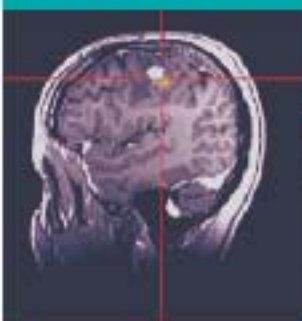


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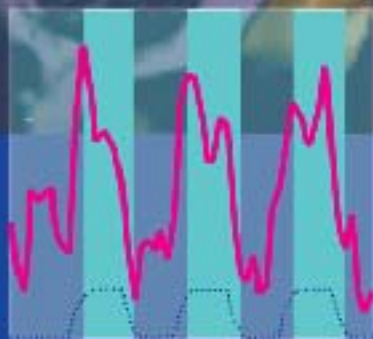
A. L. Baert
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K. Sartor



Clinical Functional MRI

**Presurgical
Functional Neuroimaging**

C. Stippich
Editor



 Springer

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Diagnostic Imaging

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Clinical Functional MRI

Presurgical Functional Neuroimaging

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Foreword by

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With 123 Figures in 200 Separate Illustrations, 151 in Color

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To my beloved family

Alexandra, Tim and Jan

home,
source of energy and contentment



Foreword

After functional mapping of the brain by magnetic resonance imaging (MRI) was found to be feasible in the early 1990s, many neuroscientists involved in research on brain function became interested in functional MRI (fMRI). In contrast to positron emission computed tomography (PET), which was used for many years to study brain function, fMRI is not based on ionizing radiation and thus can be repeated as often as necessary in patients or normal volunteers. The novel imaging method gained further in popularity when stronger magnets, stronger and faster gradients and more advanced software for data analysis became available. Although many (neuro)radiologists had access to the hardware, relatively few also had the necessary background and drive to apply fMRI in a meaningful way. Not surprisingly, the new research field was therefore largely taken over by neuroscientists with time on their hands.

This dominance, which sometimes makes it hard for neuroradiologists to gain recognition for their (largely clinical) research on fMRI, still continues to this day. As long as the local MRI capacity is such that the clinical imaging demands are met and neuroradiologists are in a position to pursue their own research, no real problem occurs; in the ideal situation, there would be suitable MRI hardware reserved entirely for research. However, whenever neuroradiologists with their primary responsibilities to patient care compete with neuroscientists for MRI time, problems are guaranteed. Although under the pressure of a tight schedule resulting from clinical demands plus the “working in” of neurologic emergencies, neuroradiologists are generally blamed for the shrinking of research time. This seems unfair, as neuroradiologists alone can do little about this. The problem can only be reduced, and eventually perhaps solved, in an atmosphere of mutual respect and understanding, that is, under conditions where neuroscientists, neuroclinicians and neuroradiologists work closely and amicably together.

Such is the atmosphere in which Christoph Stippich, a neuroradiologist with a background in magnetoencephalography, works and in which he conceived this book, at the Neurology, Neurosurgery and Neuroradiology department of the University of Heidelberg’s “Kopfclinic” (which is also situated in close proximity to the EENT and Radiooncology departments). Stippich’s idea was to clarify and then compile what is reliable and relayable current knowledge of presurgical neuroimaging, specifically fMRI. Given his experience of many years in this field, he is eminently suited for the editorship of such a book. The result of his endeavour and that of his collaborators, some of them world renowned, is so remarkable that I am convinced of the book’s having a significant clinical impact, primarily, but not exclusively, in neurosurgery. Christoph Stippich set out to show the scientific community what a determined neuroradiologist can do in an area dominated by “true” neuroscientists, and he has succeeded!

Preface

Over the past decade, functional magnetic resonance imaging (fMRI) has undergone a continuing process of technical and methodological maturation and refinement, facilitating its application in a clinical environment. One of the earliest and best validated clinical applications of fMRI was, and remains, presurgical assessment of brain function in patients with brain tumors and epilepsies. There is a substantial body of evidence that fMRI is suited to localizing different body representations in the primary motor and somatosensory cortex, as well as to localizing and lateralizing language function prior to surgery. This diagnostic information permits function-preserving and safe treatment. However, fMRI cannot be considered an established diagnostic neuroimaging modality as yet. To this end, a consensus on standardization of imaging procedures, data processing, data evaluation, and medical interpretation of imaging findings is mandatory. Various dedicated hard- and software components require medical certification and, last but not least, recommendations or guidelines need to be issued by the relevant medical associations. Until then, it is each investigator's responsibility to establish his/her own routines and standards. This requires a profound knowledge of all topics relevant to the presurgical application of fMRI.

There are several textbooks available relating to (clinical) fMRI covering neurophysiology, neuroanatomy, neurosurgery, neurology, neuropsychology, (neuro)radiology, etc., as well as various aspects of functional neuroimaging, most of the latter being dedicated to neuroscientific research. In addition, the abundant original literature published on presurgical fMRI is somewhat heterogeneous, yielding partly conflicting results, which in turn makes it difficult and time-consuming for the reader to extract the clinically relevant information. Furthermore, fMRI is not the sole method in the field of functional neuroimaging. There are other powerful tools such as EEG/MEG, PET, or SPECT that complement each other when combined in a meaningful way. The same holds true for MR spectroscopy and diffusion tensor imaging (DTI). Consequently, dealing with fMRI is intrinsically complex, multimodal, and multidisciplinary.

The motivation for writing this book was the idea of creating a comprehensive text covering the whole field of presurgical fMRI from physiological, anatomical, and methodological basics up to neuroplasticity. Besides compiling the current knowledge on presurgical fMRI, the core of this book has a clear focus on practical issues, providing guidance for those less familiar with the field. Experienced investigators may profit from the various strategies, tips, and tricks given, as well as from a deeper insight into different areas directly linked to presurgical fMRI. For easier reading, this book has been designed as an assembly of successive chapters, each dealing with a specific topic and providing a

particular point of view on presurgical fMRI. Therefore, it is not necessary to go through the whole book – areas of specific interest can be selected easily from the “keypoints” sections and from extensive illustrations.

Each chapter has been written by experienced clinicians and researchers, some world renowned in their respective fields. It has been a great pleasure writing this book together and we hope that it will be of value for all working, or intending to work, in the field of clinical functional neuroimaging, and in particular with presurgical fMRI.

Last, but not least, I would like to thank Professor Klaus Sartor for encouraging me to edit this book and Dr. Maria Blatow for her support and assistance.

Heidelberg

CHRISTOPH STIPPICH

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Introduction to Presurgical Functional MRI

CHRISTOPH STIPPICH

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1.1

Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is a modern, non-invasive imaging technique to measure and localize specific functions of the human brain without application of radiation (BANDETTINI et al. 1992; KWONG et al. 1992). Brain function is assessed indirectly with high spatial resolution via detection of local hemodynamic changes in capillaries (MENON et al. 1995) and draining veins (FRAHM et al. 1994) of so-called “functional areas”, e.g. regions of the human brain that govern motor, sensory, language or memory functions. Here, specific stimulation of the respective neurofunctional system is required – spontaneous brain activity can not be measured. The blood-oxygen-level-dependent (BOLD) technique makes use of blood as an intrinsic contrast (OGAWA et al. 1990; OGAWA et al. 1992; OGAWA et al. 1993), rendering intravenous application of paramagnetic contrast agents (BELLIVEAU et al. 1991) or radioactive substances unnecessary (MAZZIOTTA et

al. 1982; RAICHLE 1983; Fox et al. 1986; HOLMAN and DEVOUS 1992). Although the underlying physiological mechanisms of neurovascular coupling are not ultimately understood, there seems to be a very good correspondence of BOLD-signals and actual neuronal activity (LOGOTHETIS et al. 2001; LOGOTHETIS 2002; LOGOTHETIS 2003; LOGOTHETIS and PFEUFFER 2004; LOGOTHETIS and WANDELL 2004). New powerful gradient systems and the development of ultrafast MR-sequences enable examination of the entire brain in clinically defensible time frames. Better functionality of data processing and immediate data analysis (so-called real time fMRI) facilitate usability of fMRI in the clinical context (FERNANDEZ et al. 2001; WEISKOPF et al. 2003; STEGER and JACKSON 2004; MOLLER et al. 2005). Thus, functional neuroimaging not only offers a variety of novel options for clinical diagnostics and research, but also opens up a new diagnostic field of radiology and neuroradiology, shifting paradigms from strictly morphological imaging to measurement and visualization of brain function (STIPPICH et al. 2002; THULBORN 2006).

1.2

Blood Oxygenation Level Dependent (BOLD) fMRI

Enhanced synaptic activity resulting from stimulation of neurons leads to a local increase in energy and oxygen consumption in functional areas. The following local hemodynamic changes transmitted via neurovascular coupling are measured by fMRI with high spatial accuracy:

- Increase of regional cerebral blood volume (rCBV)
- Increase of regional cerebral blood flow (rCBF)
- Relative increase of oxyhemoglobin in capillary and venous blood

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In principle, fMRI measurements can be accomplished with different techniques; BOLD-fMRI being the most frequently used in human brain is therefore often referred to as the “standard”-technique (THULBORN et al. 1996; THULBORN 1998; THULBORN 2006). Bolus-tracking measures rCBV making use of external contrast agents (BELLIVEAU et al. 1991); spin-tagging assesses rCBF using arterial blood for intrinsic contrast (DETRE et al. 1992). The BOLD-technique (OGAWA et al. 1990; OGAWA et al. 1992; OGAWA et al. 1993) takes advantage of the different magnetic properties of oxygenated (oxy-Hb) and deoxygenated (deoxy-Hb) hemoglobin to generate image contrast. Paramagnetic deoxy-Hb produces local field inhomogeneities in the measurable range of MRI resulting in signal decrease in susceptibility-weighted MR-sequences (T2*), whereas diamagnetic oxy-Hb does not interfere with the external magnetic field. Specific neuronal stimulation augments local cerebral oxygen consumption, which initially results in a decrease of oxy-Hb and an increase in deoxy-Hb in the functional area. To provide the active neurons with oxygenated blood, perfusion (rCBF, rCBV) in capillaries and draining veins is enhanced within several seconds. This mechanism not only equalizes the initial decrease of local oxy-Hb concentration, but over-compensates it (FOX and RAICHLE 1986) and deoxy-Hb is progressively washed out, which is reflected by a reduction of local field inhomogeneity and a raise of BOLD-signal in T2* weighted MR images (TURNER et al. 1991).

BOLD-measurements are currently exerted with ultrafast single-shot echo-planar-imaging (EPI) sequences as gradient echo (GE) or spin echo (SE) (STIPPICH et al. 2002). GE sequences usually achieve higher BOLD-signals predominantly from venous origin; whereas SE sequences measure lower BOLD-signals also arising from the capillary bed in brain parenchyma (HULVERSHORN et al. 2005; HULVERSHORN et al. 2005). Temporal resolution in paradigms with blocked- or parametric design corresponds to the chosen block duration, but could be substantially improved (<100 ms) by introduction of event-related measurements (BUCKNER et al. 1996). Yet, fMRI cannot attain temporal resolution of electroencephalography (EEG) (BERGER 1929; GEVINS 1995; GEVINS et al. 1995) or magnetoencephalography (MEG) (HARI and ILMONIEMI 1986; HÄMÄLÄINEN et al. 1993), but does not necessitate complicated model-based calculation for source localization and offers higher spatial preci-

sion due to direct correlation to surface anatomy. Signal intensity and realizable spatial resolution vary with magnetic field strength. MR scanners with magnetic field strengths under 1.0 Tesla (T) are not suitable for BOLD-imaging. The broadly available 1.5 T scanners allow reliable measurements of cortical activation provided that powerful gradient systems (possibly >30 mT/m) are on hand, while new high magnetic field scanners with 3 T or more even permit functional imaging of subcortical structures and brain stem (THULBORN 1999; ZAMBREANU et al. 2005). Advantages of fMRI over positron emission tomography (PET) (MAZZIOTTA et al. 1982; RAICHLE 1983; FOX et al. 1986) or single-photon emission computer tomography (SPECT) (HOLMAN and DEVIOUS 1992) – other methods measuring brain activity indirectly with lower spatial/temporal resolution (glucose- or oxygen-metabolism, blood flow/perfusion changes) – are its non-invasiveness, lack of radiation, repeatability and broad availability of clinical scanners.

Due to the low signal to noise ratio (SNR) it is mandatory to perform multiple repeated stimulations during one fMRI measurement in order to obtain robust BOLD-signals. Statistical correlation of BOLD-signal time courses with the chosen stimulation protocol (paradigm) enables identification of those brain areas that show hemodynamic changes in synchrony with the task. A requisite for this is further processing of fMRI data, which is normally done after the measurements with freely available or commercial software (COX 1996; FRISTON 1996; GOLD et al. 1998; ROBERTS TP 2003). However, none of these programs has a certification for medical use so far. Most manufacturers of clinical high magnetic field scanners nowadays offer options for “online” processing of fMRI data (“real time fMRI”) (FERNANDEZ, DE GREIFF et al. 2001; MOLLER, FREUND et al. 2005). Since functionality of those programs varies considerably, the appropriate choice largely depends on individual criteria. However, any data processing software for fMRI should at least offer image alignment, motion correction, temporal and spatial data smoothing, multiple statistical tests to assess functional activation and options for spatial normalization (STIPPICH, HEILAND et al. 2002). Furthermore, in presurgical fMRI tools for superimposing functional on morphological images and for data export (e.g. neuronavigation) are essential. Chapter 2 describes physiological bases and methodological-technical aspects of fMRI in the context of clinical applications.

