with normal mental and physical development. One year after the head injury, his IQ assessed by a pediatric psychologist was 74, and he was able to walk with assist leg brace. Figure 3 shows the sequential long-term follow-up photographs of the patient. At the age of 16, 8 years after the accident, he was able to serve as a member of a basketball team of his high school.

Case 2

An 18-year-old man suffered severe head injury due to motorbike accident. On admission, his consciousness was ElV1M3 (GCS) and the left pupil was dilated. An emergency CT scan showed subarachnoid hemorrhage in the basal cisterns (Fig. 5). CT scan on the following day revealed

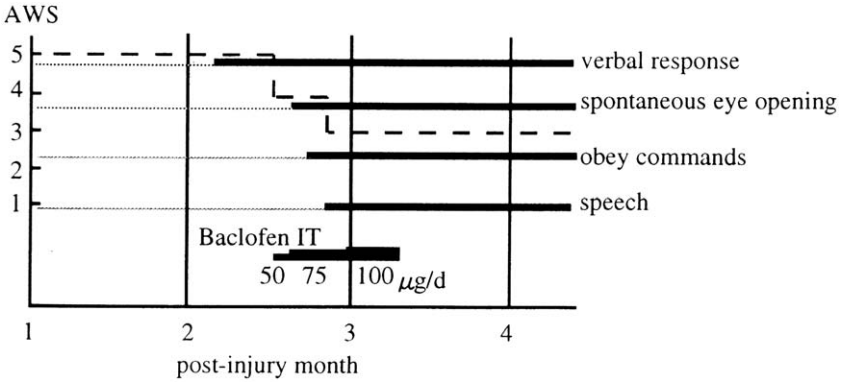


Fig. 4. Time course of neurological changes in case 1.

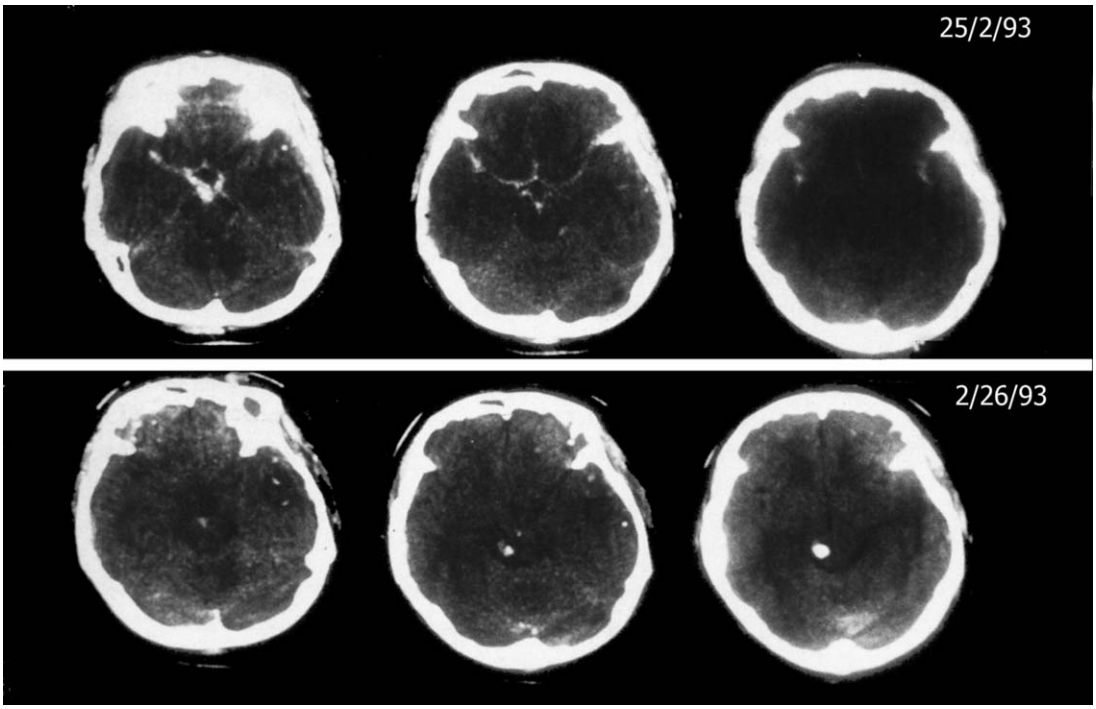


Fig. 5. A computed tomographic scan of case 2.

clearance of the subarachnoid hemorrhage but spotty hemorrhages appeared in the left side of the midbrain. He was treated conservatively with barbiturate coma therapy but on the third day, he underwent splenectomy because of associated intraperitoneal bleeding. His consciousness was E2V2M4 (GCS) 1.5 months after the accident. He showed marked spasticity of the extremities and both arms were in flexed position, and the legs showed extension posture. Ashworth scale of the extremities was 4–5. We started ITB injections through a daily lumbar puncture 1.5 months after the injury. The initial dose was 50 μg/day for 5 days, which controlled the spasticity effectively.

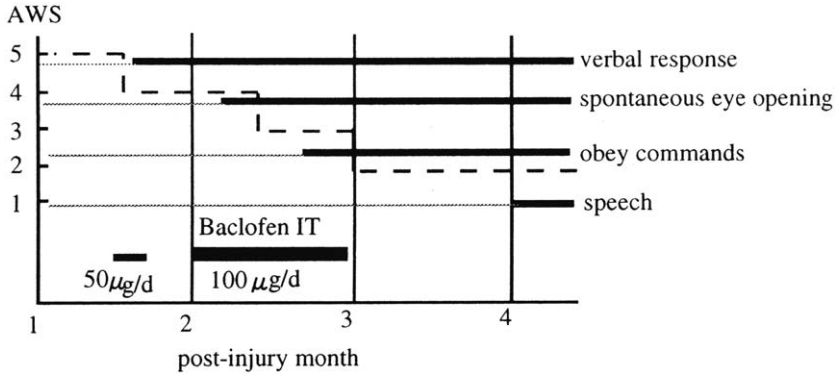


Fig. 6. Time course of neurological changes in case 2.

On the fifth day, he began to respond vaguely to verbal commands. He became able to open and close his eyes slowly to our commands. The dose was increased to 100 μg/day and the injection was continued for 23 days. He started to open his eyes spontaneously after five injections of 100 μg baclofen. On the 18th day, he became able to put out his fingers to verbal commands and he also became able to take foods orally. The patient was on prophylactic anticonvulsant (250 mg of phenytoin per day) and there were no clinical seizure attacks during the course. The clinical course is summarized in Fig. 6. He was discharged on foot to a rehabilitation center 6 months after the injury. Three years after the accident, he was living independently.

Discussion

The patients reported here are young and the durations of consciousness disturbance were 2–3 months, which does not fully fit to the criteria of PVS (Ashwal, 2004, 2005). Therefore, the recovery of their consciousness may have been a spontaneous natural course. However, all the attended doctors unanimously had a frank opinion that the dramatic improvement of consciousness was unexpectedly triggered with ITB injections and this was not merely a coincidence.

Becker et al. (1997) administered spinal ITB to relieve severe spasticity of supraspinal origin such as anoxic encephalopathy and severe brain injury. In their series of 13 patients, there were three patients whose consciousness improved dramatically after the treatment with ITB (Becker, 1996, personal communication). They also reported that severe autonomic dysfunction during the acute or subacute stage of severe brain injury is effectively controlled with ITB (Becker et al., 1997, 2000) and such use of ITB is supported by others (Baguley et al., 2004; Cuny et al., 2001).

In animal experiments of spinal cord injury, on the other hand, baclofen is known to improve axonal conduction of demyelinated axons (Nockels and Young, 1992). This experimental finding is interesting in that the present cases showed lesions compatible with diffuse axonal injury (Tong et al., 2004), and it can be suggested that the axonal conduction might have been improved with baclofen. As spontaneous recovery from PVS is an exceptional event and it is a big socioeconomical problem, any possible treatment for the recovery of consciousness is worth trying. The present experience, therefore, indicates that further investigation about effects of ITB on improvement of consciousness is crucial in patients with severe spasticity of supraspinal origin.

The initial purposes of ITB in the present cases were to relieve spasticity, to prevent organic contractures, and to facilitate rehabilitation. As shown here, Ashworth scale improved with the treatment and in this sense, the treatment was successful. Such application of ITB as in subacute stage of severe brain damage would be of

importance in terms of functional outcome of the patients. This view is also supported by Turner (2003). When we treated these patients, continuous infusion pump was not available in Japan, and we had to inject baclofen through repeated lumbar punctures. Such bolus injection gives sharp rise of baclofen concentration in the cerebrospinal fluid, and baclofen may reach to the intracranial space and act to the brain itself.

As for spasticity control, spinal cord stimulation (SCS) has long been used and extensively studied before the introduction of ITB treatment (Broseta et al., 1987; Dimitrijevic et al., 1986a, b; Illis et al., 1983; Koulousakis et al., 1987; Maiman et al., 1987; Pinter et al., 2000; Siegfried, 1980). However, SCS is abundant because of modest long-term effect (Gottlieb et al., 1985; Katz, 1988). SCS is generally indicated for control of intractable neuropathic pain (Deer, 2001; Meyerson et al., 1997; Meyerson and Linderoth, 2000; Olsson et al., 2008), and it also shows antispastic effect to some extent. Although the precise mechanism of SCS remains unsolved, release of inhibitory neurotransmitters such as GABA and glycine are suggested for the basic mechanism of SCS (Cui et al., 1996; Simpson et al., 1991, 1993; Stiller et al., 1996). Glycine is a neurotransmitter of the Renshaw cells in the spinal dorsal horn and it is used to be applied to the treatment of spasticity (Smith et al., 1979; Stern and Bokonjic, 1974). Glycine is also tried experimentally for the relief of neuropathic pain (Huang and Simpson, 2000; Simpson et al., 1997; Zeilhofer, 2005). Baclofen not only relieves spasticity but also reduces neuropathic pain (Gwak et al., 2006; Herman et al., 1992; Slonimski et al., 2004; Taira and Hori, 2007; Taira et al., 1994), and combination of SCS and ITB enhances pain suppression (Lind et al., 2007; Meyerson et al., 1997). Thus, baclofen and SCS resemble to each other in terms of antispastic effect, analgesic action for neuropathic pain, and involvement of the spinal GABA and glycine systems. It has also been reported that SCS may improve consciousness in patients with PVS (Fujii et al., 1998; Funahashi et al., 1989; Kanno et al., 1987, 1988, 1989; Liu et al., 2008; Matsui et al., 1989). It is also interesting that SCS may increase cerebral blood flow and may improve ischemic damage of the brain (Hosobuchi, 1985, 1991; Inoue et al., 2000; Liu et al., 2008; Matsui and Hosobuchi, 1989; Nagamachi et al., 2006; Visocchi, 2006, 2008; Visocchi et al., 1994). Therefore, it is highly suggested that the recovery of consciousness after intrathecal administration of baclofen is triggered by the similar mechanisms as in SCS in patients with PVS. Because the effect of SCS is basically segmental while baclofen acts diffusely on the spinal cord, ITB may show stronger and widespread effects.

In PVS or MCS patients, the extent of brain damage is not uniform, and consequently standardization or randomization of such patients for ITB treatment in terms of assessing the effect on consciousness recovery is not feasible. ITB is not yet, of course, a recommended treatment for aiming at improving impaired consciousness, and we need more accumulation of cases with detailed assessment of chronological changes of consciousness state after ITB treatment. Improvement of prolonged consciousness disturbance with any kinds of treatment is considered as serendipity, but serendipity comes only to prepared mind.

References

Albright, A. L., Gilmartin, R., Swift, D., Krach, L. E., Ivanhoe, C. B., & McLaughlin, J. F. (2003). Long-term intrathecal baclofen therapy for severe spasticity of cerebral origin. *Journal of Neurosurgery*, *98*, 291–295.

Albright, A. L., Turner, M., & Pattisapu, J. V. (2006). Best-practice surgical techniques for intrathecal baclofen therapy. *Journal of Neurosurgery*, *104*, 233–239.

Alden, T. D., Lytle, R. A., Park, T. S., Noetzel, M. J., & Ojemann, J. G. (2002). Intrathecal baclofen withdrawal: A case report and review of the literature. *Child's Nervous System*, *18*, 522–525.

Anderson, K. J., Farmer, J. P., & Brown, K. (2002). Reversible coma in children after improper baclofen pump insertion. *Paediatric Anaesthesia*, *12*, 454–460.

Ashwal, S. (2004). Pediatric vegetative state: Epidemiological and clinical issues. *NeuroRehabilitation*, *19*, 349–360.

Ashwal, S. (2005). Recovery of consciousness and life expectancy of children in a vegetative state. *Neuropsychological Rehabilitation*, *15*, 190–197.

Baguley, I. J., Cameron, I. D., Green, A. M., Slewa-Younan, S., Marosszeky, J. E., & Gurka, J. A. (2004). Pharmacological management of Dysautonomia following traumatic brain injury. *Brain Injury*, *18*, 409–417.

Bardutzky, J., Tronnier, V., Schwab, S., & Meinck, H. M. (2003). Intrathecal baclofen for stiff-person syndrome: Life-threatening intermittent catheter leakage. *Neurology*, *60*, 1976–1978.

Becker, R., Alberti, O., & Bauer, B. L. (1997). Continuous intrathecal baclofen infusion in severe spasticity after traumatic or hypoxic brain injury. *Journal of Neurology*, *244*, 160–166.

Becker, R., Benes, L., Sure, U., Hellwig, D., & Bertalanffy, H. (2000). Intrathecal baclofen alleviates autonomic dysfunction in severe brain injury. *Journal of Clinical Neuroscience*, *7*, 316–319.

Becker, R., Sure, U., Petermeyer, M., & Bertalanffy, H. (1999). Continuous intrathecal baclofen infusion alleviates autonomic dysfunction in patients with severe supraspinal spasticity. *Journal of Neurology, Neurosurgery, and Psychiatry*, *66*, 114.

Berard, C., Sindou, M., Berard, J., & Carrier, H. (1998). Selective neurotomy of the tibial nerve in the spastic hemiplegic child: An explanation of the recurrence. *Journal of Pediatric Orthopaedics B*, *7*, 66–70.

Boots, R. J., Lipman, J., O'Callaghan, J., Scott, P., & Fraser, J. (2000). The treatment of tetanus with intrathecal baclofen. *Anaesthesia and Intensive Care*, *28*, 438–442.

Broseta, J., Garcia-March, G., Sanchez-Ledesma, M. J., Barbera, J., & Gonzalez-Darder, J. (1987). High-frequency cervical spinal cord stimulation in spasticity and motor disorders. *Acta Neurochirurgica Supplement (Wien)*, *39*, 106–111.

Coffey, R. J., Edgar, T. S., Francisco, G. E., Graziani, V., Meythaler, J. M., Ridgely, P. M., et al. (2002). Abrupt withdrawal from intrathecal baclofen: Recognition and management of a potentially life-threatening syndrome. *Archives of Physical Medicine and Rehabilitation*, *83*, 735–741.

Cui, J. G., Linderoth, B., & Meyerson, B. A. (1996). Effects of spinal cord stimulation on touch-evoked allodynia involve GABAergic mechanisms. An experimental study in the mononeuropathic rat. *Pain*, *66*, 287–295.

Cuny, E., Richer, E., & Castel, J. P. (2001). Dysautonomia syndrome in the acute recovery phase after traumatic brain injury: Relief with intrathecal Baclofen therapy. *Brain Injury*, *15*, 917–925.

Dario, A., & Tomei, G. (2007). Management of spasticity in multiple sclerosis by intrathecal baclofen. *Acta Neurochirurgica Supplement*, *97*, 189–192.

Deer, T. R. (2001). Current and future trends in spinal cord stimulation for chronic pain. *Current Pain and Headache Reports*, *5*, 503–509.

Dimitrijevic, M. M., Dimitrijevic, M. R., Illis, L. S., Nakajima, K., Sharkey, P. C., & Sherwood, A. M. (1986a). Spinal cord stimulation for the control of spasticity in patients with chronic spinal cord injury: I. Clinical observations. *Central Nervous System Trauma*, *3*, 129–144.

Dimitrijevic, M. R., Illis, L. S., Nakajima, K., Sharkey, P. C., & Sherwood, A. M. (1986b). Spinal cord stimulation for the control of spasticity in patients with chronic spinal cord injury: II. Neurophysiologic observations. *Central Nervous System Trauma*, *3*, 145–152.

Dones, I., Nazzi, V., & Broggi, G. (2006). The guidelines for the diagnosis and treatment of spasticity. *Journal of Neurosurgical Sciences*, *50*, 101–105.

Elovic, E., & Kirshblum, S. C. (2003). Managing spasticity in spinal cord injury: Safe administration of bridge boluses during intrathecal baclofen pump refills. *Journal of Spinal Cord Medicine*, *26*, 2–4.

Engrand, N., Guerot, E., Rouamba, A., & Vilain, G. (1999). The efficacy of intrathecal baclofen in severe tetanus. *Anesthesiology*, *90*, 1773–1776.

Fasano, V. A., Broggi, G., Barolat-Romana, G., & Sguazzi, A. (1978). Surgical treatment of spasticity in cerebral palsy. *Child's Brain*, *4*, 289–305.

Francisco, G. E. (2001). Intrathecal baclofen therapy for stroke-related spasticity. *Topics in Stroke Rehabilitation*, *8*, 36–46.

Francisco, G. E., Latorre, J. M., & Ivanhoe, C. B. (2007). Intrathecal baclofen therapy for spastic hypertonia in chronic traumatic brain injury. *Brain Injury*, *21*, 335–338.

Francois, B., Vacher, P., Roustan, J., Salle, J. Y., Vidal, J., Moreau, J. J., et al. (2001). Intrathecal baclofen after traumatic brain injury: Early treatment using a new technique to prevent spasticity. *Journal of Trauma*, *50*, 158–161.

Francisco, G. E., Yablon, S. A., Schiess, M. C., Wiggs, L., Cavalier, S., & Grissom, S. (2006). Consensus panel guidelines for the use of intrathecal baclofen therapy in poststroke spastic hypertonia. *Topics in Stroke Rehabilitation*, *13*, 74–85.

Fujii, M., Sadamitsu, D., Maekawa, T., Uesugi, S., Ozaki, S., Koizumi, H., et al. (1998). Spinal cord stimulation therapy at an early stage for unresponsive patients with hypoxic encephalopathy. *No Shinkei Geka*, *26*, 315–321.

Funahashi, K., Komai, N., Ogura, M., Kuwata, T., Nakai, M., & Tsuji, N. (1989). Effects and indications of spinal cord stimulation on the vegetative syndrome. *No Shinkei Geka*, *17*, 917–923.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK coma recovery scale-revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation*, *85*, 2020–2029.

Gottlieb, G. L., Myklebust, B. M., Stefoski, D., Groth, K., Kroin, J., & Penn, R. D. (1985). Evaluation of cervical stimulation for chronic treatment of spasticity. *Neurology*, *35*, 699–704.

Gul, S. M., Steinbok, P., & McLeod, K. (1999). Long-term outcome after selective posterior rhizotomy in children with spastic cerebral palsy. *Pediatric Neurosurgery*, *31*, 84–95.

Gwak, Y. S., Tan, H. Y., Nam, T. S., Paik, K. S., Hulsebosch, C. E., & Leem, J. W. (2006). Activation of spinal GABA receptors attenuates chronic central neuropathic pain after spinal cord injury. *Journal of Neurotrauma*, *23*, 1111–1124.

Herman, R. M., D'Luzansky, S. C., & Ippolito, R. (1992). Intrathecal baclofen suppresses central pain in patients with spinal lesions. A pilot study. *Clinical Journal of Pain*, *8*, 338–345.

Hosobuchi, Y. (1985). Electrical stimulation of the cervical spinal cord increases cerebral blood flow in humans. *Applied Neurophysiology*, *48*, 372–376.

Hosobuchi, Y. (1991). Treatment of cerebral ischemia with electrical stimulation of the cervical spinal cord. *Pacing and Clinical Electrophysiology*, *14*, 122–126.

Hoving, M. A., van Raak, E. P., Spincemaille, G. H., Palmans, L. J., Sleypen, F. A., & Vles, J. S. (2007). Intrathecal baclofen in children with spastic cerebral palsy: A double-blind, randomized, placebo-controlled, dose-finding study. *Developmental Medicine and Child Neurology*, *49*, 654–659.

Huang, W., & Simpson, R. K. (2000). Long-term intrathecal administration of glycine prevents mechanical hyperalgesia in a rat model of neuropathic pain. *Neurological Research*, *22*, 160–164.

Illis, L. S., Read, D. J., Sedgwick, E. M., & Tallis, R. C. (1983). Spinal cord stimulation in the United Kingdom. *Journal of Neurology, Neurosurgery, and Psychiatry*, *46*, 299–304.

Inoue, M., Nakase, H., Hirabayashi, H., Hoshida, T., & Sakaki, T. (2000). Effect of stimulation of the dorsal aspect of the cervical spinal cord on local cerebral blood flow and EEG in the cat. *Neurological Research*, *22*, 386–392.

Kalmar, K., & Giacino, J. T. (2005). The JFK coma recovery scale-revised. *Neuropsychological Rehabilitation*, *15*, 454–460.

Kan, P., Gooch, J., Amini, A., Ploeger, D., Grams, B., Oberg, W., et al. (2008). Surgical treatment of spasticity in children: Comparison of selective dorsal rhizotomy and intrathecal baclofen pump implantation. *Child's Nervous System*, *24*, 239–243.

Kanno, T., Kamei, Y., Yokoyama, T., & Jain, V. K. (1987). Neurostimulation for patients in vegetative status. *Pacing and Clinical Electrophysiology*, *10*, 207–208.

Kanno, T., Kamei, Y., Yokoyama, T., Shoda, M., Tanji, H., & Nomura, M. (1988). [Effects of neurostimulation on the reversibility of neuronal function: Experience of treatment for vegetative status]. *No Shinkei Geka*, *16*, 157–163.

Kanno, T., Kamel, Y., Yokoyama, T., Shoda, M., Tanji, H., & Nomura, M. (1989). Effects of dorsal column spinal cord stimulation (DCS) on reversibility of neuronal function—Experience of treatment for vegetative states. *Pacing and Clinical Electrophysiology*, *12*, 733–738.

Katz, R. T. (1988). Management of spasticity. *American Journal of Physical Medicine and Rehabilitation*, *67*, 108–116.

Kawecki, Z., Kwiatkowski, S., Grzegorzewski, P., & Szlachta Jezioro, I. (2007). Sudden improvement of all neurological functions after general anesthesia and two-day intrathecal infusion of baclofen in a child with primary brain-stem injury. *Przegl Lek*, *64*(Suppl. 2), 13–14.

Kolaski, K., & Logan, L. R. (2007). A review of the complications of intrathecal baclofen in patients with cerebral palsy. *NeuroRehabilitation*, *22*, 383–395.

Koulousakis, A., Buchhaas, U., & Nittner, K. (1987). Application of SCS for movement disorders and spasticity. *Acta Neurochirurgica Supplement (Wien)*, *39*, 112–116.

Kroin, J. S., Penn, R. D., Beissinger, R. L., & Arzbaecher, R. C. (1984). Reduced spinal reflexes following intrathecal baclofen in the rabbit. *Experimental Brain Research*, *54*, 191–194.

Lance, J. W. (1980). The control of muscle tone, reflexes, and movement: Robert Wartenberg Lecture. *Neurology*, *30*, 1303–1313.

Lance, J. W. (1990). What is spasticity? *Lancet*, *335*, 606.

Lance, J. W., & Burke, D. (1974). Mechanisms of spasticity. *Archives of Physical Medicine and Rehabilitation*, *55*, 332–337.

Lewis, K. S., & Mueller, W. M. (1993). Intrathecal baclofen for severe spasticity secondary to spinal cord injury. *Annals of Pharmacotherapy*, *27*, 767–774.

Lind, G., Schechtmann, G., Winter, J., & Linderoth, B. (2007). Drug-enhanced spinal stimulation for pain: A new strategy. *Acta Neurochirurgica Supplement*, *97*, 57–63.

Liu, J. T., Tan, W. C., & Liao, W. J. (2008). Effects of electrical cervical spinal cord stimulation on cerebral blood perfusion, cerebrospinal fluid catecholamine levels, and oxidative stress in comatose patients. *Acta Neurochirurgica Supplement*, *101*, 71–76.

Loubser, P. G., Narayan, R. K., Sandin, K. J., Donovan, W. H., & Russell, K. D. (1991). Continuous infusion of intrathecal baclofen: Long-term effects on spasticity in spinal cord injury. *Paraplegia*, *29*, 48–64.

Maiman, D. J., Mykleburst, J. B., & Barolat-Romana, G. (1987). Spinal cord stimulation for amelioration of spasticity: Experimental results. *Neurosurgery*, *21*, 331–333.

Matsui, T., Asano, T., Takakura, K., Yamada, R., & Hosobuchi, Y. (1989). Beneficial effects of cervical spinal cord stimulation (cSCS) on patients with impaired consciousness: A preliminary report. *Pacing and Clinical Electrophysiology*, *12*, 718–725.

Matsui, T., & Hosobuchi, Y. (1989). The effects of cervical spinal cord stimulation (cSCS) on experimental stroke. *Pacing and Clinical Electrophysiology*, *12*, 726–732.

McLaughlin, J. F., Bjornson, K. F., Astley, S. J., Graubert, C., Hays, R. M., Roberts, T. S., et al. (1998). Selective dorsal rhizotomy: Efficacy and safety in an investigator-masked randomized clinical trial. *Developmental Medicine and Child Neurology*, *40*, 220–232.

Meyerson, B. A., Cui, J. G., Yakhnitsa, V., Sollevi, A., Segerdahl, M., Stiller, C. O., et al. (1997). Modulation of spinal pain mechanisms by spinal cord stimulation and the potential role of adjuvant pharmacotherapy. *Stereotactic and Functional Neurosurgery*, *68*, 129–140.

Meyerson, B. A., & Linderoth, B. (2000). Mechanisms of spinal cord stimulation in neuropathic pain. *Neurological Research*, *22*, 285–292.

Meythaler, J. M., Guin-Renfroe, S., Brunner, R. C., & Hadley, M. N. (2001). Intrathecal baclofen for spastic hypertonia from stroke. *Stroke*, *32*, 2099–2109.

Motta, F., Stignani, C., & Antonello, C. E. (2008). Upper limb function after intrathecal baclofen treatment in children with cerebral palsy. *Journal of Pediatric Orthopaedics*, *28*, 91–96.

Nagamachi, S., Fujita, S., Nishii, R., Futami, S., Wakamatsu, H., Yano, T., et al. (2006). Alteration of regional cerebral blood flow in patients with chronic pain—Evaluation before and after epidural spinal cord stimulation. *Annals of Nuclear Medicine*, *20*, 303–310.

Nockels, R., & Young, W. (1992). Pharmacologic strategies in the treatment of experimental spinal cord injury. *Journal of Neurotrauma*, *9*(Suppl. 1), S211–S217.

Olsson, G. L., Meyerson, B. A., & Linderoth, B. (2008). Spinal cord stimulation in adolescents with complex regional pain syndrome type I (CRPS-I). *European Journal of Pain*, *12*, 53–59.

Park, T. S., & Johnston, J. M. (2006). Surgical techniques of selective dorsal rhizotomy for spastic cerebral palsy. Technical note. *Neurosurgical Focus*, *21*, e7.

Peacock, W. J., & Arens, L. J. (1982). Selective posterior rhizotomy for the relief of spasticity in cerebral palsy. *South African Medical Journal*, *62*, 119–124.

Peacock, W. J., & Staudt, L. A. (1991). Functional outcomes following selective posterior rhizotomy in children with cerebral palsy. *Journal of Neurosurgery*, *74*, 380–385.

Penn, R. D., & Kroin, J. S. (1984). Intrathecal baclofen alleviates spinal cord spasticity. *Lancet*, *1*, 1078.

Penn, R. D., & Kroin, J. S. (1985). Continuous intrathecal baclofen for severe spasticity. *Lancet*, *2*, 125–127.

Penn, R. D., & Kroin, J. S. (1987). Long-term intrathecal baclofen infusion for treatment of spasticity. *Journal of Neurosurgery*, *66*, 181–185.

Penn, R. D., & Mangieri, E. A. (1993). Stiff-man syndrome treated with intrathecal baclofen. *Neurology*, *43*, 2412.

Penn, R. D., Savoy, S. M., Corcos, D., Latash, M., Gottlieb, G., Parke, B., et al. (1989). Intrathecal baclofen for severe spinal spasticity. *The New England Journal of Medicine*, *320*, 1517–1521.

Pinter, M. M., Gerstenbrand, F., & Dimitrijevic, M. R. (2000). Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 3. Control Of spasticity. *Spinal Cord*, *38*, 524–531.

Ridley, B. (2006). Intrathecal baclofen therapy: Challenges in patients with multiple sclerosis. *Rehabilitation Nursing*, *31*, 158–164.

Rifici, C., Kofler, M., Kronenberg, M., Kofler, A., Bramanti, P., & Saltuari, L. (1994). Intrathecal baclofen application in patients with supraspinal spasticity secondary to severe traumatic brain injury. *Functional Neurology*, *9*, 29–34.

Romijn, J. A., van Lieshout, J. J., & Velis, D. N. (1986). Reversible coma due to intrathecal baclofen. *Lancet*, *2*, 696.

Salazar, M. L., & Eiland, L. S. (2008). Intrathecal baclofen withdrawal resembling serotonin syndrome in an adolescent boy with cerebral palsy. *Pediatric Emergency Care*, *24*, 691–693.

Santos, M. L., Mota-Miranda, A., Alves-Pereira, A., Gomes, A., Correia, J., & Marcal, N. (2004). Intrathecal baclofen for the treatment of tetanus. *Clinical Infectious Diseases*, *38*, 321–328.

Sarà, M., Pistoia, F. (2009). Defining consciousness: Lessons from patients and modern techniques. *Journal of Neurotrauma*, March 26, Epub ahead of print.

Sarà, M., Pistoia, F., Mura, E., Onorati, P., Govoni, S. (2009). Intrathecal baclofen in patients with persistent vegetative state: Two hypotheses. *Archives of Physical Medicine and Rehabilitation*, *90*, 1245–1249.

Sarà, M., Sacco, S., Cipolla, F., Onorati, P., Scoppetta, C., Albertini, G., et al. (2007). An unexpected recovery from permanent vegetative state. *Brain Injury*, *21*, 101–103.

Sgouros, S. (2007). Surgical management of spasticity of cerebral origin in children. *Acta Neurochirurgica Supplement*, *97*, 193–203.

Shirley, K. W., Kothare, S., Piatt, J. H., Jr., & Adirim, T. A. (2006). Intrathecal baclofen overdose and withdrawal. *Pediatric Emergency Care*, *22*, 258–261.

Siegfried, J. (1980). Treatment of spasticity by dorsal cord stimulation. *International Rehabilitation Medicine*, *2*, 31–34.

Silbert, P. L., Matsumoto, J. Y., McManis, P. G., Stolp-Smith, K. A., Elliott, B. A., & McEvoy, K. M. (1995). Intrathecal baclofen therapy in stiff-man syndrome: A double-blind, placebo-controlled trial. *Neurology*, *45*, 1893–1897.

Simpson, R. K., Jr., Gondo, M., Robertson, C. S., & Goodman, J. C. (1997). Reduction in thermal hyperalgesia by intrathecal administration of glycine and related compounds. *Neurochemical Research*, *22*, 75–79.

Simpson, R. K., Jr., Robertson, C. S., & Goodman, J. C. (1993). Segmental recovery of amino acid neurotransmitters during posterior epidural stimulation after spinal cord injury. *The Journal of the American Paraplegia Society*, *16*, 34–41.

Simpson, R. K., Jr., Robertson, C. S., Goodman, J. C., & Halter, J. A. (1991). Recovery of amino acid neurotransmitters from the spinal cord during posterior epidural stimulation: A preliminary study. *The Journal of the American Paraplegia Society*, *14*, 3–8.

Sindou, M., Abdennebi, B., & Sharkey, P. (1985). Microsurgical selective procedures in peripheral nerves and the posterior root-spinal cord junction for spasticity. *Applied Neurophysiology*, *48*, 97–104.

Sindou, M., & Mertens, P. (1988). Selective neurotomy of the tibial nerve for treatment of the spastic foot. *Neurosurgery*, *23*, 738–744.

Slonimski, M., Abram, S. E., & Zuniga, R. E. (2004). Intrathecal baclofen in pain management. *Regional Anesthesia and Pain Medicine*, *29*, 269–276.

Smith, J. E., Hall, P. V., Galvin, M. R., Jones, A. R., & Campbell, R. L. (1979). Effects of glycine administration on canine experimental spinal spasticity and the levels of glycine, glutamate, and aspartate in the lumbar spinal cord. *Neurosurgery*, *4*, 152–156.

Steinbok, P. (2006). Selection of treatment modalities in children with spastic cerebral palsy. *Neurosurgical Focus*, *21*, e4.

Steinbok, P. (2007). Selective dorsal rhizotomy for spastic cerebral palsy: A review. *Child's Nervous System*, *23*, 981–990.

Stern, P., & Bokonjic, R. (1974). Glycine therapy in 7 cases of spasticity. A pilot study. *Pharmacology*, *12*, 117–119.

Stiller, C. O., Cui, J. G., O'Connor, W. T., Brodin, E., Meyerson, B. A., & Linderoth, B. (1996). Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats. *Neurosurgery*, *39*, 367–374. discussion 374–5

Taira, T., & Hori, T. (2003). Clinical application of drug pump for spasticity, pain, and restorative neurosurgery: Other clinical applications of intrathecal baclofen. *Acta Neurochirurgica Supplement*, *87*, 37–38.

Taira, T., & Hori, T. (2007). Intrathecal baclofen in the treatment of post-stroke central pain, dystonia, and persistent vegetative state. *Acta Neurochirurgica Supplement*, *97*, 227–229.

Taira, T., Ochiai, T., Goto, S., & Hori, T. (2006). Fifteen year experience of intrathecal baclofen treatment in Japan. *Acta Neurochirurgica Supplement*, *99*, 61–63.

Taira, T., Tanikawa, T., Iseki, H., Kawabatake, H., Kawamura, H., Ueda, A., et al. (1997). Dramatic recovery from coma after intrathecal baclofen. *Stereotactic and Functional Neurosurgery*, *67*, 109.

Taira, T., Tanikawa, T., Kawamura, H., Iseki, H., & Takakura, K. (1994). Spinal intrathecal baclofen suppresses central pain after a stroke. *Journal of Neurology, Neurosurgery, and Psychiatry*, *57*, 381–382.

Tong, K. A., Ashwal, S., Holshouser, B. A., Nickerson, J. P., Wall, C. J., Shutter, L. A., et al. (2004). Diffuse axonal injury in children: Clinical correlation with hemorrhagic lesions. *Annals of Neurology*, *56*, 36–50.

Tunali, Y., Hanimoglu, H., Tanriverdi, T., Hanci, L., & Hanci, M. (2006). Intrathecal baclofen toxicity and deep coma in minutes. *Journal of Spinal Cord Medicine*, *29*, 237–239.

Turner, M. S. (2003). Early use of intrathecal baclofen in brain injury in pediatric patients. *Acta Neurochirurgica Supplement*, *87*, 81–83.

Visocchi, M. (2006). Spinal cord stimulation and cerebral haemodynamics. *Acta Neurochirurgica Supplement*, *99*, 111–116.

Visocchi, M. (2008). Neuromodulation of cerebral blood flow by spinal cord electrical stimulation: The role of the Italian school and state of art. *Journal of Neurosurgical Sciences*, *52*, 41–47.

Visocchi, M., Cioni, B., Pentimalli, L., & Meglio, M. (1994). Increase of cerebral blood flow and improvement of brain motor control following spinal cord stimulation in ischemic spastic hemiparesis. *Stereotactic and Functional Neurosurgery*, *62*, 103–107.

Young, R. (1994). Spasticity: A review. *Neurology*, *44*(Suppl. 9), S12–S20.

Young, R. R., & Delwaide, P. J. (1981a). Drug therapy: Spasticity (first of two parts). *The New England Journal of Medicine*, *304*, 28–33.

Young, R. R., & Delwaide, P. J. (1981b). Drug therapy: Spasticity (second of two parts). *The New England Journal of Medicine*, *304*, 96–99.

Zeilhofer, H. U. (2005). The glycinergic control of spinal pain processing. *Cellular and Molecular Life Sciences*, *62*, 2027–2035.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 22

Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals ☆

A. Demertzi[1], C. Schnakers[2], D. Ledoux[3], C. Chatelle[1], M.-A. Bruno[1], A. Vanhaudenhuyse[1], M. Boly[1], G. Moonen[4] and S. Laureys[1,*]

[1]*Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège, Liège, Belgium*
[2]*Coma Science Group, Cyclotron Research Center and Neuropsychology Department, University of Liège, Liège, Belgium*
[3]*Coma Science Group, Cyclotron Research Center and Intensive Care Department, University of Liège, Liège, Belgium*
[4]*Department of Neurology, CHU University Hospital, Liège, Belgium*

Abstract: Pain management in severely brain-damaged patients constitutes a clinical and ethical stake. At the bedside, assessing the presence of pain and suffering is challenging due to both patients' physical condition and inherent limitations of clinical assessment. Neuroimaging studies support the existence of distinct cerebral responses to noxious stimulation in brain death, vegetative state, and minimally conscious state. We here provide results from a European survey on 2059 medical and paramedical professionals' beliefs on possible pain perception in patients with disorders of consciousness. To the question ''Do you think that patients in a vegetative state can feel pain?,'' 68% of the interviewed paramedical caregivers ($n = 538$) and 56% of medical doctors ($n = 1166$) answered ''yes'' (no data on exact profession in 17% of total sample). Logistic regression analysis showed that paramedical professionals, religious caregivers, and older caregivers reported more often that vegetative patients may experience pain. Following professional background, religion was the highest predictor of caregivers' opinion: 64% of religious ($n = 1009$; 850 Christians) versus 52% of nonreligious respondents ($n = 830$) answered positively (missing data on religion in 11% of total sample). To the question ''Do you think that patients in a minimally conscious state can feel pain?'' nearly all interviewed caregivers answered ''yes'' (96% of the medical doctors and 97% of the paramedical caregivers). Women and religious caregivers reported more often that minimally conscious patients may experience pain. These results are discussed in terms of existing definitions of pain and suffering, the remaining uncertainty on the clinical assessment of pain as a subjective first-person experience and recent functional neuroimaging findings on nociceptive processing in disorders of

☆Both A. Demertzi and C. Schnakers have contributed equally to this study.

*Corresponding author.
Tel.: +32 4 366 23 16; Fax: +32 4 366 29 46.;
E-mail: steven.laureys@ulg.ac.be

DOI: 10.1016/S0079-6123(09)17722-1

consciousness. In our view, more research is needed to increase our understanding of residual sensation in vegetative and minimally conscious patients and to propose evidence-based medical guidelines for the management of possible pain perception and suffering in these vulnerable patient populations.

Keywords: pain; brain injury; disorders of consciousness; survey; neuroimaging; ethics; end-of-life; vegetative state

Introduction

The International Association for the Study of Pain (IASP, 1994) defines pain as ''an unpleasant sensory and emotional experience associated with real or potential tissue damage.'' As stressed by the IASP, the inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain may also be reported in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though pain most often has a proximate physical cause. Pain is a subjective first-person experience with both physical and affective aspects (Kupers et al., 2005). It is a sensation in a part or parts of the body, which is, always unpleasant and, therefore, an emotional experience. Pain and suffering are not interchangeable constructs. However, the concept of suffering is surprisingly ill defined and given relatively little attention in medicine. A person might experience significant pain-related suffering from a relatively low-level noxious stimulation if she or he believes the implications are ominous, interminable, and beyond their control (Turk and Wilson, 2009). Cassell (1991) defined suffering as ''the state of severe distress associated with events that threaten the intactness of the person.'' Pain by itself does not seem to be sufficient to cause suffering; rather it seems that the person's interpretation of the symptoms is crucial. We will here consider (as expressed by the Multi-Society Task Force on PVS, 1994) that pain and suffering refer to the unpleasant experiences that occur in response to stimulation of peripheral nociceptive receptors and their peripheral and central afferent pathways or that they may emanate endogenously from the depths of human self-perception.

The management of pain and suffering in disorders of consciousness (DOCs) is challenging because, by definition, patients in a vegetative state (VS) or minimally conscious state (MCS) cannot verbally or nonverbally communicate their feelings or experiences (e.g., McQuillen, 1991; Bernat, 2006; Laureys and Boly, 2007). The VS is a condition of preserved wakefulness contrasted with absent voluntary interaction with the environment (Jennett and Plum, 1972). The MCS was only recently defined (Giacino et al., 2002) and is characterized by discernible but fluctuating signs of awareness without consistent communication with the environment. How can we know if patients in VS or in MCS feel pain or suffering? The perceptions of pain and suffering are conscious experiences: the wakeful unconsciousness of vegetative patients, by definition, precludes these experiences. Of course, there is a theoretical problem to evaluate the subjective experience of pain (and any other conscious perception or thought) in another person. At the patient's bedside, we are limited to evaluate the behavioral responsiveness to pain. If patients never show any sign of voluntary movement in response to noxious stimuli it will be concluded they do not experience pain. They may, however, be aroused by noxious stimuli by opening their eyes if they are closed, quickening their breathing, increasing heart rate and blood pressure, and occasionally show grimace-like or crying-like behavior. As all these abilities are also seen in infants with anencephaly (The Medical Task Force on Anencephaly, 1990; Payne and Taylor, 1997) they are considered to be of subcortical origin and not necessarily reflecting conscious perception of pain. We also know from studies in general anesthesia that motor or

autonomic responses are no reliable indicators of consciousness (e.g., Halliburton, 1998).

DOC patients classically are bed- or chair-bound and may suffer from spasticity, contractures, fractures, pressure sores, soft tissue ischemia, peripheral nerve injuries, complex regional pain syndrome, central pain syndromes, and post-surgical incisional pain (Schnakers and Zasler, 2007). Since they cannot communicate their potential painful state, the existence of pain is clinically inferred from observing their spontaneous behavior or their motor responses to noxious stimulation. Stereotyped responses (i.e., slow generalized flexion or extension of the upper and lower extremities), flexion withdrawal (i.e., withdrawal of the limb away from the point of the stimulation), and localization responses (i.e., the nonstimulated limb locates and makes contact with the stimulated body part at the point of stimulation) are linked to, respectively, brainstem, subcortical, or cortical activity (e.g., Stevens and Nyquist, 2006). No response after intense noxious stimulation reveals a deep stage of coma; stereotyped responses are considered as ''automatic'' unconscious reflexes, whereas localization of noxious stimulation is usually considered as indicative of conscious perception (Posner et al., 2007).

Repeated clinical examinations by trained and experienced examiners are paramount for the behavioral assessment of pain. To date, several scales are used for assessing pain in noncommunicative individuals with end-stage dementia, in newborns and in sedated intensive care patients, but no scale was developed to assess pain in DOCs (Schnakers et al., 2009b). We therefore recently proposed the Nociception Coma Scale as a standardized and validated tool measuring motor, verbal, and visual responses and facial expression in response to pain (Schnakers et al., 2009a). However, the absence of a behavioral response cannot be taken as an absolute proof of the absence of consciousness (McQuillen, 1991; Bernat, 1992) and inferring pain and suffering solely by observing behavioral responses may be misleading, especially in patients with extreme motor impairment or with fluctuating levels of vigilance (e.g., Majerus et al., 2005). Given these limitations of our bedside clinical assessment of pain in noncommunicative brain injured patients, inherent to the first-person subjective dimension of pain, we will next review the usefulness of functional neuroimaging methods in the study of pain and suffering in VS and MCS.

Neuroimaging of pain

Since brain responses are the final common pathway in behavioral responses to pain (unconscious and conscious), we believe that the application of functional imaging will allow us to study pain in an objective manner and to propose evidence-based guidelines on the use of analgesia and symptom management in DOCs (e.g., Borsook and Becerra, 2006; Laureys et al., 2006; Laureys and Boly, 2008). In healthy controls, studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed that pain cannot be localized in an isolated ''pain centre'' but rather encompasses a neural circuitry, the pain ''neuromatrix'' (Jones et al., 1991; Peyron et al., 2000). More specifically, two distinct cerebral networks have been identified to be involved in pain perception: (i) a lateral pain system or sensory network, encompassing lateral thalamic nuclei, primary and secondary somatosensory, as well as posterior parietal cortices; and (ii) a medial pain system or affective network, which involves the medial thalamus, anterior cingulate, and prefrontal cortices; the insular cortices playing an intermediate role (Hofbauer et al., 2001). For example, increased activity in the insular and anterior cingulate cortices prior to painful stimulation has been linearly associated with increased painfulness (Boly et al., 2007). Inversely, a hypnotic-induced absence of activation in these areas was associated with reduced subjective pain reports (Vanhaudenhuyse et al., 2009). These and other studies are increasing our understanding of the neural correlates of the sensory and affective components of pain (e.g., see review in Kupers et al., 2005), but it should be noted that at present our understanding of suffering (i.e., distress associated with events that threaten the intactness of the person; Cassell, 1991) is very limited and barely studied.

Recent neuroimaging studies have shown that DOCs are characterized by distinct cerebral patterns in response to sensory stimulation (e.g., Laureys et al., 2004; Laureys, 2005a; Giacino et al., 2006; Schiff, 2007; Owen, 2008). In 15 VS patients, our group found no evidence of noxious stimulation-related downstream activation beyond primary somatosensory cortex (Laureys et al., 2002). More importantly, functional connectivity assessment showed that the observed cortical activation subsisted as an island, dissociated from the pain matrix and the higher-order cortices that are currently thought to be necessary for conscious awareness (as shown by studies on conscious perception in healthy controls and on loss of consciousness in sleep and anesthesia; e.g., Baars et al., 2003; Boveroux et al., 2008; Laureys, 2005b). However, another study reported additional activation of secondary somatosensory and insula cortices in VS patients (Kassubek et al., 2003), implying the possibility of affective experiences of pain.

In striking contrast to what we observed in VS, MCS patients showed activation in not only midbrain, thalamus, and primary somatosensory cortex but also in secondary somatosensory, insular, posterior parietal, and anterior cingulate cortices (Fig. 1). The spatial extent of the activation in MCS patients was comparable to controls and no brain region showed less activation in MCS as compared to healthy individuals. A functional connectivity assessment of insular cortex demonstrated its preserved connections with a large set of associative areas encompassing posterior parietal, motor and supplementary motor, striatum, and dorsolateral prefrontal and temporal associative cortices as observed in controls (Boly et al., 2005). These neuroimaging data show large differences in brain activation between VS and MCS patients, despite a similar bedside behavioral evaluation. In the next section, we report differences in healthcare workers' beliefs toward possible pain in DOCs.

Attitudes toward pain perception

To our knowledge, no data exist on the thoughts of physicians and paramedical personnel toward pain perception in patients in VS as compared to MCS. We here present results from a questionnaire survey on attitudes on DOCs, which was distributed during lectures at medical and scientific conferences and meetings ($n = 48$) within

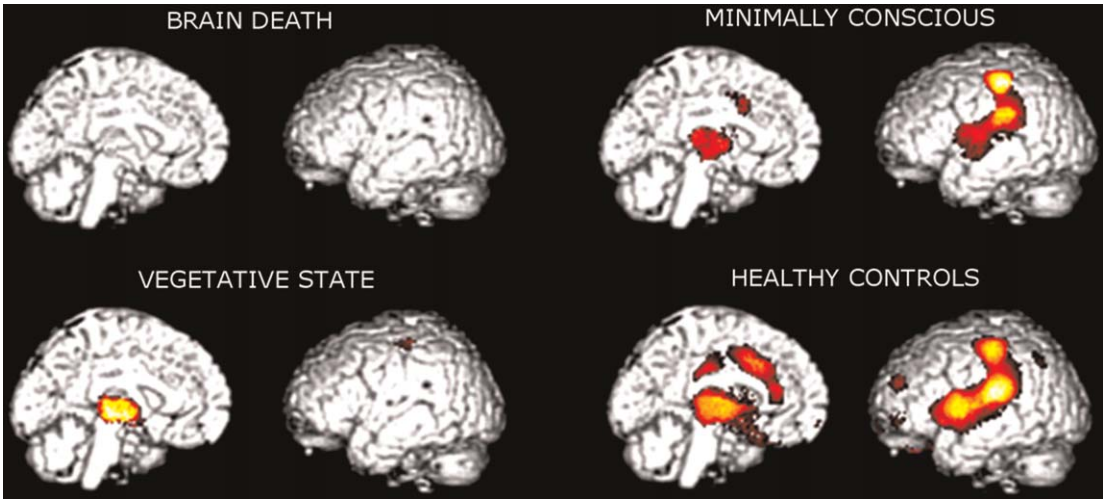


Fig. 1. Cerebral activation to noxious stimulation in brain death (adapted from Laureys, 2005a with permission), the VS (Laureys et al., 2002 with permission), and the MCS (Boly et al., 2008 with permission) as compared to healthy volunteers. Note: (i) the absence of activation in brain death; (ii) the preserved but low-level subcortical and primary cortical activation in the VS (the primary cortical activation was disconnected from the rest of the brain), and (iii) the near-normal activation in the minimally conscious state.

Europe (data were collected by SL, AD, MAB, AV, MAB, and DL between June 2007 and April 2009). Participation to the survey was voluntary and anonymous. Participants were first introduced to the clinical definitions of DOCs and were then asked to provide 'yes' or 'no' answers to 16 questions related to consciousness, VS, MCS, and locked-in syndrome. We here report the replies obtained in European medical and paramedical professionals to the questions ''Do you think that patients in a vegetative state can feel pain?'' and ''Do you think that patients in a minimally conscious state can feel pain?'' — the questions related to consciousness and the brain have been reported elsewhere (Demertzi et al., 2009). Recorded demographic data included age, gender, nationality, profession, and religious beliefs. Nationalities were categorized into three geographical regions based on previous classification criteria (Sprung et al., 2003): Northern (Denmark, Estonia, Finland, Lithuania, Netherlands, Norway, Poland, Russia, Sweden, United Kingdom), Central (Austria, Belgium, Czech Republic, Germany, Hungary, Luxembourg, Moldavia, Romania, Serbia, Slovakia, Slovenia, Switzerland), and Southern Europe (Bulgaria, Croatia, Cyprus, France, FYROM, Greece, Italy, Portugal, Spain, Turkey). Statistical analyses were performed using SPSS v.16.0 software packages. Multiple logistic regression (stepwise backward; i.e., independent variables are removed from the equation at consecutive steps; entry, $p = 0.05$ and removal, $p = 0.1$) was used to assess associations between obtained answers to the two questions and age, gender, profession, region, and religiosity. Chi-square tests assessed differences within categorical variables. Results were considered significant at $p < 0.05$ (two-sided).

The study sample included 2059 medical and paramedical professionals coming from 32 European countries (see Table 1 for demographic data). As a whole, the sampled participants replied more often that MCS patients could feel pain than that VS patients could feel pain ($\chi^2(1) = 7.9$, $p < 0.001$). Participants' opinions were much more consistent for pain perception in MCS (96% of the total sample considered MCS patients can feel pain), while responses were much more discordant for VS (59% considered vegetative patients could feel pain). Paramedical caregivers ($n = 538$) replied more often that patients in a VS could feel pain than did medical doctors ($n = 1166$) (68% versus 56%; $\chi^2(1) = 23.07$, $p < 0.001$; Fig. 2a). Following professional background, religion was the highest predictor of caregivers' opinion: 64% of religious ($n = 1009$; 94% Christians) versus 52% of nonreligious respondents ($n = 830$) answered positively (see Fig. 3a). There was no effect of religion practice (317 were practicing and 664 were not practicing their religion) on attitudes toward pain perception in the VS ($\chi^2(1) = 0.261$, $p = 0.609$). Logistic regression analysis showed that paramedical professionals, religious caregivers, and older caregivers reported more often that vegetative patients may experience pain (Table 2). To the question ''Do you think that patients in a minimally conscious state can feel pain?'' nearly all interviewed caregivers answered ''yes'' (96% of the medical doctors and 97% of the paramedical caregivers; Fig. 2b). Logistic regression analysis showed that women and religious caregivers reported more often that minimally conscious patients may experience pain. For attitudes on pain in MCS, the difference between medical

Table 1. Demographic characteristics of the study sample ($n = 2059$)

Age, mean ± SD (range), years	43 ± 12 (18–83)
Gender, no. (%)	
Women	993 (47%)
Men	962 (48%)
Missing	104 (5%)
Respondents by geographical region, no. (%)	
Northern Europe	283 (13%)
Central Europe	1011 (49%)
Southern Europe	470 (24%)
Missing	295 (14%)
Profession, no. (%)	
Medical professionals	1196 (58%)
Paramedical professionals	548 (27%)
Missing	315 (15%)
Religiosity, no. (%)	
Religious respondents	1033 (50%)
Non-religious respondents	849 (41%)
Missing	177 (9%)

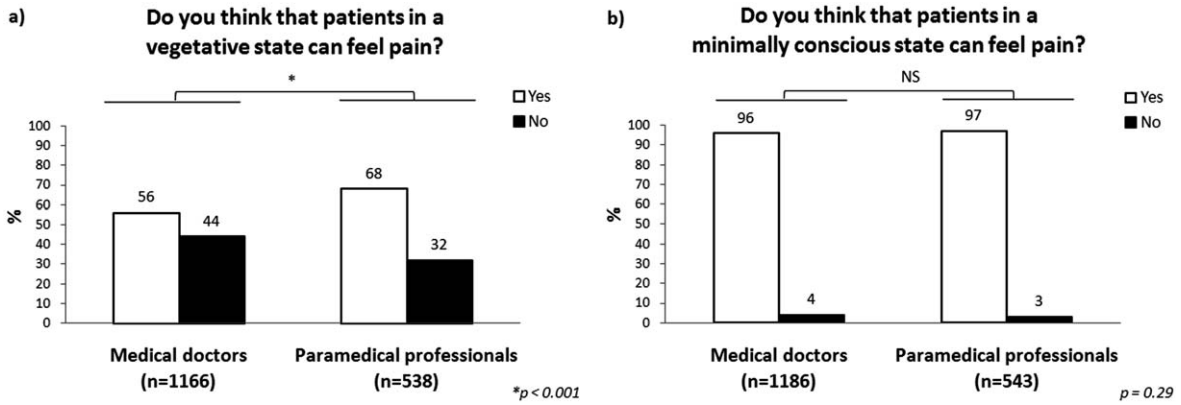


Fig. 2. Attitudes toward pain perception in the vegetative and the minimally conscious as expressed by European medical and paramedical professionals.

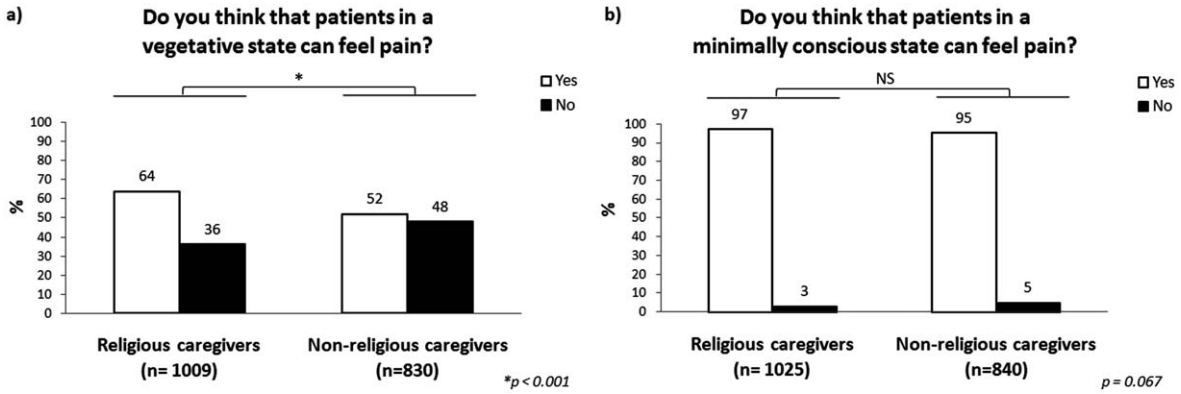


Fig. 3. The effect of religion on attitudes toward pain perception in patients with DOCs.

and paramedical professionals was not significant ($\chi^2(1) = 1.07$, $p = 0.295$).

According to our survey, healthcare workers have different beliefs about possible pain perception in MCS as compared to VS patients. This finding implies that, despite the recent introduction of MCS (Giacino et al., 2002), the medical community regards MCS and VS as two separate clinical entities characterized by different pain perception profiles. The major differences in physicians' beliefs about pain in VS as compared to MCS are supported by results from the functional neuroimaging data discussed above (Laureys et al., 2002; Boly et al., 2008). However, our survey showed that a high proportion of medical doctors (56%) and paramedical professionals (68%) considered that VS patients feel pain. The observed differences in viewpoint depending on professional background might be related to many factors including differences in proximity to the patient, time spent at the bedside, sensibilities, and education. Previous American studies reported a smaller minority of physicians holding these views. Payne et al. (1996) surveyed 170 physicians from the American Academy of Neurology and 150 from the American Medical Directors Association and reported that only 30% believed VS patients experience pain (they found no differences between academic and non-academic physicians). Similarly, an unpublished survey by the American Neurological Association reported that 31% of its members

Table 2. Logistic regression results on participants' characteristics (age, gender, region, professional background, religiosity) and ''Yes'' versus ''No'' answers to the questions on pain perception in VS and MCS

Question predictors	Odds ratio[a]	95% Confidence interval		*p*-value
Do VS patients feel pain?[b]				
Age	1.01	1.00	1.02	0.05
Women	1.25	0.99	1.58	0.06
Northern Europe	1			
Central Europe	0.81	0.58	1.14	0.24
Southern Europe	1.1	0.76	1.6	0.6
Paramedical professionals	1.56	1.2	2	<0.001
Religious respondents	1.37	1.1	1.7	0.004
Do MCS patients feel pain?[c]				
Women	2.38	1.33	4.26	0.003
Religious respondents	1.83	1.05	3.18	0.031

[a]For the continuous variables, the odds ratio equals the relative change in the odds ratio when the variable is increased by one unit.
[b]Stepwise backward (Step 1).
[c]Stepwise backward (Step 4).

were ''uncertain'' about whether VS patients could experience pain (31%) and suffering (26%) (Daroff, 1990). Tresch et al. (1991) found that only 22% of the relatives of patients in VS believed that their relative could experience pain and suffering. We can only speculate about possible explanations for the seemingly increased proportion of physicians considering that VS patients feel pain. It maybe that the recent publication of the diagnostic criteria for the MCS (Giacino et al., 2002) or the highly mediatized report of a VS patient ''playing tennis in her head'' (Owen et al., 2006) may have changed physicians opinions. In addition, cultural and religious differences could underlie the observed discrepancies between our European study and the older American surveys.

Physician and caregivers' opinions on patients' pain perception was significantly influenced by religious beliefs. We have previously shown that personal philosophical convictions are of major influence on our views on the relationship between consciousness and the brain (Demertzi et al., 2009). Such personal beliefs have also been shown to weight on physicians' clinical decisions (e.g., see Jennett, 2002). In line with our findings on the influence of religion and age on beliefs on pain perception in VS, other studies on, for example, end-of-life decisions in intensive care patients have shown that older and more experienced doctors and doctors with religious convictions (i.e., Christians) more often refused to opt for treatment limitations (Christakis and Asch, 1995; Sprung et al., 2003).

Considering our results on varying beliefs about pain perception in DOCs, physicians and healthcare workers' views on pain and symptom management may also be affected. Since nearly half of the interviewed doctors express that VS patients do not feel pain, they could be expected to act accordingly by, for instance, not providing analgesic medication in these patients. These issues become even more important in cases when VS patients are agreed to be withdrawn from life-supporting treatment, such as artificial nutrition and hydration. In these cases (e.g., Terri Schiavo) patients may be left without administration of opioids or other analgesic drugs during their dying process (Fins, 2006; Laureys, 2005a) on the grounds that they are deployed from experiencing suffering from hunger and thirst (Ahronheim and Gasner, 1990). In light of an incomplete picture of pain perception in VS patients, the existing risk for misdiagnosis (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2009c), the inconclusive drug-related effects in DOCs (Demertzi et al., 2008) and the limitations in interpreting neuroimaging results (Poldrack, 2008;

Laureys and Boly, 2007), pain prophylaxis and treatment have been proposed for all patients suffering from DOCs (Schnakers and Zasler, 2007; Schnakers et al., 2009b).

The reported discrepancies in opinions about pain perception in VS patients may also be related to the absence of a unanimously accepted definition of pain and suffering. The Multi-Society Task Force on PVS (1994) considered that grimace-like or crying-like behaviors are not likely to reflect conscious awareness of pain or suffering ''unless they are consistent, sustained, and definitive in nature.'' They differentiated between pain and nociception, in that the latter is merely a response to noxious stimulation that can be present without conscious awareness and stated that nociceptive stimulation may elicit unconscious postural responses, as well as other motor, autonomic, and endocrinologic reflexive responses without evoking the experience of pain and suffering if the brain has lost its capacity for self-awareness (Multi-Society Task Force on PVS, 1994). The IASP (1994) definition of pain also refers to cognitive and affective properties of pain, stressing the importance of subjectivity and environmental influences in the experience of pain. Some authors support the view that pain can be regarded as any response to a noxious stimulus (e.g., see Anand and Craig, 1996) — but it is clear that not just any reaction to changes in the environment can be considered as conscious (e.g., brain-death-associated reflexes and automatisms; Laureys, 2005a; Jain and DeGeorgia, 2005). Others have hypothesized, based on observations from children with hydrancephaly (Shewmon et al., 1999) newborns (Anand and Hickey, 1987) and fetuses (Derbyshire, 2008), that midbrain structures may mediate consciousness, supporting the claim that cortical activity is not necessary for conscious perception (Merker, 2007).

In conclusion, our survey shows clear differences in medical professionals' beliefs on pain perception in VS patients as compared to MCS patients. Nearly all respondents considered that MCS patients can feel pain and medical doctors and paramedical professionals largely concur. In contrast, the beliefs on pain perception in VS patients were much more divided. Paramedical professionals, religious participants, and older caregivers reported more often that VS patients may experience pain. In light of many controversies around pain (and hence pain management) in VS and MCS patients, an increase in scientific evidence is essential to enhance our understanding and to permit the development of adapted standards of care and improved clinical guidelines for these challenging and vulnerable noncommunicative patients with DOCs.

Acknowledgments

This work was supported by the Belgian Ministry of Health (SPF Santé Publique), Belgian Fonds de la Recherche Scientifique (FRS), European Commission (DISCOS, Mindbridge, COST), Belgian French Community Concerted Research Action, McDonnell Foundation, Mind Science Foundation, Reine Elisabeth Medical Foundation, and University and University Hospital of Liège. S. Laureys is Senior Research Associate, C. Schnakers and M. Boly are Postdoctoral Researchers, C. Chatelle and M. A. Bruno are Research Fellows, and D. Ledoux is Clinical Associate at FRS.

References

Ahronheim, J. C., & Gasner, M. R. (1990). The sloganism of starvation. *Lancet*, *335*, 278–279.

Anand, K. J., & Craig, K. D. (1996). New perspectives on the definition of pain. *Pain*, *67*, 3–6. Discussion 209–11.

Anand, K. J., & Hickey, P. R. (1987). Pain and its effects in the human neonate and fetus. *The New England Journal of Medicine*, *317*, 1321–1329.

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*, 13–16.

Baars, B. J., Ramsoy, T. Z., & Laureys, S. (2003). Brain, conscious experience and the observing self. *Trends in Neurosciences*, *26*, 671–675.

Bernat, J. L. (1992). The boundaries of the persistent vegetative state. *Journal of Clinical Ethics*, *3*, 176–180.

Bernat, J. L. (2006). Chronic disorders of consciousness. *Lancet*, *367*(9517), 1181–1192.

Boly, M., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., et al. (2007). Baseline brain activity

fluctuations predict somatosensory perception in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 12187–12192.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, F., Luxen, A., et al. (2005). Cerebral processing of auditory and noxious stimuli in severely brain injured patients: Differences between VS and MCS. *Neuropsychological Rehabilitation*, *15*, 283–289.

Boly, M., Faymonville, M. E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., et al. (2008). Perception of pain in the minimally conscious state with PET activation: An observational study. *Lancet Neurology*, *7*, 1013–1020.

Borsook, D., & Becerra, L. R. (2006). Breaking down the barriers: fMRI applications in pain, analgesia and analgesics. *Molecular Pain [electronic resource]*, *2*, 30.

Boveroux, P., Bonhomme, V., Boly, M., Vanhaudenhuyse, A., Maquet, P., & Laureys, S. (2008). Brain function in physiologically, pharmacologically and pathologically altered states of consciousness. *International Anesthesiology Clinics*, *46*, 131–146.

Cassell, E. J. (1991). Recognizing suffering. *The Hastings Center Report*, *20*, 24–31.

Childs, N. L., Mercer, W. N., & Childs, H. W. (1993). Accuracy of diagnosis of persistent vegetative state. *Neurology*, *43*, 1465–1467.

Christakis, N. A., & Asch, D. A. (1995). Physician characteristics associated with decisions to withdraw life support. *American Journal of Public Health*, *85*, 367–372.

Daroff, R. B. (1990). The American Neurological Association survey results on PVS. Paper presented at 115th Annual Meeting, Atlanta.

Demertzi, A., Liew, C., Ledoux, D., Bruno, M. A., Sharpe, M., Laureys, S., et al. (2009). Dualism persists in the science of mind. *Annals of the New York Academy of Sciences*, *1157*, 1–9.

Demertzi, A., Vanhaudenhuyse, A., Bruno, M. A., Schnakers, C., Boly, M., Boveroux, P., et al. (2008). Is there anybody in there? Detecting awareness in disorders of consciousness. *Expert Review of Neurotherapeutics*, *8*, 1719–1730.

Derbyshire, S. W. (2008). Fetal pain: Do we know enough to do the right thing? *Reproductive Health Matters*, *16*, 117–126.

Fins, J. J. (2006). Affirming the right to care, preserving the right to die: Disorders of consciousness and neuroethics after Schiavo. *Palliative & Supportive Care*, *4*, 169–178.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*, 349–353.

Giacino, J., Hirsch, J., Schiff, N., & Laureys, S. (2006). Functional neuroimaging applications for assessment and rehabilitation planning in patients with disorders of consciousness. *Archives of Physical Medicine and Rehabilitation*, *87*, 67–76.

Halliburton, J. R. (1998). Awareness during general anesthesia: New technology for an old problem. *Certified Registered Nurse Anesthetist*, *9*, 39–43.

Hofbauer, R. K., Rainville, P., Duncan, G. H., & Bushnell, M. C. (2001). Cortical representation of the sensory dimension of pain. *Journal of Neurophysiology*, *86*, 402–411.

International Association for the Study of Pain. (1994). *Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Task force on taxonomy*. Seattle: IASP Press.

Jain, S., & DeGeorgia, M. (2005). Brain death-associated reflexes and automatisms. *Neurocritical Care*, *3*, 122–126.

Jennett, B. (2002). *The vegetative state. Medical facts, ethical and legal dilemmas*. Cambridge: Cambridge University Press.

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet*, *1*, 734–737.

Jones, A. K., Brown, W. D., Friston, K. J., Qi, L. Y., & Frackowiak, R. S. J. (1991). Cortical and subcortical localization of response to pain in man using positron emission tomography. *Proceedings of Royal Society of London B: Biological Sciences*, *244*, 39–44.

Kassubek, J., Juengling, F. D., Els, T., Spreer, J., Herpers, M., Krause, T., Moser, E., et al. (2003). Activation of a residual cortical network during painful stimulation in long-term postanoxic vegetative state: A ^{15}O-H_2O PET study. *Journal of the Neurological Sciences*, *212*, 85–91.

Kupers, R., Faymonville, M.-E., & Laureys, S. (2005). The cognitive modulation of pain. *Progress in Brain Research*, *150*, 251–269.

Laureys, S. (2005a). Death, unconsciousness and the brain. *Nature Reviews Neuroscience*, *11*, 899–909.

Laureys, S. (2005b). The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences*, *9*, 556–559.

Laureys, S., & Boly, M. (2007). What is it like to be vegetative or minimally conscious? *Current Opinion in Neurology*, *20*, 609–613.

Laureys, S., & Boly, M. (2008). The changing spectrum of coma. *Nature Clinical Practice Neurology*, *4*, 544–546.

Laureys, S., Faymonville, M. E., Peigneux, P., Damas, P., Lambermont, B., Del Fiore, G., et al. (2002). Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage*, *17*, 732–741.

Laureys, S., Giacino, J. T., Schiff, N. D., Schabus, M., & Owen, A. M. (2006). How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs? *Current Opinion in Neurology*, *19*, 520–527.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*, 537–546.

Majerus, S., Gill-Twaites, H., Andrews, K., & Laureys, S. (2005). Behavioral evaluation of consciousness in severe brain damage. *Progress in Brain Research*, *150*, 397–413.

McQuillen, M. P. (1991). Can people who are unconscious or in the ''vegetative state'' perceive pain? *Issues in Law & Medicine*, *6*, 373–383.

Merker, B. (2007). Consciousness without a cerebral cortex: A challenge for neuroscience and medicine. *The Behavioral and Brain Sciences*, *30*, 63–81. Discussion 81–134.

Owen, A. M. (2008). Disorders of consciousness. *Annals of the New York Academy of Sciences*, *1124*, 225–238.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Payne, K., Taylor, R. M., Stocking, C., & Sachs, G. A. (1996). Physicians' attitudes about the care of patients in the persistent vegetative state: A national survey. *Annals of Internal Medicine*, *125*, 104–110.

Payne, S. K., & Taylor, R. M. (1997). The persistent vegetative state and anencephaly: Problematic paradigms for discussing futility and rationing. *Seminars in Neurology*, *17*, 257–263.

Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta- analysis. *Neurophysiologie Clinique*, *30*, 263–288.

Poldrack, R. A. (2008). The role of fMRI in cognitive neuroscience: Where do we stand? *Current Opinion in Neurobiology*, *18*, 223–227.

Posner, J., Saper, C., Schiff, N., & Plum, F. (2007). *Plum and Posner's diagnosis of stupor and coma*. New York: Oxford University Press.

Schiff, N. D. (2007). Bringing neuroimaging tools closer to diagnostic use in the severely injured brain. *Brain*, *130*, 2482–2483.

Schnakers, C., Chatelle, C., Vanhaudenhuyse, A., Majerus, S., Ledoux, D., Boly, M., et al. (2009a). The nociception coma scale: A new tool to assess pain in disorders of consciousness. *Pain* (under revision).

Schnakers, C., Faymonville, M. E., & Laureys, S. (2009b). Ethical Implications: Pain, coma, and related disorders. In W. P. Banks (Ed.), *Encyclopedia of consciousness* (Vol. 1, pp. 243–250). Oxford: Elsevier.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., et al. (2009c). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, *9*, 35.

Schnakers, C., & Zasler, N. D. (2007). Pain assessment and management in disorders of consciousness. *Current Opinion in Neurology*, *20*, 620–626.

Shewmon, D. A., Holmes, G. L., & Byrne, P. A. (1999). Consciousness in congenitally decorticate children: Developmental vegetative state as self-fulfilling prophecy. *Developmental Medicine and Child Neurology*, *41*, 364–374.

Sprung, C. L., Cohen, S. L., Sjokvist, P., Baras, M., Bulow, H. H., Hovilehto, S., et al. (2003). End-of-life practices in European intensive care units: The Ethicus study. *Journal of the American Medical Association*, *290*, 790–797.

Stevens, R. D., & Nyquist, P. A. (2006). Coma, delirium, and cognitive dysfunction in critical illness. *Critical Care Clinics*, *22*, 787–804.

The Medical Task Force on Anencephaly. (1990). The infant with anencephaly. *The New England Journal of Medicine*, *322*, 669–674.

The Multi-Society Task Force on PVS. (1994). Medical aspects of the persistent vegetative state (2). *The New England Journal of Medicine*, *330*, 1572–1579.

Tresch, D. D., Sims, F. H., Duthie, E. H., Jr., & Goldstein, M. D. (1991). Patients in a persistent vegetative state: Attitudes and reactions of family members. *Journal of the American Geriatrics Society*, *39*, 17–21.

Turk, D. C., & Wilson, H. D. (2009). Pain, suffering, pain-related suffering-are these constructs inextricably linked? *Clinical Journal of Pain*, *25*, 353–355.

Vanhaudenhuyse, A., Boly, M., Balteau, E., Schnakers, C., Moonen, G., Luxen, A., et al. (2009). Pain and non-pain processing during hypnosis: A thulium-YAG event related fMRI study. *Neuroimage*, *47*, 1047–1054.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 23

Life can be worth living in locked-in syndrome

D. Lulé[1,2,*], C. Zickler[1], S. Häcker[1], M.A. Bruno[2], A. Demertzi[2], F. Pellas[3], S. Laureys[2] and A. Kübler[4]

[1]*Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany*
[2]*Coma Science Group, Cyclotron Research Centre, University of Liège, Liège, Belgium*
[3]*Médecine Rééducative, Hôpital Caremeau, CHU Nîmes, Cedex, France*
[4]*Institute of Psychology I, Biological Psychology, Clinical Psychology and Psychotherapy, University of Würzburg, Würzburg, Germany; Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany*

Abstract: The locked-in syndrome (LIS) describes patients who are awake and conscious but severely deefferented leaving the patient in a state of almost complete immobility and loss of verbal communication. The etiology ranges from acute (e.g., brainstem stroke, which is the most frequent cause of LIS) to chronic causes (e.g., amyotrophic lateral sclerosis; ALS). In this article we review and present new data on the psychosocial adjustment to LIS. We refer to quality of life (QoL) and the degree of depressive symptoms as a measure of psychosocial adjustment. Various studies suggest that despite their extreme motor impairment, a significant number of LIS patients maintain a good QoL that seems unrelated to their state of physical functioning. Likewise, depression is not predicted by the physical state of the patients. A successful psychological adjustment to the disease was shown to be related to problem-oriented coping strategies, like seeking for information, and emotional coping strategies like denial — the latter may, nevertheless, vary with disease stage. Perceived social support seems to be the strongest predictor of psychosocial adjustment. QoL in LIS patients is often in the same range as in age-matched healthy individuals. Interestingly, there is evidence that significant others, like primary caregivers or spouses, rate LIS patients' QoL significantly lower than the patients themselves. With regard to depressed mood, ALS patients without symptoms focus significantly more often on internal factors that can be retained in the course of the disease contrary to patients with depressive symptoms who preferably name external factors as very important, such as health, which will degrade in the course of the disease. Typically, ALS patients with a higher degree of depressive symptoms experience significantly less "very pleasant" situations. The herein presented data strongly question the assumption among doctors, health-care workers, lay persons, and politicians that severe motor disability necessarily is intolerable and leads to end-of-life decisions or euthanasia. Existing evidence supports that biased clinicians provide less-aggressive medical treatment in LIS patients. Thus, psychological treatment for depression, effective strategies for coping with the disease, and support concerning the maintenance of the social network are needed to cope with the disease. Novel communication devices and assistive technology now offers an increasing number of LIS patients to resume a meaningful life and an active role in society.

*Corresponding author.
Tel.: 0049 731 500 63076; Fax: 0049 731 500 63064;
E-mail: dorothee.lule@uni-ulm.de

DOI: 10.1016/S0079-6123(09)17723-3

keywords: quality of life; depression; locked-in syndrome (LIS); amyotrophic lateral sclerosis; brainstem stroke; euthanasia; end-of-life

Introduction

The term locked-in syndrome (LIS) was first introduced by Plum and Posner in 1983 and describes patients who are awake and conscious but selectively deefferented, that is, have no means of producing speech, limb or facial movements. The American Congress of Rehabilitation Medicine (1995) defined LIS as a neurological impairment characterized by the presence of sustained eye opening (bilateral ptosis should be ruled out as a complicating factor), quadriplegia or quadriparesis, aphonia or severe hypophonia, preserved cognitive function, and a primary and elementary code of communication that use eye movement or blinking. The LIS can be subcategorized according to the severity of the motor impairment in: (1) *classical* LIS, characterized by quadriplegia and aphonia with preserved consciousness and vertical eye movements or blinking; (2) *incomplete* LIS, characterized by remnants of voluntary motion other than vertical eye movements; and (3) *total* LIS, characterized by complete immobility (including eye movements) with preserved consciousness (Bauer et al., 1979). Acute pontine lesions following vascular pathology are its most common cause (Plum and Posner, 1983; Laureys et al., 2005). LIS can also be observed in progressive neurologic pathologies like end-stage amyotrophic lateral sclerosis (ALS) (Ludolph and Dengler, 1999). It has been traditionally stated that long-term survival in LIS is rare (Ohry, 1990). Mortality is indeed high in acute LIS of vascular origin (87% within the first 4 months; Patterson and Grabois, 1986) and mean survival rate in ALS is 3–5 years with only a short period of time in LIS (Ludolph and Dengler, 1999). However, individuals in LIS may survive for long periods of time, sometimes exceeding 20 years (Doble et al., 2003; León-Carrión et al., 2002; Laureys et al., 2005). Doble et al. (2003) reported a 10-year survival of 83% and 20-year survival of 40% in 29 stabilized (i.e., surviving more than 1 year) LIS patients. Data from the French Association for Locked-In Syndrome (ALIS; www.alis-asso.fr) on 250 patients showed that mean time spent in LIS was 6 ± 4 years (range 14 days–27 years; Laureys et al., 2005). With improving medical technology, life with severe physical impairment can be significantly prolonged — for example, by application of noninvasive and invasive ventilation in ALS. Noninvasive ventilation prolongs life for 250 up to 300 days and has therefore the same life-prolonging effect as Riluzole, the only approved drug in ALS (Bourke et al., 2006). However, motor recovery is futile in a progressive motor neuron disease like ALS and the hope for motor recovery is limited in LIS of vascular origin (Doble et al., 2003). Despite the severe persisting motor deficits in classic LIS, some patients may present improvement (classically showing a distal to proximal progression) and recover voluntary control of head, finger, or foot (Richard et al., 1995; Laureys et al., 2005). Overall, the level of care remains extensive in chronic LIS and patients classically remain dependent on others for activities of daily living.

Autonomy and physical functioning has long been seen as the prerequisite of a life worth living (Chin et al., 1999). In recent years this was adjusted and life was defined to be worth living if there was a perspective of gaining autonomy (e.g., Bruno et al., 2008a, b). Studies show that QoL often equates with social rather than physical interaction or autonomy (Laureys et al., 2005). The arising question from our definition of ''a life worth living'' is what the consequences are for people with such extreme motor impairment, in which the probability for regaining autonomy in daily life is very limited. We may have to revise our classical idea of autonomy emphasizing that *mental* autonomy can be maintained even in a state of high dependence on others, in which much if not all physical autonomy is lost. The present work will review the available literature and present new

data on psychological adjustment of patients with severe states of motor impairment leading a life depending on others — including both LIS following an acute brainstem lesion and following chronic motor neuron diseases such as ALS.