1.3

Presurgical fMRI

Presurgical fMRI is carried out to facilitate function preserving and safe treatment in patients with brain tumors and epilepsies by noninvasively localizing and lateralizing specific brain functions or epileptic activity. This diagnostic information is not available from morphological brain imaging or invasive measures prior to treatment. Consequently presurgical fMRI measurements are always performed in individual patients to achieve a “functional” diagnosis. They thereby differ fundamentally from the fMRI experiments in basic neuroscience research where usually normal or altered brain function is investigated in group studies. The experimental set-up as well as data processing and evaluation need to be adapted to the clinical environment so that patients – who may present with neurological or cognitive deficits – can be examined successfully in a standardized way. It is important to note that fMRI can not be considered a definitively established method routinely used in clinical diagnostic neuroimaging. Clinical fMRI should be carried out in the framework of scientific studies until the hardware and software components for medical applications have been certified and official recommendations or guidelines have been issued by relevant medical associations. Until then, individual routines and standards need to be established for measuring techniques and examination protocols, data processing and evaluation, as well as for medical interpretation and documentation of clinical fMRI findings. As a basic principle, clinical fMRI examinations should be performed, evaluated and interpreted by trained and experienced examiners with particular expertise in this area, since careless use of this very promising technique could endanger patients.

To facilitate the access to presurgical fMRI diagnostics, Chapter 3 extensively treats morphological and functional neuroanatomy. In addition to a detailed systematic description of surface anatomy and cytoarchitecture of the human brain, important morphological criteria for straightforward identification of different anatomical structures are discussed and functional neuroanatomy of motor and language systems is presented. Chapters 4 and 5 then go into presurgical diagnostics in patients with brain tumors and epilepsies, which are at present the most widely used and best validated clinical applications of fMRI. Particular notice is given to practical and meth-

odological-technical aspects of presurgical fMRI (Sect. 4.3) as well as to specific requirements of fMRI diagnostics in patients with rolandic brain tumors (Sect. 4.4) or lesions with critical spatial relationship to language areas (Sect. 4.5). Diagnostic aims and selection criteria for patients are discussed, clinically tested examination protocols are proposed (STIPPICH et al. 1999; STIPPICH et al. 2000; STIPPICH, OCHMANN, SARTOR et al. 2002; STIPPICH et al. 2003b; STIPPICH et al. 2004; STIPPICH et al. 2005) and their applications are illustrated with example cases. Further, potentials and limits of presurgical fMRI are depicted (Sect. 4.6). Chapter 5 covers particular aspects of presurgical fMRI in patients with epilepsies, as EEG-correlated fMRI for the localization of epileptogenic foci (Sect. 5.4) and presurgical fMRI of memory function (Sect. 5.2).

With the help of functional landmarks provided by fMRI, the spatial relationship between brain tumor or epileptogenic zone and functional areas can be evaluated preoperatively, which facilitates selection of the most cautious therapy. It permits planning and implementation of the most radical and at the same time function-preserving operation, particularly if these functional landmarks are available for functional neuronavigation (see Chap. 6). This goal is rarely achieved with morphological information alone, especially in the presence of brain malformation, anatomical variants, disturbed or destroyed anatomy due to tumor growth or pathology related neuroplastic changes of brain function (see Chap. 9). In any case the “precentral knob” is the only reliable anatomical landmark for a functional area, namely the motor hand representation (YOUSRY et al. 1997; FESL et al. 2003). There are no morphological landmarks for areas related to cognitive brain functions such as language or memory (OJEMANN et al. 1989; OJEMANN 1991). Due to the vast physiological inter-individual anatomical variability (AMUNTS et al. 1999; AMUNTS et al. 2000) and the dependence on various individual factors, functional areas are traditionally mapped intraoperatively by means of electrophysiological methods (PENFIELD W 1937; PENFIELD W 1950; WOOLSEY et al. 1979; OJEMANN et al. 1989; OJEMANN 1991; UEMATSU et al. 1992; CEDZICH et al. 1996; DUFFAU et al. 1999). However, this information is preoperatively inaccessible and surgery duration is therefore significantly prolonged. fMRI on the other hand yields relevant diagnostic information on anatomy, pathology and function prior to surgery in one single examination.

The indication for presurgical fMRI results from

- Clinical signs and symptoms
- The limitations of morphological imaging
- The necessity to measure and visualize normal, modified neuroplastic, and pathological (e.g. epileptic) brain activity

There is a large body of evidence from validation studies with established reference procedures (see Chap. 7) and multimodal investigations comparing fMRI to other methods of functional neuroimaging (see Chap. 8) suggesting reliability of fMRI in (pre-surgical) localization of functional areas in primary motor and somatosensory cortices and in determination of Broca and Wernicke language areas, if indications and limits of the method are considered. Additional attention needs to be paid to technique related inaccuracies due to the superposition of functional and morphological images, the referencing of fMRI data in neuronavigation systems or to surgery induced localization errors following removal of brain tissue or loss of cerebrospinal fluid (brain shift) (REINGES et al. 2004; WITTEK et al. 2005). In Chapter 10 pitfalls, drawbacks and possible sources of artifacts in clinical BOLD-fMRI are presented and practical suggestions for successful presurgical fMRI diagnostics are given.

Safety of surgical procedures in functional areas or their proximity can be improved by concomitant visualization of functional landmarks and important fiber tracts (e.g. pyramidal tract, arcuate fascicle) using diffusion tensor imaging (DTI) (COENEN et al. 2001; HOLODNY et al. 2001; KRINGS et al. 2001; STIPPICH et al. 2003a; ULMER et al. 2004; HOLODNY et al. 2005; SHINOURA et al. 2005). The same holds true for the combined use of fMRI and EEG (TOWLE et al. 2003), MEG (KOBBER et al. 2001; GRUMMICH et al. 2006) or PET (BAUMANN et al. 1995; BITTAR et al. 1999). Tumor induced hemodynamic changes can lead to erroneous fMRI localization and missing or artificial BOLD-signals (HOLODNY et al. 1999; HOLODNY et al. 2000; SCHREIBER et al. 2000; KRINGS et al. 2002; ULMER et al. 2004). Electrophysiological techniques are unsusceptible to these problems, since they directly measure electromagnetic fields resulting from synaptic activity (BERGER 1929; HARI and ILMONIEMI 1986; HÄMÄLÄINEN et al. 1993). However, localization of electromagnetic sources requires complicated modeling and calculations and is therefore limited in precision and accuracy.

Currently, resection borders cannot be determined reliably on the basis of fMRI activations,

since spatial extent of BOLD-clusters varies with the chosen statistical threshold. Nonetheless, fMRI is capable of precisely localizing the center of gravity of a functional area and therefore grants the essential information on anatomical structures that need to be preserved during surgery. Supplementary information for the determination of appropriate resection borders is offered by mapping of tumor metabolism in nuclear medicine.

When applied in a standardized way, fMRI has the diagnostic potential to contribute substantially to the planning and implementation of function-preserving therapies in patients with brain tumors and epilepsies (LEE et al. 1999; GAILLARD et al. 2000; GRABOWSKI TJ 2000; HIRSCH et al. 2000; SUNAERT and YOUSRY 2001; BAXENDALE 2002; BINDER et al. 2002; RUTTEN et al. 2002; STIPPICH et al. 2003; VAN WESTEN et al. 2005; STIPPICH, RAPPS et al. 2007; THULBORN 2006). Prior to and during neurosurgical interventions fMRI can help to reduce the need for invasive diagnostic procedures, as intra-arterial WADA-test (WADA and RASMUSSEN 1960; RAUSCH et al. 1993; BENBADIS et al. 1998; ABOU-KHALIL and SCHLAGGAR 2002) or intraoperative electrocorticography (PENFIELD W 1937; CEDZICH et al. 1996; DUFFAU et al. 2002; DUFFAU et al. 2003). Whether the embedding of fMRI in presurgical diagnostics can indeed diminish surgery related morbidity and mortality should be investigated in prospective clinical trials. Prerequisites are a consensus on measuring techniques, analysis procedures and medical evaluation of clinical fMRI as well as the establishment of official recommendations and guidelines by the assigned medical associations.

References

- Abou-Khalil B, Schlaggar BL (2002). Is it time to replace the Wada test? *Neurology* 59(2):160–161
- Amunts K, Malikovic A, et al (2000). Brodmann's areas 17 and 18 brought into stereotaxic space-where and how variable? *Neuroimage* 11(1):66–84
- Amunts K, Schleicher A, et al (1999). Broca's region revisited: cytoarchitecture and intersubject variability. *J Comp Neurol* 412(2):319–341
- Bandettini PA, Wong EC, et al (1992). Time course EPI of human brain function during task activation. *Magn Reson Med* 25(2):390–397
- Baumann SB, Noll DC, et al (1995). Comparison of functional magnetic resonance imaging with positron emission tomography and magnetoencephalography to identify the motor cortex in a patient with an arteriovenous malformation. *J Image Guid Surg* 1(4):191–197

- Baxendale S (2002) The role of functional MRI in the presurgical investigation of temporal lobe epilepsy patients: a clinical perspective and review." *J Clin Exp Neuropsychol* 24(5): 664-76
- Belliveau JW, Kennedy Jr DN, et al (1991) Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* 254(5032):716-719
- Benbadis SR, Binder JR, et al (1998) Is speech arrest during wada testing a valid method for determining hemispheric representation of language? *Brain Lang* 65(3):441-446.
- Berger H (1929) Über das Elektroenzephalogramm des Menschen. *Arch Psychiatr Nerven* 87:527-570
- Binder JR, Achten E, et al (2002) Functional MRI in epilepsy. *Epilepsia* 43(Suppl 1):51-63
- Bittar RG, Olivier A, et al (1999) Presurgical motor and somatosensory cortex mapping with functional magnetic resonance imaging and positron emission tomography. *J Neurosurg* 91(6):915-921
- Buckner RL, Bandettini PA, et al (1996) Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proc Natl Acad Sci USA* 93(25):14878-14883
- Cedzich C, Taniguchi M, et al (1996) Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region. *Neurosurgery* 38(5):962-970
- Coenen VA, Krings T, et al (2001) Three-dimensional visualization of the pyramidal tract in a neuronavigation system during brain tumor surgery: first experiences and technical note. *Neurosurgery* 49(1):86-92; discussion 92-93
- Cox RW (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29(3):162-173
- Detre JA, Leigh JS, et al (1992) Perfusion imaging. *Magn Reson Med* 23(1):37-45
- Duffau H, Capelle L, et al (2003) Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. *J Neurosurg* 98(4):764-778
- Duffau H, Capelle L, et al (1999) Intra-operative direct electrical stimulations of the central nervous system: the Salpetriere experience with 60 patients. *Acta Neurochir (Wien)* 141(11):1157-1167
- Duffau H, Capelle L, et al (2002) Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* 125(Pt 1):199-214
- Fernandez G, de Greiff A, et al (2001) Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. *Neuroimage* 14(3):585-594
- Fesl G, Moriggl B, et al (2003) Inferior central sulcus: variations of anatomy and function on the example of the motor tongue area. *Neuroimage* 20(1):601-610
- Fox PT, Mintun MA, et al (1986) Mapping human visual cortex with positron emission tomography. *Nature* 323(6091):806-809
- Fox PT and Raichle ME (1986) Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci USA* 83(4):1140-1144
- Frahm J, Merboldt KD, et al (1994) Brain or vein - oxygenation or flow? On signal physiology in functional MRI of human brain activation. *NMR Biomed* 7(1-2):45-53
- Friston K (1996) Statistical parametric mapping and other analyses of functional imaging data. *Brain mapping: the methods*. MJ Toga AW. New York, Academic press: 363-386
- Gaillard WD, Bookheimer SY and M Cohen (2000) The use of fMRI in neocortical epilepsy. *Adv Neurol* 84:391-404
- Gevins A (1995) High-resolution electroencephalographic studies of cognition. *Adv Neurol* 66:181-195; discussion 195-198
- Gevins A, Leong H, et al (1995) Mapping cognitive brain function with modern high-resolution electroencephalography. *Trends Neurosci* 18(10):429-436
- Gold S, Christian B, et al (1998) Functional MRI statistical software packages: a comparative analysis. *Hum Brain Mapp* 6(2):73-84
- Grabowski TJ (2000) Investigating language with functional neuroimaging. *Brain mapping: the systems*. MJ Toga AW. San Diego, San Francisco, New York, Boston, London, Sydney, Tokio: Academic Press: 425-461
- Grummich P, Nimsky C, et al (2006) Combining fMRI and MEG increases the reliability of presurgical language localization: A clinical study on the difference between and congruence of both modalities. *Neuroimage* 32(4):1793-1803
- Hämäläinen M, Ilmoniemi RJ, et al (1993) Magnetoencephalography -theory, instrumentation and applications to noninvasive studies of the working human brain. *Review of modern physics* 65:413-487
- Hari R and Ilmoniemi RJ (1986) Cerebral magnetic fields. *Crit Rev Biomed Eng* 14(2):93-126
- Hirsch J, Ruge MI, et al (2000) An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. *Neurosurgery* 47(3):711-721; discussion 721-722
- Holman BL and Devous Sr. MD (1992) Functional brain SPECT: the emergence of a powerful clinical method. *J Nucl Med* 33(10): 1888-1904
- Holodny AI, Gor DM, et al (2005) Diffusion-tensor MR tractography of somatotopic organization of corticospinal tracts in the internal capsule: initial anatomic results in contradistinction to prior reports. *Radiology* 234(3): 649-653
- Holodny AI, Schulder M, et al (1999) Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol* 20(4):609-612
- Holodny AI, Schulder M, et al (2000) The effect of brain tumors on BOLD functional MR imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol* 21(8):1415-1422
- Holodny AI, Schwartz TH, et al (2001) Tumor involvement of the corticospinal tract: diffusion magnetic resonance tractography with intraoperative correlation. *J Neurosurg* 95(6):1082
- Hulvershorn J, Bloy L, et al (2005) Spatial sensitivity and temporal response of spin echo and gradient echo bold contrast at 3 T using peak hemodynamic activation time. *Neuroimage* 24(1):216-223
- Hulvershorn J, Bloy L, et al (2005) Temporal resolving power

- of spin echo and gradient echo fMRI at 3T with apparent diffusion coefficient compartmentalization. *Hum Brain Mapp* 25(2):247–258
- Kober H, Nimsky C, et al (2001) Correlation of sensorimotor activation with functional magnetic resonance imaging and magnetoencephalography in presurgical functional imaging: a spatial analysis. *Neuroimage* 14(5):1214–1228
- Krings T, Reinges MH, et al (2001) Functional and diffusion-weighted magnetic resonance images of space-occupying lesions affecting the motor system: imaging the motor cortex and pyramidal tracts. *J Neurosurg* 95(5):816–824
- Krings T, Reinges MH, et al (2002) Factors related to the magnitude of T2* MR signal changes during functional imaging. *Neuroradiology* 44(6):459–466
- Kwong KK, Belliveau JW, et al (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA* 89(12): 675–679
- Lee CC, Ward HA, et al (1999) Assessment of functional MR imaging in neurosurgical planning. *AJNR Am J Neuroradiol* 20(8):1511–1519
- Logothetis NK (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos Trans R Soc Lond B Biol Sci* 357(1424):1003–1037
- Logothetis NK (2003) The underpinnings of the BOLD functional magnetic resonance imaging signal. *J Neurosci* 23(10):3963–3971
- Logothetis NK, Pauls J, et al (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412(6843):150–157
- Logothetis NK and Pfeuffer J (2004) On the nature of the BOLD fMRI contrast mechanism. *Magn Reson Imaging* 22(10):1517–1531
- Logothetis NK and Wandell BA (2004) Interpreting the BOLD signal. *Annu Rev Physiol* 66:735–769
- Mazziotta JC, Phelps ME, et al (1982) Tomographic mapping of human cerebral metabolism: auditory stimulation. *Neurology* 32(9):921–937
- Menon RS, Ogawa S, et al (1995) BOLD based functional MRI at 4 Tesla includes a capillary bed contribution: echo-planar imaging correlates with previous optical imaging using intrinsic signals. *Magn Reson Med* 33(3): 453–459.
- Moller M, Freund M, et al (2005) Real time fMRI: a tool for the routine presurgical localisation of the motor cortex. *Eur Radiol* 15(2):292–295
- Ogawa S, Lee TM, et al (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA* 87(24):9868–9872
- Ogawa S, Menon RS, et al (1993) Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophys J* 64(3):803–812
- Ogawa S, Tank DW, et al (1992) Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci USA* 89(13):5951–5
- Ojemann G, Ojemann J, et al (1989) Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg* 71(3):316–326
- Ojemann GA (1991) Cortical organization of language. *J Neurosci* 11(8):2281–2287
- Penfield W (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60:389–443
- Penfield W (1950) The cerebral cortex of man. New York, MacMillan: 57 ff
- Raichle ME (1983) Positron emission tomography. *Annu Rev Neurosci* 6:249–267
- Rausch R, Silfvenius H, et al (1993) Intra-arterial amobarbital procedures. Surgical treatment of the epilepsies. *JJ Engel*. New York, Raven Press: 341–357
- Reinges MH, Nguyen HH, et al (2004) Course of brain shift during microsurgical resection of supratentorial cerebral lesions: limits of conventional neuronavigation. *Acta Neurochir (Wien)* 146(4):369–377; discussion 377
- Roberts TP (2003). Functional magnetic resonance imaging (fMRI) processing and analysis. *ASNR Electronic Learning Center Syllabus*: 1–23
- Rutten GJ, Ramsey NF, et al (2002) Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. *Ann Neurol* 51(3):350–360
- Schreiber A, Hubbe U, et al (2000) The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement. *AJNR Am J Neuroradiol* 21(6):1055–1063
- Shinoura N, Yamada R, et al (2005) Preoperative fMRI, tractography and continuous task during awake surgery for maintenance of motor function following surgical resection of metastatic tumor spread to the primary motor area. *Minim Invasive Neurosurg* 48(2):85–90
- Steger TR and Jackson EF (2004) Real-time motion detection of functional MRI data. *J Appl Clin Med Phys* 5(2):64–70
- Stippich C, Hofmann R, et al (1999) Somatotopic mapping of the human primary somatosensory cortex by fully automated tactile stimulation using functional magnetic resonance imaging. *Neurosci Lett* 277(1):25–28
- Stippich C, Kapfer D, et al (2000) Robust localization of the contralateral precentral gyrus in hemiparetic patients using the unimpaired ipsilateral hand: a clinical functional magnetic resonance imaging protocol. *Neurosci Lett* 285(2):155–159
- Stippich C, Heiland S, et al (2002) Functional magnetic resonance imaging: Physiological background, technical aspects and prerequisites for clinical use. *Rofo* 174(1):43–49
- Stippich C, Kress B, et al (2003a) Preoperative functional magnetic resonance tomography (fMRI) in patients with rolandic brain tumors: indication, investigation strategy, possibilities and limitations of clinical application. *Rofo* 175(8):1042–1050
- Stippich C, Mohammed J, et al (2003b) Robust localization and lateralization of human language function: an optimized clinical functional magnetic resonance imaging protocol. *Neurosci Lett* 346(1–2):109–113
- Stippich C, Ochmann H and Sartor K (2002) Somatotopic mapping of the human primary sensorimotor cortex during motor imagery and motor execution by functional magnetic resonance imaging. *Neurosci Lett* 331(1):50–54
- Stippich C, Rapps N et al (2007) Feasibility of routine preoperative functional magnetic resonance imaging for localizing and lateralizing language in 81 consecutive patients with brain tumors. *Radiology* in press

- Stippich C, Romanowski A, et al (2004) Fully automated localization of the human primary somatosensory cortex in one minute by functional magnetic resonance imaging. *Neurosci Lett* 364(2):90–93
- Stippich C, Romanowski A, et al (2005) Time-efficient localization of the human secondary somatosensory cortex by functional magnetic resonance imaging. *Neurosci Lett* 381(3):264–268
- Sunaert S and Yousry TA (2001) Clinical applications of functional magnetic resonance imaging. *Neuroimaging Clin N Am* 11(2):221–236, viii
- Thulborn K (2006) Clinical functional Magnetic Resonance Imaging. *Current Protocols in Magnetic Resonance Imaging*. EM Haacke, John Wiley & Sons, Inc
- Thulborn, KR (1998) A BOLD move for fMRI. *Nat Med* 4(2): 155–156
- Thulborn KR (1999) Clinical rationale for very-high-field (3.0 Tesla) functional magnetic resonance imaging. *Top Magn Reson Imaging* 10(1):37–50
- Thulborn KR, Davis D, et al (1996) Clinical fMRI: implementation and experience. *Neuroimage* 4(3 Pt 3):S101–107
- Towle VL, Khorasani L, et al (2003) Noninvasive identification of human central sulcus: a comparison of gyral morphology, functional MRI, dipole localization, and direct cortical mapping. *Neuroimage* 19(3):684–697
- Turner R, Le Bihan D, et al (1991) Echo-planar time course MRI of cat brain oxygenation changes. *Magn Reson Med* 22(1):159–166
- Uematsu S, Lesser R, et al (1992) Motor and sensory cortex in humans: topography studied with chronic subdural stimulation. *Neurosurgery* 31(1):59–71; discussion 71–72
- Ulmer JL, Hacein-Bey L, et al (2004) Lesion-induced pseudodominance at functional magnetic resonance imaging: implications for preoperative assessments. *Neurosurgery* 55(3):569–579; discussion 580–581
- Ulmer JL, Salvan CV, et al (2004) The role of diffusion tensor imaging in establishing the proximity of tumor borders to functional brain systems: implications for preoperative risk assessments and postoperative outcomes. *Technol Cancer Res Treat* 3(6):567–576
- Van Westen D, Skagerberg G, et al (2005) Functional magnetic resonance imaging at 3T as a clinical tool in patients with intracranial tumors. *Acta Radiol* 46(6):599–609
- Wada J and T Rasmussen (1960) Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. Experimental and clinical observations. *J Neurosurg* 17:266–282
- Weiskopf N, Veit 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(3):577–586
- Wittek A, Kikinis R, et al (2005) Brain shift computation using a fully nonlinear biomechanical model. *Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv* 8(Pt 2):583–590
- Woolsey CN, Erickson TC, and WE Gilson (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. *J Neurosurg* 51(4):476–506
- Yousry TA, Schmid UD, et al (1997) Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain* 120 (Pt 1):141–157
- Zambreanu L, Wise RG, et al (2005) A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. *Pain* 114(3):397–407

Localization of Brain Activity using Functional Magnetic Resonance Imaging

RAINER GOEBEL

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KEY POINTS

Magnetic resonance imaging (MRI) is based on magnetic excitation of body tissue and the reception of returned electromagnetic signals from the body. Excitation induces phase-locked precession of protons with a frequency proportional to the strength of the surrounding magnetic field as described by the Larmor equation. This fact can be exploited for spatial encoding by applying magnetic field gradients along spatial dimensions on top of the strong static magnetic field of the scanner. The obtained frequency-encoded information for each slice is accumulated in two-dimensional k space which can be transformed into image space by Fourier analysis.

Functional MRI (fMRI) makes it possible to localize brain function since increased local neuronal activity leads to a surprisingly strong increase in local blood flow, which itself results in measurable increases in local magnetic field homogeneity. Increased local blood flow delivers chemical energy (glucose and oxygen) to the neurons. The temporary increase and decrease of local blood flow, triggered by increased neuronal activity, is

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called the hemodynamic response starting 2–4 s after stimulus onset. Increased local blood flow results in an oversupply of oxygenated hemoglobin in the vicinity of increased neuronal activity. The oversupply flushes deoxygenated hemoglobin from the capillaries and the downstream venules. Deoxygenated hemoglobin is paramagnetic, reducing the homogeneity of the local magnetic field and resulting in a weaker MRI signal than would be measurable without it. Oxygenated hemoglobin is diamagnetic and does not strongly reduce field homogeneity. Since the increased local blood flow replaces deoxygenated hemoglobin with oxygenated hemoglobin, local field homogeneity increases, leading to a stronger MRI signal as compared to a non-activated state. Measured functional brain images thus reflect neuronal activity changes as blood-oxygenation-level-dependent (BOLD) contrast.

Functional images are acquired using the fast echo planar imaging (EPI) pulse sequence allowing acquisition of a 64×64 image matrix in less than 100 ms. To sample signal changes over time, a set of slices typically covering the whole brain is measured repeatedly. Activation of neurons results in a BOLD signal increase of only about 1%–5% and lies buried within strong physical and physiological noise fluctuations of similar size. Proper preprocessing steps, including 3D motion correction and removal of drifts, reduce the effect of artifacts increasing the signal-to-noise ratio (SNR). In order to reliably detect stimulus-

related effects, proper statistical data analysis is performed. In order to estimate response profiles, condition-related time course episodes may be averaged in various regions of interest (ROIs). The core statistical tool in fMRI data analysis is the General Linear Model (GLM) making analysis of blocked and event-related experimental designs possible. To run a GLM, a design matrix (model) has to be constructed containing reference functions (predictors, model time courses) for all effects of interest (conditions), as well as confounds. The GLM fits the created model to the data independently for each voxel's data (time course), providing a set of beta values estimating the effects of each condition. These beta values are compared with each other using contrasts resulting in a statistical value at each voxel. The statistical values of all voxels form a three-dimensional statistical map. To protect against wrongly declaring voxels as significant, statistical maps are thresholded properly by taking into account the multiple comparison problem. This problem is caused by the large number of independently performed statistical tests (one for each voxel).