Quality of life

Successful adjustment to a diagnosis can be measured as a degree of quality of life (QoL). According to the World Health Organization (WHO) ''quality of life is defined as the individual's perception of their position in life. (…) It is a broad ranging concept affected in a complex way by a person's physical health, psychological state, level of independence and their relationship to salient features of their environment'' (The WHOQOL Group, 1995). In the field of neurology and neuro-critical care, QoL has only been studied relatively recently. Communication limitations make QoL assessments in LIS patients particularly difficult (Murrell, 1999). Additionally, QoL measures may not be sensitive enough to capture specific issues relating to the disease. This seems especially true for patients with a LIS. A common approach to refining the concept of QoL is to restrict its definition to health-related QoL. The common understanding of a good QoL implies being in good health and experiencing subjective well-being and life satisfaction (Goode, 1994). According to this concept, LIS patients could not have a high QoL due to their low level of physical functioning. In reality, patients' perceptions of personal health, well-being, and life satisfaction are often discordant with their objective health status and disability (Albrecht and Higgins, 1977; Albrecht, 1994). Accordingly, LIS patients report a QoL often comparable to age-matched healthy controls and other chronically ill patients without severe motor impairment (Kübler et al., 2005; Rabkin et al., 2000; Lulé et al., 2008; Laureys et al., 2005). The self-reported subjectively experienced QoL of LIS patients with ALS is neither associated with physical functioning nor can it be predicted by this factor (Kübler et al., 2005; Lulé et al., 2008; Matuz et al., submitted). Notably, with the progression of the disease, patients with higher physical restrictions indicated a higher QoL than patients who were less impaired (Lulé et al., 2008).

We here report unpublished data on QoL measured in 30 ALS patients by means of the Schedule for the Evaluation of Individual Quality of Life Direct Weighting (SEIQoL-DW; Hickey et al., 1996) and the seiquol index score (SIS). Patients' age ranged from 37 to 72 years (mean 58 ± 8.9 years; 16 females). Physical restrictions were measured with the ALS functional rating scale revised form (ALS-FRS; Cedarbaum et al., 1999). We observed that QoL was *better* in patients with more severe motor impairment (Pearson correlation $r_{part} = -0.43$; $p < 0.05$, corrected for age). This correlation could be attributed to artificial ventilation: ALS patients who were on artificial ventilation (either noninvasive or invasive; $n = 13$) experienced a higher QoL compared to patients without ventilation ($n = 17$) (mean SIS $= 77.4 \pm 18.0$ SD versus 64.2 ± 14.8; univariate ANOVA with age as covariate, $F_{1/27} = 5.0$, $p < 0.05$; Zickler, unpublished). Note that a SIS of 77 is in the range of results obtained in healthy controls (McGee et al., 1991). Our finding may be explained by the possible beneficial symptomatic effects of ventilation, including lessening daytime fatigue and reduced anxiety.

In line with these findings in ALS, we observed in 17 patients with a LIS caused by a vascular brainstem lesion (mean age, 44 ± 6; range, 33–57 years; 5 females; LIS duration, 6 ± 4 years) that patients' subjective QoL was not related to physical impairment nor could it be predicted by this factor (Ghorbel et al., unpublished). According to the employed Short Form-36 questionnaire (SF-36; Ware et al., 1993) and compared to age-matched French control subjects (Leplege et al., 1998), LIS patients unsurprisingly showed maximal limitations in physical activities and significant limitations in usual role activities because of health problems, and in social activities due to physical or emotional problems. They also showed significant limitations in usual role activities because of emotional problems and scored significantly less on the vitality items (dealing with energy and fatigue). With the exception of the vitality score, all these items showed a significant floor effect (frequent use of the lowest possible score).

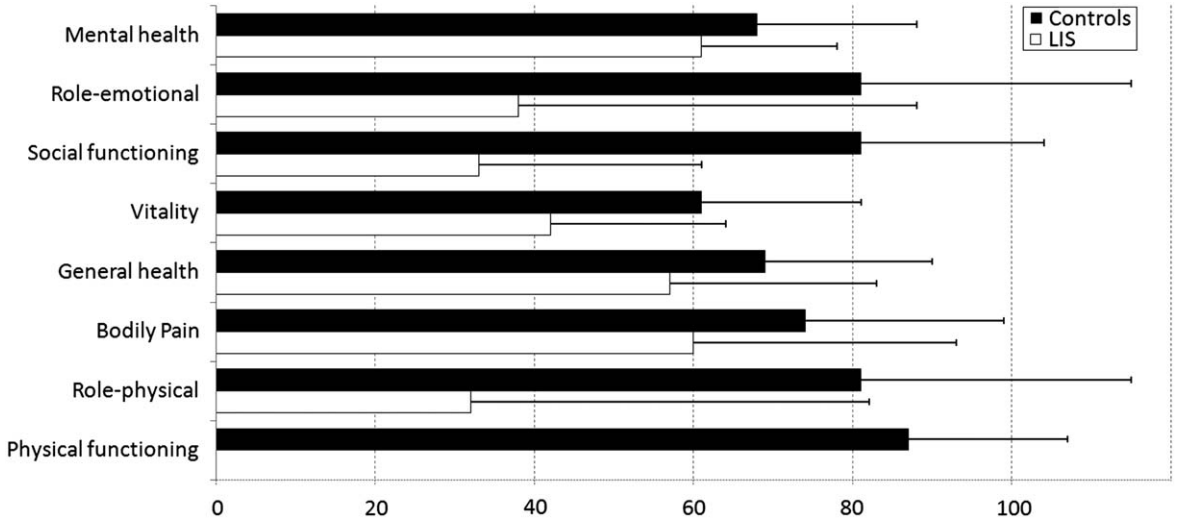


Fig. 1. Short Form-36 self-rated quality of general health status in 17 chronic locked-in patients (caused by brainstem stroke) as compared to healthy age-matched French controls (part of these data were reported in Laureys et al., 2005 with permission from Coma Science group, University of Liége).

Interestingly, self-scored perception of mental health (evaluating mental well-being and psychological distress), personal general health, and bodily pain were close to control values (Fig. 1). We also observed that perception of mental health and the presence of physical pain was correlated to the frequency of suicidal thoughts ($r = -0.67$ and 0.56, respectively, $p < 0.05$).

This "disability paradox" refers to the fact that people with serious and persistent disability report that they experience a good QoL (Albrecht and Devlieger, 1999). In contrast, advanced-stage carcinoma patients show a subjective QoL that seems significantly lower as compared to ALS patients (Fegg et al., 2005) and which continues to decline as the disease leads to progressive physical impairment (Frick et al., 2007; Jenewein et al., 2008). Patients with severe paralysis leading in its most extreme form to a LIS seem to experience a subjective QoL that is better than that of patients with terminal cancer, and comparable to that of patients with nonterminal chronic disease (McGee et al., 1991; Moons et al., 2004). The published literature and the data here presented (summarized in Table 1) suggest that patients at any stage of physical restrictions can subjectively experience a high QoL.

Family members or significant others tend to assume that patients' QoL is poor and underestimate the QoL of patients with chronic illness (McDonald et al., 1996; Sprangers and Aaronson, 1992; Trail et al., 2003). It was shown that when significant others were asked to evaluate the QoL of a patient with severe motor impairment, they rated a significantly lower QoL than did the patients themselves (Kübler et al., 2005). These findings support the assumption of Ganzini and Block (2002) that healthy people may present a defense mechanism having difficulty imagining the feelings and experiences of severely impaired patients. Albrecht and Devlieger (1999) stated that QoL is dependent on establishing and maintaining a harmonious set of relationships within the person's social context and external environment. Appropriate medical and technical intervention as well as social support may strongly influence the QoL of patients with very severe motor impairment. When ALS patients were asked about the determinants of their subjective QoL, health and mobility were factors most often mentioned by patients with clinically relevant depressive symptoms. This indicates that depressed ALS patients seem to define their QoL to a great extent as a function of "external

Table 1. Studies on adaptation to LIS (following brainstem lesion and ALS2)

Study	Number of patients	Etiology	Mean age (years; range)	Good self-scored QoL	Self-scored depression	Time since onset (range or mean)
Doble et al. (2003)	27	Brainstem lesion	34 (1–70)	7/13 (54%)[a]	5/13 (38%)[d]	12–132 months
León-Carrión et al. (2002)	44	Brainstem lesion	47 (22–77)	21/48 (48%)[a]	6/44 (13%)[d]	62 months
Bruno et al. (2008b)	11	Brainstem lesion	43 (27–61)	''Not lower than controls''[b]	NA	84 months
Ghorbel et al. (unpublished) and Laureys et al. (2005)	17	Brainstem lesion	44 (33–57)	''Not lower than controls''[c]	NA	72 months
Bruno and Laureys (unpublished)	53	Brainstem lesion	46 (22–69)	NA	5/53 (9%)	72 months
Zickler (unpublished)	30	ALS	58 (37–72)	23/30 (77%)[c]	9/30 (30%)[e]	41 months
Hacker (unpublished)	33	ALS	58 (37–72)	28/33 (85%)	8/33 (24%)	40 months
Hammer et al. (2008)	39	ALS	58 (37–72)	33/39 (85%)[c]	11/39 (28%)[e]	44 months
Lule et al. (2008)	30	ALS	59 (39–71)	21/30 (70%)[c]	4/30(13%)[e]	NA

NA = not available
[a]As assessed using open questions.
[b]As assessed using ACSA scale.
[c]As assessed using , SF-36, or SEIQoL.
[d]Depression was evaluated using open questions: the question was asked ''Is the patient depressed: often, sometimes, never.''
[e]Depression was evaluated using the ALS depression inventory, ADI (Kübler et al., 2005).

experiences'' that are no longer accessible (i.e., health and mobility). For patients without symptoms of depression, ''internal'' experiences, such as personal well-being, seem to be more important for their QoL (Lulé et al., 2008). Importantly, these areas can remain intact even as the disease progresses. These findings underline the close relationship of QoL and affective state (e.g., depression) and provided support (e.g., social, medical, technical aids). Severely impaired ALS patients more often named communication and medical care as determinants of QoL than did mildly to moderately impaired ALS patients — who did not name these areas as determinants of their QoL at all (Lulé et al., 2008). This suggests that specific determinants become increasingly important for patients' subjective QoL, while physical impairment worsens. Such an adaptation to disease is referred to as response shift (Sprangers and Schwartz, 1999).

Psychological adaptation in LIS

Psychological adaptation to extreme motor impairment is mediated by coping strategies, coping resources, and social support (Matuz et al., submitted) and thus is the prerequisite for a high QoL in LIS. Factors which help to cope with the disease are various and may change in the course of the disease. Avoidance showed to be a successful strategy at the beginning of the disease, but became nonadaptive as the disease progressed (Matuz et al., submitted). In accordance with our previous studies (Lulé et al., 2008), Neudert and colleagues confirmed that ALS patients shift their priorities with respect to QoL and focus more on social aspects (Neudert et al., 2001). Such an adaptive response shift was also found by Zickler (unpublished). With the progression of the disease, ALS patients named family and social contact more frequently as a determining factor of their subjective QoL. Data from Zickler (unpublished) showed the importance of family contacts (comparison between first and second interview 3 months later; $Chi^2(1) = 4.9$, $p = 0.05$, Fisher's exact) and social contacts (second interview $Chi^2(1) = 5.08$, $p = 0.05$). ALS patients named their friends and social environment as determinants of their QoL more often than age-matched healthy controls, who more often mentioned their occupation and

Fig. 2. Satisfaction with factors determining quality of life. Schedule for the evaluation of individual QoL in ALS patients ($n = 30$) and healthy subjects ($n = 30$). The degree of satisfaction in each area was rated on a seven-point Likert scale ranging from 0 (could not be worse) to 100 (could not be better). Adapted from Lulé et al. (2008) with permission from Medical Psychology and Neurobiology, University of Tübingen, and Coma Science group, University of Liége.

financial status. Finally, we observed that ALS patients were more satisfied with their families than healthy control subjects (Lulé et al., 2008; Fig. 2). When patients in LIS of vascular origin were interviewed with the Reintegration to Normal Living Index (Wood-Dauphinee and Williams, 1987), 70% of patients assumed that their role in their family meets their needs and those of their family members (study on 53 patients; mean age, 46 ± 10; range, 22–69 years; 17 females; LIS duration, 6 ± 5 years; Bruno and Laureys, unpublished). Quite in contrast to the assumption of medical doctors, caregivers, and lay people, the physical state does not predict psychological adjustment. Social support, coping strategies, and coping resources predict more than 50% of the variance in psychological adaptation to chronic disease measured as QoL and severity of depression (Matuz et al., submitted). The subjective feeling of control over one's life and the feeling of a purposeful life irrespectively of the actual physical conditions seem to be strong determinants of a good QoL in patients with severe physical impairment (Albrecht and Devlieger, 1999; Matuz et al., submitted). It seems that many LIS patients develop successful adaptive strategies with respect to their needs and priorities in different stages of the disease (Lulé et al., 2008; Matuz et al., submitted). In the ''International classification of Impairment, Disease, and Handicap'' the World Health Organization states that disease, impairment, activity, and life satisfaction are defined as separate aspects of health. The presented data strongly support this notion dissociating physical restrictions from residual QoL in LIS patients.

Depression rate

Depression is a well-described psychological disorder permitting effective psychotherapeutic and pharmacologic treatment (e.g., De Jong-Meyer et al., 2007). Similarly to QoL, the presence of depression can be regarded as a measure of adjustment to the circumstances of the disease. Comparable to the findings for QoL previously discussed, there is evidence that the incidence of depressive symptoms in patients with severe physical impairment is not associated with physical function. This was true for LIS patients when assessed by means of a short self-report on depression (Ghorbel, unpublished; Laureys et al., 2005) as well as for ALS patients when using a

disease-specific screening instrument for depression (Lulé et al., 2008). Likewise, the severity of depressive symptoms in ALS patients was not associated with the time since diagnosis (Kübler et al., 2005; Lulé et al., 2008). For patients with carcinoma, however, depressive symptoms have been reported to correlate with the extent of physical impairment (Frick et al., 2007). The prevalence of depression diagnosed with a structured interview according to DSM-IV criteria among ALS patients is around 9–11% (Ganzini et al., 1999; Rabkin et al., 2000, 2005; Kurt et al., 2007; Hammer et al., 2008) — which is only slightly higher than that observed in the general population (4–7%, Narrow et al., 2002, Kessler et al., 2003) yet lower than among patients with multiple sclerosis (up to 46%, Feinstein and Feinstein, 2001; Galeazzi et al., 2005). Disease-independent factors like level of education (number of school years) correlated significantly with the prevalence of depression in ALS. The higher the education, the lower was the prevalence of depression for ALS patients (Lulé et al., 2008). Although correlations do not tell anything about causal relationships, it might be speculated that better educated people have a better ability to develop functional coping strategies.

Depression and QoL seem anticorrelated in patients with severe motor impairment (Lulé et al., 2008; Kübler et al., 2005) — confirming the well-known relationship of affective state and QoL (Badger, 2001; Kübler et al., 2005). Not only LIS patients with full-blown depression but also with depressed mood should be treated and not be left alone with feelings of hopelessness and despair. This claim is underlined by data showing that an interaction of stress factors like depression and despair cause a mortality risk 6.8 times higher than in patients without these stressors (McDonald et al., 1994). Nevertheless, ALS patients are dramatically undertreated in two ways: first, depression is often left undiscovered; and second, when pharmacologically treated, the dose of antidepressants is too low, and treatment effect is not followed up (Kurt et al., 2007). Psychological interventions tailored to the specific needs of LIS patients which take also into account the progressive nature of ALS are not yet available. In the absence of an empirical basis for the fatalistically postulated causal relationship between the loss of physical function and depression (Goldstein et al., 2006), we conclude that depression is not a widespread phenomenon among LIS patients but when it is identified it should be adequately treated.

Social participation

One of the strongest factors which help to cope with severe motor impairment as seen in LIS and ALS is social support. Matuz and colleagues (submitted) demonstrated that perceived social support is the most powerful predictor for a good QoL and low depression rate. The same was shown by Häcker (unpublished) in a study encompassing 33 ALS patients (mean age, 58 ± 9.0; range, 37–72 years; 18 females; ALS-FRS mean, 20.0 ± 11.0; range, 0–38; diagnosed since 40 ± 31; range, 1–126 months): patients perceiving social support ($n = 24$) rated their QoL significantly higher than patients ($n = 9$) who did not experience the benefit of social support (SIS mean 75.7 ± 11.8 versus 60.7 ± 20.2; univariate ANOVA with age as covariate, $F_{1/25} = 11.9$; $p = 0.002$). Perceived social support could explain almost one-third of the variance between both groups (partial $\text{Eta}^2 = 0.32$).

With the help of family and friends, many LIS patients lead meaningful lives and show strong social participation. Vocational and avocational activities listed by these persons included, among others, visiting with family members, visit vacation home, e-mail, telephone, and teaching. One individual, an attorney, used Morse code eye blinks interpreted by a caregiver so that he could provide legal opinions and keep up with colleagues through fax and e-mail. Another helped to teach maths and spelling to third graders using a mouth stick to trigger an electronic voice device (Doble et al., 2003; Laureys et al., 2005; León-Carrión et al., 2002). In a survey of 44 people diagnosed with LIS, 73% enjoyed going out and 81% met with friends at least twice a month (León-Carrión et al., 2002). Häcker (unpublished) showed that 71% of ALS LIS patients were able

to participate in recreational activities (hobbies, crafts, sports, reading, television, games, computers, etc.) as they wanted to. Given that most LIS patients need support by others, those numbers imply that there must be, and normally are, other people that help and organize this type of activity for people with LIS (León-Carrión et al., 2002).

Alternative communication devices

Another decisive factor for successful adjustment strategies in LIS patients is communication — classically and most basically via an eye movement code (León-Carrión et al., 2002; Laureys et al., 2005). Those functions are usually retained in LIS patients with pontine lesions (León-Carrión et al., 2002) and are usually preserved in ALS patients (Ludolph and Dengler, 1999). However, this way of communication always requires the help of a second person who needs to be willing and capable to follow this time-consuming procedure. Furthermore, LIS patients with progressive etiology like ALS may loose control of eye movement in the end-stage of the disease and are therefore dependent on alternative ways of communication. Assistive communication devices that can be controlled even with one single movement have drastically changed the lives of people with LIS in the last years (Doble et al., 2003; Kübler et al., 2008). Instead of passively responding to the requests of others, the patients can initiate conversation and interaction. Camera-guided systems which scan eye movement or infrared eye movement sensors can be coupled to on-screen virtual keyboards and allow LIS patients not only to communicate via spelling systems on a computer (which can be coupled to a text-to-speech synthesizer to give the LIS patient a ''voice'') but also to control their environment (lights, doorbell, wheelchair, telephone, etc.) (Laureys et al., 2005). To provide LIS patients with a device for communication and control independent of any muscular input, brain–computer interfaces (BCI) have been developed and are continuously improved. Brain activity linked to specific imagery or evoked by sensory stimulation is recorded, filtered, classified, and translated into command signals to control a device (Dornhege et al., 2007). BCIs have been used by LIS patients to communicate (Birbaumer et al., 1999; Neumann et al., 2003; Nijboer et al., 2008), to surf on the Internet (Karim et al., 2006; Mugler et al., 2008), and even to paint (Kübler et al., 2008). BCI-controlled devices also permitted patients with spinal cord injury to regain movement (e.g., grasping could be restored with a BCI linked to functional electric stimulation; Pfurtscheller et al., 2003) and control a wheelchair (Galán et al., 2008; Iturrate et al., 2009). Devices are currently being developed using multiple input channels (speech, muscular and eye movement, and brain activity recording) and with multiple output options (movement, environmental control, communication, or Internet access), which can be easily adapted to the individual's needs (e.g., see www.tobi-project.org). We predict that in near future LIS patients will have even more options to be included in the world of electronic information transfer and social networking.

Wish to die

The discussed studies on successful adaptation in severely disabled patients like LIS and ALS have strong implications for the management, end-of-life decisions, and euthanasia in these challenging patients. Reports from LIS patients contradict the widespread opinion that patients with severe physical impairment inevitably suffer from poor QoL, depression, despair, and hopelessness which, consequently lead to the wish to die. In fact, the wish to die and the request for euthanasia is low, albeit existing, in LIS. In a study on spinal cord injury patients, 95% reported to be glad to be alive (Hall et al., 1999). In retrospective studies in ALS (Kühnlein et al., 2008; Neudert, unpublished) and LIS patients with brainstem lesions (Doble et al., 2003) there was almost no evidence for euthanasia requests although around 35% may have had periodic suicidal thoughts. In the longest surviving group of LIS patients with brainstem lesion (studied after 11 years), 54% had never considered euthanasia, 46% had previously considered it but none of the patients voted

against resuscitation if necessary (Doble et al., 2003). These data demonstrate that almost all of the patients chose to continue living despite severe physical limitations. In reply to the question ''would you like to receive antibiotics in case of pneumonia?'' 80% answered ''yes'' and to the question ''would you like to reanimation to be tempted in case of cardiac arrest?'' 62% answered positively (Bruno and Laureys, unpublished).

The decision not to undergo life-prolonging treatment in severely disabled patients is due to the fear of loss of autonomy and control and to the worry that the lack of mobility and impaired communication will lead to social isolation (Ganzini and Block, 2002). Moreover, it is often assumed that severely paralyzed patients have a poor QoL, particularly when they are on life-sustaining treatment (McDonald et al., 1996). The data presented here and the fact that ventilated ALS patients reported enjoying a significant higher QoL than nonventilated patients contradicts this notion (Lulé et al., 2008; Zickler, unpublished). Many useful therapeutic measures are available, including communication devices that help the patient to maintain autonomy and QoL (Miller et al., 1999; Voltz and Borasio, 1997) by generating a feeling of control over one's own fate. Patients who experience a more internal locus of control also seemed to show less symptoms of depression (Nedele, unpublished).

While the right of individuals to withdraw from treatment should not be questioned, the reviewed data call into question the assumption among some health-care providers and policy makers that severe disability is necessarily perceived as intolerable by the patient her- or himself. Preliminary results from our study on clinicians' perception of LIS show that in 97 interviewed health-care workers the majority (66%) considered that ''being LIS is worse than being in a vegetative or minimally conscious state'' (Bruno et al., 2008b). These prejudices toward LIS may be clinically consequential. Biased health-care workers may provide less-aggressive medical treatment or influence the patient's family in ways not appropriate to the situation (Doble et al., 2003). Information on LIS may be inadequately communicated and the available treatment modalities may be underutilized (Ganzini and Block, 2002). Some authors have argued that optimized palliative care would reduce the number of requests for a hastened death (Ganzini and Block, 2002; Bascom and Tolle, 2002). The understanding of successful adaptation to a life in LIS or ALS is the essential prerequisite for debates about euthanasia and the will to live, especially in the vulnerable nonresponsive patients or the rare cases of complete LIS (e.g., Schnakers et al., 2009) or in the utterly challenging problem of LIS in children (for review see Bruno et al., 2009). As the philosopher Soren Kierkegard put it in 1859, ''If you really want to help somebody, first you must find out where he is. This is the true secret of caring … Helping somebody implies … [that] you must understand what he understands.''

Conclusion

Superficially involved for the short-term of clinical surveillance clinicians may tend to assume that LIS patients will die anyway or would choose to die if they only knew what the clinicians knew (Laureys et al., 2005). Ganzini and Block (2002) suspect that this is due to a psychological defense mechanism: healthy people have difficulty imagining the feelings and experiences of a severely impaired patient and may assume that the patient's QoL is poor (McDonald et al., 1996). As a result, discussions on QoL, withdrawing or withholding of care, end-of-life decisions, and euthanasia are often based on prejudices and the input of the patients themselves is sometimes lacking. Decisions on hastening death or refusal of life-sustaining treatments are still too often made, or at least strongly influenced, by physicians and relatives (Moss et al., 1993; Borasio and Voltz, 1998). Biased clinicians might provide less-aggressive medical treatment and influence the family according to their own biased view of a life in LIS (Doble et al., 2003; Laureys et al., 2005). Likewise, insufficiently informed ALS patients are regularly advised by physicians to refuse intubation and withhold life-saving interventions (Trail et al., 2003). We thus argue that LIS patients — whose competence and cognitive capabilities still

too often are underestimated (e.g., Schnakers et al., 2008) — have to be exhaustively informed about their options to continue life (or not). We need to increase our efforts to integrate these extremely motor handicapped patients in social life and offer the patients who fail to adapt with adaptive coping strategies. The presented data provide evidence that a life with LIS can be worth living, provided the organization of medical, emotional, and social support (including adapted communication devices). LIS patients may regain a productive life and become active members of society; they may return to live at home and can start a new, different, but meaningful life.

Acknowledgments

This work was supported by funds by the European Commission (DISCOS, Mindbridge, and COST), McDonnell Foundation, Mind Science Foundation, and the Belgian Fonds de la Recherche Scientifique (FRS). S. Laureys and M. A. Bruno are, respectively, Senior Research Associate and Research Fellow at FRS.

References

Albrecht, G. L. (1994). Subjective health assessment. In C. Jenkinson (Ed.), *Measuring health and medical outcomes* (pp. 7–26). London: UCL Press.

Albrecht, G. L., & Devlieger, P. J. (1999). The disability paradox: High quality of life against all odds. *Social Science and Medicine*, *48*, 977–988.

Albrecht, G. L., & Higgins, P. (1977). Rehabilitation success: The interrelationships of multiple criteria. *Journal of Health and Social Behavior*, *18*, 36–45.

American Congress of Rehabilitation Medicine. (1995). Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. *Archives of Physical Medicine and Rehabilitation*, *76*, 205–209.

Badger, T. A. (2001). Depression, psychological resources, and health-related quality of life. *Journal of Clinical Geropsychology*, *7*, 189–200.

Bascom, P. B., & Tolle, S. W. (2002). Responding to requests for physician assisted suicide: These are uncharted waters for both of us. *Journal of the American Medical and Association*, *288*, 91–98.

Bauer, G., Gerstenbrand, F., & Rumpl, E. (1979). Varieties of the locked-in syndrome. *Journal of Neurology*, *221*(2), 77–91.

Birbaumer, N., Ghanayim, N., Hinterberger, T., Iversen, I., Kotchoubey, B., Kübler, A., et al. (1999). A spelling device for the paralysed. *Nature*, *398*, 297–298.

Borasio, G. D., & Voltz, R. (1998). Discontinuation of mechanical ventilation in patients with amyotrophic lateral sclerosis. *Journal of Neurology*, *245*, 717–722.

Bourke, S. C., Tomlinson, M., Williams, T. L., Bullock, R. E., Shaw, P. J., & Gibson, G. J. (2006). Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: A randomised controlled trial. *The Lancet Neurology*, *5*, 140–147.

Bruno, M.-A., Bernheim, J., Schnakers, C., & Laureys, S. (2008a). Locked-in: Don't judge a book by its cover. *Journal of Neurology Neurosurgery and Psychiatry*, *79*, 2.

Bruno, M. A. & Laureys, S. (unpublished). Quality of Life in LIS with pontine lesion.

Bruno, M. A., Pellas, F., Schnakers, C., Bernheim, J., Damas, F., Majerus, S., et al. (2009). Locked-in syndrome in children. *Pediatric Neurology* (in press).

Bruno, M. A., Pellas, F., Schnakers, C., Van Eeckhout, P., Bernheim, J., Pantke, K. H., et al. (2008b). Blink and you live: The locked-in syndrome. *Review Neurology (Paris)*, *164*, 322–335.

Cedarbaum, J. M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., et al. (1999). The ALSFRS-R: A revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *Journal of the Neurological Sciences*, *169*, 13–21.

Chin, A. E., Hedberg, K., Higginson, G. K., & Fleming, D. W. (1999). Legalized physician-assisted suicide in Oregon — The first year's experience. *New England Journal of Medicine*, *340*, 577–583.

De Jong-Meyer, R., Hautzinger, M., Kühner, C., & Schramm, E. (2007). *Evidenzbasierte Leitlinie zur Psychotherapie Affektiver Störungen (Evidence based guidelines for psychotherapy of affective disorders)*. Göttingen: Hogrefe.

Doble, J. E., Haig, A. J., Anderson, C., & Katz, R. (2003). Impairment, activity, participation, life satisfaction, and survival in persons with locked-in syndrome for over a decade: Follow-up on a previously reported cohort. *Journal of Head Trauma Rehabilitation*, *18*, 435–444.

Dornhege, G., del, R., Millan, J., Hinterberger, T., McFarland, D., & Müller, K. R. (Eds.). (2007). *Toward brain–computer interfacing*. Cambridge, MA: MIT press.

Fegg, M. J., Wasner, M., Neudert, C., & Borasio, G. D. (2005). Personal values and individual quality of life in palliative care patients. *Journal of Pain and Symptom Management*, *30*, 154–159.

Feinstein, A., & Feinstein, K. (2001). Depression associated with multiple sclerosis. Looking beyond diagnosis to symptom expression. *Journal of Affective Disorders*, *66*, 193–198.

Frick, E., Tyroller, M., & Panzer, M. (2007). Anxiety, depression and quality of life of cancer patients undergoing radiation therapy: A cross-sectional study in a community hospital outpatient centre. *European Journal of Cancer Care*, *16*, 130–136.

Galán, F., Nuttin, M., Lew, E., Ferrez, P. W., Vanacker, G., Philips, J., et al. (2008). A brain-actuated wheelchair: Asynchronous and non-invasive brain-computer interfaces for continuous control of robots. *Clinical Neurophysiology*, *119*, 2159–2169.

Galeazzi, G. M., Ferrari, S., Giaroli, G., Mackinnon, A., Merelli, E., Motti, L., et al. (2005). Psychiatric disorders and depression in multiple sclerosis outpatients: Impact of disability and interferon beta therapy. *Neurological Sciences*, *26*, 255–262.

Ganzini, L., & Block, S. (2002). Physician-assisted death a-last resort? *New England Journal of Medicine*, *346*, 1663–1665.

Ganzini, L., Johnston, W. S., & Hoffman, W. F. (1999). Correlates of suffering in amyotrophic lateral sclerosis. *Neurology*, *52*, 1434–1440.

Ghorbel, S. (unpublished). Statut fonctionnel et qualité de vie chez le locked-in syndrome a domicile. In: *DEA Motricité Humaine et Handicap*, *Laboratory of Biostatistics*, *Epidemiology and Clinical Research.* Dissertation in Medicine. Université Jean Monnet Saint-Etienne, Montpellier, France.

Goldstein, L. H., Atkins, L., Landau, S., Brown, R. G., & Leigh, P. N. (2006). Longitudinal predictors of psychological distress and self-esteem in people with ALS. *Neurology*, *67*, 1652–1658.

Goode, D. (1994). The national quality of life for persons with disabilities project: A quality of life agenda for the United States. In D. Goode (Ed.), *Quality of life for persons with disabilities* (pp. 139–161). Cambridge: Brookline Press.

Häcker, S. (unpublished). *Depressivität und subjektive Lebensqualität bei schwerster körperlicher Beeinträchtigung — Eine empirsche Arbeit über Patienten mit amyotropher Lateralsklerose (Depression and subjective quality of life given severest physical impairment — An empirical study on patients with amotrophic lateralsclerosis)*. Unpublished diploma thesis in Psychology. University of Tübingen, Germany.

Hall, K. M., Knudsen, S. T., Wright, J., Chaarlifue, S. W., Graves, D. E., & Werner, P. (1999). Follow-up study of individuals with high tetraplegia (C1–C4) 14 to 24 years post injury. *Archives of Physical Medicine and Rehabilitation*, *80*, 1507–1513.

Hammer, E. M., Häcker, S., Hautzinger, M., Meyer, T. D., & Kübler, A. (2008). Validity of the ALS-depression-inventory (ADI-12)—A new screening instrument for depressive disorders in patients with amyotrophic lateral sclerosis. *Journal of Affective Disorders*, *109*, 213–219.

Hickey, A. M., Bury, G., O'Boyle, C. A., Bradley, F., O'Kelly, F. D., & Shannon, W. (1996). A new short form individual quality of life measure (SEIQoL-DW): Application in a cohort of individuals with HIV/AIDS. *British Medical Journal*, *313*, 29–33.

Iturrate, I., Antelis, J. M., Kübler, A., & Minguez, J. (2009). A noninvasive brain-actuated wheelchair based on a P300 neurophysiological protocol and automated navigation. *IEEE Transactions on Robotics*, *99*, 1–14.

Jenewein, J., Zwahlen, R. A., Zwahlen, D., Drabe, N., Moergeli, H., & Büchi, S. (2008). Quality of life and dyadic adjustment in oral cancer patients and their female partners. *European Journal of Cancer Care*, *17*, 127–135.

Karim, A. A., Hinterberger, T., Richter, J., Mellinger, J., Neumann, N., Flor, H., et al. (2006). Neural Internet: Web surfing with brain potentials for the completely paralyzed. *Neurorehabilitation and Neural Repair*, *20*, 508–515.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., et al. (2003). National comorbidity survey replication. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *Journal of the American Medical Association*, *289*, 3095–3105.

Kübler, A., Furdea, A., Halder, S., & Hösle, A. (2008). Brain painting—BCI meets art. In G. R. Müller-Putz, C. Brunner, R. Leeb, G. Pfurtscheller, & C. Neuper (Eds.), *4th International Brain–Computer Interface Workshop and Training Course* (pp. 361–366). Austria: Verlag der Technischen Universität Graz: Graz University of Technology.

Kübler, A., Winter, S., Ludolph, A. C., Hautzinger, M., & Birbaumer, N. (2005). Severity of depressive symptoms and quality of life in patients with amyotrophic lateral sclerosis. *Neurorehabilitation and Neural Repair*, *19*, 182–193.

Kühnlein, P., Kübler, A., Raubold, S., Worell, M., Kurt, A., Gdynia, H. J., et al. (2008). Palliative care and circumstances of dying in German ALS patients using non-invasive ventilation. *Amyotrophic Lateral Sclerosis*, *9*, 91–98.

Kurt, A., Nijboer, F., Matuz, T., & Kübler, A. (2007). Depression and anxiety in individuals with amyotrophic lateral sclerosis: Epidemiology and management. *CNS Drugs*, *21*, 279–291.

Laureys, S., Pellas, F., Van Eeckhout, P., Ghorbel, S., Schnakers, C., Perrin, F., et al. (2005). The locked-in syndrome: What is it like to be conscious but paralyzed and voiceless? *Progress in Brain Research*, *150*, 495–511.

León-Carrión, J., van Eeckhout, P., Domínguez-Morales Mdel, R., & Pérez-Santamaría, F. J. (2002). The locked-in syndrome: A syndrome looking for a therapy. *Brain Injury*, *16*, 571–582.

Leplege, A., Ecosse, E., Verdier, A., & Perneger, T. V. (1998). The French SF-36 Health Survey: Translation, cultural adaptation and preliminary psychometric evaluation. *Journal of Clinical Epidemiology*, *51*, 1013–1023.

Ludolph, A. C., & Dengler, R. (1999). Geschichte, epidemiologie und diagnostische kriterien (History, epidemiology and diagnostic guidelines). In R. Dengler, A. Ludolph, & S. Zierz (Eds.), *Amyotrophe lateralsklerose* (2nd ed., pp. 1–16). Stuttgart: Thieme.

Lulé, D., Häcker, S., Ludolph, A. C., Birbaumer, N., & Kübler, A. (2008). Ergebnisse zu Depression und Lebensqualität bei der amyotrophen Lateralsklerose. *Deutsches Ärzteblatt International*, *105*, 397–403.

Matuz, T., Birbaumer, N., Hautzinger, M., & Kübler, A. (submitted). Coping with amyotrophic lateral sclerosis: An integrative view.

McDonald, E. R., Hillel, A., & Wiedenfeld, S. A. (1996). Evaluation of the psychological status of ventilatory-supported patients with ALS/MND. *Palliative Medicine*, *10*, 35–41.

McDonald, E. R., Wiedenfeld, S. A., Hillel, A., Carpenter, C. L., & Walter, R. A. (1994). Survival in amyotrophic lateral sclerosis. The role of psychological factors. *Archives of Neurology*, *51*, 17–23.

McGee, H. M., O'Boyle, C. A., Hickey, A., O'Malley, K., & Joyce, C. R. (1991). Assessing the quality of life of the individual: The SEIQoL with a healthy and a gastroenterology unit population. *Psychological Medicine*, *21*, 749–759.

Miller, R. G., Rosenberg, J. A., Gelinas, D. F., Mitsumoto, H., Newman, D., Sufit, R., et al. (1999). Practice parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology: ALS Practice Parameters Task Force. *Neurology*, *52*, 1311–1323.

Moons, P., Marquet, K., Budts, W., & De Geest, S. (2004). Validity, reliability and responsiveness of the ''Schedule for the Evaluation of Individual Quality of Life-Direct Weighting'' (SEIQoL-DW) in congenital heart disease. *Health and Quality of Life Outcomes*, *2*, 27.

Moss, A. H., Casey, P., Stocking, C. B., Roos, R. P., Brooks, B. R., & Siegler, M. (1993). Home ventilation for amyotrophic lateral sclerosis patients: Outcomes, costs, and patient, family, and physician attitudes. *Neurology*, *43*, 438–443.

Mugler, E., Bensch, M., Halder, S., Rosenstiel, W., Bogdan, M., Birbaumer, N., et al. (2008). Control of an internet browser using the P300 event-related potential. *International Journal of Bioelectromagnetism*, *10*, 56–63.

Murrell, R. (1999). Quality of life and neurological illness: A review of the literature. *Neuropsychology Review*, *9*, 209–229.

Narrow, W. E., Rae, D. S., Robins, L. N., & Regier, D. A. (2002). Revized prevalence estimates of mental disorders in the United States: Using a clinical significance criterion to reconcile 2 surveys' estimates. *Archives of General Psychiatry*, *59*, 115–123.

Nedele, P. (unpublished). *Kognitionen, Emotionen und Bewältigung im Alltag von Patienten mit ALS: Eine empirische Arbeit bei Patienten mit amyotropher Lateralsklerose (ALS). (Cognition, emotions and coping in daily life: An empirical study in patients with amyotrophic lateral sclerosis (ALS)*. Unpublished diploma thesis of Psychology. University of Tübingen, Germany.

Neudert, C. (unpublished). Verlauf und palliativmedizinische Behandlung in der Terminalphase bei Patienten mit Amyotropher Lateralsklerose. Dissertation in Medicine, University of Munich, Germany.

Neudert, C., Wasner, M., & Borasio, G. D. (2001). Patients' assessment of quality of life instruments: A randomized study of SIP, SF-36 and SEIQoL-DW in patients with amyotrophic lateral sclerosis. *Journal of Neurological Sciences*, *191*, 103–109.

Neumann, N., Kübler, A., Kaiser, J., Hinterberger, T., & Birbaumer, N. (2003). Conscious perception of brain states: Mental strategies for brain–computer communication. *Neuropsychologia*, *41*, 1028–1036.

Nijboer, F., Sellers, E. W., Mellinger, J., Jordan, M. A., Matuz, T., Furdea, A., et al. (2008). A P300-based brain–computer interface for people with amyotrophic lateral sclerosis. *Clinical Neurophysiology*, *119*, 1909–1916.

Ohry, A. (1990). The locked-in syndrome and related states. *Paraplegia*, *28*, 73–75.

Patterson, J. R., & Grabois, M. (1986). Locked-in syndrome: A review of 139 cases. *Stroke*, *17*, 758–764.

Pfurtscheller, G., Müller, G. R., Pfurtscheller, J., Gerner, H. J., & Rupp, R. (2003). Thought'-control of functional electric stimulation to restore hand grasp in a patient with tetraplegia. *Neuroscience Letters*, *351*, 33–36.

Plum, F., & Posner, J. B. (1983). *The diagnosis of stupor and coma*. Philadelphia, PA: Davis, FA.

Rabkin, J. G., Albert, S. M., Del Bene, M. L., O'Sullivan, I., Tider, T., Rowland, L. P., et al. (2005). Prevalence of depressive disorders and change over time in late-stage ALS. *Neurology*, *65*, 62–67.

Rabkin, J. G., Wagner, G. J., & Del Bene, M. (2000). Resilience and distress among amyotrophic lateral sclerosis patients and caregivers. *Psychosomatic Medicine*, *62*, 271–279.