In recent years, parallel imaging techniques have been developed, which make simultaneously acquiring MRI data with two or more receiver coils possible. Parallel imaging can be used to increase temporal or spatial resolution. It also helps to reduce EPI imaging artifacts, such as geometrical distortions and signal dropouts in regions of different neighboring tissue types.

Since its invention in the early 1990s, functional magnetic resonance imaging (fMRI) has rapidly assumed a leading role among the techniques used to localize brain activity. The spatial and temporal resolution provided by state-of-the-art MR technology and its non-invasive character, which allows multiple studies of the same subject, are some of the main advantages of fMRI over the other functional neuroimaging techniques that are based on changes in blood flow and cortical metabolism (e.g. positron emission tomography, PET). fMRI is based on the discovery of OGAWA et al. (1990), that magnetic resonance imaging (MRI, also called nuclear magnetic resonance imaging) can be used in a way that makes it possible to obtain signals depending on the level of blood oxygenation. The measured signal is therefore also called “BOLD” signal (BOLD = blood oxy-

genation level-dependent). Since locally increased neuronal activity leads to increased local blood flow, which again changes local blood oxygenation, fMRI enables indirect measurements of neuronal activity changes. With appropriate data analysis and visualization methods, these BOLD measurements enable conclusions to be drawn about the localization and dynamics of brain function.

This chapter describes the basic principles and methodology of fMRI. After a description of the physical principles of MRI at a conceptual level, the physiology of the BOLD contrast mechanism is described. The subsequent, major part of the chapter provides an introduction to the current strategies of statistical image analysis techniques with a focus on the analysis of single-subject data because of its relevance for presurgical mapping of human brain function.

2.1

Physical Principles of MRI

MRI enables visualization of both anatomical and functional data of the human brain. This section shortly describes the main concepts of the physical principles of MRI. More detailed descriptions of the physical basis of MRI are available in several introductory texts, e.g. HUETTEL et al. (2004), BANCETTINI et al. (2000), BROWN and SEMELKA (1999), NESSAIVER (1997) and SCHILD (1990).

A typical whole body MR scanner has a hollow bore (tube) about 1 m in diameter. Inside that bore a cylinder is placed containing the primary magnet producing a very strong static, homogeneous magnetic field (B_0). Today, nearly all scanners create the magnetic field with superconducting electromagnets whose wires are cooled by cryogenics (e.g. liquid helium). Most standard clinical scanners used to image the human brain possess a magnetic field strength of 1.5 Tesla, which is 30,000 times the strength of the Earth's magnetic field (1 Tesla = 10,000 Gauss). In recent years, installation of tomographs with 3.0 Tesla has become common in major hospitals and research centres. In a few research labs, the human brain is imaged at ultra-high fields such as 7 and 9.4 Tesla. At higher field strengths it gets increasingly difficult to create a homogenous magnetic field, which is necessary for accurate spatial decoding of the raw measurement data. Since homogenous fields are easier to create for scanners with small bores, scanners with higher magnetic fields (10–20 Tesla) are currently only available for animal use. Besides the main magnet, additional coils are located inside the cylinder including shimming coils, gradient coils and a radio frequency (RF) coil. The shimming coils are used to shape the magnetic field increasing its homogeneity. The gradient coils are used to temporarily change the magnetic field linearly along any direction which is essential for spatial localization (see below). The RF coil is used to send radio frequency pulses into the subject.

In a typical brain scanning session, a subject or patient in supine position is slowly moved into the scanner bore using a maneuverable table. Scanning of anatomical and functional images is managed from a terminal in a control room by specifying slice positions and by running appropriate MRI pulse sequences. The control room usually has a window behind the computer terminal, which enables observation of the scanner room. Before the subject is

moved into the scanner, the head is placed in a small replaceable coil, called the head coil. This coil surrounds the head and is used to send radio frequency pulses into the subject as well as to receive electromagnetic echos. When receive-only head coils are used, the radio frequency pulses are provided by the RF coil in the cylinder of the scanner. The head coil is an example of a volume coil, which are designed such that the sensitive volume (e.g. brain) experiences a fairly uniform RF field. Surface coils are receive-only RF coils that are placed directly upon the surface of the anatomy to be imaged. They provide very high signal to noise in their immediate vicinity but recorded images suffer from extreme non-uniformity because the obtained signal intensity drops rapidly with distance and approaches zero about one coil diameter away from the coil. Phased array coils are an attempt to combine the positive properties of volume and surface coils by combining images from two or more surface coils to produce a single image (see Sect. 2.4.1).

The physical principles of MRI are the same for anatomical and functional imaging. What makes functional imaging special is described in Sect. 2.2. The operation of MRI can be described in two major themes. The first theme refers to the excitation and recording of electromagnetic signals reflecting the properties of the measured object. The second theme refers to the construction of two- and three-dimensional images reflecting how the measured object properties vary across space.

2.1.1

Spin Excitation and Signal Reception

MRI is based on the magnetic excitation of body tissue and the recording of returned electromagnetic signals from the body. All nuclei with an odd number of protons are magnetically excitable. The atom of choice for MRI is ^1H , the most common isotope of hydrogen having a nucleus with only one proton. Hydrogen protons are ideally suited for MRI because they are abundant in human tissue and possess particularly favorable magnetic properties. Water is the largest source of protons in the body, followed by fat. Protons have magnetic properties because they possess a spin: they rotate like a spin top around their own axes inducing a small directed magnetic field. In a normal environment, the magnetic fields of the spins in the human body are oriented randomly and, thus, cancel each other out. If, however, the body of

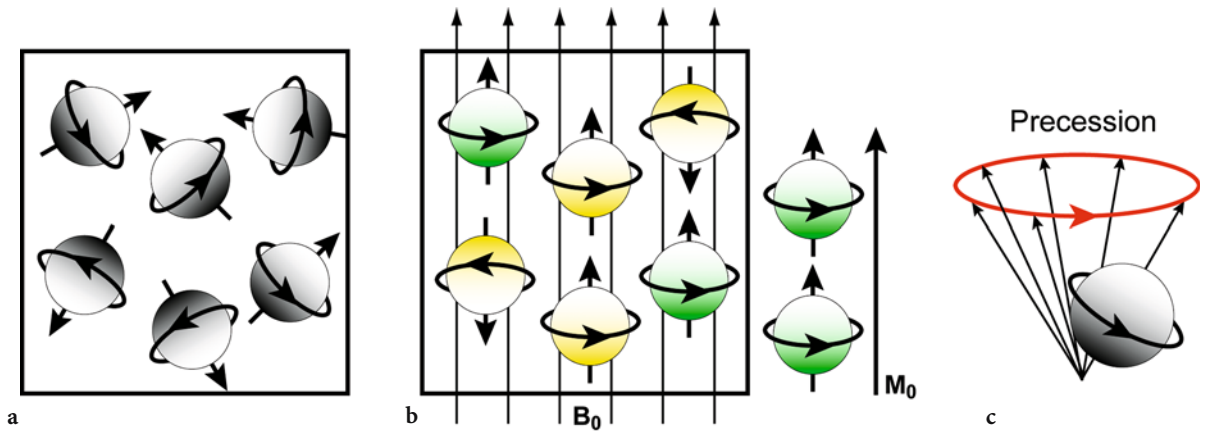


Fig. 2.1a–c. Spinning protons are little magnets because of the spin property. **a** Without an external magnetic field, the directions of the spins are randomly distributed. **b** When placed within a large magnetic field, the spins align either with the field (parallel) or against the field (antiparallel). A slight excess of spins align with the external magnetic field resulting in a net magnetic field parallel to the external magnetic field. **c** A spin is actually not aligning its axis of rotation with the external magnetic field as shown in (a) and (b), but rotates around the direction of the field. This motion is called precession.

a subject is placed in the strong static magnetic field of an MRI tomograph (called B_0), the spins orient themselves in line with that field, either parallel or antiparallel (Fig. 2.1). Since a slightly larger proportion of spins align parallel to the scanner magnetic field, the body gets magnetized. The excess number of spins aligned with the external magnetic field is proportional to the strength of the external magnetic field and is in the order of 10^{15} spins at 1.5 Tesla in a $2 \times 2 \times 2$ mm volume of water. The total magnetic field of the excess spins is called M_0 . Just as a spinning top wobbles about its axis, the spinning protons wobble, or precess, about the axis of the external B_0 field (Fig. 2.1c). The precession frequency of the protons depends on the strength of the surrounding magnetic field. More precisely, the precession frequency ω is directly proportional to the strength of the external magnetic field and is defined by the Larmor Equation:

$$\omega_0 = \gamma B_0$$

The symbol ω_0 is known as the precessional, Larmor or resonance frequency. The symbol γ refers to the gyromagnetic ratio, which is a constant unique to every atom. For hydrogen protons, $\gamma = 42.56$ MHz per Tesla. At the magnetic field strength of a 3-Tesla scanner, the precession frequency of hydrogen protons is thus 128 MHz.

If an applied electromagnetic pulse has the same frequency as the proton's precession frequency, then the protons get "excited" by absorbing the transmit-

ted energy. This important principle is called resonance and gives the method magnetic resonance imaging its name. Since the precession frequency is in the range of radio frequency waves, the applied electromagnetic pulse is also called a radio frequency (RF) pulse. As an effect of excitation, spins flip from the parallel (lower energy) state to the antiparallel (higher energy) state. The RF pulse furthermore lets the excited protons precess in phase. As a result, the magnetization vector M_0 moves down towards the x-y plane (Fig. 2.2). The x-y plane is perpendicular to the static magnetic field and is also referred to as the transverse plane. The angle, α , of rotation towards the x-y plane is a function of the strength and duration of the RF pulse. If $\alpha = 90^\circ$, the magnetization vector is completely moved into the x-y plane with an equal amount of spins aligned parallel and antiparallel (Fig. 2.2b). Since the protons precess in phase, i.e. they point in the same direction within the x-y plane, the magnetic fields of the spins add up to form a net magnetic field M_{xy} in the x-y plane. This transversal component of the rotating electromagnetic field can be measured (received) in the receiver coil (antenna) because it induces a detectable current flow.

The established in-phase precession is, however, not stable after the RF transmitter is turned off. Because of interactions between the magnetic fields of the protons, the transverse magnetization decays within a few tens of milliseconds. These spin-spin interactions lead to slightly different local magnetic field strengths and, thus, to slightly different precession frequencies leading to phase shifts between

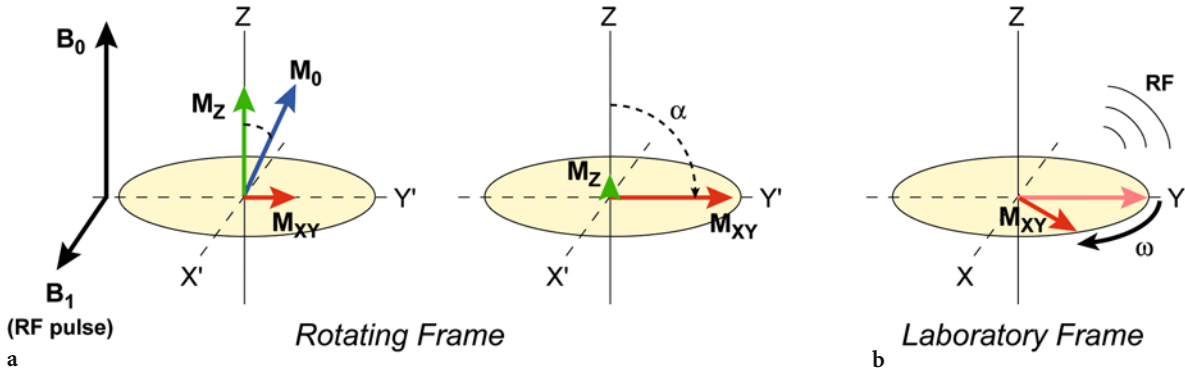


Fig. 2.2a,b. Spins in the lower energy state can be excited by an electromagnetic pulse at the resonance frequency ω_0 forcing the spins absorbing the transmitted energy to precess in phase. **a** As an effect of excitation, the net magnetic field M_0 (blue vector) smoothly tips down towards the x-y plane. The longitudinal component M_z (green vector) decreases over time while the transverse component M_{xy} (red vector) increases. This view assumes that the observer is moving with the precessing protons (rotating frame of reference). **b** Viewed from outside (laboratory frame of reference), the net magnetization vector rotates with angular velocity ω_0 given by the Larmor equation. The rotating magnetic field in the x-y plane emits radiofrequency waves, which can be measured by a receiver coil.

the precessing spins (dephasing). The dephasing process is also called transversal relaxation. It progresses initially rapidly but slows down over time following an exponential function with time constant T_2 with values in the range of 30–150 ms. Due to magnetic field inhomogeneities in the static magnetic field and in physiological tissue, the spins get out of phase actually faster than T_2 and therefore the measured raw signal in the receiver coil, the free induction decay (FID), decays with the shorter time constant T_2^* (Fig. 2.3):

$$M_{xy} = M_0 e^{-t/T_2^*}$$

The fact that local field inhomogeneities lead to different precession frequencies increasing the speed of dephasing is an important observation for fMRI because local field inhomogeneities also depend on the local physiological state, especially the state of local blood oxygenation, which itself depends on the state of local neuronal activity. Measurements of changing local magnetic field inhomogeneities (T_2^* parameter), thus, provide indirect measurements of local neuronal activity.

The speed of spin dephasing is determined by random effects as well as by fixed effects due to magnetic field inhomogeneities. The dephasing effect of constant magnetic field inhomogeneities can be reversed by application of a 180° RF pulse. A time duration of $t = \tau$ is allowed to elapse while the spins go out of phase. Then a 180° RF pulse is applied flipping the dephased spin vectors about the X' or Y' axis in the

rotating frame of reference. As an effect of the pulse, the order of the spins is reversed (Fig. 2.4). At the echo time $TE = 2\tau$, the vectors are back in phase producing a large signal, the spin echo. This process is similar to a race situation in which participants run with different (but constant) speed. At time τ they get a signal (" 180° pulse") to turn around and go back; assuming they continue in the same speed, they will all arrive at the starting line at the same time (2τ).

The amplitude of the obtained spin echo will be smaller than the amplitude during the FID because part of the signal is inevitably lost due to random spin-spin interactions (T_2 decay). As soon as the spins are all back in phase at the echo time, they immediately start to go out of phase again. An additional 180° RF pulse will generate a second echo (Fig. 2.4). This process can be continued as long as enough signal is available. By setting the time of the 180° pulse, the amplitude of the T_2 signal can, thus, be assessed at any moment in time.

Besides dephasing, the spins reorient themselves with the direction of the strong static magnetic field of the scanner since the excited spins slowly go back into the low energy state realigning with the external magnetic field. This reorientation process is called longitudinal relaxation and progresses slower than the dephasing process. The increase (recovery) of the longitudinal component M_z follows an exponential function with time constant T_1 with values in the range of 300–2000 ms:

$$M_z = M_0 (1 - e^{-t/T_1})$$

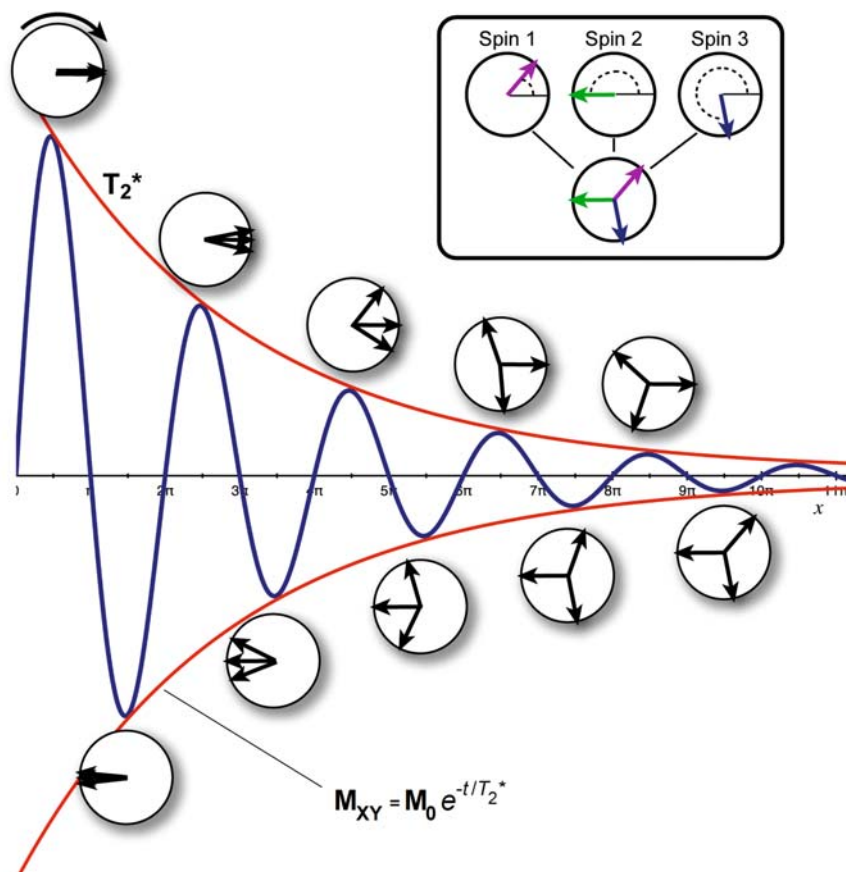


Fig. 2.3. The signal amplitude (red curve) of the measured raw MR signal, the free induction decay (FID), decays exponentially with time constant T_2^* . The raw signal itself is oscillating at the resonance frequency (blue curve). The signal is lost due to dephasing as indicated by the phase coherence plots (circles) with three representative, superimposed spins (see inset). The amplitude of the signal at any moment in time is determined by the sum of the spin vectors. When the spins are all in phase (left side), the maximum signal is obtained, i.e. the vector sum equals M_0 . When the spins are completely out of phase (right side), the signal is completely lost, i.e. the sum of the spin vectors equals zero.

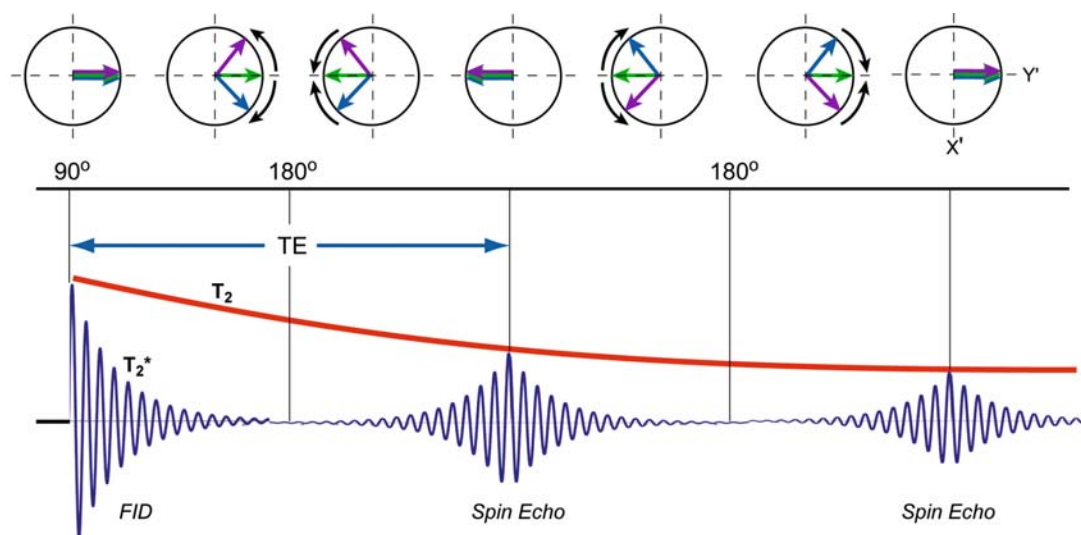


Fig. 2.4. The effect of constant magnetic field inhomogeneities can be reversed by application of a 180° RF pulse, which flips the dephased vectors about the X' axis. This is indicated in the upper row with three spin vectors, one precessing at the resonance frequency (green vector), one precessing slightly faster (violet vector), and one precessing slightly slower (blue vector) leading to dephasing. The 180° RF pulse reverses the order of the spins, but not the direction of rotation. The faster spin now runs behind catching up over time, while the slower spin runs ahead slowly falling back. At time TE (echo time), the vectors are back in phase producing a large signal, the spin echo. A second 180° RF pulse will generate a second echo (right side). The maximum amplitude of the echos gets smaller over time because signal is inevitably lost due to random spin-spin interactions (T_2 decay, red curve).

Note that the absorbed RF energy is not only released in a way that it can be detected outside the body as RF waves; part of the energy is given to the surrounding tissue, called the lattice. The spin-lattice interactions determine the speed of T_1 recovery, which is unique to every tissue. Tissue-specific T_1 and T_2 values enable MRI to differentiate between different types of tissue when using properly designed MRI pulse sequences.

2.1.2

Image Reconstruction

The described principles of magnetic resonance do not explain how one can obtain images of the brain. This requires attributing components of the signal to those positions in space from which they originated. Although not identical for all measurement sequences, the principles for localizing signal sources typically contains the combined application of three fundamental techniques, selective excitation of a slice, frequency encoding and phase encoding. Each of these steps enables localization of the signal's source with respect to one spatial dimension. Paul C. Lauterbur and Peter Mansfield were awarded the 2003 Nobel Prize in Medicine for their discovery that magnetic field gradients can be used for spatial encoding. The gradient coils of the MRI scanner make it possible to add a magnetic field to the static magnetic field, which causes the field strength to vary linearly with distance from the center of the magnet. According to the Larmor equation, spins on one side are exposed to a higher magnetic field and precess faster, while spins on the other side are exposed to a lower magnetic field and precess slower than spins in the center (Fig. 2.5b).

2.1.2.1

Selective Slice Excitation

A magnetic field gradient is used to select a slice of the imaged object (slice selection gradient). Since spins precess with different frequencies along a gradient, protons can be excited selectively: An applied electromagnetic pulse of a certain frequency band will excite only those protons along the gradient precessing at the same frequency band. Spins outside that range will precess at different frequencies and will, thus, not absorb the transmitted RF energy. The selectively excited protons are located in a slice oriented perpendicular to the gradient direction. A gradient

along the z-axis will result in an axial slice, a gradient along the x-axis in a sagittal slice, and a gradient along the y-axis in a coronal slice. Oblique slices can be obtained by applying two or three gradients simultaneously. The position and thickness of the selected slice depends on the slope of the applied gradient and the frequency band of the applied RF pulse. After selective slice excitation, the measured echo will be restricted to a compound signal from the excited protons within the slice. For subsequent spatial encoding, the slice selection gradient is turned off.

2.1.2.2

Frequency Encoding

While receiving the signal (FID or echo) from the excited slice, a magnetic field gradient can be applied along one of the two remaining spatial dimensions. This second gradient, running along one dimension of the excited slice, is called frequency encoding gradient. Note that this gradient is not used to selectively excite protons, but to encode a spatial dimension for those protons already excited in the slice. Due to the applied gradient, the protons within the slice precess with different frequencies along the respective dimension allowing differentiating spatial positions in the received signal (Fig. 2.5). The frequency encoding gradient is also called read-out gradient since it is tuned on during reception of the signal from the protons. The strength of the signal at each frequency is directly related to the strength of the signal at the encoded spatial position. The measured composite time domain signal consists of the sum of all frequency responses. The Fourier transform (FT) can be used to extract the strength of the signal at each frequency (amplitude and phase information) from the composite signal. Since space has been frequency encoded, the FT provides the strength of the signal at different spatial positions. The obtained frequency-specific information can thus be used to form a spatial image (Fig. 2.5b). In such an image, the grey level is used to represent the strength of the signal at each picture element (pixel).