Richard, I., Pereon, Y., Guiheneu, P., Nogues, B., Perrouin-Verbe, B., & Mathe, J. F. (1995). Persistence of distal motor control in the locked in syndrome. Review of 11 patients. *Paraplegia*, *33*, 640–646.

Schnakers, C., Majerus, S., Goldman, S., Boly, M., Van Eeckhout, P., Gays, S., et al. (2008). Cognitive function in the locked in syndrome. *Journal of Neurology*, *255*, 323–330.

Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., et al. (2009). Detecting consciousness in a total locked-in syndrome: An active event related paradigm. *Neurocase*, *25*, 1–7.

Sprangers, M. A., & Aaronson, N. K. (1992). The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: A review. *Journal of Clinical Epidemiology*, *45*, 743–760.

Sprangers, M. A. G., & Schwartz, C. E. (1999). Integrating response shift into health-related quality of life research: A theoretical model. *Social Science and Medicine*, *48*, 1507–1515.

The WHOQOL Group. (1995). The World Health Organization quality of life assessment (WHOQOL): Position paper from the World Health Organization. *Social Science and Medicine*, *41*, 1403–1409.

Trail, M., Nelson, N. D., Van, J. N., Appel, S. H., & Lai, E. C. (2003). A study comparing patients with amyotrophic lateral sclerosis and their caregivers on measures of quality of life, depression, and their attitudes toward treatment options. *Journal of the Neurological Sciences*, *209*, 79–85.

Voltz, R., & Borasio, G. D. (1997). Palliative therapy in the terminal stage of neurological disease. *Journal of Neurology*, *244*, 2–10.

Ware, J. E., Snow, K. K., & Kosinski, M. (1993). *SF-36 Health survey manual and interpretation guide*. Boston, MA: The Health Institute, New England Medical Center.

Wood-Dauphinee, S., & Williams, J. I. (1987). Reintegration to normal living as a proxy to quality of life. *Journal of Chronic Diseases*, *40*, 491–499.

Zickler, C. (unpublished). *Depression und subjektive Lebensqualität bei Patienten mit amyotropher Lateralsklerose — Veränderungen im Zeitraum von drei Monaten (Depression and subjective quality of life in patients with amyotrophic lateral sclerosis — changes within three months)*. Unpublished diploma thesis in Psychology. University of Tübingen, Germany.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 24

Defining personal loss after severe brain damage

Isabelle Lutte*

Medico-legal Department, Faculty of Medicine, Université Libre de Bruxelles and Coma Science Group, Cyclotron Research Centre, University of Liège, Belgium

Abstract: The impact of disorders of consciousness in terms of compensation for patients' personal non-economic injuries often raises vigorous debates in legal courts. Attributing personal loss to non-communicating brain damaged patients based on assessment of residual levels of consciousness remains controversial. Is the loss of consciousness in vegetative or minimally conscious state a condition to be compensated for? Does alteration of consciousness diminish the seriousness of injury? To answer these challenging medico-legal questions, three distinct aspects are here taken into consideration: (i) the recognition that disorders of consciousness constitute a personal injury for non-communicative patients; (ii) the scope of the compensation for this injury and (iii) the purpose of the compensation granted.

Keywords: law; liability; damage; personal loss; personal injuries; compensation; Belgium; Austria; Germany; Switzerland; France; Great-Britain

Introduction

The impact that disorders of consciousness (i.e. coma, vegetative state, minimally conscious state) have on patients in terms of compensation for their personal (non-economic) injuries often raises vigorous debates in courts. Following severe brain injury, is unconsciousness a condition to be compensated for? Does alteration of consciousness diminish the seriousness of injury? In other words, is it justifiable to reject or reduce compensation for non-material injuries and suffering in non-communicative patients on the grounds that they suffer from disorders of consciousness? To answer these questions, the following three distinct aspects should be taken into consideration: (i) the recognition that disorders of consciousness constitute a personal injury for non-communicative patients; (ii) the scope of the compensation for this injury and (iii) the purpose of the compensation granted.

The principles

The conditions of liability

Liability rests on the union of three conditions: (1) the operative event or the fault, (2) the damage and (3) a cause and effect link between the fault and the alleged damage. We will here limit our topic to the question of damage.

The damage

Damage refers to the loss of an advantage or to the infringement of a legitimate interest. This damage is often plural; it can be material

*Corresponding author.
Tel.: 0032 2 790 42 41; Fax: 0032 2 790 42 41;
E-mail: ilutte@thelius.be

DOI: 10.1016/S0079-6123(09)17724-5

(economic) or moral (non-economic), direct or by repercussion, immediate or deferred. Damage is also designated as the negative difference between two situations in which the victims find themselves as a result of the operative event causing their damage or the faulty action, and in which they were before the occurrence of this event or this action. Any negative difference, however minimal, entitles them for compensation.

The present article focuses on the non-economic (moral) damage, the definition of which is not easy. In a broad sense, non-material damage designates all the victim's infringements of interests, other than professional or economic. 'It is the very essence of the victim, body and soul, which is affected by damages referred to as non-economic, moral, personal or extra-patrimonial' (Lambert–Faivre, 2000). The definition of André (1986) cites, among non-material damages, 'the loss of the pleasures, recreations and satisfactions that life can bring when one is healthy in mind and body'. We will see that this loss is indeed real in a person suffering from disorders of consciousness. In a more restrictive sense, non-material damage is an expression which designates the mental suffering of the victim, who experiences mental suffering inherent in the disability itself, following an impairment of her or his physical integrity.

Evaluation in concreto and full compensation of the damage

The evaluation of damage is governed by the principle of full compensation of the sustained injury. This principle obliges the perpetrators of the harmful event to restore the victims to the state in which they would have found themselves if the operative event had not occurred, and if the fault had not been committed. The in concreto character of the evaluation of damage makes it necessary to investigate concretely the nature of the effects that the impairment of physical integrity has on the victim's habitual activities (Papart and Ceulemans, 2004). However, in terms of physical injuries, the damaged body tissue is hardly replaceable and, often, cannot be repaired. The exact evaluation of non-material damage is utopian. 'How can one put a figure, in an exact way, on the non-material damage resulting from the loss of an eye, a hand, or the possibility of procreation?' (Fagnart, 1993). How can non-material damage be repaired? In addition, the 'compensation' can only be carried out by equivalent, by granting the victims reparation intended to compensate for impairment of their bodily integrity (either physical or mental) and, in the view of some, to 'console the victims'. Let us clarify to that point that, in reality, it cannot be a matter of consolation: this is of no relevance to the courts. Granting indemnification is rather a response to the objective of compensation in search for an equilibrium, which aims to counterbalance the 'loss' suffered on behalf of the victim, without claiming either to restore her/his physical integrity or to afford her/him consolation. Even if this equilibrium is difficult to achieve, a difficulty in calculation or evaluation cannot obscure the right of the victims to obtain compensation (even by substitution) for their injury. Nobody would refuse to grant a prosthesis to a victim whose leg had been amputated on the grounds that this prosthesis, a mere substitute, cannot restore the victim to the situation in which she/he would have been without the amputation.

The recognition of personal injuries of the unconscious victim

Attributing personal loss to non-communicating patients based on residual levels of consciousness is controversial. This opposition is best reflected in the following two theses: the subjective thesis and the objective thesis.

The subjective thesis

According to the subjective thesis, the injury is attached to the person who sustains it. Thus, it has been held that it is incongruous to recompense the physical suffering of a person no longer aware of her/his body (French Council of State, 1997). No compensation is due if the victims are not aware of their state and injury. In the ruling of 13 October 1999, the Supreme Court of Belgium,

evaluating the extent of the non-material injury of the victims, resolved that the judge can, by an assessment based on facts, consider the victims' diminished state of consciousness resulting from their state of mental health. By this way of reasoning, the Supreme Court seemed to approve the so-called subjective thesis. A recent review of the various decisions pronounced in this matter has allowed us to establish that the judicial approach to the compensation of an unconscious victim is strongly influenced by the subjective thesis (Table 1).

The partisans of such a thesis, basing their argument on the obligation to repair the injury in concreto, support the reasoning according to which a diminished state of consciousness necessarily diminishes the injury of the victim. Thus, they feel authorized to reduce the compensation for the pain, mental injury, aesthetic injury and loss of amenity of such victims. Only the conscious injury is held to exist and be 'repairable'.

This thesis elicits three observations. First, the evidence for such a sustained absence of consciousness resembles more to a colossus with feet of clay than a genuine certainty. It is appropriate to bear in mind that even if the scientific literature provides a catalogue of concepts or definitions with regard to the different altered states of consciousness, the barrier is not only tenuous, but also fluctuating between what is or is not considered conscious. A patient in coma can pass into a vegetative state, then into a minimally conscious state, possibly to fall again into a state of unconsciousness (Laureys et al., 2004). This implies that consciousness is not and cannot be envisaged as an all-or-nothing phenomenon; rather, it is located on a continuum (Laureys and Boly, 2008). This feature of consciousness has not escaped a portion of jurisprudence. Thus, in the ruling of 15 May 2000 the Court of Appeals of Brussels stated that 'it has not been scientifically proven that a person in *coma* is totally unconscious . The starting point, then, should be that this person experiences the same injury as a victim who can express her or his suffering' (Court of Appeals of Brussels, 2001). Nowadays, the only scientific certainty of absence of consciousness is the state of brain death, a state leading to the recognition of the patient's death (Laureys, 2005). Second, if the recognition of personal injury were dependent on the victim's consciousness, there would be good reason to claim that the injury

Table 1. Review of Belgian Court rulings related to the compensation of personal injuries in disorders of consciousness

Court	Date	Journal	Diagnosis	Decisions
Bruxelles (Court of Appeal)	23/11/1988	*R.G.A.R.* 1990, no. 11.678	Coma	Accepted
Bruxelles (Criminal Court)	10/02/1989	*R.G.A.R.* 1991, no. 11.879	Coma	Accepted
Bruxelles (Court of Appeal)	18/10/1989	*Bull. Ass.* 1990, p. 177	Coma	Rejected
Anvers (Criminal Court)	20/10/1992	*Bull. Ass.* 1993, p. 108	Coma	Accepted
Liège (Court of Appeal)	25/02/1992	*Bull. Ass.* 1992, p. 537	Coma	Rejected
Courtrai (Criminal Court)	23/10/1992	*Bull. Ass.* 1993, p. 112	Coma	Rejected
Anvers (Court of Appeal)	24/01/1997	*T.A.V.W.* 2000, p. 144	Coma	Accepted
Tournai (Police Court)	28/04/2000	*E.P.C.* 2003, II.1, Tournai, p. 9	Absence of evidence of conscience	Rejected
Bruxelles (Court of Appeal)	15/04/2000	*T.A.V.W.* 2001, p. 308	Absence of evidence of absolute lack of conscience	Accepted
Arlon (Criminal Court)	29/06/2001	*E.P.C* 2004, II.2, Arlon, p. 9	Coma	Rejected
Tournai (Criminal Court)	07/12/2001	*E.P.C.* 2003, Suppl. 8, p. 19	Absence of evidence of conscience	Rejected
Liège (Police Court)	08/06/2004	*E.P.C* 2006, II.1, Liège, p. 27	Unconsciousness	Rejected
Namur (Criminal Court)	15/02/2005	*R.G.A.R* 2006 no. 14.123	Disorder of the consciousness	Reduced
Charleroi (Police Court)	08/05/2007	*C.R.A.* 2007, p. 373	Irreversible coma	Rejected
Termonde (Civil Court)	08/06/2007	*Bull. Ass.* 2008, p. 204	Therapeutic/artificial coma	Reduced

Note: Eight rulings refused compensation, five accepted compensation and two received reduced compensation claims.

lessens or even disappears during sleep (a state of reversible unconsciousness). Why grant compensation to a victim showing daily periods 'of reversible unconsciousness' and refuse compensation to a victim displaying an alteration or fluctuation in her/his state of consciousness? Third, the non-economic injury of an unconscious victim results from the alteration of her or his consciousness state. This injury is an objective fact and corresponds to the negative difference between the state in which the victim was before the occurrence of the brain injury and the state following it. If one resorts to the subjective thesis, such an injury is not compensated while the objective situation of the victim is profoundly modified by it. How can the absence of compensation for this damage be explained?

The objective thesis

For the partisans of the objective thesis, the recognition of the injury alone suffices to constitute a basis for a compensation request, with no reference to the victim's state of consciousness. A person, even unconscious, is nonetheless a person in possession of her/his rights. This thesis is followed by the Supreme Court of France (1979). Thus, the recognition of the victim's unconscious or quasi-unconscious state is not in itself sufficient to justify a refusal to compensate the loss of amenity, as 'compensation for injury is not a function of the victim's presentation of it, but of its recognition by the judges and its objective evaluation within the limits of the claim with which they are confronted'. This ruling has been unevenly applied in the French doctrine. Nonetheless, the French Council of State has recently applied the objective thesis in deeming that 'the circumstance that a patient is in a *chronic vegetative coma* [author's note: observe the erroneous terminology; italics added] does not lead, in itself, to the exclusion of any grounds for compensation, nor does it form an obstacle to the full compensation of the injury suffered by the victim' (Momas, 2005). Anglo-Saxon law considers that the victim's unconsciousness does not eliminate the right to compensation. The House of Lords has ruled that unconsciousness does not eliminate the actuality of the deprivations of the ordinary experiences and merits of life …' (West and v. Chephard, 1999). Doctrine agrees completely: 'Damages are awarded for the fact of deprivation, a substantial loss. The award for loss of amenities must be made on the basis of amenities lost; it is irrelevant that the plaintiff is unaware of his deprivation. […] In short, damages under this head […] are not reduced because the plaintiff has been rendered unconscious or unable to appreciate his loss' (Street, 1983). Other European countries accept the non-material injury of the unconscious person, as is the case in Germany (Supreme Court (BG), 1976), Austria (Supreme Court (OGH) 1992) and Switzerland (Supreme Court (BGH), 1982). The Supreme Court of Belgium has not yet pronounced an opinion on this question. Fagnart (2004) emphasizes, 'when it is a question of economic damage, no one has ever maintained that its reality depends on the psyche of a living person. Why should it not be the same with regard to non-economic injuries? Physical integrity, the pleasures of life, and other people's opinion are objective realities. Impairment of one of these values constitutes in itself an objective loss which should be compensated'. This view complies with the idea of damage as defined by the Supreme Court of Belgium (1955): 'Damage is an element of pure fact which consists of a diminution of assets or the privation of a benefit'. The loss of a victim's capacity to work is an objective fact and just as independent of the state of consciousness as the loss of her/his ability to benefit from the pleasures of life, such as that of sharing a meal with friends or embracing her/his children. In line with Lambert–Faivre (2000) we consider that 'while the principle remains that a victim who claims compensation for an injury must prove it, one can legally concede that the very gravity of the chronic vegetative state implies the reality of the personal injuries invoked'.

The scope of compensation for personal injuries

If the personal injury of victims who are unconscious or have an altered state of consciousness is recognized, the question of the scope of this

compensation is inevitably posed. For some, 'the assessment *in concreto* of such damage would even be unrealistic. Setting the compensation according to the actual scale of the injury is meaningless' (Viney, 1982). However, the extent of the injury to the victim who is unconscious or has an altered level of consciousness is difficult to understand in concreto. It is certain that such a victim can no longer enjoy the recreational activities of daily living (e.g. reading, watching television, going on holiday etc). These privations are hardly contestable. The unpleasantness related to this condition of unconsciousness or altered consciousness is just as obvious. Consider gastrostomy feeding, bronchial aspirations, bedsores etc. In reality, in such situations, the non-economic injury in concreto is intense: it is 100 percent. It is probably due to the maximal nature of this damage that some have thought that evaluation of the non-economic injury to a person who is unconscious or has an altered state of consciousness required recourse to a method in abstracto, in reference to what a person capable of expressing her/himself would feel (Court of Appeals of Bordeaux, 1992). But the maximal nature of an injury per se does not in any way exclude its evaluation in concreto.

The purpose of compensation for personal injuries

The question of the extent of the injury is regularly confused with that of the purpose of the compensation granted to the victim. The Supreme Court of Belgium (1990) recognizes that the right to full compensation for non-economic injury is not subject to the condition that the victim is aware that the indemnification is intended to compensate for this damage. The Supreme Court of Belgium, thus, agrees with the House of Lords: 'Damages cannot be refused because the plaintiff will be unable to enjoy the damages in view of the severity of his injuries' (Street, 1983). However, certain authors and jurisdictions of law and fact are reluctant to compensate the non-economic injury of unconscious victims. They also uphold as obstacles the impossibility for the victims or their representatives to demonstrate their injury and the danger of an undue profit. The indemnity paid is held to be a source of enrichment without cause for the victims or, indirectly, for their family.

Out of concern for an undue profit, some have thought that 'in case of prolonged coma in a chronic vegetative state, compensation for personal injuries could be suspended: if the victim regains consciousness, all her or his rights should then be respected, including compensation for the loss of amenity suffered during the period of unconsciousness; on the other hand, if the coma and the vegetative state end in death, the intransmissibility of such grounds for compensation should be put forward to the heirs' (Lambert–Faivre, 2000). Maintaining such reasoning necessarily implies the recognition of the reality of such injury and its extent, even during the period of unconsciousness. The sole concern of the author of this proposal is the misappropriation of the indemnities by persons other than the victims themselves. The mechanism of suspending the grant of indemnities until the victim returns to a conscious state would provide a guarantee that the funds would go to the right beneficiary. Such reasoning should logically lead to refusing any compensation to the mentally retarded, mentally ill and children 'who would be at risk of all sorts of injury without the possibility of compensation' (Fagnart, 2004) on the grounds that they would also have a diminished perception of their injury. In such case, there should also be concern for the misappropriation of the indemnities by the family or by other third parties making an undue profit. This reasoning elicits three observations:

(1) It does not consider the mechanisms for protection of the weaker among us, with regard to both their person and their assets. Consider parental authority, the possibility of appointing a guardian, or the status of extended minority. Moreover, the persons of legal age, who by reason of their state of health are totally or partially incapable of managing their assets, can be provided with a provisional executor by the justice of the peace. In organizing this system for provisional administration for the persons of legal

age who are incapable of managing their assets, the legislator has acted in the sole interest of the said persons of legal age, so that the provisional executor carries out his mission under the supervision of the justice of the peace. Thus, actions carried out contrary to the interest of the person protected, or considered as such, are sanctioned by relative nullity.

(2) Regardless of the systems for protection of our weaker and vulnerable citizens organized by the legislator, and consequently even in the absence of these, concern for misappropriation of indemnities or an undue profit cannot in any way entail disregard for the right of the victims to full compensation for their injury.

(3) Making reparation for non-economic injuries dependent on the victim's consciousness necessarily implies 'a discrimination which would follow from the fact that a patient in a state of vegetative coma […] would be denied compensation while a victim much more mildly impaired would be compensated, solely on the grounds that she or he has at least partially maintained her or his consciousness' (Olson, 2005). Thus, a maxim such as 'I am conscious, therefore I am entitled to compensation' cannot be upheld (Lutte and Laureys, 2008). This is the position of the Supreme Court of Belgium which, in a ruling of 4 April 1990, pronounced 'that starting, by limiting to the symbolic franc the compensation intended to rectify the non-material injury, the existence of which it recognizes in Innez Chevalier as a result of the premature disappearance of the benevolent presence of her father, solely on the aforementioned grounds that the right to compensation and the amount of the compensation intended to rectify the injury are limited due to ''the absence of perception'' on behalf of the victim, from the compensation for her injury by the payment of an indemnity, the ruling misapplied the legal concepts of non-material injury and the link of causality as well as the right to full compensation for the damage suffered, which is not subject to the condition that the victim can be aware that the compensation is intended to rectify her injury' (Supreme Court of Belgium, 1990).

Conclusion

In disorders of consciousness, although much remains unknown, scientific progress has removed several uncertainties. First, consciousness is a complex and multi-dimensional subject that cannot be envisaged as an all-or-nothing phenomenon, but is rather placed along a continuum. Patients may display fluctuating levels of consciousness, sometimes in the course of a single day. The case of brain death corresponds to a total and definitive abolition of consciousness but for patients in a vegetative or minimally conscious state, diagnostic errors are not rare (e.g. the recent study by Schnakers et al., 2009). The assessment of unconscious victims requires experience, rigour and competence. On such grounds, consciousness cannot be a determining condition for recognition of the reality of the non-economic injury to such victims. The impairment of the victims' capacity to benefit from the pleasures of life and the unpleasantness that they suffer constitute in themselves an objective injury, the compensation of which cannot be refused or reduced on the pretext of an altered state of consciousness. Any other solution would violate, in our opinion, the fundamental principle of full compensation for the injury suffered and create discrimination between the victims, to the detriment of the most deprived.

References

André, R. (1986). *La réparation du préjudice corporel*. Bruxelles: Story-Scientia.

BGH, 16 décembre 1975, N.J.W., 1976, p. 1147.

Bordeaux, 18 avril 1991, D., 1992, p. 14.

Bruxelles, 13e ch., 15 mai 2000, T.A.V.W., 2001, p. 308.

Fagnart, J.-L. (1993). Rapport de synthèse. In J.-L. Fagnart & A. Pire, (Eds.), *Problèmes actuels de la réparation du dommage corporel* (p. 266). Bruxelles: Bruylant.

Fagnart, J.-L. (2004). Définitions des préjudices non économiques. In: *Préjudices extrapatrimoniaux: Vers une*

évaluation plus précise et une plus juste indemnisation (pp. 40). Actes du colloques du Jeune Barreau de Liège.

French Council of State. (1997). *Crts Alis*.

Lambert–Faivre, Y. (2000). Droit du dommage corporel: Systèmes d'indemnisation. Dalloz.

Laureys, S. (2005). Science and society: Death, unconsciousness and the brain. *Nature Reviews Neuroscience*, *6*, 899–909.

Laureys, S., & Boly, M. (2008). The changing spectrum of coma. *Nature Clinical Practice Neurology*, *4*(10), 544–546.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*, 537–546.

Lutte, I., & Laureys, S. (2008). La conscience de la victime: Une nouvelle condition de la réparation du dommage? R.G.A.R.2008, n° 14.422.

Momas, J. (2005). Le dernier avatar de la prise en charge du pretium doloris et du préjudice d'agrément par les juges administratifs: Sa reconnaissance pour les victimes en état végétatif. *Medizinische Dokumentation*, 85–88.

Olson, T. (2005). Conclusions sur C.E. *A.D.J.A.*, 336.

Papart, T., & Ceulemans, B. (2004). *Vade-mecum du tribunal de police*. Bruxelles: Kluwer.

Street, H. (1983). *The law of torts, Londres, Butterworths*. London: Butterworths.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S. et al. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology*, *9*, 35.

Supreme court of Austria (OGH), 31 août 1992, 8 OB, 581/92.

Supreme Court of Belgium. (1955). 2 May 1955, Pasicrisie (Pas.), I, p.m 550.

Supreme Court of Belgium. (1990). 4 April 1990, *Pasicrisie* (Pas.), I, p. 913.

Supreme Court of France. (1979). 3 April 1979, Juris Classeur Périodique (J.C.P.), II, p. 1916.8

Supreme Court of Germany (Bundesgericht-BG), 16 décembre 1975, Neue Juristische Wochenschrift, (N.J.W.), 1976, p. 1147.

Supreme Court of Switzerland (Bundsgerichtshof- BGH), BG, 6 juillet 1982, Recueil officiel des arrêts du Tribunal Fédéral Suisse A.T.F./B.G.E., 108 II, p. 422.

Viney, G. (1982). Traité. *La responsabilité-effets*, *146*, 202.

West, H. & Son v. Chephard, S. in W. Van Gerven (Ed.), Tort law (1999), (pp. 103–106). Oxford: Art publishing.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 25

Moral significance of phenomenal consciousness

Neil Levy* and Julian Savulescu

Oxford Centre for Neuroethics, Littlegate House, Oxford, UK

Abstract: Recent work in neuroimaging suggests that some patients diagnosed as being in the persistent vegetative state are actually conscious. In this paper, we critically examine this new evidence. We argue that though it remains open to alternative interpretations, it strongly suggests the presence of consciousness in some patients. However, we argue that its ethical significance is less than many people seem to think. There are several different kinds of consciousness, and though all kinds of consciousness have some ethical significance, different kinds underwrite different kinds of moral value. Demonstrating that patients have phenomenal consciousness — conscious states with some kind of qualitative feel to them — shows that they are moral patients, whose welfare must be taken into consideration. But only if they are subjects of a sophisticated kind of access consciousness — where access consciousness entails global availability of information to cognitive systems — are they persons, in the technical sense of the word employed by philosophers. In this sense, being a person is having the full moral status of ordinary human beings. We call for further research which might settle whether patients who manifest signs of consciousness possess the sophisticated kind of access consciousness required for personhood.

Keywords: consciousness; persistent vegetative state; minimally conscious state; morality; right to life; access consciousness; phenomenal consciousness

Consciousness is notoriously difficult to study empirically. But unlike most other nearly intractable problems, consciousness *matters*. It matters *practically* to the quality of our lives, but also for significant ethical questions. Consider the vexed question concerning the withdrawal of the means of life (whether life support or nutrition and hydration) from patients in a persistent vegetative state (PVS). As we recently witnessed in the Terri Schiavo case, these cases are the focus of passionate debate, and this is a debate that turns, significantly, on the consciousness of the patient. Opponents of withdrawing life support often claim that PVS patients are conscious, citing spontaneous behavior by these patients as evidence; supporters of the right of family to withdraw life support maintain that PVS is incompatible with consciousness. Given this context, the recent claim by Owen et al. (2006) that they have strong evidence of consciousness in a PVS patient is extremely significant.

In this paper, we shall sound a note of caution. While the results reported are undoubtedly significant, and leave little room for doubt that some patients correctly diagnosed as PVS (i.e., who do not show the minimal behavioral responsiveness required for another diagnosis) have

*Corresponding author.
Tel.: +61 3 8344 3855; Fax: +61 3 8344 4280;
E-mail: neil.levy@philosophy.ox.ac.uk

DOI: 10.1016/S0079-6123(09)17725-7

some degree of consciousness, their ethical importance should not be exaggerated. We shall argue that given the current state of our knowledge — a state which is, we acknowledge, in flux — the research is unlikely to significantly alter the ethical debate. If PVS patients are conscious, then it is important to ensure that they do not experience aversive mental states. Accordingly, we have reason to give their analgesics and perhaps sedatives and antidepressants. But whether they are conscious or not, it can be argued that we have little reason to maintain them in existence (and perhaps even some reason to bring about the cessation of their lives), unless their mental states are at least as sophisticated as those exhibited by children, and, importantly, as connected across time. It is not merely consciousness that is required for what we shall call full moral status; it is self-consciousness, and we do not believe that we can (yet) attribute self-consciousness to any PVS patients.

Concepts of consciousness

In order to understand and properly appreciate the significance of the work of Owen and colleagues, it is necessary to recognize that consciousness is a complex phenomenon, or perhaps even a complex set of phenomena. Different thinkers denote different properties when they refer to ''consciousness,'' and different concepts of consciousness underlie different kinds of moral value. It is likely that the different concepts of consciousness refer to properties that co-occur in normal subjects under typical conditions, but given that they may dissociate, in normal and in pathological cases, we cannot assume co-occurrence without further evidence.

What do researchers like Owen mean when they say that a patient is conscious? Generally speaking, neuroscientists and clinicians implicitly work with a definition of consciousness that is vague, but which might best be summed as ''wakefulness with awareness.'' Wakefulness is relatively easily defined, at least behaviorally, and is rarely in dispute. Wakefulness is a defining feature of PVS: a patient is diagnosed as PVS when they transition out of a coma and begin a sleepwake cycle but remain unresponsive to external stimuli. ''Awareness,'' too, is defined behaviorally: a patient is aware if they make non-reflexive responses to external stimuli. The response need not be sophisticated: tracking a moving object or even fixated their gaze for long enough to rule out mere chance is enough to indicate awareness. If the response is inconsistent, the patient is said to be in a ''minimally conscious state'' (MCS), where to be minimally conscious is to have transitory conscious states (possibly sometimes of a lower quality than the conscious states of normal subjects). Now, people are free to use words however they like; if they want define ''consciousness'' as ''wakefulness with awareness'' they may do so. But we should be aware that consciousness is a word in everyday language. Accordingly, there is a risk that consciousness, as used by neuroscientists and clinicians, will be understood as denoting not, or not only, ''wakefulness with awareness'' but the other properties more usually associated with consciousness. Indeed, neuroscientists and clinicians themselves seem to assume that consciousness as *they* use it has these further qualities. But this assumption may be illegitimate.

What are these further properties? Ned Block has famously distinguished two concepts of consciousness, both of which, he asserts, have claims to being *the* folk concept: *phenomenal* consciousness and *access* consciousness (Block, 1995). Phenomenal consciousness refers to the qualitative character of experience. A state is phenomenally conscious inasmuch as there is something it is like to be in it. In contrast, information is access conscious if it is available for rational control, if it is simultaneously accessible to the decision making, planning, and volitional centers. Many neuroscientists seem committed to a global workspace model of consciousness (Baars, 1988, 1997; Dehaene and Naccache, 2001). On the global workspace account, information is conscious if it is in the global workspace, that is, simultaneously accessible to a variety of (so-called) consuming systems. Consuming systems are relatively modular and possess few links to one another; only through the conduit of the

global workspace does information became available for the rational control of thought and behavior.

Now, it is apparent that the participants in the debate over whether some patients diagnosed as PVS are conscious assume that consciousness, as they define it and test for it, has the properties that Block describes, that is, a patient who exhibits wakeful awareness is both phenomenally conscious and access conscious. For instance, they argue, on the basis of their evidence, that there is case for giving PVS patients analgesia (Whyte, 2008); since the function of analgesics is to mitigate the *experience* of pain, they clearly assume that wakeful awareness is evidence of phenomenality. Now, in general this is a warranted assumption: the three concepts of consciousness (wakeful awareness, phenomenality, and access) occur together with great regularity. But it may be that these different states can dissociate. Block has argued that sometimes the contents of the phenomenal consciousness of normal subjects are richer than the contents of their access consciousness; that is, they have phenomenal contents that are not available to the full range of consuming systems which have access to the global workspace of access consciousness. The opposite dissociation is also conceivable, that is, subjects may sometimes be access conscious of information of which they are not phenomenally conscious, perhaps, for instance, when engaging in overlearned behavior. This being so, we should not be too quick to assume that access and phenomenal consciousness co-occur in the patients tested. Thus, one challenge to researchers aiming to show that some PVS patients are conscious is to answer the question what kind of consciousness their tests reveal. As we shall see, different answers to this question have dramatically different moral implications.

A second (and more basic) challenge consists in showing that the evidence produced is of consciousness at all. The fact that a test shows that information presented to a subject is available to drive behavior is not evidence of consciousness, all by itself. The mind contains a number of what we might call ''zombie systems,'' modular systems capable of guiding behavior in response to environmental stimuli in the absence of consciousness. Classic examples include the modules involved in visual perception, which calculate distance and trajectory of objects and motivate reflexive avoidance behavior. The existence of these systems, which may account for a great deal of the behavior of normal awake subjects (Bargh and Chartrand, 1999), is a product of our evolutionary history, in which consciousness was almost certainly a relatively late arrival. We were behaving in adaptive ways for millennia before consciousness arrived, and evolution is a conservative process. Consciousness is a scarce resource, one that is apparently called on only when zombie systems do not suffice on their own; it is needed only for complex or novel behavior.

Showing that a patient is (relevantly) conscious, therefore, requires conceptual work as well as empirical results. We need to establish what behaviors require consciousness, and what kinds of consciousness are required. We also need to establish the precise relationship between access and phenomenal consciousness. It may be that once access consciousness is rich enough, its contents are ipso facto phenomenally conscious, but this remains to be demonstrated. We are not entirely ignorant here: at least we have good theories concerning the role of access consciousness, which may shed light on the relationship between the two concepts of consciousness. The function of access consciousness is likely to be the integration of information from diverse sources, making that information available to many systems (including zombie systems) in turn. Information of which a person is aware is access conscious if it is available to (enough of) the consuming systems which make up the mind. Information must achieve what Dennett (2001) calls ''cerebral celebrity'' in order to be access conscious. It may be that achieving this kind of celebrity is also necessary for phenomenal consciousness; perhaps, the richness or vividness of phenomenal consciousness is a function of the degree of global availability of information. The mark of access consciousness is flexibility of response; because a piece of information is globally available, it can drive different kinds of behavior, and behavior that is sensitive to many

different kinds of information, fed from different modules. Mere awareness, or mere response, is therefore not an indicator, by itself, of consciousness. Isolated zombie systems are perfectly capable of such responses, but isolated zombie systems are unlikely, by themselves, to give rise to any kind of consciousness.

If all this is correct, we have good reason to be suspicious of the standard behavioral tests for the detection of consciousness. At very least, their use requires validation; it must be shown that the behaviors in question are unlikely to be produced by zombie systems. One of the many reasons why the work of Owen and colleagues constitutes an advance on standard methodologies for the detection of consciousness is that they are sensitive to this kind of concern; the task they use is demanding enough to make the hypothesis that it is accomplished by zombie systems alone unlikely.

Consciousness: new evidence

Owen et al. (2006) represents a revolution in consciousness studies, not only in the results contained but also in the methodology employed. Previously, researchers who hoped to detect consciousness in patients who, for one reason or another, were unresponsive to external stimuli had used fMRI or EEG in an attempt to detect neural correlates of consciousness "the minimal set of neuronal events and mechanisms jointly sufficient for a specific conscious percept" (Koch, 2004, p. 16). This is a technique fraught with conceptual difficulties, inasmuch as it is disputed what neural processes constitute the correlates of consciousness. Owen et al. sidestep this debate brilliantly. We can reconstruct their reasoning as follows: we do not ordinarily look for the neural correlatives of consciousness in other people, because we believe that the kinds of complex cognitive processes in which they manifestly engage — talking to one another paradigmatically, but also interacting flexibly with the environment in ways that outrun overlearned processes — are clear evidence of access consciousness, and almost certainly of phenomenal consciousness as well. It is therefore not necessary to look for the neural correlates of consciousness. Instead, neuroimaging techniques can be employed to look for neural correlates of less controversial processes; if the subject gives unequivocal evidence of engaging in complex processes, of the sort which we ordinarily take to be evidence of consciousness, we will have as good reason to attribute consciousness to them as to one another outside the clinical context.

The reasoning is, we think, unassailable. If there are any doubts about their results, these doubts must focus on the particular cognitive processes selected, and on whether these processes might be carried by zombie systems, and not on the general line of argument. Let us now turn to the processes and the evidence they have produced.

There were two kinds of probes utilized by Owen and colleagues. One tested for, and successfully demonstrated, appropriate processing of ambiguous words. This evidence is not especially informative, because semantic processing is clearly the kind of thing that can be carried out by zombie systems. A number of previous studies have shown task-specific brain activation in patients: Schoenle and Witzke (2004) measured event-related potentials in the brains of PVS patients, using sentences ending in congruent or incongruent words as stimuli. In normal controls, an N400 response is elicited by the incongruent endings. Twelve percent of VS patients and 77% of what the authors describe as near VS patients exhibited the response, reflecting preserved semantic processing in these patients. Unpublished data reported by Perrin showed a P300 response — correlated reliably with recognition — to the patient's own name in PVS (Laureys et al., 2005). The evidence from Owen et al. of semantic processing in PVS is therefore unsurprising. Semantic processing is mental activity, but mental activity need not be conscious.

The second type of probe utilized produces far more impressive evidence, and attention has rightly been focused on it. The probes utilized were instruction probes, and came in two variants. One variant asked the patient to imagine playing tennis, while the other asked her to imagine

walking from room to room in her house. In each case, she was asked to engage in the task for 30 s at a time. During the tennis probe, significant activity was observed in the supplementary motor area (SMA); during the navigation task, activity was observed in the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex. In both cases, the responses were comparable to those observed in healthy controls.

The tasks the patient was asked to perform matters relatively little; any task would do, so long as it satisfied two conditions: initiation of the task must be under voluntary control and it must give rise to unambiguous neural correlates. It is plausible to maintain that the instruction following probes both satisfy these conditions (though it is sufficient for their purposes if only one of them satisfies the conditions). Might the behavior have been carried out by zombie systems nevertheless? Some critics have worried that the behavior might be produced through priming (Greenberg, 2007), that is, the processes which, in normal subjects, lead later behavior to be responsive to unconsciously processed information. In response, Owen et al. (2007) point to the sustained nature of the activity. Priming, they argue, is typically transitory, not sustained for the full 30s. But this reply is not decisive.

Owen and his critics seem to have the same view of the unconscious: it is the ''dumb'' unconscious of cognitive psychology, which engages in brief flickers of automatic behavior. But the view of the unconscious mind suggested by work in social psychology is of a set of flexible and complex systems, capable of driving intelligent behavior. Most of the actions of ordinary people — some researchers believe the *overwhelming* majority — are initiated and guided by unconscious systems. Consciousness is a limited resource and it is saved for difficult tasks. So there is another way to interpret the evidence: rather than inferring, with Owen et al., that the patient engaged in goal-directed and complex behavior, and thus must have been conscious, we can conclude that they have provided further evidence for the power of automatic systems.

Owen et al. argue that their study demonstrated that the patient was conscious because the activation in SMA and other regions persisted so long, whereas responses to primes last only a few seconds. But persisting activity by unconscious processes has been demonstrated: Bargh et al. (2001) primed subjects with stimuli related to high performance, put them to work on a word finding task, and then instructed them to stop after 2 min. Primed subjects were more likely to ignore the instruction, indicating the persistence of the unconsciously activated goal. In a variation of this study, primed subjects were interrupted at the task after 1 min and then made to wait 5 min before being given the choice of continuing the word finding task or instead performing a cartoon-rating task, which was rated as more enjoyable. Once again, subjects primed with stimuli related to high performance were more likely to return to the word finding task then controls, indicating the persistence of the unconsciously activated goal through a full 5 min of rest.

Of course, this study is in many ways disanalogous to Owen et al., most significantly in that it concerned fully conscious subjects, albeit with unconsciously primed attitudes. Nevertheless, it demonstrates that we cannot infer from the mere persistence of a mental state to the conclusion that it is conscious. There is also some evidence that instruction following can be performed in the absence of consciousness, this time by subjects who may be entirely unconscious. Automatism is characterized by complex goal-directed behavior, apparently in the absence of consciousness. Automatism can persist for long periods of time. Consider the case of Ken Parks, who in 1987 drove 23 km through the Ontario suburbs to the home of his parents-in-law, where he stabbed them both (Broughton et al., 1994). Parks was held to be acting automatistically. Behavior in automatism is less flexible and intelligent than conscious behavior; some researchers believe that the violence sometimes observed arises from an unexpected obstacle interrupting an overlearned script. But it is apparently compatible with instruction following, at least in an extended sense: Parks drove through the Ontario streets apparently safely. We do not know if he obeyed the instructions of traffic lights and stop signs, but at very least he was able to guide his actions by

the layout of the streets, all in the apparent absence of consciousness.

It should be noted that though the existence of automatism is not in doubt, there is little direct evidence of the absence of consciousness in subjects in this state. However, if the widely held theory according to which consciousness requires activation of higher-associative cortices is correct (Dehaene et al., 2006), subjects in a state of automatism are not conscious, since they do not exhibit such activation (Laureys, 2005).

Despite the reservations expressed above, we concede that the evidence presented by Owen et al. (2006) is impressive. It is indicative of a degree of complexity of behavior which is unexpected. It is evidence of instruction following, and there are grounds for regarding instruction following as evidence of consciousness. Though the objection from priming cannot be ruled out, it might be thought that on balance the evidence favors the view that their patient was consciousness. What kind of consciousness is in question? Instruction following is evidence of some degree of access consciousness, the kind of consciousness that makes possible verbal report in normal subjects. Indeed, the PVS patient is engaging in an unusual kind of verbal report. It is a further step from the claim that the subject is access conscious to the claim that she is phenomenally conscious. It remains possible, as we have seen, that zombie systems underlie the report, and further work which tests for this possibility is required (Block, 2005, 2007, suggests way in which the dissociation between access and phenomenal conscious may be empirically tractable). However, given our doubts about the actual dissociation of the kinds of consciousness, we think it is reasonable to conclude that the patient has some degree of phenomenal consciousness as well as access consciousness.