2.1.2.3

Phase Encoding

A further encoding step is required in order to be able to also separate signal components originating from different positions along the second dimension in the imaging plane. This is achieved by briefly adding another gradient to the static magnetic field

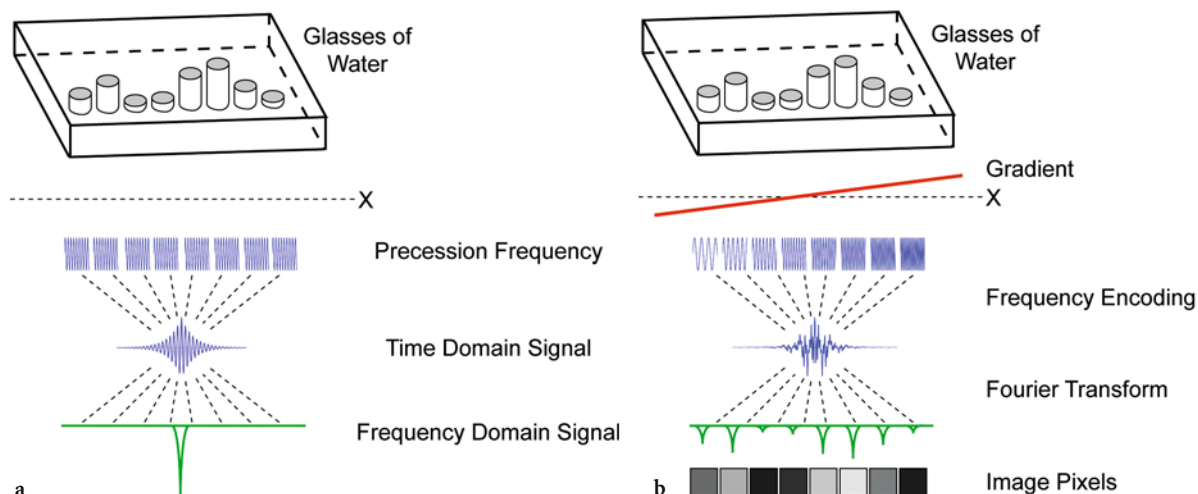


Fig. 2.5a,b. Assume that eight glasses with different amounts of water are placed in the MRI scanner along the x-axis and that a single, thick slice containing all glasses has been excited. **a** In the absence of any gradients, all of the excited protons from all glasses are spinning at the same frequency. The received signal also oscillates at that frequency and its amplitude reflects the sum of excited water protons of all glasses. Since all protons precess at the same frequency, the Fourier transform can not be used to identify signals from different spatial positions along the x-axis. **b** If a gradient is applied in the x direction, the spins will precess at frequencies that depend upon their position along the gradient. Spatial information is now frequency-encoded: The strength of the signal at each frequency is directly related to the number of excited protons from the respective glass of water. The obtained composite time domain signal is the sum of these frequencies. The Fourier Transform can now be used to determine the strength of the signal at each frequency. Since frequencies encode different spatial positions, an “image” of eight pixels can be formed. The grey values of these pixels reflect the relative amount of water in the different glasses.

oriented along the remaining (third) spatial dimension before receiving an echo. This third magnetic field gradient is called phase encoding gradient. While the frequency encoding gradient is turned on during reception of the signal, the phase encoding (PE) gradient is turned off just before receiving the echo and is, thus, not (permanently) changing the frequency at different spatial positions. This is necessary since frequency encoding gradients in two dimensions would result in ambiguous spatial encoding. Prior to read-out, the brief duration of the phase encoding gradient results in a short moment of different precession frequencies within each row of the slice. After turning off the phase encoding gradient, the protons within each row precess again with the same frequency but they will now precess with a systematic phase shift along the positions within each row. The amount of phase shift depends on the position of a proton along the encoded second image dimension. Through proper combination of frequency encoding in one dimension and phase encoding in the other dimension, all positions within a 2D image can be uniquely encoded with a desired resolution. Unfortunately a single application of the phase-encoding gradient is not sufficient

to encode the second image dimension. The process of excitation and phase-encoding must be repeated many times for a single slice. At each repetition, the strength of the phase-encoding gradient is slightly changed in order to ultimately obtain a complete frequency x phase encoding of the slice.

2.1.2.4

Two-Dimensional k Space

The data obtained from a series of excitation-recording cycles can be arranged in a two-dimensional space called k space. Each row of k space corresponds to the data of one excitation-recording cycle with a different phase-encoding step. As described above, the echo signal of one line in k space contains a frequency encoded representation of one dimension of the selected slice. While the slice selection and frequency encoding gradients are the same from cycle to cycle, the slope of the phase encoding gradient is changed by a constant value across cycles and, thus, from line to line in k space. The imposed phase shift for a specific proton depends on the strength of the phase encoding gradient and on the proton's position along the second image dimension. A series

of phase encoding steps “fills” k space in such a way that the second slice dimension ultimately also gets frequency encoded. The k space thus contains two-dimensional frequency encoded information of the slice, which can be transformed into two-dimensional image space by application of the two-dimensional Fourier transform (2D FT).

2.1.2.5

Echo-Planar Imaging

The described procedure is applied for each slice of a scanned volume. A properly specified series of electromagnetic pulses allowing to construct one or more 2D images from electromagnetic echos is called an MRI pulse sequence. The most frequently used sequence for fMRI is gradient-echo echo-planar imaging (GE-EPI). This sequence enables very rapid imaging of a slice by performing all phase-encoding steps after a single 90° excitation pulse. This sequence requires switching the read-out gradient rapidly on and off to fill k space line by line resulting in a series of (e.g. 64) small gradient echos within the duration of a single T_2^* decay. A complete image can thus be obtained in about 50–100 ms as opposed to several seconds with standard (functional) imaging sequences. GE-EPI is very sensitive to field inhomogeneities influencing the speed of dephasing (T_2^* contrast). This is essential for functional imaging (see below) but also produces image distortions, called susceptibility artifacts, which occur especially at tissue boundaries. Running EPI sequences requires a high performance (i.e. expensive) gradient system to enable very rapid gradient switching.

2.2

Physiological Principles of fMRI

Neuronal activity consumes energy, which is produced by chemical processes requiring glucose and oxygen. The vascular system supplies these substances by a complex network of large and small vessels. The arterial part of the vascular system transports oxygenated blood through an increasingly fine-grained network of blood vessels until it reaches the capillary bed where the chemically stored energy (oxygen) is transferred to the neurons. If the brain is in resting state, 30%–40% of

the oxygen is extracted from the blood in the capillary bed. The venous system transports the less oxygenated blood away from the capillary bed. Oxygen is transported in the blood via the hemoglobin molecule. If hemoglobin carries oxygen, it is called oxygenated hemoglobin (HbO_2), while it is called deoxygenated hemoglobin (Hb) when it is devoid of oxygen. While the arterial network contains almost only oxygenated hemoglobin, the capillary bed and the venous network contain a mixture of oxygenated and deoxygenated hemoglobin.

2.2.1

Neurovascular Coupling

A local increase of neuronal activity immediately leads to an increased oxygen extraction rate in the capillary bed and, thus, in an increase in the relative concentration of deoxygenated hemoglobin. This fast response to increased neuronal activity is described as the “initial dip” (Fig. 2.7). After a short time of about 3 s the increased local neuronal activity also leads to a strong increase in local blood flow. This response of the vascular system to the increased energy demand is called the hemodynamic response. Recent studies indicate that synaptic signal integration (measured by the local field potential, LFP) is a better predictor of the strength of the hemodynamic response than spiking activity (LOGOTHETIS et al. 2001; MATHIESEN et al. 2000). It thus seems likely that the hemodynamic response primarily reflects the input and local processing of neuronal information rather than the output signals (LOGOTHETIS and WANDELL 2004). Note that it is not yet completely known how the neurons “inform” the vascular system about their increased energy demand. Important theories about neuro-vascular coupling mechanisms are described, among many others, by Fox et al. (1988), BUXTON et al. (1998) and MAGISTRETTI et al. (1999). It appears likely that astrocytes play an important role because these special glial cells are massively connected with both neurons and the vascular system.

The hemodynamic response consists in increased local cerebral blood flow (CBF), as well as increased cerebral blood volume (CBV), probably as a mechanical consequence of increased blood flow. The hemodynamic response not only compensates quickly for the slightly increased oxygen extraction rate but it is so strong that it results in a substantial local *oversupply* of oxygenated hemoglobin (Figs. 2.6,

2.7). Note that it is not yet clear why the vascular system responds with a much stronger increase in cerebral blood flow than appears to be necessary. The increased CBV may help to explain the post-stimulus undershoot (Fig. 2.7) observed in typical fMRI responses (balloon model; Buxton et al. 1998). While CBF and oxygen extraction rate may quickly return to baseline, the elastic properties of the dilated venules will require many seconds until baseline size is reached. In the expanded space of the dilated vessels more deoxygenated hemoglobin will accumulate reducing the MRI signal below the pre-stimulus baseline level.

2.2.2 The BOLD Effect

The most common method of fMRI is based on the BOLD effect (OGAWA et al. 1990). This exploits the

fact that oxygenated hemoglobin has different magnetic properties to deoxygenated hemoglobin. More specifically, while oxygenated hemoglobin is diamagnetic, deoxygenated hemoglobin is paramagnetic altering the local magnetic susceptibility, creating magnetic field distortions within and around the blood vessels in the capillary bed and venules. During the hemodynamic response (oversupply phase), the oxygenated to deoxygenated hemoglobin ratio increases resulting in a more homogeneous local magnetic field. As follows from the description in Sect. 2.1, excited spins dephase slower in a more homogeneous magnetic field leading to a stronger measured MRI signal in the activated state when compared to a resting state (Fig. 2.6). The BOLD effect, thus, measures increased neuronal activity indirectly via a change in local magnetic field (in)homogeneity, which is caused by an oversupply of oxygenated blood (Fig. 2.6). Note that these field inhomogeneities are only detectable with MRI

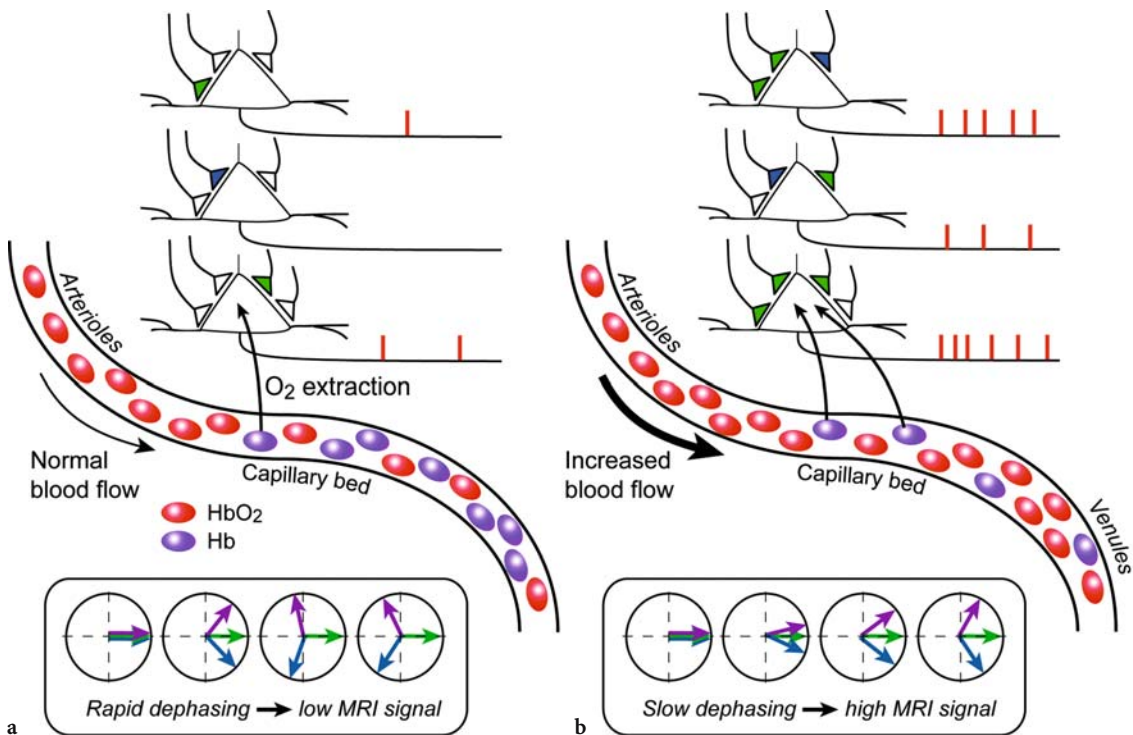
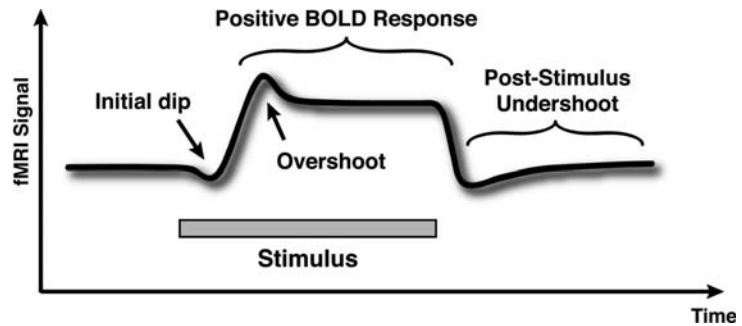


Fig. 2.6a,b. From neural activity to BOLD MRI responses. **a** If a cortical region is in baseline mode, neural activity – including synaptic signal integration and spike generation – is low (*upper part*). Cerebral blood flow (CBF) is at a basal level. A constant oxygen extraction rate fueling neural activity leads to a fixed deoxygenated hemoglobin (Hb) to oxygenated hemoglobin (HbO₂) ratio in the capillary bed and venules. Since Hb is paramagnetic, it distorts the magnetic field. The Hb-related magnetic field inhomogeneities lead to rapid dephasing of excited spins resulting in a low MRI signal level (*lower part*). **b** If the cortical region is in activated state, synaptic signal integration and spiking activity increases, leading to an increased oxygen extraction rate (*upper part*). CBF strongly increases delivering oxygen beyond local need, which essentially flushes Hb away from the capillary bed (*middle part*). Since HbO₂ does not substantially distort the homogeneity of the local magnetic field, excited spins dephase slower than in the baseline state (*lower part*) resulting in an enhanced MRI signal (BOLD effect).

Fig. 2.7. Idealized time course of the hemodynamic response following a long (approximately 20 s) stimulation event. The theoretically expected initial dip is not reliably measured in human fMRI studies. For long stimulation events, the signal often rises initially to a higher value (*overshoot*) than the subsequently reached plateau. When the stimulus is turned off, the signal often falls below the baseline signal level (*undershoot*), which is then approached slowly.



because of the different magnetic properties of oxygenated and deoxygenated hemoglobin. The change in the local HbO_2/Hb ratio and its associated change in magnetic field homogeneity, thus, acts as an endogenous marker of neural activity.

2.2.3

The BOLD Hemodynamic Response

The time course of evoked fMRI signals, reflecting the BOLD hemodynamic response, is well-studied for primary visual cortex (V1). After application of a short visual stimulus of 100 ms, the observed (positive) signal response starts to rise after 2–3 s (oversupply phase) and reaches a maximum level after 5–6 s. About 10 s later, the signal again reaches the baseline level. As compared to the neuronal response of about 100 ms duration, the corresponding fMRI response is thus characterized by a delayed, gradual response profile extending as long as 20 s. Despite this sluggish response, the latency of response onsets appear to reflect quite precisely neuronal onset times (MENON and KIM 1999): If the left and right visual field are stimulated sequentially with a stimulus onset asynchrony of only 100 ms, response profiles from the right and left primary visual cortex are systematically shifted according to the applied temporal offset. More generally, the fMRI signal may reflect the flow of information processing across different brain areas as a sequence of shifted response profiles. Estimates of the temporal resolution with respect to onset delays are more in the order of hundreds of milliseconds than in the order of seconds (FORMISANO and GOEBEL 2003).

Assuming a linear time invariant (LTI) system, one can predict the expected time course of arbitrary long stimulation periods from the known response to a short stimulus. The response to a very short stimulus is called the impulse response function or, in the context of fMRI, the BOLD hemodynamic

response function (HRF). The output (expected fMRI response) of a LTI system is obtained by convolving the input time course (e.g. stimulation “box-car” time course) with an impulse response function (Fig. 2.9). For primary visual cortex (V1), BOYNTON et al. (1996) showed that the measured responses to stimuli with varying amplitudes and durations could indeed be predicted well from the response profile obtained from a short visual stimulus. A well-suited function to model the hemodynamic impulse function is the probability density function (pdf) of the gamma distribution scaled by parameter A :

$$y(x; A, \tau, \sigma) = A x^{\tau/\sigma - 1} \frac{e^{-x/\sigma}}{\sigma^{\tau/\sigma} \Gamma(\tau/\sigma)}$$

Parameters τ and σ define the onset and dispersion of the response peak, respectively. While BOYNTON et al. (1996) used a single gamma function to characterize the impulse response function, the sum of two gamma functions (FRISTON et al. 1998) make it possible to also capture the undershoot usually observed in fMRI responses. The first gamma function typically peaks 5 s after stimulus onset ($\tau = 6$), while the second gamma function peaks 15 s after stimulus onset ($\tau = 16$, see Fig. 2.8). After convolution of a stimulus time course with the impulse function (Fig. 2.9), the calculated time course can be directly used as a reference function for statistical data analysis (see Sect. 2.3.3).

Note that the linear system assumption is reasonably valid only for stimuli with sufficient temporal separation. For a series of short stimuli separated by intervals shorter than 2–4 s, non-linear interaction effects have to be expected (e.g. ROBSON et al. 1998). Note further that calculation (convolution) of expected time courses requires as input the valid specification of the time course of assumed neuronal response profiles, which is often not simply a copy of stimulus timing. A simple box-car time course, for example, assumes that neurons in a stimulated cor-

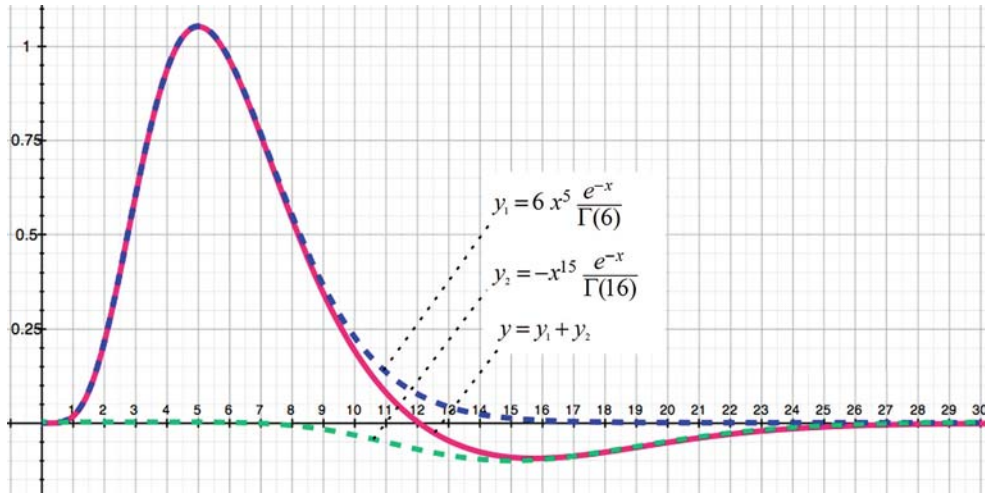


Fig. 2.8. The two-gamma function enables modelling of typical hemodynamic impulse responses. One gamma function models the peak (τ) and dispersion (σ) of the positive BOLD response while the second gamma function models the peak and dispersion of the undershoot response. Parameter A scales the amplitudes of the individual gamma functions.

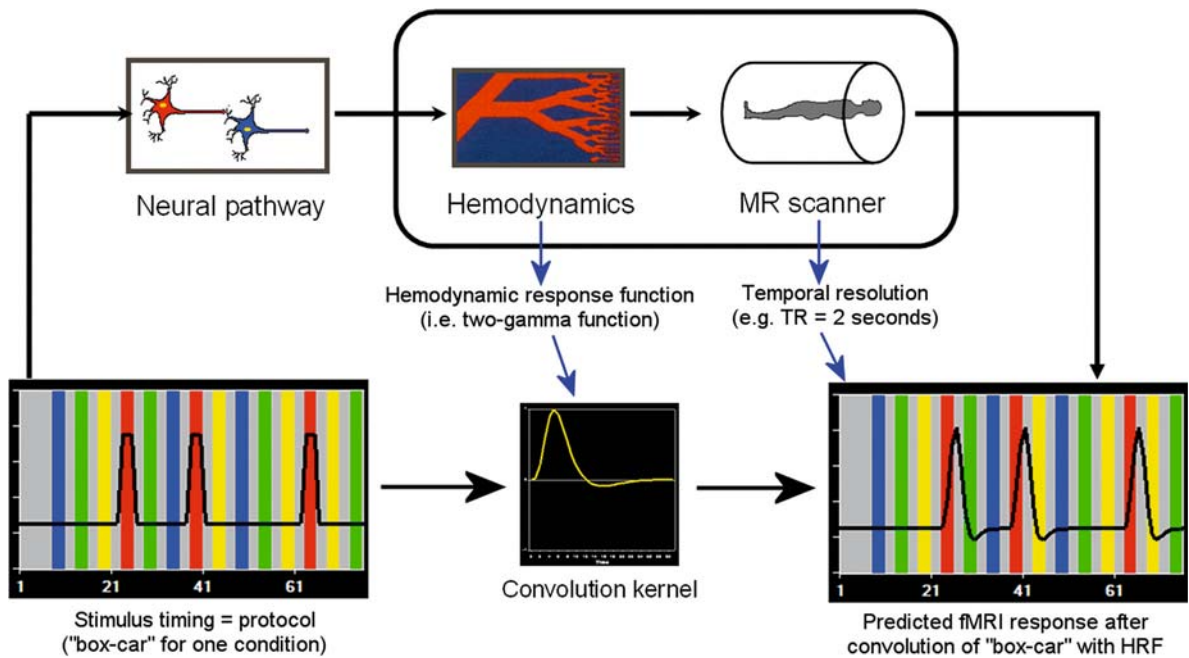


Fig. 2.9. Calculation of expected fMRI signal response for one condition of a protocol using convolution. The calculated response depends on the chosen model for the BOLD hemodynamic response function (HRF), e.g. two gamma function (*middle part*). The expected response is obtained by convolution of the box-car time course (*left*) with the chosen HRF. The convolved time course is downsampled to the temporal resolution (sampling intervals) of the fMRI measurements given by the volume TR value (*right*).

tical area are active with constant amplitude in prolonged “on” periods. It is well known, however, that this assumption is too simplistic for neurons in early sensory areas. For higher cortical areas, e.g. frontal areas involved in working memory, the neuronal response profile might differ substantially with respect to stimulus timing. Assuming that neuronal responses are correctly specified, it appears reasonable to use the same hemodynamic response function for all brain regions to predict expected BOLD signal time courses since neuro-vascular coupling should be similar in different brain areas. If it is difficult to specify proper “neuronal” input response profiles, a more general approach should be used (e.g. deconvolution analysis, see Sect. 2.3.3).

While fMRI responses clearly reflect the oversupply phase of the hemodynamic response, the theoretically expected initial dip (Fig. 2.7) has not been reliably detected in standard human fMRI measurements (for animal studies, see, e.g. KIM et al. 2000). This component of the idealized hemodynamic response is thus not included in the standard single or two gamma convolution kernels (Fig. 2.8). Data analysis of almost all fMRI studies is therefore based on the signals coming from the much stronger positive BOLD response.

2.3 fMRI Data Analysis

A major goal of fMRI measurements is the localization of the neural correlates of sensory, motor and cognitive processes. Another major goal of fMRI measurements is the characterization of the response profile in various regions-of-interest (ROIs) by retrieving plots of averaged signal time courses for different experimental conditions. Inspection of the shape of (averaged) time courses may also help to separate signal fluctuations due to measurement artefacts from stimulus-related hemodynamic responses. In order to obtain fMRI data with relatively high temporal resolution, functional time series are acquired using fast MR sequences sensitive to BOLD contrast. As described above, most fMRI experiments use the gradient echo EPI sequence, which allows acquisition of a 64×64 matrix in 50–100 ms. A typical functional scan of the whole brain with 20–40 slices lasts only about 2 s on state-of-the-art MRI scanners. The data obtained from

scanning all slices once at different positions (e.g. 30 slices covering the whole brain) is subsequently referred to as a *functional volume* or a functional 3D image. The measurement of an uninterrupted series of functional volumes is referred to as a run. A run, thus, consists of the repeated measurement of a functional volume and, hence, the repeated measurement of the individual slices. The sampling interval – the time until the same brain region is measured again – is called volume TR. The volume TR specifies the temporal resolution of the functional measurements since all slices comprising one functional volume are obtained once during that time. Note, however, that the slices of a functional volume are not recorded simultaneously, which implies that data from different regions of the brain are recorded at different moments in time (see Sect. 2.3.2.2.2). During a functional experiment, a subject performs tasks typically involving several experimental conditions. A short experiment can be completed in a single run, which typically consists of 100–1000 functional volumes. Assuming a run with 500 volumes each consisting of 30 slices of 64×64 pixels and that 2 bytes are needed to store each pixel, the amount of raw data acquired per run would be $500 \times 30 \times 64 \times 64 \times 2 = 122,880,000$ bytes or roughly 117 MB. In more complex experiments, a subject typically performs multiple runs in one scanning session resulting in about 500 MB of functional data per subject per session.

Given the small amplitude of task-related BOLD signal changes of typically 1%–5%, and the presence of many confounding effects, such as signal drifts and head motion, the localization and characterization of brain regions responding to experimental conditions of the stimulation protocol is a non-trivial task. The major analysis steps of functional and associated anatomical data will be described in the following paragraphs including spatial and temporal preprocessing, statistical data analysis, coregistration of functional and anatomical data sets and spatial normalization. Although these essential data analysis steps are performed in a rather standardized way in all major software packages, including AFNI (<http://afni.nimh.nih.gov/afni/>), BrainVoyager (<http://www.brainvoyager.com/>), FSL (<http://www.fmrib.ox.ac.uk/fsl/>) and SPM (<http://www.fil.ion.ucl.ac.uk/spm/>), there is still room for improvements as will be discussed below. For the visualization of functional data, high-resolution anatomical data sets with a resolution of (or close to) cubic millimeters are often acquired in a recording session. In most cases, these anatomical volumes are

scanned using slow T1-weighted MR sequences that are optimized to produce high-quality images with very good contrast between gray and white matter. In some analysis packages, anatomical data sets do not only serve as a structural reference for the visualization of functional information but are often also used to improve the functional analysis itself, for example, by restricting statistical data analysis to gray matter voxels. The preprocessing of high-resolution anatomical data sets and their role in functional data analysis will be described in Sect. 2.3.4. Since some data analysis steps depend on the details of the experimental paradigm, the next section shortly describes the two most frequently used experimental designs.