The moral significance of consciousness

Even though we think that Owen et al. have produced impressive evidence that patients correctly diagnosed as PVS (i.e., who do not show sufficient behavioral responsiveness to qualify as conscious on the standard tests) are sometimes conscious, we want to sound a note of caution over the *moral* significance of these findings. We think that the moral issues are hardly altered at all by the findings.

The distinction between the two concepts of consciousness is important for ethics as well as cognitive science and the philosophy of mind. Consciousness is closely linked to the moral status of those capable of experiencing it, but the different kinds of consciousness underlie different kinds of moral value. Phenomenal consciousness is sufficient to make its bearer a moral *patient* (though it may not be necessary — beings with interests, like plants, who lack phenomenal consciousness might be moral patients as well; if so, however, they are a very low-grade kind of moral patient). To be a moral patient is to be a being whose welfare matters, whose welfare must be taken into account when we decide what to do. To be phenomenally consciousness makes one a moral patient because a phenomenally conscious being can experience states that have qualities of aversiveness (like pain or boredom) or of pleasantness (like joy); these are states that matter intrinsically. To undergo these states is to have experiences which matter morally, and therefore beings capable of such experiences are moral patients.

We cannot be indifferent to moral patients; we are required to take their morally relevant states into account when we decide how to act. If PVS patients are sentient, then it matters what we do to them. We can benefit them by giving pleasure and harm them by causing pain. To that extent, their moment-by-moment states are of potential value and disvalue to them: they can suffer on the assumption — *contra* Carruthers (2004) — that the badness of pain consists in its phenomenality. We are morally required to minimize the amount of pain suffered by any sentient being (to the extent to which this is compatible with our other moral obligations), where sentience is the ability to have phenomenally conscious states. One way in which the findings under discussion should affect the debate, therefore, is by indicating the use of analgesics for some PVS patients. They may suffer, and we ought to take steps to prevent or minimize their suffering.

In our view, being a moral patient *solely* on the grounds that one is capable of experiences that are aversive or pleasant is a relatively low grade of moral status. It is the status that we accord to nonhuman animals. It is widely, and in our view correctly, held that we ought to take the quality of the experiences of nonhuman animals into account in our decision making, such that, say, we cannot cause them pain unless we have a good justification for doing so. But it is also widely, and we think correctly, held that other things being equal we have little reason to maintain nonhuman animals in existence; we need little justification to (painlessly) kill them (that is not to say, of course, that there are no differences between nonhuman animals and human beings: in virtue of *having been* a person, a certain kind of respectful treatment might be due to a patient, for instance, most of us think people ought to be buried. Our claim, rather, is nonhuman animals and human beings who are merely moral patients are similar in lacking an interest in continuing to live).

According to the view we are urging, nonhuman animals, with the possible exception of the great apes and perhaps cetaceans, have a right to have their interests taken into consideration, but they do not have a right to life. By a right to life here we do not mean the full inviolability that deontologists mean by the phrase: we do not mean an inviolability that can only be defeated by nothing short of what Nozick calls ''major moral catastrophe'' (Nozick, 1974). We mean something less stringent: a right to inviolability that can be defeated only by a sufficient number of comparable goods. We do not have space to develop our conception of what it takes to defeat such a right here; suffice it to say that this is a right that cannot be defeated by any number of trivial interests, though it can be defeated by important goods. Nonhuman animals do not have any such right; they have no interest in continuing to live and therefore we can choose to kill them (once again, painlessly) for the satisfaction of trivial interests (other things being equal), normal adult human beings do have such a right. What is it about normal adult human beings that justifies this difference in their moral status?

The justification lies in the mental states of which they are capable, including, though not only, their conscious mental states. The life of a person typically matters much more than the life of a nonhuman animal because only the former is capable of very sophisticated mental states that have an ineliminably temporal component. A being acquires a full moral status, including the right to life, if its life matters to it; that is, if it is not only momentary experiences that matter — as for the being capable only of phenomenal consciousness — but also an ongoing series of experiences. A full right to life requires that it is not only experiences that matter to one, but also how one's life actually goes; that is, that satisfaction of one's interests matter to one, and this requires very sophisticated cognitive abilities, such as an ability to conceive of oneself as a being persisting through time, to recall one's past, to plan, and to have preferences for how one's life goes (Singer, 1993; McMahan, 2002). It is the connectedness and continuity of one's mental states that underwrite *personhood*, in one central sense of the word; it is insofar as each of us is a single being across (relatively long) stretches of time that we count as moral persons.

But the abilities that underlie moral personhood and full moral status are abilities that require *access* consciousness, not phenomenal consciousness. Information must be sufficiently available for rational thought and deliberation in order for a being to be able to have future-oriented desires or to conceive of itself as persisting in time. So the demonstration that the PVS patient was phenomenally conscious — that is, that she was ''consciously aware of herself and her surroundings'' (Owen et al., 2006, p. 1402) — would not alter the debate significantly unless it was also evidence for sophisticated cognitive abilities, including a sophisticated kind of access consciousness that was not the subject of evaluation of the Owen tests.

In order to justifiably attribute to a being the right to life, in the sense sketched above, we must have good reason to attribute to them not phenomenal consciousness, but a sophisticated kind of access consciousness. It is not sufficient that information be in the global workspace; there is every reason to

think that this much is true of many nonhuman animals, including many who are not capable of the sophisticated mental states required for a right to life. In addition, as we have seen, the right kinds of information must be available to the right systems to enable the organism to have extended and self-referential mental states. The organism must be capable of future-oriented desires (desires that some future state of affairs be actual) and, of plans and projects. It must be capable of preferences regarding how its life goes. These capacities require that the organism be capable not merely of phenomenal and access consciousness, but also of *self*-consciousness, because only a self-conscious being can have preferences regarding how *its* life goes. This is one reason why most nonhuman animals do not have a right to life, but great apes and cetaceans might, because the latter pass tests for self-consciousness (like the mirror test; the ability to recognize that an image in a mirror is oneself is thought to require a conception of oneself as a separate being; see Keenan et al., 2003) and the former do not.

In addition, however, it is plausible to think that a full right to life requires not just access consciousness — which, as we noted above, we think that patients who pass the tests designed by Owen et al. demonstrate — but a sustained and sophisticated kind of access consciousness; that is, for a being to possess a right to life, the information in their global workspace must be available to consuming systems for a sustained period, to enable the being to link mental states across time. It may in fact be the case that what we shall call diachronic access consciousness is a necessary condition of self-consciousness that only a being who is able to maintain a thought about a desire can refer that desire to itself and therefore be self-conscious. There is, we note, evidence for some kind of diachronic access consciousness in the patient reported in Owen et al. (2006); the patient sustained the instruction following task for a full 30s. But before we can conclude that she is self-conscious, we need evidence that her diachronic access conscious had the right *content*: that it included self-referential contents. So far as we can tell, the study does not provide such evidence, and therefore does not establish that the patient has the right kinds of sophisticated mental states that underlie full moral status.

Conclusion and future directions

Clearly, further research is needed. We do not rule out the possibility that some patients who pass the test are in a state akin to locked-in syndrome, in which, usually as a result of a brain stem stroke, a person is fully and normally unconscious but incapable of voluntary movement. Someone in this state has all the capacities which underlie a full right to life. But we do not take this claim to be established. We have expressed some doubt that the patient in the original study was conscious at all, but we concede that the room for doubt is limited. We do think that the evidence suggests strongly that some PVS patients are actually conscious. But we think that the degree of consciousness is likely to be closer to that seen in MCS, rather than in LIS. We have suggested that the transitory and fluctuating consciousness seen in some MCS patients does not underwrite full moral status because it is transitory; only in those cases in which the mental states of the person are appropriately connected to one another does she have full moral status.

If the patient is conscious, then she is a moral patient; it matters — morally — how we treat her. We cannot cause her pain unless there is good reason to do so. But we do not have a reason to maintain her in being. Indeed, given that decisions about patient treatment are made in contexts in which resources are scarce, evidence that the patient is neither self-conscious nor capable of self-consciousness might be seen to be evidence that we have a positive reason *not* to maintain her in being (we acknowledge, of course, that there is no direct evidence that any PVS patient is *not* conscious). But we utterly reject the view that we need evidence for the absence of consciousness before we can justifiably conclude that consciousness is lacking. Sometimes absence of evidence *is* evidence of absence; were that not the case induction, a fundamental part of the scientific method in which one concludes on the basis of the

fact that past experiences have had a certain feature that future experiences will too would be impossible (for a defence of this claim, see Sober, 1981). Given the current state of consciousness studies, we believe that we can — fairly — reliably conclude from the absence of certain kinds of neural responses to the absence of states of consciousness.

We conclude with some reflections on the moral importance of the research examined here, as well as related work. We have argued that if the research shows that the patient is phenomenally consciousness but not self-conscious, we have reason to take her experiences into consideration but not to keep her alive. But we have not ruled out the possibility that some PVS patients will be shown to have more sophisticated cognitive capacities, which would allow us justifiably to attribute full moral status to them. Moreover, it may be that evidence of consciousness in PVS is not evidence of full moral status at the time of the test, but predictive of later recovery, perhaps even recovery of full moral status. Obviously, we have good reason to maintain a person in life if they have good prospects of such a recovery. Given, however, that MCS (unless it is a transition stage) is not a state that gives a patient moral personhood, it is no benefit to them to be in it.

Obviously, a great deal of further research is necessary. In particular, we hope to see research aimed at demonstrating the sophisticated kind of access consciousness that underlies full moral personhood. Such tests would demonstrate the availability of self-referential information to the patient across time; they would therefore probe for desires which are about how the patient's life goes, and not merely for immediate experiences, for hopes or fears regarding future times. We see no way to test for these capacities without the development of a communication paradigm that would enable the probing of self-consciousness and temporally persisting information. Unfortunately, we believe that this is a case in which failure to elicit the information would not be absence of evidence that is evidence of absence: there are many reasons why someone who is conscious might fail to be capable of sophisticated communication. But success at eliciting such information would put the moral status of PVS patients beyond any doubt.

References

Baars, B. J. (1988). *A cognitive theory of consciousness*. Cambridge: Cambridge University Press.

Baars, B. J. (1997). In the theatre of consciousness: Global workspace theory, a rigorous scientific theory of consciousness. *Journal of Consciousness Studies*, *4*, 292–309.

Bargh, J. A., & Chartrand, T. L. (1999). The unbearable automaticity of being. *American Psychologist*, *54*, 462–479.

Bargh, J. A., Gollwitzer, P. M., Lee-Chai, A. Y., Barndollar, K., & Troetschel, R. (2001). The automated will: Nonconscious activation and pursuit of behavioral goals. *Journal of Personality and Social Psychology*, *81*, 1014–1027.

Block, N. (1995). On a confusion about a function of consciousness. *Behavioral and Brain Sciences*, *18*, 227–287.

Block, N. (2005). Two neural correlates of consciousness. *Trends in Cognitive Sciences*, *9*, 46–52.

Block, N. (2007). Consciousness, accessibility, and the mesh between psychology and neuroscience. *Behavioral and Brain Sciences*, *30*, 481–499.

Broughton, R., Billings, R., Cartwright, R., Doucette, D., Edmeads, J., Edwardh, M., et al. (1994). Homicidal somnambulism: A case report. *Sleep*, *17*, 253–264.

Carruthers, P. (2004). Suffering without subjectivity. *Philosophical Studies*, *121*, 99–125.

Dehaene, D., & Naccache, L. (2001). Towards a cognitive neuroscience of consciousness: Basic evidence and a workspace framework. *Cognition*, *79*, 1–37.

Dehaene, S., Changeux, J.-P., Naccache, L., Sackur, J., & Sergent, C. (2006). Conscious, preconscious, and subliminal processing: A testable taxonomy. *Trends in Cognitive Science*, *10*, 204–211.

Dennett, D. C. (2001). Are we explaining consciousness yet? *Cognition*, *79*, 221–237.

Greenberg, D. L. (2007). Comment on ''detecting awareness in the vegetative state''. *Science*, *315*, 1221.

Keenan, J. P., Falk, D., & Gallup, G. G., Jr. (2003). *The face in the mirror: The search for the origins of consciousness*. New York: Harper Collins Publisher.

Koch, C. (2004). *The quest for consciousness: A neurobiological approach*. Englewood, CO: Roberts and Company.

Laureys, S. (2005). The neural correlates of (un)awareness lessons from the vegetative state. *Trends in Cognitive Science*, *9*, 556–559.

Laureys, S., Perrin, F., Schnakers, C., Boly, M., & Majerus, S. (2005). Residual cognitive function in comatose, vegetative and minimally conscious states. *Current Opinion in Neurology*, *18*, 726–733.

McMahan, J. (2002). *The ethics of killing: Problems at the margins of life*. Oxford: Oxford University Press.

Nozick, R. (1974). *Anarchy, state and utopia*. New York: Basic Books.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., Jolles, D., et al. (2007). Response to comments on "detecting awareness in the vegetative state". *Science*, *315*, 1221.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Schoenle, P. W., & Witzke, W. (2004). How vegetative is the vegetative state? Preserved semantic processing in vegetative state patients: Evidence from N 400 event-related potentials. *Neurorehabilitation*, *19*, 329–334.

Singer, P. (1993). *Practical ethics*. Cambridge: Cambridge University Press.

Sober, E. (1981). The principle of parsimony. *British Journal for the Philosophy of Science*, *32*, 145–156.

Whyte, J. (2008). Clinical implications of the integrity of the pain matrix. *Lancet Neurology*, *7*, 979–980.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 26

The ethics of measuring and modulating consciousness: the imperative of minding time

Joseph J. Fins*

Division of Medical Ethics, Weill Medical College of Cornell University, New York, NY, USA

Abstract: Using *time* as an over-arching metaphor, and drawing upon resources in the sciences, humanities, and the history of medicine, the author addresses the neuroethics of measuring and modulating consciousness. Static and evolving views of time dating to the Ancients are contrasted and applied to severe brain injury. These temporal worldviews are tracked progressively in the philosophies of Democritus and Heraclitus, Hippocrates and Galen, and the neurosurgeon, Wilder Penfield on into the modern era as they relate to current perceptions related to disorders of consciousness. These disorders, typified by the vegetative and minimally conscious states, can be viewed as either fixed and immutable or in flux depending upon social currents and scientific knowledge. Variable perspectives are examined in light of right-to-die cases involving permanently vegetative patients like Quinlan and Schiavo and contrasting ''late'' recoveries involving patients in the minimally conscious state. The author suggests that disorders of consciousness should not be viewed categorically as static entities but rather assessed as a reflection of a synchrony of time and biology that we are just beginning to understand. He stresses the relationship of temporality to clinical evaluation, diagnosis assessment, and prognostication and their association to new methods in functional neuroimaging. These time stamps have profound implications for systems of care and reimbursement mechanisms, which often mistakenly conflates futility with chronicity. This conflation is increasingly being challenged by patients who emerge from the minimally conscious state after conventional temporal expectations for improvement had transpired. These cases often referred to as ''late emergences'' point to the importance of better understanding the natural history of these conditions and the tempo of associated recoveries.

Keywords: brain injury; disorders of consciousness; vegetative state; minimally conscious state; time; ethics; neuroethics; right-to-die; Quinlan; Schiavo

> Time is to Clock as Mind is to Brain.
> Dava Sobel

A time of discovery

In life and in medicine, there are elements that go together. Our German hosts would say that *Der Hammer und der Nagel passen zusammen.* The hammer and nail go together. In Medicine, we couple diagnosis and treatment; they go together. And so it is with my assigned task of

*Corresponding author.
Tel.: (212) 746-4246; Fax: (212) 746-8738;
E-mail: jjfins@med.cornell.edu

DOI: 10.1016/S0079-6123(09)17726-9

addressing the ethics of measuring and modulating consciousness.

Although we have just begun this work in earnest, I have little doubt that measurement will become a diagnostic task and modulation will evolve into a therapeutic one. And it is quite likely that certain measurement methods, such as those that have been pioneered by Adrian Owen et al. (2006), will become effective therapies and communication devices for those with profoundly discordant behavioral and cognitive capabilities.

From an ethical standpoint, linking measurement and modulation in this clinical fashion clearly promotes synergisms: all of these elements go together in the service of patients with disorders of consciousness. In linking assessment and intervention, we will help meet the long neglected needs (Fins, 2003) of a population too often equated with near death states; conscious individuals marginalized to the sidelines of community who are exiled from humanity.

Although this fiduciary obligation is a worthy instrumental link, viewing this relationship solely within the narrow framework of therapeutics misses the larger theme of discovery, which ties measurement and movement together. It is helpful to look for broader relationships that would account for this process of inquiry and the acts of discovery, which have been central to our collective work.

And here I would suggest consideration of the analogic concepts of latitude and longitude, representing their own sort of global stereotaxy. This tandem speaks to the Age of Discovery undertaken by European navigators in search of the New World and as such, is a fitting association as we embark upon our own exploration of inner space. Like the ancient mariners, we too are mapping territories we could but once hardly imagine, much less visualize, either structurally or functionally.

As we look to the future, it is important to remember just how far discovery has come in such a short time. It is only 91 years since the Hopkins neurosurgeon, Walter Dandy, experimented with the ventriculogram to visualize central structures (Dandy, 1918; Kilgore and Elster, 1995). Wilder Penfield in his memoir, *No Man Alone*, writes of his excitement traveling down to Baltimore in 1921 in order to learn this new method. His words convey the excitement of novelty and reminds us that our own quest is still less than a century old. Penfield recalls:

> I watched while the ventricular fluid was drawn off and the air injected by a long, hollow needle inserted through a hole in the skull, deep into the ventricular cavity within the brain. The air, which replaced the fluid, did not seem to disturb the patient at all. It cast a clearly outlined shadow when X-rays were made of the head. The shadow showed the exact shape and position of the ventricular cavities within the brain.
>
> It was clear to me now that this was an important step forward, a surgical method of locating tumors and, even more important in my view, of studying the brain…
>
> (Penfield, 1977, p. 76)

More recently, the third edition of *The Diagnosis of Stupor and Coma* (Plum and Posner, 1982) is a time stamp for how far we have come in imaging the brain over the past several decades. In the 1982 iteration, the modern reader will find grainy black and white image of CT scans of the brain with large clunky pixilated blocks comprising the images. Our perspective contrasts with the text's rather hopeful statement about resolution: ''CT scanning is an ideal way to view the anatomy of the brain and to identify either abnormal structures (larger than 5 mm in diameter) or shifts of normal structures.'' (Plum and Posner, 1982, p. 73).

And since that tentative start we have seen in the past decade functional studies which reveal the absence and presence of neural networks depending upon brain state, the elucidation of language processing (Schiff et al., 2005; Owen et al., 2006) and the advent of structural changes which may be associated with recovery of cognitive function (Voss et al., 2006).

Given these notable achievements, it is not hyperbolic to suggest that we have indeed entered into an Age of Cognitive Exploration as glorious as that of the Age of Discovery. But latitude and longitude do more than suggest an analogy to the early navigators, it points us to what made it possible for them to determine their location when at sea far away from a home port. It points us to the importance of *time*.

Dava Sobel, in her critically acclaimed volume, *Longitude* writes that while latitude could be discerned by the Ancients by looking merely at the elevation of the stars in the sky, determining longitude was a far more difficult matter. She notes that:

> The measurement of longitude meridians, in comparison, is tempered by time. To learn one's longitude at sea, one needs to know what time it is aboard ship and also the time at the home port or another place of known longitude — at the very same moment. The two clocks enable the navigator to convert the hour difference into a geographical separation…
>
> Precise knowledge of the hour in two different places at once — a longitude prerequisite so easily accessible today from any pair of cheap wristwatches was utterly unattainable up to and including the era of pendulum clocks…
>
> (Sobel, 2007, pp. 4–5)

Sobel continues by recounting the challenge of timekeeping with a pendulum clock on a rolling ship deck amidst the additional challenges of extremes in temperature, barometric pressure and gravitational pull encountered at sea. These barriers were overcome with the advent of a reliable chronometer in the early 18th century.

Just as time tempered space and allowed for the precise localization of latitude and longitude, it is also integral to understanding consciousness and the relationship between its measurement and modulation. Drawing upon resources in the sciences and the humanities, I want to address the interplay of time and consciousness as it relates to: cultural and historical perceptions, clinical assessment, and systems of care.

Cultural and historical perceptions

One of the great challenges we have all encountered in our work is its relevance. I would wager that there is not a single clinician in this room who has not encountered the perception of nihilism that so closely affixes to patients with disorders of consciousness. Despite our progress in neuroimaging characterizing these brain states and our therapeutic forays utilizing pharmacology and neuromodulation, our ranks remain small and the utility of our work is still questioned.

Families who chose to be hopeful are counseled to expect less function, not more. Consider the advice offered by The Mayo Clinic's Drs. Wijdicks and Rabinstein for meeting with families whose loved ones are comatose:

> The attending physician of a patient with a devastating neurologic illness will have to come to terms with the futility of care … Those families who are unconvinced should be explicitly told they should have markedly diminished expectations for what intensive care can accomplish and that withdrawal of life support or abstaining from performing complex interventions is more commensurate with the neurologic status
>
> (Wijdicks and Rabinstein, 2007).

One mother who we interviewed at Weill Cornell Medical College in an IRB approved study of families touched by disorders of consciousness told us of her initial experiences after her 19-year-old son was hit by a drunk driver while he was walking on the sidewalk:

> Mother: And actually I had a neurologist tell me ''your son is basically just an organ donor now.''

> JJF: And when did that happen?
>
> Mother: Within the first 72 hours. She said, ''well he doesn't have the reflexes of a frog.''
>
> JJF: He doesn't have the reflexes of a …?
>
> Mother: Of a frog… She said ''you should really just consider him being an organ donor. That's the best thing you can do for your son.'' And I said, ''I completely disagree with you. I'm not making him an organ donor. Go back in there and do the best you can.''
>
> (Weill Cornell Transcripts, 2007–2008, IN314WN).

Even as we gather here in Berlin to celebrate our progress since the last symposium in *Progress in Brain Research* five years ago, such marginalization continues. What accounts for the truncated prognoses, the enduring skepticism about the work and its applicability to real patients and families burdened by disorders of consciousness?

There are at least two explanations and each takes account of time. The first is that clinicians who see patients early into the course of their injury do not see longitudinal outcomes. These clinicians are appropriately concerned about *acute* prognoses and the provision of proportionate care, recognizing the inherently serious and fragile state of patients with severe brain injury early in their course. They see patients at their worst, devoid of consciousness, which in other contexts is often the marker of end-stage disease and a clear prompt for end-of-life decision making like the designation of Do Not Resuscitate (DNR) Orders (Fins, 2007a). Clinicians habituated to respecting preferences at the end of life, and not prolonging the dying process, can *believe* that they are being patient advocates by routinely steering families to less aggressive curative care and on to palliative measures. While this is often appropriate in the neuro-intensive care unit, it is essential that acute care clinicians avoid prognostic errors about patients solely on the basis of a loss of consciousness.

As well-intentioned as they might be, these clinicians may in fact be victims of a *temporal error* by falsely analogizing the loss of consciousness that occurs with head injury to that which accompanies end-stage degenerative conditions like Alzheimer's disease or are the sequelae of the metabolic encephalopathies associated with terminal medical illnesses such as end-stage renal disease, metastatic cancer or sepsis. The loss of consciousness that occurs in these medical conditions is the penultimate deterioration before death. In contrast, the loss of consciousness in brain injury — while it can be the immediate harbinger of conventional or whole brain death — may also be the start of a process of recovery whose variability depends upon etiology.

The second reason for such errors is also related to time but due to more of a fixed perspective on its passage rather than an outright temporal error. Since the Ancients, conceptions of time have been either static or evolving. On the one hand there were the atomists who did not place time among their first principles. Instead, their conceptualization of time was due to a reconfiguration of atoms, which made up matter. According to Milic Capek:

> … Democritus regarded time as ''an appearance presenting itself under the aspect of night and day''; if he called time ''uncreated,'' he meant by it that notion (on which, in his view, time depended) is without beginning. With such a view of time and with their anticipation of the law of constancy of matter, the atomists greatly strengthened the static and substantialist modes of thought (Capek, 1973, pp. 389–398).

This static view, stressing the immutability of matter, found opposition in the perspective of Heraclitus who stressed dynamic fluidity. His antisubstantialist view was quite modern, emphasizing change, evolution and flux (Capek, 1973). He famously observed that, ''You cannot step twice into the same river.'' (Heraclitus, 1999).

For the modern era concerned about patients with disorders of consciousness, the point is to learn from the Ancients and appreciate the contrast between the atomists with their static notion of things and the Heracliteans who emphasized the process of evolution and becoming. Though they knew little about disorders of consciousness, this dichotomy of views is richly analogous to the two camps of modern medicine which embraces either a static view of brain states or appreciates that recovery and progress is possible.

I believe that this same tension was captured by Wilder Penfield in his design of the entrance hall of the Montreal Neurological Institute (MNI). Invoking the Ancients, as we have just done, Penfield takes a decidedly anti-static stance when it comes to prognosis and brain injury. In his inaugural address of September 27, 1934, commemorating the opening of the MNI, he explains the important symbolism of the entrance hall in an essay entitled, ''The Significance of the Montreal Neurological Institute'' (see Fig. 1).

In his address, Penfield describes the ceiling in his cathedral to neuroscience… Against the backdrop of a fresco with ''neuroglia cells after a drawing by the great Italian neurologist Camillo Golgi'' is ''the head of Aires the Ram, which in astrological terms presides over the brain'' and four hieroglyphic figures, thought to be ''the earliest reference to the brain anywhere in human records.'' Encircling all of this is an outer ring in which Galen — in Greek — refutes the Hippocratic aphorism that ''a wound involving the brain is invariably fatal.'' Penfield observed the importance of Galen's contrarian views given the regard he held the great physician from Cos:

> … Galen called no man master save only Hippocrates, but he took exception to the latter's statement that a wound involving the brain is invariably

Fig. 1. Entrance Hallway, Montreal Neurological Institute (Penfield, 1936).

> fatal in the above words which Dr. Francis (*Classicist and Nephew of Sir William Osler*) has translated, ''But I have seen a severely wounded brain healed.''
>
> (Penfield, 1936, pp. 42–43).

Not to miss the importance of Galen's defiance, Penfield signals his own point of view by adding the noteworthy endorsement of his own mentor and teacher (Fins 2008a, b), the legendary Sir William Osler:

> Osler said of Galen, ''There is no ancient physician in whose writings are contained so many indications of modern methods of research.'' It is pleasing to have from his pen, eighteen centuries old, the statement that the brain after all is a tissue like other tissues with capacity for healing; a promise that it too many yield to the physician and surgeon who come to understand the principles involved
>
> (Penfield, 1936, pp. 42–43).

Make no mistake about it; Penfield was clear about whose side he was on. His view was Galenic not Hippocratic when it came to brain injury. He saw the injured brain as an evolving entity amenable to intervention and improvement. In his cosmology, injuries were not immutable and fixed, they evolve and were treatable.

Unfortunately for those who have gathered here — and are fellow travelers in the lineage of Heraclitus, Galen, and Penfield — in modern society, static views continue to challenge a dynamic view of the injured brain. For better or worse, brain injuries — and disorders of consciousness in particular — have taken on iconic status becoming cultural talismans that achieve certain societal ends by being fixed in place.

As previously articulated, the utter *and fixed* futility of the vegetative state became the ethical and legal justification for the genesis of the right-to-die movement in the United States (Fins, 2003, 2006a). Although this right has become synonymous with broader rubric of patient self-determination in the decades since *Quinlan*, the origins of the right had its roots in a *prognostic* assessment of a future in the vegetative state.

In considering her irretrievable loss of a cognitive sapient state, Judge Hughes of the New Jersey Supreme Court drew heavily on the expert testimony of the court-appointed neurologist, Fred Plum, who was co-originator of the diagnosis with the late Brian Jennett (Jennett and Plum, 1972). In his decision, Judge Hughes noted:

> … It was indicated by Dr. Plum that the brain works in essentially two ways, the vegetative and the sapient. He testified:
>
> … We have an internal vegetative regulation … We have a more highly developed brain which is uniquely human which controls our relation to the outside world, our capacity to talk, to see, to feel, to sing, to think. Brain death necessarily must mean the death of both of these functions of the brain, vegetative and sapient…
>
> We have no hesitancy in deciding … that no external compelling interest of the State should compel Karen to endure the unendurable, only to vegetate a few more measurable months with no realistic possibility of returning to any semblance of *cognitive or sapient life*
>
> (Matter of Karen Quinlan, 1976).

The cultural import of this decision in shaping bioethical norms cannot be overstated (Cantor, 2001). It ensconced the right to die in American life, institutionalized hospital bioethics committees and changed practice patterns at life's end (Fins, 2006a). Unfortunately, the right to die was a fragile one. It was highly contextual and hinged on the near certain futility of ongoing treatment of those in the vegetative state. If vegetative patients, or even those who resembled vegetative patients, were seen as able to improve, that right could be undermined and challenged. This was the case in the Terri Schiavo saga where American ''right-to-life'' proponents sought to associate disingenuously an unimpeachable diagnosis of a

permanent vegetative state with the more favorable minimally conscious state (MCS) diagnosis (Giacino et al., 2002) in order to undermine the legitimacy of her prior wishes (Fins and Plum, 2004; Fins, 2006b).

On the opposite side of the political spectrum, the need to sustain a right to die, in a society with such strong pro-life currents, provides an on-going incentive for the ''pro-choice'' segment to twinge the diagnosis of disorders of consciousness with an ideological coloring. This tends to view all vegetative states as fixed and immutable, ignoring seemingly small clinical nuances that might make important diagnostic distinctions as some patients progress from VS to MCS (Fins, 2007b).

In the clinical context this failure often results in global pronouncements about disorders of consciousness, which are over-arching and often value-laden, such as comments about ''hopes for a meaningful recovery'' (Fins, 2005). Although such predispositions may reflect implicit values, or more nefariously political views, they represent — at their core — *temporal* errors and a failure to appreciate that the diagnosis of disorders of consciousness is *Heraclitean*, with diagnoses remaining in flux after injury.

Clinical assessment

Disorders of consciousness should not be viewed categorically as static entities but rather as a reflection of a synchrony of time and biology we are only beginning to understand. In some case permanence will take hold, though in other settings consciousness will change and evolve over time en route to recovery. It is well appreciated for this readership that the vegetative state becomes permanent when it has lasted 3 months following an anoxic injury and 12 months after a traumatic insult has occurred (Multi-Society Task Force on PVS, 1994). Before those temporal milestones are reached, patients can move — often unobserved (Fins et al., 2007a) — into the MCS. MCS is marked by definitive — albeit intermittent — evidence of consciousness as evidenced by demonstrations of intention, attention, memory, and awareness of self, others or the environment (Giacino et al., 2002).

Appreciating this temporal framework is a good starting place for the interpretation of novel findings such as the remarkable case presented by Owen et al. (2006) of a woman in the vegetative state who demonstrated integrated network responses of neuroimaging following traumatic brain injury (TBI) five months earlier. Investigators elicited significant activity in the supplementary motor areas when she was asked to play tennis mentally. When asked to imagine walking through her house she activated the parahippocampal gyrus, posterior parietal cortex, and the lateral premotor cortex. Finally, when presented with linguistically unclear sentences she activated the middle and superior temporal gyrus bilaterally as well as the left inferior frontal region. All of these network responses were ''indistinguishable'' from normals.

Although these findings represented a striking discordance between what was observed behaviorally and that demonstrated on fMRI, the patient's responsiveness was consistent with the Multi-Society Task Force diagnostic and prognostic guidelines which noted that the vegetative state becomes permanent 12 months after traumatic injury. At five months it remained possible that the patient was in the processing of transitioning to MCS. The images of integrated network responses, before there were behavioral manifestations of the same, could be interpreted as evidence of a liminal state between VS and MCS. My colleague and I interpreted it as consistent with a ''non-behavioral minimally conscious state.'' (Owen et al., 2006; Multi-Society Task Force on PVS, 1994; Fins and Schiff, 2006). Whether one agrees with this designation, what is important is that the neuroimaging evidence for a state transition was consistent with current temporal expectations about the potential for recovery into MCS before the 12-month marker of permanence occurs following TBI.

It is especially critical to be aware of these prognostic time stamps because absent these temporal markers it is difficult to interpret neuroimaging data. If another behaviorally vegetative patient demonstrated these responses years

after our current expectations of permanence had passed, we would need to postulate at least two explanations.

The first explanation might be that the Multi-Society categories were incorrect. This is unlikely based on the differential biology of the vegetative and MCSs as demonstrated by Steven Laureys et al. (2002) in a paper on pain response. Using PET and concurrent recordings of evoked potentials, the vegetative brain was compared to normal controls. The response of the vegetative patients was limited to the level of the mid brain, contralateral thalamus and primary sensory areas and *functionally disconnected* from activations of secondary somatosensory areas and higher-level associative areas seen in normal controls.

The second, and more probable explanation is that the observed recoveries were somehow unreliable or misleading. Bryan Jennett's analysis of data on late recoveries indicates that most reports were incomplete, unverified, or based on single case reports. Most importantly, he indicates that, ''Some alleged late recoveries might in fact have been late discoveries of earlier recovery'' (Jennett, 2001, pp. 63–64).

Notice the use of *chronological* terms in Dr. Jennett's elegant sentence. It suggests that what was observed late in the course of injury may in fact have been a missed diagnosis of higher function missed on an earlier examination, thus distorting or complicating our understanding of the epidemiology of these conditions (Fins et al., 2007a). These concerns are compounded as we introduce neuroimaging into the assessment process. Network responses, which are only discernible by neuroimaging and not by the conventional neurological examination could lead to the erroneous conclusion that their appearance coincided with the performance of the neuroimaging study and did not predate it.

This is a logical analysis based on the biological differences between VS and MCS brains (Laureys et al., 2002), the review of ''late recoveries'' done by the Multi-Society Task Force on PVS (1994) and the late Dr. Jennett's (2001) analysis. It is also an assessment that points to the compelling need to define the natural history of recovery and the public health importance of establishing longitudinal registries (Fins et al., 2007b) integrating behavioral metrics and neuroimaging data to assess the recovery of both latent and manifest function *over time* (Fins et al., 2008).

The errors which occur in the diagnostic differentiation of VS from MCS, which make such a clarion call for longitudinal assessment, have their basis in the *temporal* inconsistency of MCS itself. Putting aside the confounding dimensions of neuroimaging assessment, the frequency of bedside behaviors, which cinch the diagnosis and differentiate the MCS from the VS patient are themselves episodic. Their lack of clockwork reproducibility makes it difficult for the examiner to make the diagnosis quickly or accurately on a single occasion. To distinguish MCS from VS requires multiple moments in time.

Assessment of an individual patient in MCS requires the rigor of multiple exams as well as an awareness of the patient's *timing*. It is well appreciated that the processing speed of patients who have sustained TBI can be slowed. A large meta-analysis of 41 studies and 823 persons with severe brain injury recently concluded, ''that the time taken to process even simple stimuli is affected by a severe TBI and that the contribution of this deficit to performance on tests of attention cannot be ignored'' (Mathias and Wheaton, 2007). More recently, investigators studying brain injured U.S. service members found that diminished ''processing speed contributes significantly to performance on some measures of executive functioning in a sample of TBI veterans with and without post traumatic stress disorder (PTSD)'' (Nelson et al, 2009).

These data point to the need to be especially sensitive to response time when examining patients with severe injury. These patients may not be in our accustomed time zones but in a delayed frame marked by a degree of latency. Their slowed response time may lead clinicians to miss affirmative indications of cognitive capacity, albeit demonstrated at a slower pace.

I remember quite vividly examining a patient with a neurologist colleague during a therapeutic trial of zolpidem. The patient's diagnosis had been the vegetative state. After the drug had been administered, we sought to assess command

following by asking the patient to stick out his tongue. After more than the usual delay, my colleague turned away to his doctor's bag for the next item he would need in the examination. As he did this, my eyes were fixed on the patient who then executed the command. The patient's action was delayed way beyond the normal temporal window for a response. Despite the delay, his action had profound implications for his diagnosis, suggesting that, at least on zolpidem, he was responsive and now in the MCS.

The clinical — and ethical — importance of time cannot be overstated. Had we utilized a normal time frame we would have missed the response and the realization that this patient was at least minimally conscious. I suggest "at least minimally conscious" because once a patient shows some degree of awareness, the response could be indicative of a capability to do much more. Consider the case of a patient who is in a brain trauma unit receiving occupational therapy. The therapist, herself a poet, asked her students to write a poem. Often after an interminable delay, a time when most would give up on a writing effort, the patient comes up with a poignant and parsimonious Haiku-like sentiment. An excerpt from a poem entitled, "Transience" by John Wosinski captures the temporal displacement of brain injury:

> Endless cycles of
> Birth, growth, atrophy
> and death
> But not necessarily
> in that order.
>
> (Corbett, 2006)

The therapist collected her charges' poetry to demonstrate that profound physical disability does not always correlate with an equally significant cognitive impairment (Corbett, 2006). Readers of the equally elegant and sparse *The Diving Bell and the Butterfly* know this. This memoir of the locked-in state makes clear that patients who at first appear inert, or as Jean-Dominique Bauby put it, like a "zombie father", sometimes need a bit more time to demonstrate their capabilities. Their slowed cognitive response coupled with impaired motor function can obscure a conscious life (Bauby, 1998, p. 69).

At the bedside — and soon in the neuroimaging suite — clinicians will need to take account of latency and slowed processing speed to avoid depriving conscious individuals of their rightful place within our shared community.

Systems of care

As important as it is to be cognizant of when time is diagnostically determinative, it is equally important to appreciate when it is not necessarily a factor. Although we are accustomed to inversely correlate the *chronicity* of a condition with the likelihood of additional recovery, Lammi and colleagues have shown that emergence out of MCS (Giacino et al., 2002) is unpredictable and occurs in a rather open-ended fashion 2–5 years after injury (Lammi et al., 2005). They have found that the reacquisition of functional communication and object manipulation (Taylor et al., 2007), *not* time, predicts emergence from MCS:

> The low correlation coefficients between duration of MCS and the outcome measures suggest that prognostic statements based on length of time a person is in the MCS cannot be made with confidence
>
> (Lammi et al., 2005).

Nowhere is the dis-synchrony of time and recovery more plaintively revealed than in the musing of Donald Herbert, the brain-injured Buffalo fire fighter who began to speak fluently after a decade in the MCS (Blake, 2007; Fins, 2008c). After learning that a decade had passed, the forlorn father of four sons lamented, "I've been gone long time …"

Beyond the pathos of Donny Herbert's story and the fire fighter's misplaced sense of culpability for being an absent father, the work of Lammi and colleagues is a critically important finding because it points to the *dis-synchrony* of patient recovery with the provision of care and reimbursement.

At least in the Unites States, patients with disorders of consciousness are denied benefits or additional time in the hospital because when they fail to demonstrate medical progress based on expectations of progress derived from somatic illness or injury. Under a bureaucratic rubric of ''medical necessity'' governing payment, if a patient fails to improve demonstrably, services are cut as institutions are put under pressure to discharge patients (Granger et al., 2009). Simply put, medical necessity applies a somatic time frame to cognitive injuries that do not obey conventional temporal expectations.

Although a 1999 National Institutes of Health (NIH) consensus panel on TBI advocated that ''Persons with TBI should have access to rehabilitation services through the entire course of recovery, which may last for many years after the injury,'' (NIH, 1999) the on-going temporal discordance fostered by conventions like ''medical necessity'' coupled with the uncertain pace of cognitive recovery leaves a heavy financial burden — including the risk of personal bankruptcy — on patients and families touched by TBI (Relvea-Chew et al., 2009).

The problem is that medical necessity is derived from illnesses for which the natural history is known and predictable. If a patient is getting rehabilitation after hip replacement, the course and pace of recovery is relatively well understood. A failure to progress at certain intervals is predictive of a low likelihood benefiting from additional rehabilitative services. This relationship may not be as certain in cognitive rehabilitation for several reasons. First, the pace of recovery may not adhere to somatic standards. Second what is observed by overt behavioral criteria may belie with what is actually happening inside the patient's brain. The wife of a patient in the Locked-In-Syndrome put it this way:

> I see some improvement. They stopped his physical therapy, they just do occupational therapy and I would rather see the physical therapy back. I don't understand their logic for not doing it. You know, they were saying like, you know, he's not making an effort to roll or get to, try to get from the bed to a chair, you know. (He) might never get from the bed to a chair. His whole left side does not move at all. And his right only pushes. He can do thumbs up, if you say give me thumbs up he can give me thumbs up. He tries to roll his hands over, he can wiggle his fingers goodbye, he can rock his foot. Um, shrugs his shoulder. And I still think this part of physical therapy, as much as it is occupational therapy, according to them, there words to me were from the therapist is that they can't do physical therapy forever. [pause] Now, I was like very upset over that. Because why can't you do physical therapy forever? If the brain is so complex, what he might not do today he might do 3 months from now. But if you don't continue to do it with him he's not gonna do it at all. You know what I'm saying?
>
> (Weill Cornell Transcripts, 2007–2008, IN321D).

These barriers to care are further amplified because of the temporal stamp we lay upon the *places* where individuals receive care. Patients receive aggressive scientifically informed and curative interventions in acute care settings. The Oxford English Dictionary defines acute as ''coming rapidly to a crisis.'' In contrast, ''chronic'' is firstly defined as ''of or relating to time'' and secondarily ''lasting a long time, lingering, inveterate'' (Oxford, 1987). Thus labeled, is it any wonder that our expectations for improvement or recovery are so low for those who have found themselves in chronic care? Indeed, the lingering, inveterate quality of the designation is reminiscent of the immutability of the fixed period of the Ancients Atomists against which Heraclitus railed.

The problem is that these temporal perceptions about acute and chronic care are reinforced by how patients are sequestered and distributed within our health care system, where context so often influences diagnosis, prognosis, and

recovery. When we label outcomes as a ''late emergence'' or marvel at a ''late induced recovery'' from interventions like neuromodulation (Schiff et al., 2007, 2009) or a pharmaceutical trial (Whyte et al., 2005) we need to ask ourselves, *late by whose standards*?

If ''late'' reflects the natural history and timing of emergence, by natural or assisted means, why do we view its arrival pejoratively before we know what neuroscience might predict as an expected time of arrival? To label recoveries late or otherwise, before basic prognostic information is available, is to imply that recovery should have happened earlier. The absence of these ''early'' recoveries only serve to affirm the mistaken notion that improvement should have already taken place and that brain injuries are static and immutable. These perceptions are increasingly scientifically untenable and only serve to run out the clock for hope and expectation. Would it not be better if our expectations for what might be possible were concordant with the actual tempo of recovery experienced by patients with these disorders?

Acknowledgments

Dr. Fins is the recipient of an Investigator Award in Health Policy Research (*Minds Apart: Severe Brain Injury and Health Policy*) from The Robert Wood Johnson Foundation. He also gratefully acknowledges grant support from: the Buster Foundation (*Neuroethics and Disorders of Consciousness*); the Richard Lounsbery Foundation (*Sustaining and Building Research Infrastructure for the Study of Disorders of Consciousness at Weill Cornell Medical College and Rockefeller University*); and The Jerold B. Katz Foundation.

The author extends thanks to Dr. Steven Laureys for his invitation to contribute to this issue of *Progress in Brain Research*, Dr. Nicholas D. Schiff for his counsel and collegiality and Jennifer Hersh for her research assistance. Dr. Fins is especially grateful to Amy B. Ehrlich for her critical insights and to the family members who have shared their experiences with such a spirit of altruism.

References

Bauby, J.-D. (1998). *The diving bell and the butterfly*. New York: Vintage International.

Blake, R. (2007). *The day Donny Herbert woke up*. New York: Harmony Books.

Cantor, N. L. (2001). Twenty-five years after Quinlan: A review of the jurisprudence of death and dying. *Journal of Law Medicine & Ethics*, *29*(2), 182–196.

Capek, M. (1973). Time. In P. P. Wiener (Ed.), *Dictionary of the history of ideas* (Vol. IV), New York: Charles Scribner's Sons, Publishers.

Corbett, C. (2006). *Literary review* (Winter, Vol. III). Lake Katrine, NY: The Northeast Center for Special Care.

Dandy, W. E. (1918). Ventriculography following the injection of air into the cerebral ventricles. *Annals of Surgery*, *68*, 5–11.

Fins, J. J. (2003). Constructing an ethical stereotaxy for severe brain injury: Balancing risks, benefits and access. *Nature Reviews Neuroscience*, *4*, 323–327.

Fins, J. J. (2005). Rethinking disorders of consciousness: New research and its implications. *The Hastings Center Report*, *35*(2), 22–24.

Fins, J. J. (2006a). *A palliative ethic of care: Clinical wisdom at life's end*. Sudbury, MA: Jones and Bartlett.

Fins, J. J. (2006b). Affirming the right to care, preserving the right to die: Disorders of consciousness and neuroethics after Schiavo. *Supportive & Palliative Care*, *4*(2), 169–178.

Fins, J. J. (2007a). Ethics of clinical decision making and communication with surrogates. In J. Posner, C. Saper, N. D. Schiff, & F. Plum (Eds.), *Plum and Posner's diagnosis of stupor and coma* (4th ed.), New York: Oxford University Press.

Fins, J. J. (2007b). Border zones of consciousness: Another immigration debate? *American Journal of Bioethics-Neuroethics*, *7*(1), 51–54.

Fins, J. J. (2008a). A leg to stand on: Sir William Osler and Wilder Penfield's ''Neuroethics''. *American Journal of Bioethics*, *8*(1), 37–46.

Fins, J. J. (2008b). ''Humanities are the Hormones'': Osler, Penfield and ''Neuroethics'' Revisited. *American Journal of Bioethics*, *8*(1), w5–w8.

Fins, J. J. (2008c). A review of: The day Donny Herbert woke up. *Journal of the American Medical Association*, *299*(8), 959–960.

Fins, J. J., Illes, J., Bernat, J. L., Hirsch, J., Laureys, S., Murphy, E., et al. (2008). Neuroimaging and disorders of consciousness: Envisioning an ethical research agenda. *American Journal of Bioethics*, *8*(9), 3–12.

Fins, J. J., Master, M. G., Gerber, L. M., & Giacino, J. T. (2007a). The minimally conscious state: A diagnosis in search of an epidemiology. *Archives of Neurology*, *64*(10), 1400–1405.

Fins, J. J., & Plum, F. (2004). Neurological diagnosis is more than a state of mind: Diagnostic clarity and impaired consciousness. *Archives of Neurology*, *61*(9), 1354–1355.

Fins, J. J., & Schiff, N. D. (2006). Shades of gray: New insights from the vegetative state. *The Hastings Center Report*, *36*(6), 8.

Fins, J. J., Schiff, N. D., & Foley, K. M. (2007b). Late recovery from the minimally conscious state: Ethical and policy implications. *Neurology*, *68*, 304–307.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*, 349–353.

Granger, C. V., Carlin, M., Diaz, P., Dorval, J., Forer, S., Kessler, C., et al. (2009). Medical necessity: Is current documentation practice and payment denial limiting access to inpatient rehabilitation? *American Journal of Physical Medicine & Rehabilitation*, *88*(9), 755–765.

Heraclitus. (1999). *The art and thought of Heraclitus*. In C. H. Kahn (Ed.) (p. 53). Cambridge, UK: Cambridge University Press.

Jennett, B. (2001). *The vegetative state* (pp. 63–64). Cambridge, UK: Cambridge University Press.

Jennett, B., & Plum, F. (1972). Persistent vegetative state after brain damage: A syndrome in search of a name. *Lancet*, *299*(7753), 734–737.

Kilgore, E. J., & Elster, A. D. (1995). Walter Dandy and the history of ventriculography. *Radiology*, *194*, 657–660.

Lammi, M. H., Smith, V. H., Tate, R. L., & Taylor, C. M. (2005). The minimally conscious state and recovery potential: A follow-up study 2 to 5 years after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *86*(4), 746–754.

Laureys, S., Faymonville, M. E., Peigneux, P., Damas, P., Lambermont, B., Del Fiore, G., et al. (2002). Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage*, *17*(2), 732–741.

Mathias, J. L., & Wheaton, P. (2007). Changes in attention and information-processing speed following severe traumatic brain injury: A meta-analytic review. *Neuropsychology*, *21*(2), 212–223.

Matter of Karen Quinlan. (1976). 70 N.J. 10, 355 A.2d 677.

Multi-Society Task Force on PVS. (1994). Medical aspects of the persistent vegetative state (2). The Multi-Society Task Force on PVS. *New England Journal of Medicine*, *330*(22), 1572–1579.

Nelson, L. A., Yoash-Gantz, R. E., Pickett, T. C., & Campbell, T. A. (2009). Relationship between processing speed and executive performance among OEF/OIF Veterans: Implications for postdeployment rehabilitation. *The Journal of Head Trauma Rehabilitation*, *24*(1), 32–40.

NIH Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury. (1999). Rehabilitation of persons with traumatic brain injury. *Journal of the American Medical Association*, *282*, 974–983.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*(5792), 1402.

Penfield, W. (1936). The significance of the Montreal Neurological Institute. In Neurological Biographies and Addresses (Foundation Volume, Published for the Staff, to commemorate the Opening of the Montreal Neurological Institute, of McGill University). London: Humphrey Milford/Oxford University Press.

Penfield, W. (1977). *No man alone*. Boston, MA: Little, Brown and Company.

Plum, F., & Posner, J. B. (1982). *The diagnosis of stupor and coma* (3rd ed.). Philadelphia, PA: F.A. Davis Company.

Relvea-Chew, A., Hollingworth, W., Chan, L., Comstock, B. A., Overstreet, K. A., & Jarvik, J. G. (2009). Personal bankruptcy after traumatic brain injury or spinal cord injury: The role of medical debt. *Archives of Physical Medicine and Rehabilitation*, *90*(3), 413–419.

Schiff, N. D., Giacino, J. T., & Fins, J. J. (2009). Deep brain stimulation, neuroethics and the minimally conscious state: Moving beyond proof of principle. *Archives of Neurology*, *66*(6), 697–702.

Schiff, N. D., Giacino, J. T., Kalmar, K., Victor, J. D., Baker, K., Gerber, M., et al. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, *448*(7153), 600–603.

Schiff, N. D., Rodriguez-Moreno, D., Kamal, A., Kim, K. H., Giacino, J. T., Plum, F., et al. (2005). fMRI reveals large-scale network activation in minimally conscious patients. *Neurology*, *64*(3), 514–523.

Sobel, D. (2007). *Longitude*. New York: Walker & Company.

Taylor, C. M., Aird, V. H., Tate, R. L., & Lammi, M. H. (2007). Sequence of recovery during the course of emergence from the minimally conscious state. *Archives of Physical Medicine and Rehabilitation*, *88*(4), 521–525.

The Shorter Oxford English Dictionary. (1987). In C. T. Onions (Ed.). New York: Clarendon Press/Oxford University Press.

Voss, H. U., Uluc, A. M., Dyke, J. P., Watts, R., Kobylarz, E. J., McCandliss, B. D., et al. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *Journal of Clinical Investigation*, *116*(7), 2005–2011.

Weill Cornell Transcripts. (2007–2008). Patient/Family Interviews. IRB approved study.

Whyte, J., Katz, D., Long, D., DiPasquale, M. C., Polansky, M., Kalmar, K., et al. (2005). Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: A multicenter study. *Archives of Physical Medicine and Rehabilitation*, *86*(3), 453–462.

Wijdicks, E. F. M., & Rabinstein, A. A. (2007). The family conference: End-of-life guidelines at work for comatose patients. *Neurology*, *68*, 1092–1094.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 27

Theoretical approaches to the diagnosis of altered states of consciousness

Melanie Boly[1,*], Marcello Massimini[2] and Giulio Tononi[3]

[1]*Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège, CHU Sart Tilman Hospital, Liège, Belgium*
[2]*Department of Neurophysiology, University of Milan, Milan, Italy*
[3]*Department of Psychiatry, University of Wisconsin, Madison, WI, USA*

Abstract: Assessing the level of consciousness of noncommunicative brain-damaged patients is difficult, as one has to make inferences based on the patients' behavior. However, behavioral responses of brain-damaged patients are usually limited not only by their cognitive dysfunctions, but also by their frequent motor impairment. For these reasons, it is essential to resort to para-clinical markers of the level of consciousness. In recent years, a number of studies compared brain activity in comatose and vegetative state patients to that in healthy volunteers, and in other conditions of reduced consciousness such as sleep, anesthesia, or epileptic seizures. Despite the increasing amount of experimental results, no consensus on the brain mechanisms generating consciousness has yet been reached. Here, we discuss the need to combine a theoretical approach with current experimental procedures to obtain a coherent, parsimonious explanation for the loss of consciousness in several different conditions, such as coma, vegetative state, sleep, anesthesia, and epileptic seizures. In our view, without a theoretical account of how conscious experience is generated by the brain, it will remain difficult to understand the mechanisms underlying the generation of consciousness, and to predict reliably its presence or absence in noncommunicative brain-damaged patients. In this context, we review current theoretical approaches to consciousness, and how well they fit with current evidence on the neural correlates of experience. Specifically, we emphasize the principled approach provided by the Integrated Information Theory of Consciousness (IITC). We describe the different conditions where the theory predicts markedly reduced states of consciousness, and discuss several technical and conceptual issues limiting its applicability to measuring the level of consciousness of individual patients. Nevertheless, we argue that some of the predictions of the theory are potentially testable using available imaging techniques.

Keywords: consciousness; integrated information theory; vegetative state; minimally conscious state; diagnostic framework

In clinical practice, unconsciousness is defined as the absence of any sign of perception of self or environment (Laureys and Boly, 2008). Clinical conditions meeting these criteria include coma and vegetative state (VS). Patients in a minimally

*Corresponding author.
Tel.: +324 366 2316; Fax: +324 366 2946;
E-mail: mboly@student.ulg.ac.be

DOI: 10.1016/S0079-6123(09)17727-0

conscious state (MCS) show nonreflexive behaviors but are unable to communicate (Giacino et al., 2002). To date, patients in altered states of consciousness such as in coma, VS, and MCS continue to pose great diagnostic and management problems (Laureys and Boly, 2007). Several studies have indeed shown how difficult is the clinical diagnosis of consciousness at the bedside, and this difficulty is reflected in a high rate of misdiagnosis among these noncommunicative patients (up to 43%) (Laureys et al., 2004). This high frequency of diagnostic errors can be partially explained by the fact that we can only infer the patient's consciousness from motor responses obtained at the bedside, searching for response to command or ''purposeful'' behaviors. However, there is no clinical consensus on which behavior has to be considered as ''reflexive'' or ''meaningful'' in this context. Furthermore, patients' motor responsiveness is often impaired in parallel to cognitive dysfunction, leading to frequent underestimation of their actual level of awareness in clinical conditions (Owen et al., 2006).

These clinical diagnosis issues emphasize the need to find objective para-clinical markers of consciousness in order to compensate for the lack of clinical reliability at the bedside. A number of studies thus investigated brain function in coma, VS, and MCS patients, showing differences between patients groups and healthy volunteers (Boly et al., 2004; Boly et al., 2008a; Laureys et al., 1999; Owen et al., 2005b; Schiff et al., 2002b). However, several studies have also shown that brain activity patterns of individual VS and MCS patients are extremely variable (Coleman et al., 2007; Di et al., 2007). Pathophysiological mechanisms and/or brain lesions leading to coma or VS are also heterogeneous, leading to even bigger difficulties in finding consistent para-clinical markers of unconsciousness in these patients' populations. Moreover, in the absence of consensus on the neural correlates of conscious perception, and in the absence of a subjective report, even an abnormal pattern of brain activity compared to a normal control population is to date not sufficient to ensure the presence or absence of consciousness in individual noncommunicative patients.

The need for a scientific theory of consciousness

Over the past few years, several studies have appeared that aimed at comparing brain function in several conditions of no or reduced consciousness, such as coma and VS, anesthesia, sleep, and epileptic seizures (Baars et al., 2003; Boly et al., 2008b; Boveroux et al., 2008; Davis et al., 2007; Laureys, 2005). These studies have often pointed to a complex of brain regions, mostly involving a frontoparietal network bilaterally, as a potential locus for consciousness, as suggested by a relative deactivation in relation to loss of consciousness. However, there are exceptions to this general rule. For example, during the tonic phase of generalized tonico-clonic seizures, loss of consciousness is not related to a deactivation, but rather to a diffuse increase in metabolism in the same frontoparietal cortices. Moreover, a relative deactivation of a frontoparietal complex involved in attention and executive function might be the inevitable consequence of loss of consciousness, even though consciousness itself might be generated in a more restricted set of areas (Tononi and Laureys, 2008). Thus, at present there is still no consensus on what would constitute a reliable marker of consciousness in the absence of the subject's report. In our view, to move closer to this goal, it is important to complement clinical and experimental investigations with a theoretical approach aiming at understanding consciousness — what it is and how it can be generated — at a fundamental level: one could say that theories without experiments are lame, but experiments without theories are blind (Tononi, 2008a). For instance, only a theoretical framework can go beyond a provisional list of candidate mechanisms or brain areas and account, in a coherent manner, for key but puzzling facts about consciousness and the brain, coming from classical neurology as well as from neuroimaging experiments (Tononi, 2008a). These include the preeminence of the corticothalamic system in generating consciousness as opposed to the irrelevance of the cerebellar system, despite the latter's remarkable complexity; the loss of consciousness in NREM sleep despite the persistence of neuronal firing at levels similar to quiet wakefulness; the fact that

afferent and efferent pathways do not seem to contribute directly to experience; the existence of a large amount of ''unconscious'' neural activity in cortico-subcortical loops, despite the central role of these loops in parsing inputs and outputs from consciousness; the splitting of consciousness after sections of the corpus callosum; and the loss of consciousness during generalized seizures despite the presence of intense hypersynchronous neuronal activity. Moreover, only a theoretical stance can offer some guidance in evaluating the quantity and quality of consciousness in clinical conditions such as the MCS, or instances of the VS with brain ''islands'' of preserved functionality (Schiff et al., 2002a).

Several theoretical viewpoints about consciousness have been proposed over the last few years. Here, we will limit our description to theories that attempt to find an explanation for loss of consciousness during coma, sleep, anesthesia, or epilepsy, by accounting for some available neuroscientific data. A first category of theories emphasizes one given neural activity pattern, or one particular brain function, as being the likely mechanism sufficient to generate conscious perception. Examples of proposed mechanisms would be activation of higher order association cortices (Owen et al., 2005a), long-range synchronization of brain activity in fast frequencies (Engel and Singer, 2001; Tallon-Baudry, 2004), dynamic formation of neural coalitions (Crick and Koch, 2003), or high level of cortical depolarization with background high-frequency activity (Llinas et al., 1998).

A second category of theories is related to the concept of a ''global workspace,'' and can be viewed as a theater metaphor of mental functioning (Baars, 1988; Baars, 2005). According to Baars et al. (2003), once conscious sensory content is established, it is distributed widely to a decentralized ''audience'' of expert networks — executive interpreters, involving parietal and prefrontal cortices. Consequently, conscious perception should involve widespread brain sources, and unconscious sensory processing should be much more limited. In the same line, loss of consciousness in states like coma, VS, sleep, and anesthesia should be explained by decreased activity in ''observing self'' frontoparietal regions (Baars et al., 2003).

A different viewpoint on global workspace theory is provided by Dehaene, Naccache, and Changeux (Dehaene and Changeux, 2004; Dehaene and Changeux, 2005; Dehaene et al., 2006; Dehaene and Naccache, 2001). These authors explicitly limit themselves the application of global workspace theory to the case of ''access consciousness,'' and state that their ''global neuronal workspace'' is essentially a theory of conscious content (Dehaene and Changeux, 2004). They specify that this theory does not attempt to describe the mechanisms of the ''state of consciousness, usually considered as a continuous variable (coma, sleep, drowsiness, awake state …)'' (Dehaene and Changeux, 2004). In a later work, in line with Llinas et al. (1998), they suggest that the level of consciousness should be determined by the amount of spontaneous fast frequency oscillatory activity in the thalamocortical system (Dehaene and Changeux, 2005).

Despite their attempt to find coherent explanations of the mechanisms of generation of consciousness in the brain, the previously cited theories generally fail to account in a coherent manner for all the observations accumulated in neurological, neurophysiological, and neuroimaging experiments over the last few years. A particularly problematic case for these theories is, for example, to explain loss of consciousness during generalized tonico-clonic seizures. The tonic phase of this affection has indeed been shown to be characterized by increased metabolic activity and long-range synchronization in fast frequencies, in higher order associative areas like frontoparietal cortices (Blumenfeld, 2008; Blumenfeld et al., 2003). According to the previously described theories, such a pattern of highly active and synchronous brain activity in higher order frontoparietal cortices would have no reason to lead to unconsciousness (Tononi, 2008a). On the contrary, this pattern of brain activity should rather lead to a higher level of consciousness, because of an intense synchronized activity, or ''binding,'' in frontoparietal cortices. Theories linking consciousness to widespread brain activity would also fail to explain reports of widespread cerebral activity, and even

hypersensitivity, in response to sensory stimulation observed both during anesthesia and during sleep (Alkire, 2008; Kakigi et al., 2003; Kroeger and Amzica, 2007), or reports of widespread brain activation and gamma band synchronization in response to subliminal stimuli in awake volunteers (Diaz and McCarthy, 2007; Luo et al., 2009). Finally, theories linking consciousness to a high level of brain depolarization and fast rhythmic background brain activity would fail to explain consciousness impairment resulting from ketamine-induced anesthesia, occurring despite increased cerebral fast rhythmic activity and brain metabolism compared to normal wakefulness (Itoh et al., 2005; Langsjo et al., 2005; Maksimow et al., 2006). They would also not be in line with findings of loss of consciousness induced by inhalation agents, occurring despite increased gamma power in the EEG (Alkire, 2008; Imas et al., 2005).

Thus, it appears to be difficult to provide a coherent account for most of the key clinical observations on loss of consciousness in coma, sleep anesthesia, and generalized seizures without ad hoc assumptions (e.g., that synchrony is good but too much synchrony, as in seizures, is bad). We now turn in more detail to the Integrated Information Theory of Consciousness (IITC), as it offers a single perspective that, at least in principle, can provide a parsimonious account for many empirical observations starting, as it were, from first principles.

Introduction to information integration theory of consciousness

Let us define consciousness as ''what disappears when we fall into dreamless sleep'' (Tononi and Edelman, 1998; Tononi and Massimini, 2008). This commonsensical, intuitive definition is clearly related to the clinical one according to which unconsciousness is the ''absence of perception of self and environment'' (Laureys et al., 2004). In this sense, consciousness would be defined as any kind of experience, from the simplest perception (pure darkness and silence) to the most complex one (say a bustling market scene). The IITC claims that, at the fundamental level, consciousness *is* integrated information, and that its quality is given by the informational relationships generated by a complex of elements (Tononi, 2004; Tononi, 2008a). These claims stem from realizing that information and integration are the essential properties of our own experience. Note that we will only consider here the part of the theory concerning the quantity or level of consciousness. Further details on how the theory addresses qualitative aspects of conscious experience can be found in Tononi (2008a).

The IITC claims that consciousness is independent of specific cognitive functions. This claim seems to fit neurological evidence in favor of a dissociation between consciousness and specialized processes like episodic memory, language, introspection or reflection, sense of space, sense of body, sense of self, or sensorimotor processing, or attention (Tononi and Laureys, 2008). In short, consciousness can be dissociated from episodic memory in the case of amnesic patients, who lack memory encoding, but yet are still conscious of themselves and their environment. Consciousness can also be dissociated from language in aphasic patients, because even globally aphasic patients retain a preserved perception of their environment. In the same manner, introspection and reflection are not necessarily associated with each and every conscious experience: self-consciousness can sometimes be absent, for example, when watching an absorbing movie or when engaged in cognitively demanding sensorimotor categorization experiments (Goldberg et al., 2006). A dissociation between consciousness and sense of space can be found in Balint's syndrome. A similar dissociation can be found in patients with spatial neglect, in whom attention, rather than perception, seems to be impaired. Indeed, neglect patients manifest deficits preferentially in presence of competing stimuli, but usually remain able to perceive a stimulus if it is presented isolated (Phan et al., 2000). A dissociation between consciousness and the sense of body or self can be found in out-of-body experiences, where a subject has the experience of not being located in his own body (Blanke et al., 2002). A dissociation between consciousness and

sensorimotor processing can be found for instance during dreaming, where the subject has vivid experiences despite the absence of sensorimotor interactions with the external world (Tononi, 2008b). Finally, it seems that consciousness cannot be equated with attention: several studies have shown that attended stimuli can be processed by the brain in the absence of awareness, while stimuli can be perceived in the absence of attention, that is, in the case of environmental features processed in the peripheral visual field (Koch and Tsuchiya, 2007).

According to IITC, what is instead specific to consciousness are the following two constitutive properties: (i) consciousness is highly informative, because each conscious experience constitutes a discrimination among a large repertoire of alternative experiences; (ii) consciousness is highly integrated, because each conscious experience is unified and cannot be decomposed into elements that can be experienced independently. We will develop these concepts in the following paragraphs, and briefly discuss their mathematical implementation.

Information: the photodiode thought experiment

IITC states that consciousness is highly informative, in the sense that each conscious experience is implicitly discriminated by ruling out a very large number of alternatives. According to the theory, the more alternatives you can rule out, the more informative is your conscious experience, and the higher your level of consciousness. A useful thought experiment (Fig. 1, upper panel) is to imagine the performance of a photodiode compared to one of us, when facing a blank screen (Tononi, 2008a). The photodiode is a simple light-sensitive device, composed of a sensor that responds to light with an increase in current and a detector connected to the sensor that says ''light'' if the current is above a certain threshold and ''dark'' otherwise. In front of a screen switching alternately from black to white, the photodiode would perform as well as we in discriminating ''light'' from ''dark.'' Obviously, however, it is implausible that the photodiode would be conscious of the screen. The difference between us and the photodiode is that when we look at a blank screen, we have a choice among many alternatives, and not just a few like the photodiode. The discrimination you can perform is thus much more informative than the photodiode, who has a limited level of surprise. The key here is to realize that the number of discriminations that can be potentially available affects the meaning of the discrimination at hand, the one between light and dark. For example, the photodiode has no mechanism to discriminate colored from achromatic light, even less to tell which particular color the light might be. As a consequence, all light is the same to it, as long as it exceeds a certain threshold. In short, the only specification a photodiode can make is whether things are this or that way: any further specification is impossible because it does not have mechanisms for it. Therefore, when the photodiode detects ''light,'' such ''light'' cannot possibly mean what it means for us; it does not even mean that it is a visual attribute. By contrast, when we see ''light'' in full consciousness, we are implicitly being much more specific: we simultaneously specify that things are this way rather than that way (light as opposed to dark), that whatever we are discriminating is not colored (in any particular color), does not have a shape (any particular one), is visual as opposed to auditory or olfactory, sensory as opposed to thought-like, and so on. To us, then, light has much more meaning, precisely because we have mechanisms that can discriminate this particular state of affairs we call ''light'' against a large number of alternatives, and we can do so in a specific way (Tononi, 2008a). According to the IITC, it is all this added meaning, provided implicitly by *how* we discriminate pure light from all these alternatives, that increases the level of consciousness.

How can we express this information in mathematical terms? To address this issue, we have to look more closely at the photodiode. Indeed, even if it has only two alternatives, the photodiode is the smallest device able to perform a discrimination, and looking at its mechanism can help building the blocks for further discussion. Let us look in more detail at how the photodiode performs a given discrimination, for example,

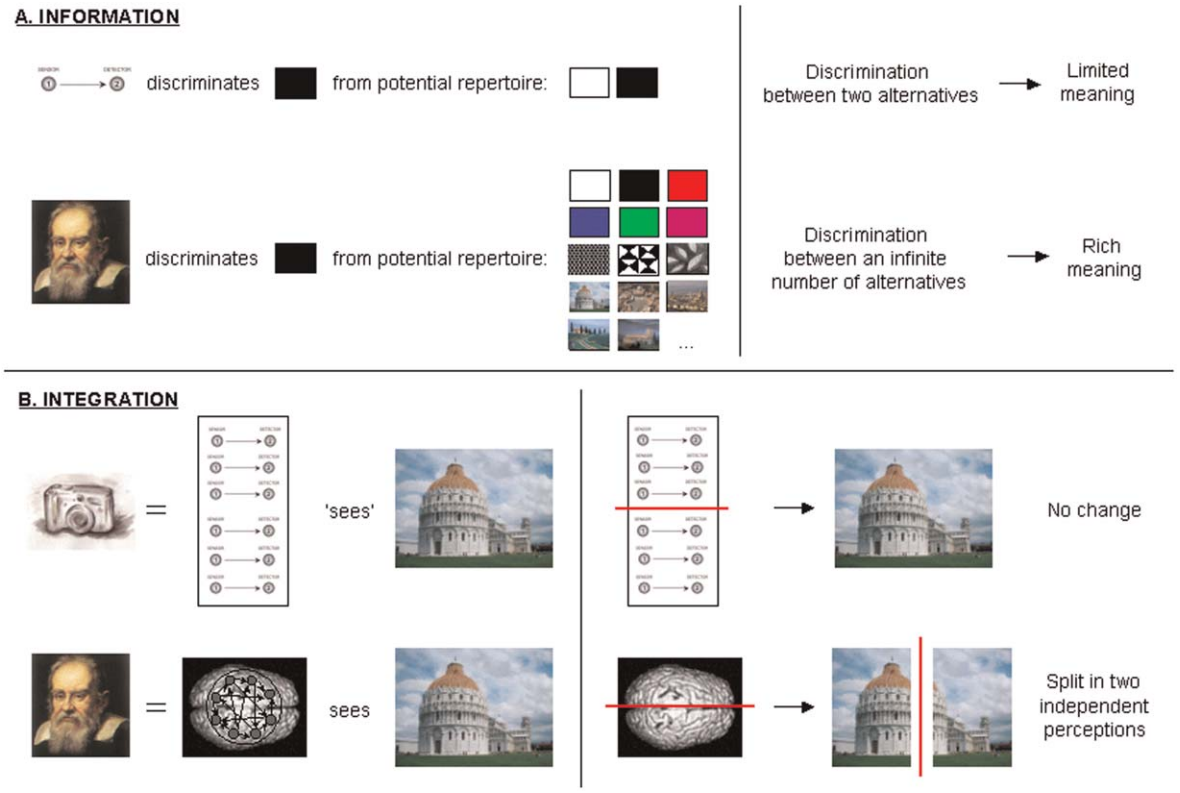


Fig. 1. Information and integration are fundamental properties of conscious experience. (A) Information: the photodiode thought experiment. IITC states that consciousness is highly informative, because each conscious experience is implicitly discriminated by ruling out an infinite number of other available alternatives. According to the theory, the more alternatives you can rule out, the more informative is your conscious experience, and the higher your level of consciousness. This concept is illustrated when comparing a photodiode, simple light-sensitive device to anyone of us (here Galileo Galilei, for the sake of the example), facing a blank screen. According to the theory, the key difference between us and the photodiode relies in the fact that when specifying "dark," the photodiode discriminates between only two alternatives, while we discriminate it from a large repertoire of other available percepts. This difference affects the meaning of the discrimination performed, and the amount of information generated. (B) Integration: the camera thought experiment. By multiplying the number of photodiodes, like in the case of a camera, one can considerably increase the amount of information generated. The difference between us and the camera is that the information generated by each photodiode is not communicated to the whole system, that is, the information the systems generates is not integrated. This is reflected by the fact that if one would separate the camera in two parts with an infinitely thin line, this would not impair its function, nor diminish the amount of information generated. If the same procedure is applied to the brain, this will result in a split in two independent consciousnesses, similarly to what is observed in split-brain patients. Integration of information allows to perform a single discrimination at the scale of the whole system, in order to generate a unified perception.

when it reports "dark" (Fig. 2). Because of the architecture of this device (the presence of a causal interaction between its elements that we call a mechanism), the fact that the photodiode sensor signals "dark" at a given time t implies that at the previous time step (time $t-1$), its sensor unit had to be silent. Thus, the photodiode, by virtue of its causal mechanism and current state, specifies an *actual* repertoire (of states it could have come from) that is smaller than the repertoire of states potentially available to it (*potential* repertoire). This reduction of uncertainty constitutes the "effective information" generated by the system. Effective information is measured in bits, and it can be calculated as the difference (relative entropy) between two

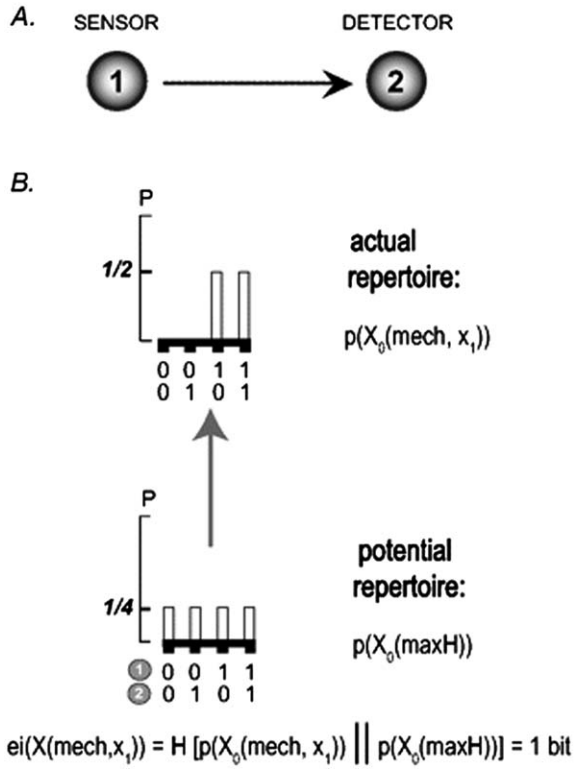


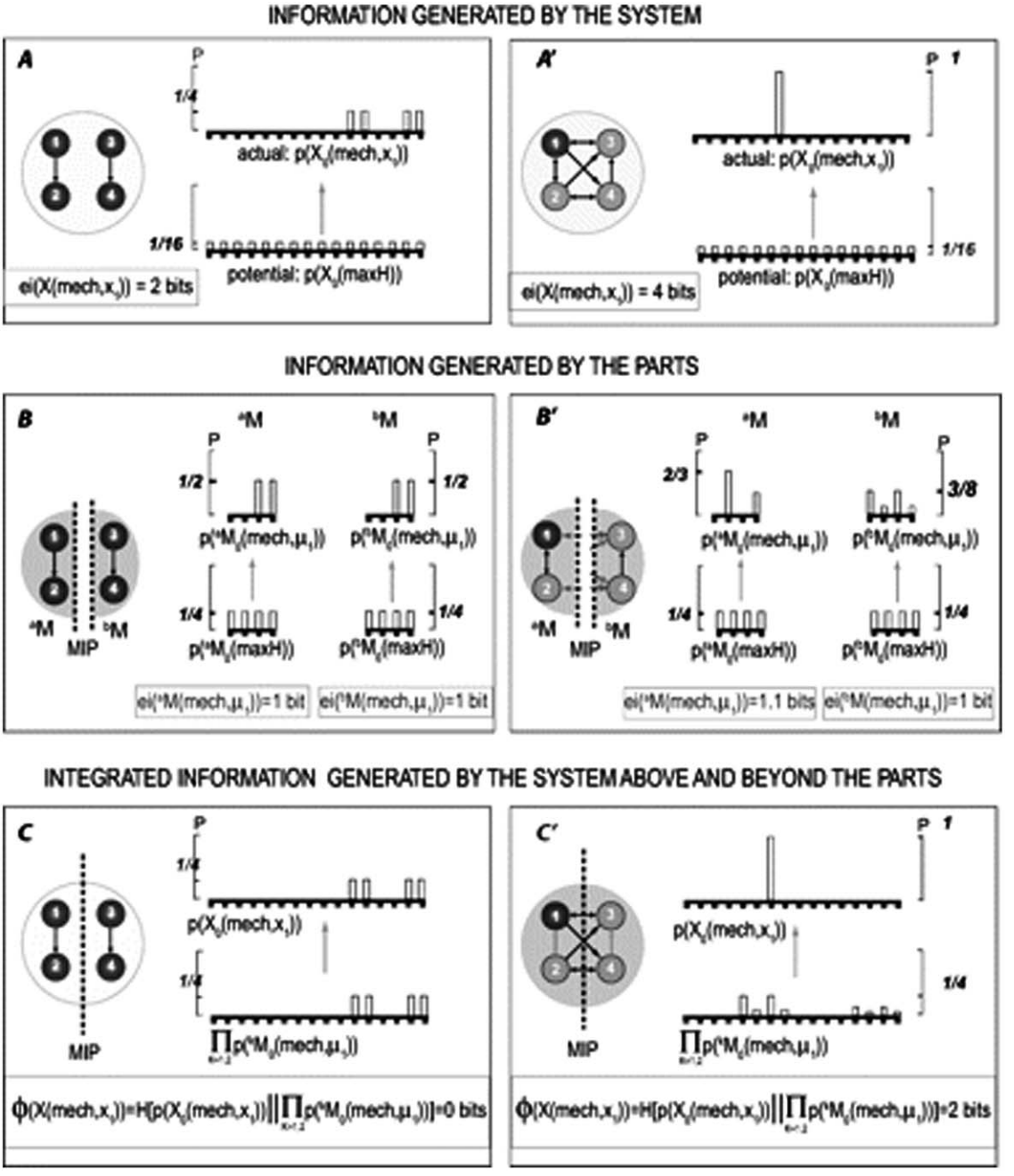
Fig. 2. Measuring effective information. (A) A ''photodiode'' consisting of a sensor and detector unit. The photodiode's mechanism is such that the detector unit turns on if the sensor's current is above a threshold. Here both units are on (binary 1, indicated in gray). (B) For the entire system (sensor unit, detector unit) there are four possible states: (00, 01, 10, 11). The potential distribution $p(X_0(\max H)) = (1/4, 1/4, 1/4, 1/4)$ is the maximum entropy distribution on the four states. Given the photodiode's mechanism and the fact that the detector is on, the sensor must have been on. Thus, the photodiode's mechanism, and its current state, specifies the following distribution: two of the four possible states (00, 01) are ruled out; the other two states (10, 11) are equally likely, since they are indistinguishable to the mechanism (the prior state of the detector makes no difference to the current state of the sensor). The actual distribution is therefore $p(X_0(\text{mech}, x_1)) = (0, 0, 1/2, 1/2)$. Relative entropy (Kullback–Leibler divergence) between two probability distributions p and q is $H[p|q] = \sum_i p_i \log 2\, p_i/q_i$, so the effective information $\text{ei}(X(\text{mech}, x_1))$ associated with output $x_1 = 1$ is 1 bit (effective information is the entropy of the actual relative to the potential distributions). Adapted with permission from Tononi (2008a).

probability distributions (the actual and potential repertoires). For instance, the photodiode reporting ''dark'' generates 1 bit of effective information (Fig. 2). Clearly, a system such as our brain (or some privileged part of it) that has a much larger potential repertoire of states (corresponding to all possible experiences) and a powerful set of causal mechanisms capable of discriminating among them so as to rule all of them out except for, say, a state of pure darkness and silence will generate much more than a mere photodiode.

Integration: the camera thought experiment

In a system constituted of several elements interacting through causal interactions, another problem has to be faced: the information has to be integrated in order to allow a single discrimination to be available simultaneously to the whole system. This integration of the information available across the system accounts for the unified character of conscious experience as perceived in our daily life. A second thought experiment that helps to clarify this issue involves a digital camera (Fig. 1, lower panel). A camera can be considered as an army of millions of photodiodes, each one generating 1 bit of effective information. The repertoire of states available to the camera is large, so the information it generates can be very high — several millions bits. However, it still seems implausible that a camera would be able to consciously perceive the visual scene. According to the IITC, the difference between us and the camera is that each photodiode generates 1 bit of information independently, and the information generated by the system as a whole (the camera) can be decomposed without loss into the information generated by each photodiode independently, that is, the information the camera generates is not integrated. When we perceive a visual scene, by contrast, we perceive it as a whole, and our experience cannot be subdivided into independent sub-experiences. A discrimination is performed by the system as a whole, between this particular visual scene and all the other possible alternatives.

How can this observation be translated in mathematical terms? Figure 3 shows two systems constituted of several elements interacting with each other through causal mechanisms. One can see that the system on the left is not integrated,


INFORMATION GENERATED BY THE SYSTEM
A
P
1/4
actual: p(X_0(mech,x_0))
1/16
potential: p(X_0(maxH))
ei(X(mech,x_0)) = 2 bits
A'
P 1
actual: p(X_0(mech,x_0))
1/16
potential: p(X_0(maxH))
ei(X(mech,x_0)) = 4 bits
INFORMATION GENERATED BY THE PARTS
B
^aM
^bM
P
1/2
p(^aM_0(mech,μ_a))
p(^bM_0(mech,μ_b))
1/4
p(^aM_0(maxH))
p(^bM_0(maxH))
MIP
ei(^aM(mech,μ_a))=1 bit
ei(^bM(mech,μ_b))=1 bit
B'
^aM
^bM
P
2/3
3/8
1/4
MIP
ei(^aM(mech,μ_a))=1.1 bits
ei(^bM(mech,μ_b))=1 bit
INTEGRATED INFORMATION GENERATED BY THE SYSTEM ABOVE AND BEYOND THE PARTS
C
P
1/4
p(X_0(mech,x_0))
1/4
∏ p(^kM_0(mech,μ_k))
MIP
ϕ(X(mech,x_0))=H[p(X_0(mech,x_0))||∏ p(^kM_0(mech,μ_k))]=0 bits
C'
P 1
p(X_0(mech,x_0))
1/4
∏ p(^kM_0(mech,μ_k))
MIP
ϕ(X(mech,x_0))=H[p(X_0(mech,x_0))||∏ p(^kM_0(mech,μ_k))]=2 bits

because it can be decomposed in two different subsystems that do not interact with each other. This simple example already shows that conceptually, the way to check if a system is integrated is by searching for its weakest link in terms of interactions. Specifically, one can partition the system in all possible ways and find the ''cut'' that least diminishes the information generated by the system as a whole (the informational ''weakest link''). This way to partition the system is called the minimum information partition (MIP). For the system on the left, the MIP is obviously obtained when separating the elements in a vertical manner: no information is lost after this cut (the system generates as much information as before the cut). For the system on the right, on the other hand, one has to compute all the possible partitions and calculate the difference between the information generated by the system as a whole (the actual repertoire of the system) and the information generated independently by the parts (the product of the actual repertoires of the parts). The partition for which this difference is minimal is the MIP, and the amount of information generated by the system above the MIP is ''integrated information'' or φ. According to the IITC, consciousness is integrated information, and φ can be seen as a measure of the level of consciousness of a given system, generated when entering in a particular state. Note that φ is an intrinsic property of a given system entering in a particular state, due to the presence of causal interactions between its elements.

Finally, once φ has been calculated for different subsets of elements, one can identify *complexes*. Specifically, a complex is a set of elements that generate integrated information that is not fully contained in some larger set of higher φ. A complex, then, can be properly considered to form a single entity having its own intrinsic ''point of view'' (as opposed to being treated as a single entity from an outside, extrinsic point of view). Since integrated information is generated *within* a complex and not outside its boundaries, experience is necessarily private and related to a single point of view or perspective (Tononi, 2004; Tononi and Edelman, 1998). A given physical system, such as a brain, is likely to contain more than one complex, many small ones with low values, and perhaps a few large ones. In fact, at any given time there may be a single *main complex* of comparatively much higher φ that underlies the dominant experience (a main complex is such that its subsets have strictly lower φ). Indeed, a main complex can be embedded into larger complexes of lower φ. Thus, a complex can be casually connected, through *ports-in* and *ports-out*, to elements that are not part of it. Indeed, according to the IITC, such elements can indirectly influence the state of the main complex without contributing directly to the conscious experience that it generates (Tononi and Sporns, 2003).

At this stage, it is hard to say precisely which cortical circuits may behave as a large complex of high φ, and which instead may remain

Fig. 3. Integrated information. *Left-hand side:* two photodiodes in a digital camera. (A) Information generated by the system as a whole. The system as a whole generates 2 bits of effective information by specifying that n_1 and n_3 must have been on. (B) Information generated by the parts. The minimum information partition (MIP) is the decomposition of a system into (minimal) parts, that is, the decomposition that leaves the least information unaccounted for. Here the parts are two photodiodes. (C) The information generated by the system as a whole is completely accounted for by the information generated by its parts. In this case, the actual repertoire of the whole is identical to the combined actual repertoires of the parts (the product of their respective probability distributions), so that relative entropy is zero. The system generates no information above and beyond the parts, so it cannot be considered a single entity. *Right-hand side:* an integrated system. Elements in the system are on if they receive two or more spikes. The system is in state $x_1 = 4000$. (A′) The mechanism specifies a unique prior state that can cause state x_1, so the system generates 4 bits of effective information. All other initial states are ruled out, since they cause different outputs. (B′) Effective information generated by the two minimal parts considered as systems in their own right. External inputs are treated as extrinsic noise. (C′) Integrated information is information generated by the whole (black arrows) over and above the parts (gray arrows). In this case, the actual repertoire of the whole is different from the combined actual repertoires of the parts, and the relative entropy is 2 bits. The system generates information above and beyond the parts, so it can be considered a single entity (a complex). Adapted with permission from Tononi (2008a).

informationally insulated. One limitation for the direct testing of the theory is the need to find a principled way to determine the proper spatial and temporal scales to measure informational relationships and integrated information. An informed guess (Tononi, 2008a) would, however, likely position the relevant spatial scale at the grain size of neurons or minicolumns, and the relevant time scale at periods of tens to hundreds of milliseconds. For both theoretical and practical reasons, the measure of φ remains unrealistic in real biological systems.

Conditions where IITC predicts markedly reduced levels of consciousness

Even if measuring the φ value for biological systems is to date impossible, computer simulations on simple systems allow already making predictions about systems architecture and activity patterns that may be associated with high or low values of information integration. We will review these conditions in the following sections.

Neuroanatomy

Computer simulations suggest that the optimal configuration of a system to generate high φ should combine functional segregation and integration in a balanced manner. According to the theory, systems characterized by excessively abundant anatomical connectivity, resulting in a loss of individual specificity of the system's individual elements, are expected to have low values of φ. On the other hand, φ is expected to be low for systems with a modular organization — such as that of the cerebellum — and to be higher for systems combining specialization and integration — such as the corticothalamic system.

Anatomical or functional disconnections among the system's elements should also lead to a decrease of φ in the system. A complete disconnection of some elements from the system, while the elements by themselves could still be activated, would have virtually the same effect than the destruction or permanent inactivation of these elements. In line with this prediction, computer simulations confirm that functional disconnection can reduce the size of a complex and reduce its capacity to integrate information (Tononi, 2004).

Finally, according to the theory, for a given number of interacting elements, systems built of strictly feed-forward architecture generate φ values lower than systems combining feed-forward and feedback connections. Thus, it is conceivable that the abundant reentrant connections that are thought to exist in the human brain would be ideally suited to generate high levels of information integration.

Neurophysiology

In addition to neuroanatomical constraints, IITC also predicts that the amount of integrated information generated by a system depends on its firing pattern, and should be higher for balanced firing states. Simulations indicate that a system with only a low number of elements firing generates low values of φ, even if the system has complex architecture. Low levels of activity are likely to be found in some deep coma, but have mostly been observed during deep anesthesia. On the other hand, if the whole system is in a state where every element fires, the available repertoire of discriminable states of the system is also expected to be greatly reduced. This particular mechanism could explain the loss of consciousness observed in generalized seizures (Fig. 4).

A combination of these two mechanisms (excessively low and excessively high firing) occurs in the presence of bistable dynamics, a condition which, according to IITC, also impairs the capacity of a system to integrate information. The term bistability means that in response to local activation, the system can only respond in a whole-or-none manner, with no gradations in the firing patterns between these two states. Bistable dynamics are actually found in the corticothalamic system during slow wave sleep, and are expressed in the EEG by the presence of high amplitude slow waves. In line with the predictions of the theory, loss of consciousness during sleep has been related to slow wave activity power in the EEG (Tononi, 2008b).

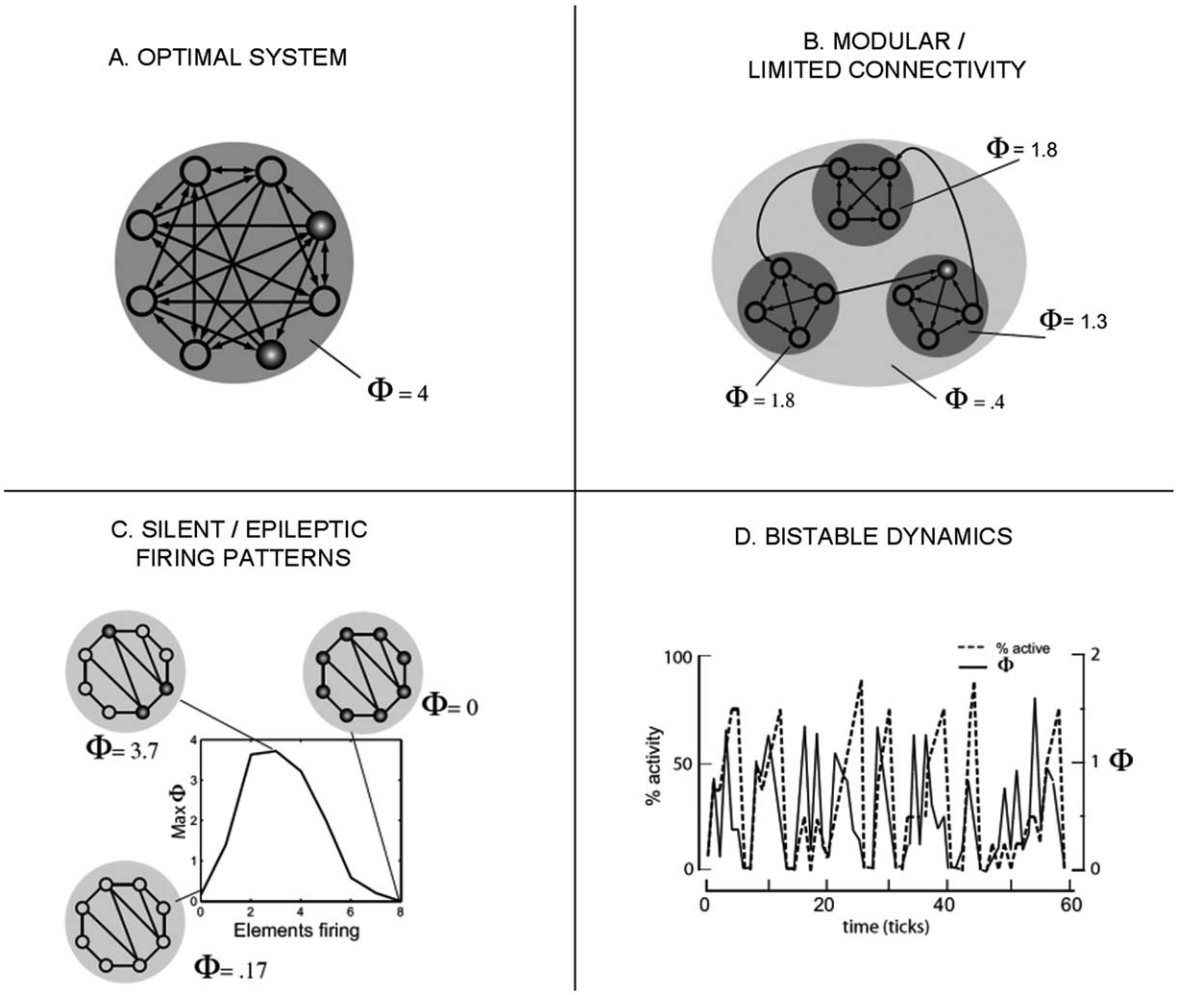


Fig. 4. Conditions where IIT predicts low levels of consciousness. (A) An optimal system to generate integrated information is a system combining integration and differentiation, firing in a balanced manner. (B) Breakdown of anatomical connectivity between parts of an integrated system results in a splitting of the system in smaller independent modules, generating less integrated information. (C) Excessively low or high levels of firing in a system typically result in a dramatic decrease of φ vales generated by a system, even if the system's architecture is properly designed to generate high φ values in balanced firing states. (D) Bistable dynamics typically lead to lower φ values in integrated systems. Partly adapted with permission from Tononi (2008a).

Location of the main complex — an informed guess

According to the theory, to assess the level of consciousness generated by a system, that is, the amount of integrated information it generates, one has first to identify the so-called main complex. In principle, the identification of the main complex requires a computational approach, where φ is measured for all possible partitions of the system. However, as previously mentioned, this computation is to date still out of our reach in real brains. As a starting hypothesis, one could propose to investigate the functional consequences of altered brain activity patterns involving most of the corticothalamic system. Indeed, it is undisputed and certainly not new that broad lesions or inactivations of the corticothalamic system abolish consciousness, whereas lesions of other parts of the brain do not (Tononi and

Laureys, 2008). Beyond this, it is still difficult to identify with confidence specific regions of the corticothalamic system that are necessary and sufficient to sustain conscious experience. Yet, one could predict that higher order associative areas such as frontal, or more likely, parietal cortices may play a privileged role. These areas have indeed been recently shown to be among the most densely connected areas of the human brain, both in structural (Hagmann et al., 2008) and in functional (Buckner et al., 2009) measurements. On the contrary, computer simulations suggest that subcortical loops and afferent pathways would be less likely to play a crucial role (Tononi, 2005). When investigating altered states of consciousness, one could thus try to classify patients by looking for global alterations of connectivity or firing patterns in a large part of the corticothalamic system, encompassing bilateral frontoparietal cortices. It may, however, turn true that the parts of the brain crucially involved in the generation of conscious experience (constituting the main complex) are limited to a smaller part of the corticothalamic complex. Future experiments may provide useful information on which parts of the brain are critically necessary for the generation of conscious perception.

Available in vivo brain imaging techniques and potential applications

Positron emission tomography

According to IITC, minimal levels of neuronal firing throughout the brain should lead to reduced levels of consciousness. Diffusely decreased neuronal firing throughout the brain is expected to globally decrease brain metabolism as measured in PET studies. Practically, according to the theory, consciousness is thus likely to vanish in the presence of diffuse hypometabolism in large parts of the corticothalamic system.

On the other hand, according to IITC, a state of hyperactivity of the system is also expected to lead to reduced consciousness. Diffuse cerebral hypermetabolism can be observed, for example, in absence or generalized tonico-clonic seizures (Blumenfeld, 2008; Engel et al., 1982). In our experience (unpublished data), cerebral hypermetabolism can also be observed in some non-epileptic MCS patients, resuming to a normal level during recovery of consciousness.

By a theoretical point of view, however, brain metabolism cannot be considered as a reliable marker of consciousness at the individual level, since it is not a direct reflect of neural firing, but can also be influenced by other factors, such as for instance membrane potential depolarization. Thus, even if the information provided by PET is undoubtedly useful, it may be advantageously complemented by other imaging techniques, such as functional MRI or EEG.

Functional MRI

Resting state functional MRI connectivity measurements in large-scale brain networks may help identifying patients in which connectivity patterns are severely altered. According to IITC, major impairment of connectivity is expected to reduce the brain's ability to integrate information, and thus the level of consciousness. In line with this hypothesis, studies of our group and others show that connectivity in default network is decreased in some VS patients compared to controls (Boly et al., 2009; Cauda et al., 2009; see Soddu et al., 2009). Normative data should be acquired to evaluate to which extent brain connectivity patterns have to be altered in order to lead to clinical unconsciousness.

On the contrary, according to IITC, the presence of a near-to-normal level of connectivity in large-scale brain networks is necessary but not sufficient to ensure normal consciousness. Indeed, the presence of firing patterns such as bistable dynamics or excessive hypersynchronous firing are important conditions where IITC also predicts a low level of consciousness, despite preserved connectivity in the system. In line with this prediction, a recent study showed preserved connectivity in frontoparietal cortices during non-REM sleep (a condition characterized by the presence of bistable dynamics) as compared to wakefulness (Larson-Prior et al., 2009).

EEG

According to IITC, in order to generate high φ in a given system, not only the amount of integration

(connectivity) matters but also the information present in the system. Computer simulations suggest that even if a system has the proper connectivity architecture to generate high φ in balanced firing states, the presence of activity patterns such as low firing, hyperactivity, or bistable dynamics is expected to markedly impair the capacity of the system to integrate information. To date, a systematic assessment of the prevalence of firing patterns such as very low firing, seizures, or bistable dynamics in scalp EEG of patients in MCS and VS has not been performed. Future experiments should, for example, investigate the correlation between the presence of widespread bistable dynamics throughout the brain and behavioral responsiveness in brain-damaged patients. These widespread bistable dynamics should likely be reflected by high amplitude slow waves in spontaneous EEG. High-density EEG recordings and source reconstruction should evaluate if the presence of these slow waves correspond to a diffuse increase in delta frequency involving most of the brain (Murphy et al., 2009). In the same line, silent or seizure-like patterns should be present in a widespread bilateral cortical network in order to significantly impair the brain's ability to generate information. These firing patterns are likely to be preferentially found in VS patients, and much less in MCS patients. In this context, EEG studies using high-density recordings and source reconstruction may also help better differentiating MCS from VS patients, by precising the brain topography of dysfunctional firing patterns (such as bistable dynamics, low firing, or epileptic activity). Indeed, in a first guess, firing patterns involving large parts of the corticothalamic system should preferentially be expected to markedly impair the level of consciousness. As previously mentioned, it is also possible that the part of the corticothalamic system critically necessary for the presence of consciousness could be much more limited in space. By the same token, high-density EEG and source modeling may thus help localizing the precise scale and constituents of the actual main complex in the human brain.

Perturbational approaches

According to the theory, the actual succession of states one can observe by passively looking at a system is not necessarily representative of the potential repertoire of this system. Indeed, in order to properly assess the potential repertoire of a system, one would have to observe it for an infinite time. This is obviously not feasible in real conditions. Thus, the repertoire of a system should be more efficiently approximated using a perturbational approach, that is, by recording the reaction of the system to the activation of its different subparts. Perturbational approaches also offer the advantage to uniquely record effective connectivity — changes in the system due to neuronal causal interactions.

A perturbational approach based on a combination of TMS and EEG has recently been employed to understand what changes in thalamocortical circuits when consciousness fades during slow wave sleep ((Massimini et al., 2007; Massimini et al., 2005), see also this volume). In principle, assessing the response to external stimuli in the auditory, visual or somatosensory modalities may also provide insights on the brain's capacity for integration and information. In fact, this approach goes clearly beyond the simple assessment of the spatial extent of the responses to stimulation (Boly et al., 2004; Boly et al., 2008a). In this case, according to IITC, both the extent of activation and the specificity of brain responses to different stimulations are relevant criteria to assess the capacity of the patient's brain to integrate information. We previously mentioned that the relevant temporal scale to assess information integration is likely in the order of hundreds of milliseconds, below the temporal resolution of functional MRI. On the other hand, due to this limited temporal resolution, functional MRI is also unable to reliably differentiate connectivity due to forward versus backward connections. In this perspective, assessing the brain response to external stimuli using high-density EEG recordings combined with an explicit study of neural dynamics may represent a useful complement of investigation.

A general framework

A systematic investigation of an individual patients' brain function requires not only one imaging modality in isolation, but rather a combination of techniques. Figure 5 proposes a systematic summary of the potential use of each

technique in this context. Future research should identify the most efficient combination of techniques to comprehensively evaluate brain ability to generate integrated information.

Conclusion

In our view, there is a need to combine theoretical and experimental approaches in the study of brain function in noncommunicative brain-damaged patients, in order to guide clinicians in the choice of meaningful diagnostic criteria for the level of consciousness. In particular, we emphasized the IITC approach and the predictions of this theory concerning for neural correlates of unconsciousness. We argued that though an exhaustive measure of integrated information (φ) is not yet possible in real brains, reasonable approximations can already be considered using currently available imaging techniques. The use of these approximated measures of a brain's ability to integrate information may help clinicians precising the individual patients diagnosis and identifying which patterns of brain activity are more likely to lead to unconsciousness in different conditions. This preliminary attempt to systematically implement IITC criteria for unconsciousness in real situations may also stimulate further efforts to bring theoretical neuroscience closer to the patient's bedside.

Acknowledgments

This work was supported by the Belgian Fund for Scientific Research (FNRS) and European Grant STREP LSHM-CT-2205-51818. MB is research fellow at FNRS. We thank Steven Laureys, Brigitte Dahmen, Andrea Soddu, and Eric Landsness for their help and comments.

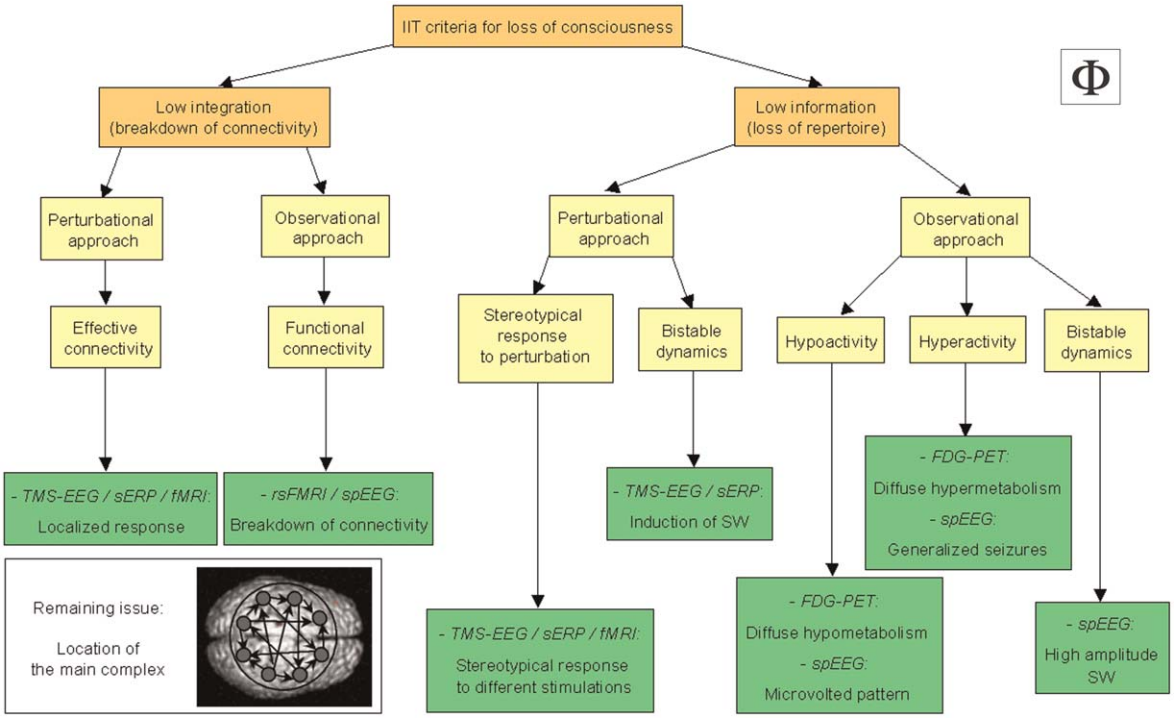


Fig. 5. A provisional practical framework to investigate brain function in noncommunicative brain-damaged patients. FDG-PET: fluoro-deoxyglucose positron emission tomography; spEEG: spontaneous electroencephalography; TMS-EEG: transcranial magnetic stimulation coupled to electroencephalography; sERP: sensory evoked related potentials; rsFMRI: resting state functional MRI; SW: slow waves. A remaining issue concerns the location of the main complex in the human brain. Future experiments may help precising which parts of the corticothalamic system are crucially necessary for the generation of conscious perception.

References

Alkire, M. T. (2008). General anesthesia and consciousness. In S. Laureys & G. Tononi (Eds.), *Neurology of consciousness: Cognitive neuroscience and neuropathology* (Vol. 1, p. 424). London: Academic Press — Elsevier.

Baars, B. J. (1988). *A cognitive theory of consciousness*. Cambridge: Cambridge University Press.

Baars, B. J. (2005). Global workspace theory of consciousness: Toward a cognitive neuroscience of human experience. *Progress in Brain Research*, 15045–15053.

Baars, B. J., Ramsoy, T. Z., & Laureys, S. (2003). Brain, conscious experience and the observing self. *Trends in Neuroscience*, *26*(12), 671–675.

Blanke, O., Ortigue, S., Landis, T., & Seeck, M. (2002). Stimulating illusory own-body perceptions. *Nature*, *419*(6904), 269–270.

Blumenfeld, H. (2008). Epilepsy and consciousness. In S. Laureys & G. Tononi (Eds.), *The neurology of consciousness* (pp. 247–260). Oxford: Elsevier Academic Press.

Blumenfeld, H., Westerveld, M., Ostroff, R. B., Vanderhill, S. D., Freeman, J., Necochea, A., et al. (2003). Selective frontal, parietal, and temporal networks in generalized seizures. *Neuroimage*, *19*(4), 1556–1566.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, P., Del Fiore, G., et al. (2004). Auditory processing in severely brain injured patients: Differences between the minimally conscious state and the persistent vegetative state. *Archives of Neurology*, *61*(2), 233–238.

Boly, M., Faymonville, M. E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., et al. (2008a). Perception of pain in the minimally conscious state with PET activation: An observational study. *Lancet Neurology*, *7*(11), 1013–1020.

Boly, M., Phillips, C., Tshibanda, L., Vanhaudenhuyse, A., Schabus, M., Dang-Vu, T. T., et al. (2008b). Intrinsic brain activity in altered states of consciousness: How conscious is the default mode of brain function? *Annals of the New York Academy of Sciences*, *1129*, 119–129.

Boly, M., Tshibanda, L., Noirhomme, Q., Vanhaudenhuyse, A., Schnakers, C., Ledoux, D., et al. (2009). Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping*, *30*(8), 2393–2400.

Boveroux, P., Bonhomme, V., Boly, M., Vanhaudenhuyse, A., Maquet, P., & Laureys, S. (2008). Brain function in physiologically, pharmacologically, and pathologically altered states of consciousness. *International Anesthesiology Clinics*, *46*(3), 131–146.

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., et al. (2009). Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*, *29*(6), 1860–1873.

Cauda, F., Micon, B. M., Sacco, K., Duca, S., D'Agata, F., Geminiani, G., et al. (2009). Disrupted intrinsic functional connectivity in the vegetative state. *Journal of Neurology, Neurosurgery & Psychiatry*, *80*(4), 429–431.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, *130*(Pt 10), 2494–2507.

Crick, F., & Koch, C. (2003). A framework for consciousness. *Nature Neuroscience*, *6*(2), 119–126.

Davis, M. H., Coleman, M. R., Absalom, A. R., Rodd, J. M., Johnsrude, I. S., Matta, B. F., et al. (2007). Dissociating speech perception and comprehension at reduced levels of awareness. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(41), 16032–16037.

Dehaene, S., & Changeux, J. P. (2004). Neural Mechanisms for Access to Consciousness. In M. Gazanniga (Ed.), *The cognitive neurosciences* (3rd ed., pp. 1145–1157). New York: Norton.

Dehaene, S., & Changeux, J. P. (2005). Ongoing spontaneous activity controls access to consciousness: A neuronal model for inattentional blindness. *PLoS Biology*, *3*(5), e141.

Dehaene, S., Changeux, J. P., Naccache, L., Sackur, J., & Sergent, C. (2006). Conscious, preconscious, and subliminal processing: A testable taxonomy. *Trends in Cognitive Sciences*, *10*(5), 204–211.

Dehaene, S., & Naccache, L. (2001). Towards a cognitive neuroscience of consciousness: Basic evidence and a workspace framework. *Cognition*, *79*(1–2), 1–37.

Di, H. B., Yu, S. M., Weng, X. C., Laureys, S., Yu, D., Li, J. Q., Qin, P. M., et al. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology*, *68*(12), 895–899.

Diaz, M. T., & McCarthy, G. (2007). Unconscious word processing engages a distributed network of brain regions. *Journal of Cognitive Neuroscience*, *19*(11), 1768–1775.

Engel, A. K., & Singer, W. (2001). Temporal binding and the neural correlates of sensory awareness. *Trends in Cognitive Sciences*, *5*(1), 16–25.

Engel, J., Jr., Kuhl, D. E., & Phelps, M. E. (1982). Patterns of human local cerebral glucose metabolism during epileptic seizures. *Science*, *218*(4567), 64–66.

Giacino, J. T., Ashwal, S., Childs, N., Cranford, R., Jennett, B., Katz, D. I., et al. (2002). The minimally conscious state: Definition and diagnostic criteria. *Neurology*, *58*(3), 349–353.

Goldberg, I. I., Harel, M., & Malach, R. (2006). When the brain loses its self: Prefrontal inactivation during sensorimotor processing. *Neuron*, *50*(2), 329–339.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., et al. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biology*, *6*(7), e159.

Imas, O. A., Ropella, K. M., Ward, B. D., Wood, J. D., & Hudetz, A. G. (2005). Volatile anesthetics enhance flash-induced gamma oscillations in rat visual cortex. *Anesthesiology*, *102*(5), 937–947.

Itoh, T., Wakahara, S., Nakano, T., Suzuki, K., Kobayashi, K., & Inoue, O. (2005). Effects of anesthesia upon 18F-FDG uptake in rhesus monkey brains. *Annals of Nuclear Medicine*, *19*(5), 373–377.

Kakigi, R., Naka, D., Okusa, T., Wang, X., Inui, K., Qiu, Y., et al. (2003). Sensory perception during sleep in

humans: A magnetoencephalograhic study. *Sleep Medicine*, *4*(6), 493–507.

Koch, C., & Tsuchiya, N. (2007). Attention and consciousness: Two distinct brain processes. *Trends in Cognitive Sciences*, *11*(1), 16–22.

Kroeger, D., & Amzica, F. (2007). Hypersensitivity of the anesthesia-induced comatose brain. *Journal of Neuroscience*, *27*(39), 10597–10607.

Langsjo, J. W., Maksimow, A., Salmi, E., Kaisti, K., Aalto, S., Oikonen, V., et al. (2005). S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. *Anesthesiology*, *103*(2), 258–268.

Larson-Prior, L. J., Zempel, J. M., Nolan, T. S., Prior, F. W., Snyder, A. Z., & Raichle, M. E. (2009). Cortical network functional connectivity in the descent to sleep. *Proceedings of the National Academy Sciences of the United States of America*, *106*(11), 4489–4494.

Laureys, S. (2005). The neural correlate of (un)awareness: Lessons from the vegetative state. *Trends in Cognitive Sciences*, *9*(12), 556–559.

Laureys, S., & Boly, M. (2007). What is it like to be vegetative or minimally conscious? *Current Opinion in Neurology*, *20*(6), 609–613.

Laureys, S., & Boly, M. (2008). The changing spectrum of coma. *Nature Clinical Practice Neurology*, *4*(10), 544–546.

Laureys, S., Goldman, S., Phillips, C., Van Bogaert, P., Aerts, J., Luxen, A., et al. (1999). Impaired effective cortical connectivity in vegetative state: Preliminary investigation using PET. *Neuroimage*, *9*(4), 377–382.

Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, *3*(9), 537–546.

Llinas, R., Ribary, U., Contreras, D., & Pedroarena, C. (1998). The neuronal basis for consciousness. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *353*(1377), 1841–1849.

Luo, Q., Mitchell, D., Cheng, X., Mondillo, K., McCaffrey, D., Holroyd, T., et al. (2009). Visual awareness, emotion, and gamma band synchronization. *Cerebral Cortex*, *19*(8), 1896–1904.

Maksimow, A., Sarkela, M., Langsjo, J. W., Salmi, E., Kaisti, K. K., Yli-Hankala, A., et al. (2006). Increase in high frequency EEG activity explains the poor performance of EEG spectral entropy monitor during S-ketamine anesthesia. *Clinical Neurophysiology*, *117*(8), 1660–1668.

Massimini, M., Ferrarelli, F., Esser, S. K., Riedner, B. A., Huber, R., Murphy, M., et al. (2007). Triggering sleep slow waves by transcranial magnetic stimulation. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(20), 8496–8501.

Massimini, M., Ferrarelli, F., Huber, R., Esser, S. K., Singh, H., & Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. *Science*, *309*(5744), 2228–2232.

Murphy, M., Riedner, B. A., Huber, R., Massimini, M., Ferrarelli, F., & Tononi, G. (2009). Source modeling sleep slow waves. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(5), 1608–1613.

Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*(5792), 1402.

Owen, A. M., Coleman, M. R., Menon, D. K., Berry, E. L., Johnsrude, I. S., Rodd, J. M., et al. (2005a). Using a hierarchical approach to investigate residual auditory cognition in persistent vegetative state. *Progress in Brain Research*, *150*, 457–471.

Owen, A. M., Coleman, M. R., Menon, D. K., Johnsrude, I. S., Rodd, J. M., Davis, M. H., et al. (2005b). Residual auditory function in persistent vegetative state: A combined PET and fMRI study. *Neuropsychological Rehabilitation*, *15*(3–4), 290–306.

Phan, M. L., Schendel, K. L., Recanzone, G. H., & Robertson, L. C. (2000). Auditory and visual spatial localization deficits following bilateral parietal lobe lesions in a patient with Balint's syndrome. *Journal of Cognitive Neurosciences*, *12*(4), 583–600.

Schiff, N. D., Ribary, U., Moreno, D. R., Beattie, B., Kronberg, E., Blasberg, R., et al. (2002a). Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain*, *125*(Pt 6), 1210–1234.

Schiff, N. D., Ribary, U., Moreno, D. R., Beattie, B., Kronberg, E., Blasberg, R., et al. (2002b). Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. *Brain*, *125*(Pt 6), 1210–1234.

Soddu, A., Boly, M., Papa, M., Laureys, S., & Malach, R. (2009). Reaching across the abyss: Recent advances in functional magnetic resonance imaging (fMRI) and their potential relevance to deficits of consciousness. In: S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications* (this volume). Progress in Brain Research. Oxford: Elsevier Press.

Tallon-Baudry, C. (2004). Attention and awareness in synchrony. *Trends in Cognitive Sciences*, *8*(12), 523–525.

Tononi, G. (2004). An information integration theory of consciousness. *BMC Neuroscience*, *5*(1), 42.

Tononi, G. (2005). Consciousness, information integration, and the brain. *Progress in Brain Research*, *150*, 109–126.

Tononi, G. (2008a). Consciousness as integrated information: A provisional manifesto. *The Biological Bulletin*, *215*(3), 216–242.

Tononi, G. (2008b). Sleep and dreaming. In S. Laureys & G. Tononi (Eds.), *The neurology of consciousness* (p. 424). London: Academic Press — Elsevier.

Tononi, G., & Edelman, G. M. (1998). Consciousness and complexity. *Science*, *282*(5395), 1846–1851.

Tononi, G., & Laureys, S. (2008). The neurology of consciousness: An overview. In S. Laureys & G. Tononi (Eds.), *The neurology of consciousness* (pp. 375–412). Oxford: Elsevier.

Tononi, G., & Massimini, M. (2008). Why does consciousness fade in early sleep? *Annals of the New York Academy of Sciences*, *1129*, 330–334.

Tononi, G., & Sporns, O. (2003). Measuring information integration. *BMC Neuroscience*, *431*.

S. Laureys et al. (Eds.)
Progress in Brain Research, Vol. 177
ISSN 0079-6123

CHAPTER 28

A new era of coma and consciousness science

Adrian M. Owen[1,*], Nicholas D. Schiff[2] and Steven Laureys[3]

[1]*MRC Cognition and Brain Sciences Unit; Impaired Consciousness Research Group, Wolfson Brain Imaging Center, University of Cambridge, UK*
[2]*Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY, USA*
[3]*Coma Science Group, Cyclotron Research Center and Department of Neurology, University of Liège, Liège, Belgium*

Abstract: In the past ten years, rapid technological developments in the field of neuroimaging have produced a cornucopia of new techniques for examining both the structure and function of the human brain in vivo. In specialized centers, many of these methods are now being employed routinely in the assessment of patients diagnosed with disorders of consciousness, mapping patterns of residual function and dysfunction and helping to reduce diagnostic errors between related conditions such as the vegetative and minimally conscious states. Moreover, such efforts are beginning to provide important new prognostic indicators, helping to disentangle differences in outcome on the basis of a greater understanding of the underlying mechanisms responsible and providing information that will undoubtedly contribute to improved therapeutic choices in these challenging populations. Of course, these emerging technologies and the new information that they provide will bring new ethical challenges to this area and will have profound implications for clinical care and medical–legal decision-making in this population of patients. We review the most recent work in this area and suggest that the future integration of emerging neuroimaging techniques with existing clinical and behavioral methods of assessment will pave the way for new and innovative applications, both in basic neuroscience and in clinical practice.

Keywords: coma; vegetative state; minimally conscious state; locked-in syndrome; functional MRI; consciousness; ethics

Introduction

It has been a tremendously exciting decade for research into disorders of consciousness. Rapid technological advances have produced a variety of novel neuroimaging approaches that allow a comprehensive assessment of brain function (e.g. cognitive performance) to be combined with detailed information about brain *structure* (e.g. anatomy) and *connectivity*. Thus, in less than ten years, low-resolution metabolic group studies and block design 'activation studies' using $H_2{}^{15}O$ positron emission tomography (PET) have largely given way to event-related functional magnetic resonance imaging (fMRI) investigations that combine high-resolution anatomical imaging with sophisticated psychological paradigms. Until recently, such methods were used primarily as a correlational tool to 'map' the cerebral changes that are associated with a particular cognitive process or function, be it an action, a reaction

*Corresponding author.
Tel.: +44 1223 355294; Fax: +44 1223 359062;
E-mail: adrian.owen@mrc-cbu.cam.ac.uk

DOI: 10.1016/S0079-6123(09)17728-2

(e.g. to some kind of external stimulation) or a thought. But recent advances in imaging technology, and in particular the ability of fMRI to detect reliable neural responses in individual participants in real time, are beginning to reveal patient's thoughts, actions or intentions based solely on the pattern of activity that is observed in their brain. New techniques such as diffusion tensor imaging (DTI) are also being used to probe the structural integrity of white matter tracts between key brain regions and emerging methods such as resting state fMRI are beginning to reveal how the intrinsic functional connectivity of the brain is altered by serious brain injury. Throughout this new volume of *Progress in Brain Research — Coma Science: Clinical and Ethical Implications*, the influence of this 'technical revolution' is palpable; from methodologically themed chapters on multimodal approaches to assessment, advances in fMRI, DTI and MRI spectroscopy through to more philosophical chapters on the problem of unreported awareness and the moral significance of phenomenal consciousness. In the following sections, we review some of the key findings in this area and discuss how novel neuroimaging methods and approaches are beginning to make a significant impact on the assessment and management of patients with disorders of consciousness. The results have profound implications for clinical care, diagnosis, prognosis and ethical and medical–legal decision-making, but are also beginning to address more basic scientific questions concerning the nature of consciousness and the neural representation of our own thoughts and intentions.

fMRI: from passive paradigms to the assessment of awareness

An accurate and reliable evaluation of the level and content of cognitive processing is of paramount importance for the appropriate management of patients diagnosed with disorders of consciousness. Objective behavioral assessment of residual cognitive function can be extremely difficult as motor responses may be minimal, inconsistent, and difficult to document, or may be undetectable because no cognitive output is possible (for a comprehensive discussion of this issue — including the limitations of behavioral assessment — see Giacino et al., 2009). This situation may be further complicated when patients with disorders of consciousness have underlying deficits in the domain of communication functions, such as aphasia (the consequences of receptive and/or productive aphasia on the already limited behavioral repertoire presented in these patients are reviewed in Majerus et al., 2009). 'Activation' methods, such as $H_2{}^{15}O$ PET and fMRI can be used to link residual neural activity to the presence of covert cognitive function. A significant development over the past ten years has been the relative shift of emphasis from PET activation studies using $H_2{}^{15}O$ methodology, to functional magnetic resonance imaging (fMRI; see Chapters by Coleman et al., 2009; Soddu et al., 2009; Sorger et al., 2009; Monti et al., 2009). Not only is MRI more widely available than PET, it offers increased statistical power, improved spatial and temporal resolution and does not involve radiation. Given the heterogeneous nature of this patient group and the clinical need to define each individual in terms of their diagnosis, residual functions and potential for recovery, these technical benefits are of paramount importance in the evaluation of disorders of consciousness.

Recent notable examples include Di et al. (2007) who used event-related fMRI to measure brain activation in seven vegetative patients and four minimally conscious patients in response to the patient's own name spoken by a familiar voice. Two of the vegetative patients exhibited no significant activity at all, three patients exhibited activation in primary auditory areas and two vegetative patients and four minimally conscious patients exhibited activity in 'higher-order' associative temporal-lobe areas. This result is encouraging, particularly because the two vegetative patients who showed the most widespread activation subsequently improved to a minimally conscious state in the following months. Staffen et al. (2006) also used event-related fMRI to compare sentences containing the patient's own name (e.g. 'Martin, hello Martin'), with sentences using

another first name, in a patient who had been vegetative for ten months at the time of the scan. Differential cortical processing was observed to the patient's own name in a region of the medial prefrontal cortex, similar to that observed in three healthy volunteers. These findings concur closely with a recent electrophysiological study, which has shown differential P3 responses to patient's own names (compared to other's names) in some vegetative patients (Perrin et al., 2006). Selective cortical processing of one's own name (when it is compared directly with another name) requires the ability to perceive and access the meaning of words and may imply some level of comprehension on the part of these patients. However, as several authors have pointed out, a response to one's own name is one of the most basic forms of language and may not depend on the higher-level linguistic processes that are assumed to underpin comprehension (Perrin et al., 2006; Owen and Coleman, 2008; Laureys et al., 2007).

Several recent studies have sought to address this problem of interpretation by adopting an 'hierarchical' approach to fMRI assessment of language processing in disorders of consciousness (Owen et al., 2005a, b; Coleman et al., 2007, in press). At the highest level, responses to sentences containing semantically ambiguous words (e.g. 'the *creak/creek* came from a *beam* in the *ceiling/sealing*') are compared to sentences containing no ambiguous words (e.g. 'her secrets were written in her diary'), in order to reveal brain activity associated with spoken language *comprehension* (Rodd et al., 2005). In one large study of 41 patients, 2 who had been diagnosed as behaviorally vegetative were shown to exhibit 'normal' fMRI activity during the speech comprehension task (Coleman et al., in press), Moreover, these fMRI findings were found to have no association with the patients' behavioral presentation at the time of investigation and thus provide additional diagnostic information beyond the traditional clinical assessment. These results illustrate how technically complex event-related fMRI designs are now being combined with well-characterized psycholinguistic paradigms to demonstrate that some of the processes involved in activating, selecting and integrating contextually appropriate word meanings may be intact in some vegetative patients, despite their clinical diagnoses.

Does the presence of 'normal' brain activation in patients with disorders of consciousness indicate a level of awareness, perhaps even similar to that which exists in healthy volunteers when exposed to the same type of information? Many types of stimuli, including faces, speech and pain will elicit relatively 'automatic' responses from the brain; that is to say, they will occur without the need for willful intervention on the part of the participant (e.g. you cannot choose to *not* recognize a face, or to *not* understand speech that is presented clearly in your native language). In addition, there is a wealth of data in healthy volunteers, from studies of implicit learning and the effects of priming (Schacter, 1994) to studies of learning and speech perception during anesthesia (Davis et al., 2007) that have demonstrated that many aspects of human cognition can go on in the absence of awareness. Even the semantic content of masked information can be primed to affect subsequent behavior without the explicit knowledge of the participant, suggesting that some aspects of semantic processing may occur without conscious awareness (Dehaene et al., 1998). By the same argument, 'normal' neural responses in patients who are diagnosed with disorders of consciousness do not *necessarily* indicate that these patients have any conscious experience associated with processing those same types of stimuli. This logic exposes a central conundrum in the study of conscious awareness and in particular, how it relates to the vegetative and minimally conscious states; our ability to know unequivocally that another being is consciously aware is determined, not by whether they are aware or not, but by their ability to communicate that fact through a recognized behavioral response (for a fuller discussion of this 'problem of unreportable awareness' see Adam Zeman's chapter, 2009).

A significant recent development in this field, therefore, has been the development of fMRI paradigms that render awareness *reportable* in the absence of an overt behavioral (e.g. motor or speech) response (Owen et al., 2006; Boly et al.,

2007). Crucially, these paradigms differ from the passive tasks described above (e.g. speech perception) because 'normal' patterns of fMRI activity are only observed when the patient exerts a willful, or voluntary, response that is not elicited automatically by the stimulus (for a fuller discussion of this issue, see Monti et al., 2009). Some of these techniques make use of the general observation that imagining performing a particular task generates a robust and reliable pattern of brain activity in the fMRI scanner that is similar to actually performing the activity itself. For example, imagining moving or squeezing the hands will generate activity in the motor and premotor cortices (Boly et al., 2007) while imagining navigating from one location to another will activate the same regions of the parahippocampal gyrus and the posterior parietal cortex that have been widely implicated in map-reading and other so-called spatial navigation tasks (Jeannerod and Frak, 1999; Aguirre et al., 1996). The robustness and reliability of these fMRI responses across individuals means that activity in these regions can be used as a neural proxy for behavior, confirming that the participant retains the ability to understand instructions, to carry out different mental tasks in response to those instructions and, therefore, is able to exhibit willed, voluntary behavior in the absence of any overt action. On this basis, they permit the identification of awareness at the single-subject level, without the need for a motor response (for discussion, see Owen and Coleman, 2008; Monti et al., 2009).

This approach was used recently to demonstrate that a young woman who fulfilled all internationally agreed criteria for the vegetative state was, in fact, consciously aware and able to make responses of this sort using her brain activity (Owen et al., 2006, 2007). Thus, when the patient was asked to imagine playing tennis or navigate her way around her house, significant activity was observed that was indistinguishable from that exhibited by healthy volunteers performing the same tasks (Boly et al., 2007).

An alternative approach that has been explored recently is to target processes that require the willful adoption of 'mind-sets' in carefully matched (perceptually identical) experimental and control conditions. Monti et al. (2009) describe a study in which healthy volunteers were presented with a series of neutral words, and alternatively instructed to just listen, or to count, the number of times a given target was repeated. The counting task revealed the frontoparietal network that has been previously associated with target detection and working memory. When tested on this same procedure, a minimally conscious patient produced a very similar pattern of activity, confirming that he could willfully adopt differential mind-sets as a function of the task condition and could actively maintain these mind-sets across time. A similar approach has been adopted recently by Schnakers et al. (2008b) who used, as targets, the patient's own name and other 'non-salient' names (e.g. similarly frequent names that had no relation to the patient or his/her family). All of the minimally conscious patients that were tested exhibited a significant response when passively listening to their own name. In addition, however, 9 of 14 patients exhibited more activity when instructed to count the number of times their own name (or another target name) occurred than when they passively heard it. This approach also allowed awareness to be identified in a case of complete locked-in syndrome (Schnakers et al., 2009).

These types of approach all illustrate a paradigmatic shift away from passive (e.g. perceptual) tasks to more active (e.g. willful) tasks in the fMRI and electroencephalography (EEG) assessment of residual cognitive function in patients with disorders of consciousness. What sets such tasks apart is that the neural responses required are not produced automatically by the eliciting stimulus, but rather, depend on time-dependent and sustained responses generated by the participant. Such behavior (albeit neural 'behavior') provides a proxy for an (e.g. motor) action and is, therefore, an appropriate vehicle for *reportable awareness* (also see Zeman, 2009; Overgaard, 2009).

fMRI as a form of communication?

One major aim of clinical assessment in disorders of consciousness is to harness and nurture any

available response, through intervention, into a form of reproducible communication, however rudimentary. The acquisition of any interactive and functional verbal or nonverbal method of communication represents an important milestone. Clinically, it demarcates the upper boundary of minimally conscious state (MCS) (see Giacino et al., 2009). More importantly, from a quality of life perspective, it allows such patients to communicate their wishes (e.g. concerning treatment options), and, therefore, to exert their right to autonomy. Thus, a key future question for functional neuroimaging is whether fMRI data could ever be used in this way; that is as a form of *communication*, replacing speech or a motor act in patients for whom such forms of behavioral expression are unavailable?

Several recent studies using fMRI suggest that this may be possible. For example, Haynes et al. (2007) asked healthy volunteers to freely decide which of two tasks to perform (to add or subtract two numbers) and to covertly hold onto that decision during a delay. After the delay they performed the chosen task, the result indicating which task they had intended to do (and eventually executed). A classifier was trained to recognize the characteristic fMRI signatures associated with the two mental states and in 80% of trials was able to decode from activity in medial and lateral regions of prefrontal cortex which of the two tasks the volunteers were intending to perform. Another previous study has shown that fMRI can be used as a 'brain–computer interface' (BCI) that allows real-time communication of thoughts (Weiskopf et al., 2004); healthy volunteers learned to regulate the fMRI signal in a particular brain area using their own fMRI signal as feedback. In general terms, a brain–computer interface is any system that translates an individual's thoughts and intentions into signals to control a computer or communicate via external hardware, thereby establishing a 'direct' connection between the brain and the external world without any need for motor output (Kubler and Neumann, 2005; for further discussion, see Sorger et al., 2009). In recent years, significant progress has been made in developing sophisticated noninvasive BCI methods for 'decoding thoughts' using both fMRI and EEG (e.g. Birbaumer and Cohen, 2007; deCharms, 2007). However, all of these methods require extensive training of participants, the decoding algorithm, or both. Moreover, accuracy rates are typically in the 60–80% range rendering them of limited use in clinical decision-making. In an exciting new development, Sorger et al. (2009) have developed a novel information encoding technique that exploits the fact that the signal-to-noise ratio in fMRI time courses is sufficiently high to reliably detect BOLD signal onsets and offsets on a single-trial level with a high degree of accuracy. Eight healthy participants 'answered' multiple-choice questions with 95% accuracy by intentionally generating single-trial BOLD responses in three tasks that were then 'decoded' in real time with respect to three influenceable signal aspects (source location, onset and offset). Although this 'proof of concept' was in healthy participants, such feats of rudimentary 'mind-reading' increase the likelihood that in the near future, some patients with disorders of consciousness may also be able to communicate their thoughts to those around them by simply modulating their own neural activity.

Resting state fMRI

Another important new direction in the use of fMRI data in the assessment of patients with disorders of consciousness is in the examination of so-called 'resting-state' data (for a comprehensive discussion of this area see Soddu et al., 2009). Recently, increasing attention has been paid to the 'intrinsic' functional connectivity of the brain, and this can be revealed by examination of fMRI data collected while the participant is not performing any active task (e.g. they are 'at rest'). Resting state data is very easy to obtain in vegetative and minimally conscious patients, as it does not require the participant to perform any task. Boly et al. (2009a, b) have recently investigated spontaneous activation in patients with disorders of consciousness and showed that resting state connectivity in the 'default network' is decreased in proportion to the degree of

consciousness impairment. Specifically, they demonstrated that cortico-thalamic BOLD functional connectivity (i.e. between posterior cingulate/precuneal cortex and medial thalamus) was notably absent, but cortico-cortical connectivity was preserved within the default network in one vegetative state patient studied 2.5 years following cardio-respiratory arrest (Boly et al., 2009a). In a second study, resting state connectivity was investigated using probabilistic independent component analysis in 14 noncommunicative brain damaged patients and 14 healthy controls (Boly et al., 2009b). Connectivity in all default network areas was found to be linearly correlated with the degree of 'clinical consciousnesses' (from healthy controls, to locked-in syndrome, to minimally conscious state, vegetative state and coma). Moreover, precuneus connectivity was found to be significantly stronger in minimally conscious patients than vegetative state patients. As might be expected given their preserved level of awareness, in locked-in syndrome patients, default network connectivity was not significantly different from controls (for further discussion see Soddu et al., 2009). In this volume, Boly et al. (2009) suggest a theoretical framework for understanding the properties that grant a system a state of consciousness, and highlight the notion of 'integration' as a necessary (but not sufficient) component of consciousness. While measures of integration have been proposed previously, the fact that these may be computationally out of reach for a system such as the brain, makes studies of intrinsic connectivity (e.g. using resting state data) a relatively crude, but informative, approximation of the levels of functional integration available at different levels of consciousness.

Using a somewhat different, but related, approach to understanding consciousness and its breakdown, Massimini et al. (2009) propose a theoretically grounded methodology for assessing a system's capability for producing consciousness. Adopting a 'perturbational approach' they suggest that the combination of transcranial magnetic stimulation (TMS) and high density EEG may make it possible to evaluate the amount of functional integration of a system — a theoretical requisite for conscious experience.

Diffusion tensor imaging

Another significant development in the last decade has been the development of various methods for assessing the structural connectivity of the brain (for a comprehensive discussion of some of these techniques, see Tshibanda et al., 2009). DTI is a noninvasive magnetic resonance technique that allows examination of white matter fiber tracts in vivo. In white matter, water diffusion is higher along the direction of fiber bundles (due to axonal organization and the myelin sheath). This *anisotropy* is measured with MRI to determine anatomical connectivity. To date, detailed histopathological studies have shown no pathological distinctions between vegetative state and some minimally conscious state patients (Jennett et al., 2001). This approach has been used to great effect recently by Voss et al. (2006) who used DTI to longitudinally characterize brain structural connectivity in a minimally conscious patient who regained expressive and receptive language 19 years after sustaining a traumatic brain injury. DTI not only revealed severe diffuse axonal injury, as indicated by volume loss in the medial corpus callosum, but also large regions of increased connectivity (relative to healthy controls) in posterior parts of the brain (i.e. precuneal areas). In a second DTI study 18 months later, these posterior regions of white matter anisotrophy were reduced in directionality. At the same time point, significant increases in anisotrophy within the midline cerebellar white matter were shown to correlate with the observed clinical improvement in motor control during the previous 18 months. These findings strongly suggest that the observed structural changes within the patient's white matter played a role in his functional recovery.

Coleman et al. (2009) have also used this technique as part of a multimodal approach to the assessment of patients with disorders of consciousness. In one minimally conscious patient described in detail, DTI revealed reduced (−38%) fractional anisotropy in comparison to healthy control subjects, indicating widespread loss of white matter integrity. Moreover DTI revealed a significantly increased apparent

diffusion coefficient in comparison to healthy volunteers, suggesting loss of cortico-cortical connectivity. Indeed, a qualitative view of white matter paths revealed a loss of the inferior temporal and inferior frontal pathways that have been shown to mediate aspects of speech comprehension in some of the psycholinguistic fMRI tasks described above (e.g. Rodd et al., 2005). Of note, a prospective cohort study of serial DTI imaging following severe traumatic brain injury and coma found that cognitive and behavioral improvement correlated with recovery of normal to supranormal fractional anisotropy in preselected white matter regions (Sidaros et al., 2008). These findings showed a directional specificity with improvements in fractional anisotropy seen only in the eigenvectors of the diffusion tensor associated with diffusion parallel to the axonal fibers; these results are consistent with the Voss et al. (2006) study and supportive of possible axonal regrowth.

In the coming years, we expect that the increasing use if routinely acquired DTI data in disorders of consciousness will yield larger prospective studies in this patient group which will ultimately determine whether the sorts of slow structural changes reported by Voss et al. (2006) occur frequently in severe traumatic brain injury and whether they have any influence on functional outcomes (e.g. see Perlbarg et al., 2009; Tollard et al., 2009; Tshibanda, 2009).

The impact on diagnosis and prognosis

As the use of multimodal imaging methods in the assessment of disorders of consciousness is translated to clinical routine, the likely effects on diagnosis and prognosis are beginning to become more apparent. The main goal of the clinical assessment in the vegetative and minimally conscious states is to determine whether the patient retains any purposeful response to stimulation, albeit inconsistent, suggesting they are at least partially aware of their environment and/or themselves. Crucially, this decision separates vegetative state from minimally conscious state patients and has, therefore, profound implications for the subsequent care of the patient and rehabilitation, as well as legal and ethical decision-making. Unfortunately, the behavior elicited by these patients is often ambiguous, inconsistent and typically constrained by varying degrees of paresis making it very challenging to disentangle purely reflexive from voluntary behaviors (for further discussion, see Giacino et al., 2009), a fact that undoubtedly contributes to the high rate of diagnostic error (37–43%) in this patient group (Andrews et al., 1996; Childs et al., 1993; Schnakers et al., 2006). In several recent cases, neuroimaging data has been entirely inconsistent with the formal clinical diagnosis which remains based on standard behavioral criteria. For example, the patient described by Owen et al. (2006), was clearly able to produce voluntary responses (albeit neural responses) to command, yet was unable to match this with any form of motor response at the bedside. Paradoxically therefore, this patient's (motor) behavior was consistent with a diagnosis of vegetative state which effectively depends on *an absence of evidence of awareness or purposeful response*, yet her brain imaging data were equally consistent with the alternative hypothesis, that she was entirely aware during the scanning procedure. Clearly the clinical diagnosis of vegetative state based on behavioral assessment was inaccurate in the sense that it did not accurately reflect her internal state of awareness. On the other hand, she was not *misdiagnosed* in the sense that no behavioral marker of awareness was missed. Similarly, the minimally conscious patient described by Monti et al. (2009) was able to 'perform' a complex working memory task in the scanner, in the sense that his brain activity revealed consistent and repeatable command following. While this 'behavior' does not necessarily alter the patient's formal diagnosis (from 'low' MCS) it certainly demonstrated a level of responsively that was not revealed by the behavioral examination.

A second question concerns the implications that emerging neuroimaging approaches may have for prognosis in this patient group. At present, predicting survival, outcome and long-term cognitive deficits in individual patients with severe brain injury based on clinical assessment is

very difficult (see extensive reviews by Whyte et al., 2009; Katz et al., 2009; Azouvi et al., 2009; Zasler, 2009). It is of interest that in the case described by Owen et al. (2006), the patient began to emerge from her vegetative state to demonstrate diagnostically relevant behavioral markers before the prognostically important 12-month threshold was reached (for a diagnosis of *permanent* vegetative state), suggesting that early evidence of awareness acquired with functional neuroimaging may have important prognostic value. Indeed, with a marked increase in the number of studies using neuroimaging techniques in patients with disorders of consciousness a consistent pattern is starting to emerge. Di et al. (2008), reviewed 15 separate $H_2{}^{15}O$ PET and fMRI studies involving 48 published cases which were classified as 'absent cortical activation', 'typical activation', (involving low level primary sensory cortices) and 'atypical activation' (corresponding to higher-level associative cortices). The results show that atypical activity patterns appear to predict recovery from vegetative state with 93% specificity and 69% sensitivity. That is to say, 9 of 11 patients exhibiting atypical activity patterns recovered consciousness, whereas 21 of 25 patients with typical primary cortical activity patterns and 4 out of 4 patients with absent activity failed to recover. This important review strongly suggests that functional neuroimaging data can provide important prognostic information beyond that available from bedside examination alone.

In another recent study of 41 patients with disorders of consciousness, Coleman et al. (in press; also see Coleman et al., 2009) found direct evidence of prognostically important information within neuroimaging data that was at odds with the behavioral assessment at the time of scanning. Thus, contrary to the clinical impression of a specialist team using behavioral assessment tools, two patients who had been referred to the study with a diagnosis of vegetative state, did in fact demonstrate clear signs of speech comprehension when assessed using fMRI. More importantly however, across the whole group of patients, the fMRI data were found to have *no association* with the behavioral presentation at the time of the investigation, but correlated significantly with subsequent behavioral recovery, six months after the scan. In this case, the fMRI data predicted subsequent recovery in a way that a specialist behavioral assessment could not. In future, the full utility of neuroimaging in this context will become clearer when even larger studies are conducted, preferably involving multiple centers using standardized techniques and paradigms.

Therapeutic advances

At present, there is no empirically proven intervention to facilitate recovery in the vegetative state and related disorders of consciousness (e.g. Schnakers et al., 2008a; also see extensive review by Zafonte et al. (2009) on pharmacotherapy of arousal and Taira (2009), on intrathecal administration of GABA agonists). The favored approach is to create a stable clinical environment for natural recovery to take place. The greatest difficulty preventing the development of treatment options is the extent and heterogeneity of pathology underlying these conditions. It is increasingly accepted; therefore, that novel treatments designed for the individual or a small group of very similar patients will be necessary. One such approach is deep brain stimulation (DBS), which uses stereotactically placed electrodes to deliver electrical stimulation to the thalamus (also see Moll et al., 2009, on subpallidal DBS-induced wakeful unawareness during anesthesia). DBS has recently been employed by Schiff et al. (2007) with startling results in a patient in post traumatic MCS. Electrical stimulation, delivered via electrodes implanted bilaterally into the central thalamus, was found to produce increased periods of arousal and responsiveness to command in a 38-year-old male who had remained in a minimally conscious state for six and a half years following the injury. The changes correlated closely with the commencement of DBS and could not be attributed to gradual recovery over time. Importantly however, the patient was at the upper boundary of the minimally conscious state before DBS was commenced. He had also produced inconsistent, but reproducible evidence of communication and

fMRI had shown preservation of cortical language networks. Yamamoto and Katayama (2005) used a similar technique on more severely impaired patients and reported positive effects in 8 out of 21 vegetative patients, who subsequently emerged from vegetative state and obeyed commands. However, in that study, DBS was commenced within 3–6 months of brain injury and it is not clear whether the behavioral improvement simply reflected natural recovery. There are now widespread calls for the methodology of Schiff et al. (2007) to be extended to a larger number of more severely impaired patients in order to evaluate the potential of this technique to facilitate recovery.

Neuroimaging and ethics

Neuroimaging of severely brain-injured, noncommunicative populations of patients raises several important ethical concerns. Foremost is the concern that diagnostic and prognostic accuracy is assured, as treatment decisions typically include the possibility of withdrawal of life support. In an excellent discussion of these issues (Fins, 2009), Joseph Fins notes that 'the utter *and fixed* futility of the vegetative state became the ethical and legal justification for the genesis of the right-to-die movement in the United States' (Fins, 2003, 2006; Fins et al., 2008). At present, although several of the neuroimaging approaches discussed in this chapter hold great promise to improve both diagnostic and prognostic accuracy, the standard approach remains the careful and repeated neurological exam by a trained examiner.

That said, in future, the routine use of techniques such as fMRI and quantitative EEG in the diagnostic process (e.g. for the detection of awareness), will raise additional issues relating to legal decision-making and the prolongation, or otherwise, of life after severe brain injury (see Levy and Savulescu, 2009; Lutte, 2009). At present, decisions concerning life support (nutrition and hydration) are generally taken once a diagnosis of *permanent* vegetative state has been made. To date, fMRI has not demonstrated unequivocal signs of awareness in any patient that has survived beyond the time point required for such a diagnosis (Owen and Coleman, 2008; Laureys and Boly, 2008). Thus, whether fMRI will ever be used in this context will only become apparent when more patients have been scanned, although if evidence for awareness were to be found in a patient who had progressed beyond the threshold for a diagnosis of permanent vegetative state, this fact would certainly have profound implications for this decision-making process. On the other hand, it is important to point out that neuroimaging is unlikely to influence legal proceedings where negative findings have been acquired. False-negative findings in functional neuroimaging studies are common, even in healthy volunteers, and they present particular difficulties in this patient population. For example, a patient may have low levels of arousal or even fall asleep during the study (e.g. see review by Bekinschtein et al. (2009) on the influence of arousal fluctuations on patients' responsiveness) or the patient may not have properly heard or understood the task instructions, leading to an erroneous negative result. Accordingly, single negative fMRI or EEG findings in patients should not be used as evidence for impaired cognitive function or *lack* of awareness.

Ethical concerns are also sometimes raised concerning the participation of severely brain–injured patients in functional neuroimaging studies (e.g. to assess pain perception; see Demertzi et al., 2009), studies that require invasive procedures (e.g. intra-arterial or jugular lines required for quantification of PET data or modeling), or the use of neuromuscular paralytics. By definition, unconscious or minimally conscious patients cannot give informed consent to participate in clinical research and written approval is typically obtained from family or legal representatives depending on governmental and hospital guidelines in each country. We side with a proposed ethical framework that emphasizes balancing access to research and medical advances alongside protection for vulnerable patient populations. Severe brain injury represents an immense social and economic problem that warrants further research. Unconscious, minimally conscious and locked-in patients are very vulnerable and deserve special procedural protections (also see

Lulé et al., 2009, on quality of life in the locked-in syndrome). However, it is important to stress that these severely brain–injured patients are also vulnerable to being denied potentially life-saving therapy if clinical research cannot be performed adequately (for further discussion, see Fins, 2009).

Conclusions

Disorders of consciousness present unique problems for diagnosis, prognosis, treatment and everyday management. In this chapter, we have reviewed a number of areas where novel neuroimaging methods and approaches are beginning to make a significant impact on the assessment and management of these patients. For example, cognitive activation studies using event-related fMRI are now being used to objectively describe (using population norms) the regional distribution of cerebral activity at rest and under various conditions of stimulation. Indeed, in several rare cases, functional neuroimaging has demonstrated *conscious awareness* in patients who are assumed to be vegetative, yet retain cognitive abilities that have evaded detection using standard clinical methods. Similarly, in some patients diagnosed as minimally conscious, functional neuroimaging has revealed residual cognitive capabilities that extend well beyond that evident from even the most comprehensive behavioral assessment. Moreover, these detailed functional images are now being combined with high-resolution information about anatomy and images of structural connectivity, acquired using techniques such as DTI, to produce an increasingly cohesive picture of normal and abnormal brain function following serious brain injury.

Although insufficient population data currently exists, evidence to include the use of such techniques in the formal diagnostic and prognostic procedure in this patient group is accumulating rapidly. The emerging view is not that brain imaging should replace behavioral assessment, but rather that it should be used, wherever possible, to acquire further information about the patient and their condition. In doing so, the current alarmingly high rate of misdiagnosis in this patient group will undoubtedly fall. Likewise, clinical teams will have the best possible information for planning and monitoring interventions to facilitate recovery.

Acknowledgments

The authors acknowledge the generous support of the James S. McDonnell Foundation. AMO is supported by the Medical Research Council (UK). NS is supported by NS02172, NS43451 and the Charles A. Dana Foundation. SL is a Research Associate at the Fonds National de la Recherche Scientifique de Belgique (FNRS).

References

Aguirre, G. K., Detre, J. A., Alsop, D. C., & D'Esposito, M. (1996). The parahippocampus subserves topographical learning in man. *Cerebal Cortex*, *6*, 823–829.

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *British Medical Journal*, *313*, 13–16.

Azouvi, P., Vallat-Azouvi, C., Belmont, A., & Azouvi, P. (2009). Cognitive deficits and long-term outcome after traumatic coma. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Bekinschtein, T., Cologan, V., Dahmen, B., & Golombek, D. (2009). You are only coming through in waves: Wakefulness variability and assessment in patients with impaired consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Birbaumer, N., & Cohen, L. G. (2007). Brain–computer interfaces: Communication and restoration of movement in paralysis. *Journal of Physiology*, *579*, 621–636.

Boly, M., Coleman, M. R., Davis, M. H., Hampshire, A., Bor, D., Moonen, G., et al. (2007). When thoughts become actions: An fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. *NeuroImage*, *36*(3), 979–992.

Boly, M., Massimini, M., & Tononi, T. (2009). How could information integration theory be applied to the differential diagnosis of patients in altered states of consciousness? In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., et al. (2009a). Functional connectivity in the default network during resting state is

preserved in a vegetative but not in a brain dead patient. *Human Brain Mapping*, *30*(8), 2393–2400.

Boly, M., Vanhaudenhuyse, A., Tshibanda, L., Bruno, M.-A., Boveroux, P., Noirhomme, Q., et al. (2009b). Default network connectivity reflects the level of consciousness in non-communicative brain damaged patients. Submitted.

Childs, N. L., Mercer, W. N., & Childs, H. W. (1993). Accuracy of diagnosis of persistent vegetative state. *Neurology*, *43*, 1465–1467.

Coleman, M. R., Davis, M. H., Rodd, J. M., Robson, T., Ali, A., Pickard, J. D., et al. (in press). Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain*.

Coleman, M. R., Monti, M. M., Bekinschtein, T., Pickard, J., & Owen, A. M. (2009). A multimodal approach to the assessment of patients with disorders of consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Coleman, M. R., Rodd, J. M., Davis, M. H., Johnsrude, I. S., Menon, D. K., Pickard, J. D., et al. (2007). Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain*, *130*, 2494–2507.

Davis, M. H., Coleman, M. R., Absalom, A. R., Rodd, J. M., Johnsrude, I. S., Matta, B. F., et al. (2007). Dissociating speech perception and comprehension at reduced levels of awareness. *Proceedings of the National Academy of Sciences*, *104*(41), 16032–16037.

deCharms, R. C. (2007). Reading and controlling human brain activation using real-time functional magnetic resonance imaging. *Trends in Cognitive Sciences*, *11*, 473–481.

Dehaene, S., Naccache, L., Le Clec, H. G., Koechlin, E., Mueller, M., Dehaene-Lambertz, G., et al. (1998). Imaging unconscious semantic priming. *Nature*, *395*, 597–600.

Demertzi, A., Schnakers, C., Ledoux, D., Chatelle, C., Bruno, M.-A., Vanhaudenhuyse, A., et al. (2009). Different beliefs about pain perception in the vegetative and minimally conscious states: A European survey of medical and paramedical professionals. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Di, H., Boly, M., Weng, X., Ledoux, D., & Laureys, S. (2008). Neuroimaging activation studies in the vegetative state: Predictors of recovery? *Clinical Medicine*, *8*, 502–507.

Di, H. B., Yu, S. M., Weng, X. C., Laureys, S., Yu, D., Li, J. Q., et al. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology*, *68*, 895–899.

Fins, F. (2009). The ethics of measuring and modulating consciousness: The imperative of minding time. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Fins, J. J. (2003). Constructing an ethical stereotaxy for severe brain injury: Balancing risks, benefits and access. *Nature Reviews Neuroscience*, *4*(4), 323–327.

Fins, J. J. (2006). *A palliative ethic of care: Clinical wisdom at life's end*. Sudbury, MA: Jones and Bartlett.

Fins, J. J., Illes, J., Bernat, J. L., Hirsch, J., Laureys, S., & Murphy, E. (2008). Neuroimaging and disorders of consciousness: Envisioning an ethical research agenda American. *American Journal of Bioethics Neuroscience*, *8*, 3–12.

Giacino, J. T., Schnakers, C., Rodriguez-Moreno, D., Schiff, N. D., & Kalmar, K., (2009). Behavioral assessment in patients with disorders of consciousness: Gold standard or fool's gold? In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Haynes, J.-D., Sakai, K., Rees, G., Gilbert, S., Frith, C., & Passingham, R. E. (2007). Hidden intentions in the human brain. *Current Biology*, *10*, 1016.

Jennett, B., Adams, J. H., Murray, L. S., & Graham, D. I. (2001). Neuropathology in vegetative and severely disabled patients after head injury. *Neurology*, *56*, 486–490.

Jeannerod, M., & Frak, V. G. (1999). Mental simulation of action in human subjects. *Current Opinions in Neurobiology*, *9*, 735–739.

Katz, D., Polyak, M., Coughlin, D., Nichols, M., & Roche, A. (2009). Natural history of recovery from brain injury after prolonged impairment of consciousness: Patients admitted to inpatient rehabilitation. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Kubler, A., & Neumann, N. (2005). Brain-computer interfaces — The key for the conscious brain locked into a paralyzed body. *Progress in Brain Research*, *150*, 513–525.

Laureys, S., & Boly, M. (2008). The changing spectrum of coma. *Nature Clinical Practice Neurology*, *4*, 544–546.

Levy, N., & Savulescu, J. (2009). The moral significance of phenomenal consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Laureys, S., Perrin, F., & Brédart, S. (2007). Self-consciousness in non-communicative patients. *Consciousness and Cognition*, *16*, 722–741.

Lulé, D., Zickler, C., Häcker, S., Bruno, M. A., Pellas, F., Demertzi, A., et al. (2009). Life may be worth living in locked-in syndrome. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Lutte, I. (2009). Defining personal loss after severe brain damage. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier

Majerus, S., Bruno, M. A., Schnakers, C., Giacino, J. T., & Laureys, S. (2009). The problem of aphasia in the assessment of consciousness in brain damaged patients. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Massimini, M., Boly, M., Casali, A., & Tononi, G. A. (2009). A perturbational approach to implement theoretical measures

of consciousness at the patient's bedside. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Moll, C. K. E., Sharott, A., Hamel, W., Münchau, A., Buhmann, C., Hidding, U., et al. (2009). Waking up the brain. A case study of stimulation-induced wakeful unawareness during anesthesia. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Monti, M. M., Coleman, M. R., & Owen, A. M. (2009). From V1 to volition: Hierarchical assessment of visual cognition and attention with fMRI. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Overgaard, M. (2009). How can we know if patients in coma, vegetative state or minimally conscious state are conscious? In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Owen, A. M., & Coleman, M. (2008). Functional imaging in the vegetative state. *Nature Reviews Neuroscience*, *9*, 235–243.

Owen, A. M., Coleman, M. R., Davis, M. H., Boly, M., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science*, *313*, 1402.

Owen, A. M., Coleman, M. R., Davis, M. H., Boly, M., Laureys, S., & Pickard, J. D. (2007). Response to comments on ''Detecting awareness in the vegetative state''. *Science*, *315*, 1221c.

Owen, A. M., Coleman, M. R., Menon, D. K., Berry, E. L., Johnsrude, I. S., Rodd, J. M., et al. (2005a). Using a hierarchical approach to investigate residual auditory cognition in persistent vegetative state. In S. Laureys (Ed.), *The boundaries of consciousness: Neurobiology and neuropathology. Progress in Brain Research* (Vol. 150, pp. 461–476). London: Elsevier.

Owen, A. M., Coleman, M. R., Menon, D. K., Johnsrude, I. S., Rodd, J. M., Davis, M. H., et al. (2005b). Residual auditory function in persistent vegetative state: A combined PET and fMRI study. *Neuropsychological Rehabilitation*, *15*(3–4), 290–306.

Perlbarg, V., Puybasset, L., Tollard, E., Lehéricy, S., Benali, H., & Galanaud, D. (2009). Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: A diffusion tensor imaging study using voxel-based approaches. *Human Brain Mapping*, in press. Available at http://www3.interscience.wiley.com/journal/122440012/abstract?CRETRY=1&SRETRY=0

Perrin, F., Schnakers, C., Schabus, M., Degueldre, C., Goldman, S., Bredart, S., et al. (2006). Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Archives of Neurology*, *63*, 562–569.

Rodd, J. M., Davis, M. H., & Johnsrude, I. S. (2005). The neural mechanisms of speech comprehension: fMRI studies of semantic ambiguity. *Cerebral Cortex*, *15*, 1261.

Schacter, D. L. (1994). Priming and multiple memory systems: Perceptual mechanisms of implicit memory. In D. L. Schacter & E. Tulving (Eds.), *Memory systems* (pp. 233–268). Cambridge, MA: MIT Press.

Schiff, N. D., Giacino, J. T., Kalmar, K., Victor, J. D., Baker, K., Gerber, M., et al. (2007). Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature*, *448*, 600–603.

Schnakers, C., Giacino, J., Kalmar, K., Piret, S., Lopez, E., Boly, M., et al. (2006). Does the FOUR score correctly diagnose the vegetative and minimally conscious states? *Annals of Neurology*, *60*, 744–745.

Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., et al. (2009). Detecting consciousness in a total locked-in syndrome: An active event related paradigm. *Neurocase*, *25*, 1–7.

Schnakers, C., Hustinx, R., Vandewalle, G., Majerus, S., Moonen, G., Vanhaudenhuyse, A., et al. (2008a). Measuring the effect of amantadine in chronic anoxic minimally conscious state. *Journal of Neurology Neurosurgery and Psychiatry*, *79*, 225–227.

Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., et al. (2008b). Voluntary brain processing in disorders of consciousness. *Neurology*, *71*, 1614–1620.

Sidaros, A., Engberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Petersen, P., et al. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: A longitudinal study. *Brain*, *131*, 559–572.

Soddu, A., Boly, M., Papa, M., Laureys, S., & Malach, R. (2009). Reaching across the abyss: Recent advances in functional magnetic resonance imaging (fMRI) and their potential relevance to deficits of consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Sorger, B., Dahmen, B., Reithler, J., Gosseries, O., Maudoux, A., Laureys, S., et al. (2009). Another kind of 'BOLD response': Answering multiple choice questions by differential single-trial fMRI responses. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Staffen, W., Kronbichler, M., Aichhorn, M., Mair, A., & Ladurner, G. (2006). Selective brain activity in response to one's own name in the persistent vegetative state. *Journal of Neurology, Neurosurgery & Psychiatry*, *77*, 1383–1384.

Taira, T. (2009). Intrathecal administration of GABA agonists in the vegetative state. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Tollard, E., Galanaud, D., Perlbarg, V., Sanchez-Pena, P., Le Fur, Y., Abdennour, L., et al. (2009). Experience of diffusion tensor imaging and 1H spectroscopy for outcome prediction in severe traumatic brain injury: Preliminary results. *Critical Care Medicine*, *37*(4), 1448–1455.

Tshibanda, J. F., Galanaud, D., Vanhaudenhuyse, A., Boly, M., Laureys, S., & Puybasset, L. (2009). MRI spectroscopy and diffusion tensor imaging in coma survivors: Promises and pitfalls. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Voss, H. U., Uluç, A. M., Dyke, J. P., Watts, R., Kobylarz, E. J., McCandliss, B. D., et al. (2006). Possible axonal regrowth in late recovery from the minimally conscious state. *The Journal of Clinical Investigation*, *116*, 2005–2011.

Weiskopf, N., Mathiak, K., Bock, S. W., Scharnowski, F., Veit, R., Grodd, W., et al. (2004). Principles of a brain-computer interface (BCI) based on real-time functional magnetic resonance imaging (fMRI). *IEEE Transactions on Biomedical Engineering*, *51*, 966–970.

Whyte, J., Gosseries, O., Chervoneva, I., DiPasquale, M. C., Giacino, J., Kalmar, K., et al. (2009). Predictors of short-term outcome in brain injured patients with disorders of consciousness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Yamamoto, T., & Katayama, Y. (2005). Deep brain stimulation therapy for the vegetative state. *Neuropsychological Rehabilitation.*, *15*(3/4), 406–413.

Zafonte, R., Hammond, F., Dennison, A., & Chew, E. (2009). Pharmacotherapy of arousal: Balancing the risks and benefits. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Zasler, N. (2009). Life expectancy and disorders of consciousness after traumatic brain injury. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Zeman, A. (2009). The problem of unreportable awareness. In S. Laureys, N. D. Schiff, & A. M. Owen (Eds.), *Coma science: Clinical and ethical implications – Progress in Brain Research* (this volume). Oxford: Elsevier.

Subject Index