2.3.1

Block and Event-Related Designs

In the early years of fMRI measurements, experimental designs were adapted from positron emission tomography (PET) studies. In the typical PET design, several trials (individual stimuli, or more generally, cognitive events) were clustered in blocks, each of which contained trials of the same condition (Fig. 2.10). As an example, one block may consist of a series of different pictures showing happy faces and another block may consist of pictures showing sad faces. The statistical analysis of such block designs compares the mean activity obtained in the different experimental blocks. Block designs were necessary

in PET studies because of the limited temporal resolution of this imaging technique requiring about 1 min to obtain a single whole-brain image. Since the temporal resolution of fMRI is much higher than PET, it has been proposed to use event-related designs (BLAMIRE et al. 1992; BUCKNER et al. 1996; DALE and BUCKNER 1997). The characteristics of these designs (Fig. 2.10) follow closely those used in event-related potential (ERP) studies. In event-related designs, individual trials of different conditions are not clustered in blocks but are presented in a random sequence. Responses to trials belonging to the same condition are selectively averaged and the calculated mean responses are statistically compared with each other. While block designs are well suited for many experiments, event-related designs offer several advantages over block designs, especially for cognitive tasks. An important advantage of event-related designs is the possibility to present stimuli in a randomized order (Fig. 2.10), which avoids cognitive adaptation strategies of the subjects. Such cognitive adaptations are likely to occur in block designs since a subject knows what type of stimuli to expect within a block after having experienced the first few trials. Another important advantage of event-related designs is that the response profile for different trial types (and even single trials) can be estimated by event-related averaging. Furthermore, event-related designs allow post-hoc sorting of individual brain responses. One important example of post-hoc sorting is the separation of brain responses for correctly vs. incorrectly performed trials.

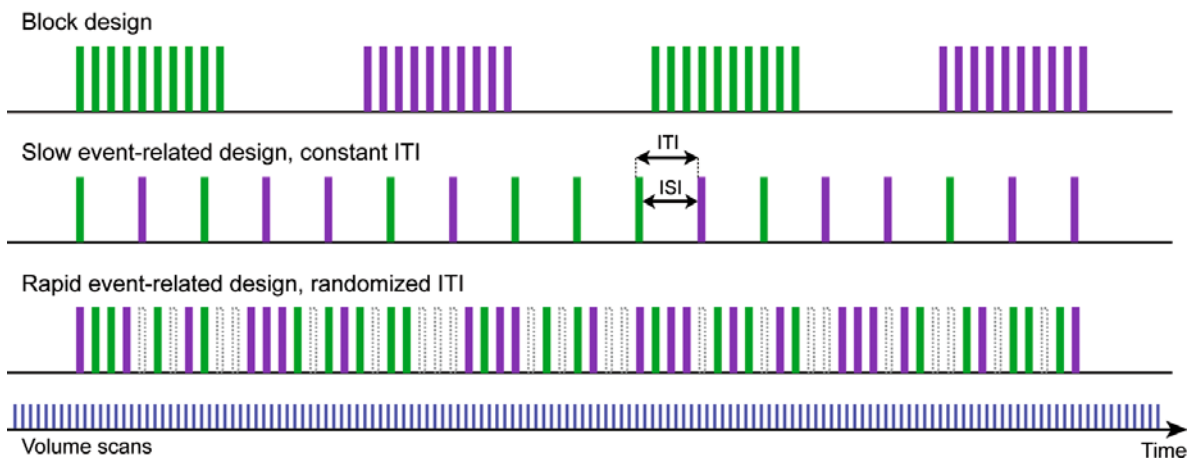


Fig. 2.10. In a block design (*upper row*), trials (events) belonging to the same condition are grouped together and are separated by a baseline block. In this example, two blocks of two main conditions (*green*, condition 1; *violet*, condition 2) are depicted. In slow event related designs, trials of different conditions appear in randomized order and are spaced sufficiently far apart to avoid largely overlapping BOLD responses. Optimal intertrial intervals (ITIs) are about 12 s. In rapid event-related designs, stimuli are closely spaced leading to substantial overlap of evoked fMRI responses. If ITIs are randomized, the evoked responses can be decomposed into condition-specific response profiles by deconvolution analysis.

The possibilities of event-related fMRI designs are comparable to standard behavioral and ERP analyses. Note, however, that the hemodynamic response extends over about 20–30 s (Fig. 2.8) after presentation of a short stimulus; if only the positive BOLD response is considered (ignoring the undershoot), the signal extends over 10–15 s. The easiest way to conduct event-related fMRI designs is to temporally separate individual trials far enough to avoid overlapping responses of successive trials. Event-related designs with long temporal intervals between individual trials are termed slow event-related designs (Fig. 2.10). For stimuli of 1–2 s duration, the optimal intertrial interval (ITI) is 12 s (BANDETTINI and COX 2000). Since it has been shown the fMRI signals of closely spaced trials add up approximately linearly (BOYNTON et al. 1996; DALE and BUCKNER 1997; see Sect. 2.2.3), it is also possible to run experiments with inter-trial intervals of 2–6 s. Designs with short temporal intervals between trials are called rapid event-related designs (Fig. 2.10). While the measured response of rapid event-related designs will contain a combination of overlapping responses from closely spaced trials, condition-specific event-related time courses can be isolated using deconvolution analysis. Deconvolution analysis works correctly only under the assumption of a linear system (see Sect. 2.3.2) and requires randomized intertrial intervals (“jitter”), which can be easily obtained by adding “null” (baseline) trials when trial sequences are created for an experiment. While simple permutation approaches produce already good event sequences for rapid event-related designs, statistical power can be maximized by using more advanced randomization procedures e.g. (WAGER and NICHOLS 2003). In general, block and event-related designs can be statistically analyzed using the same mathematical principles (see Sect. 2.3.3.3).

It is important to note that conventional fMRI data does not provide an absolute signal of brain activity limiting the quantitative interpretation of results. The major part of the signal amplitude is related to proton density and T_2 tissue contrast varying across brain regions within and between subjects. BOLD related signal fluctuations, thus, have neither a defined origin nor a unit. In light of these considerations, signal strengths in main experimental conditions can not be interpreted absolutely but have to be assessed relative to the signal strength in other main or control conditions. As a general control condition, many fMRI experiments contain a base-

line (“rest”, “fixation”) condition with “no task” for the subject. More complex control conditions differ from the main condition(s) only in a subtle cognitive component allowing isolating brain responses specific to that component. Responses to main conditions are often expressed as percent signal change relative to a baseline condition.

Furthermore, it is recommended to vary conditions instead of across subjects since the lack of an absolute signal level will increase intersubject variability. Since signal levels may vary even across runs within a scanning session of the same subject, it is recommended to present each experimental condition within each run as opposed to change conditions across runs, if possible. Some experiments require a between-subjects design, including comparisons of responses between different subject groups, e.g. males vs. females or treatment group vs. control group. If a more quantitative evaluation of hemodynamic responses is desired, standard BOLD measurements can be combined with CBF measurements using arterial spin labeling (ASL) techniques (e.g. BUXTON et al. 2004).

2.3.2

Basic Analysis Steps

2.3.2.1

Two Views on fMRI Data Sets

In order to better understand different fMRI data analysis steps, two different views on the recorded four-dimensional data sets are helpful. In one view (Fig. 2.11a), the 4D data is conceptualized as a sequence of functional volumes (3D images). This view is very useful to understand spatial analysis steps. During motion correction, for example, each functional volume of a run is aligned to a selected reference volume by adjusting rotation and translation parameters. The second view focuses on time courses of individual voxels (“voxel” = “volume element” analogous to “pixel” = picture element). This second view (Fig. 2.11b) helps to understand those preprocessing and statistical procedures, which process time courses of individual voxels. Most standard statistical analysis procedures operate in this way, including the General Linear Model (GLM). In a GLM analysis (see below), the data is processed “voxel-wise” (univariate) by fitting a model to the time course of each voxel independently.

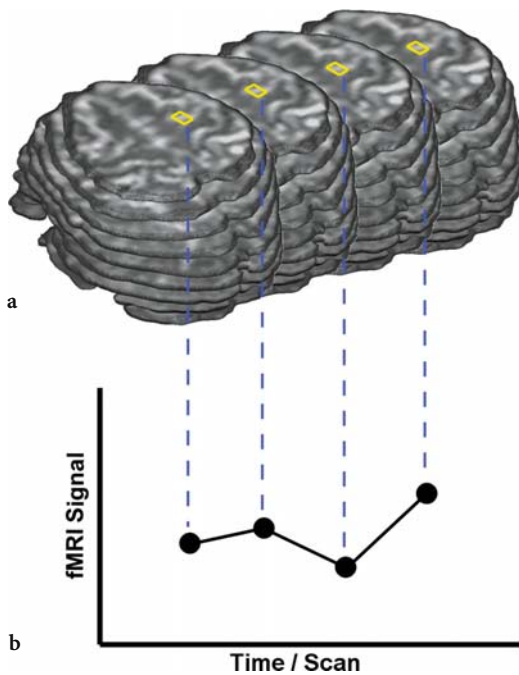


Fig. 2.11a,b. During fMRI measurements, a set of slices, often covering the whole brain, is scanned repeatedly over time. Although the repeated slice measurements look almost identical, small task-related signal fluctuations may occur at different brain regions at different moments in time (a). To visualize these subtle fluctuations, the time course of any desired brain region may be depicted (b). The smallest separate brain region one can select to display a time course in a two-dimensional image (slice) is called pixel (picture element) while the smallest region in a three dimensional “image” is called voxel (volume element).

2.3.2.2

Preprocessing of Functional Data

In order to reduce artifact and noise-related signal components, a series of mathematical operations is typically performed prior to statistical data analysis. The most essential steps of these preprocessing operations include: (1) head motion detection and correction, (2) slice scan timing correction, (3) removal of linear and non-linear trends in voxel time courses and (4) spatial and temporal smoothing of the data.

2.3.2.2.1

Detection and Correction of Head Motion

The quality of fMRI data is strongly hampered in the presence of substantial head movements. Most people reject data sets for further analysis if head motion of 5 mm or more is detected. Although head motion

can be corrected in image space, displacements of the head in the scanner reduce the homogeneity of the magnetic field, which is fine-tuned (“shimmed”) prior to functional scans for a given head position. If head movements are small, motion correction is a useful step to improve the data quality for subsequent statistical data analysis. Motion correction operates by selecting one functional volume of a run (or a volume from another run of the same scanning session) as a reference to which all other functional volumes are aligned. Most head motion algorithms describe head movements by six parameters, three translation (displacement) parameters, and three rotation parameters. These six parameters are appropriate to characterize motion of rigid bodies, since any spatial displacement of rigid bodies can be described by translation along the x, y and z-axes and rotation around these axes. These six parameters are estimated iteratively by analyzing how a source volume should be translated and rotated in order to better align with the reference volume. An often used similarity measure is the difference of intensity values of corresponding positions in the reference volume and the transformed source volume given the current translation and rotation parameters. The iterative adjustment of the parameters stops if no further improvement can be achieved, i.e. when a minimum has been found. After the final motion parameters have been detected, they can be applied to the source volume to produce a new volume replacing the original volume in the motion corrected data set. For visual inspection, fMRI software packages usually present line plots of the translation and rotation parameters across time showing how the estimated values change from volume to volume. The obtained parameter time courses may also be integrated in subsequent statistical data analysis with the aim to remove residual motion artifacts (for details, see Sect. 2.3.2).

Note that the assumption of rigid body motion is not strictly valid for fMRI data since the individual slices of a functional volume are not scanned in parallel. Since abrupt head motions may occur at any moment in time, the assumption of a rigid body is violated. Imagine, for example, that a subject does not move while the first five slices of a functional volume are scanned, then moves 2 mm along the y-axis and then lies still until scanning of that volume has been completed. The six parameters of a rigid body approach are not sufficient to capture such “within-volume” motion correctly. Fortunately, head movements from volume to volume are typically small and the assumption of a moving rigid body is thus largely valid.

2.3.2.2.2

Slice Scan Time Correction

A functional volume is considered as the data obtained at a certain time point. Slices of a functional volume are, however, scanned sequentially in standard functional (EPI) measurements distributing time within a functional volume. For a functional volume of 30 slices and a volume TR of 3 s, for example, the data of the last slice is measured almost 3 s later than the data of the first slice. Despite the sluggishness of the hemodynamic response (Fig. 2.8), an imprecise specification of time in the order of 3 s will lead to suboptimal statistical analysis, especially in event-related designs. It is, thus, desirable to preprocess the data in such a way that the resulting data appears as if all slices of a functional volume were measured at the same moment in time. Only then would it be possible to compare and integrate event-related responses from different brain regions correctly with respect to temporal parameters such as onset latency. In order to correct for different slice scan timings, the time series of individual slices are temporally “shifted” to match a reference time point, e.g. of the first or middle slice of a functional volume. The exact choice of the reference slice should be performed

with respect to the details of the stimulation protocol timing. The temporal shift of the slice time courses is performed by resampling the original data. Since this involves sampling at time points which fall between measurement time points, the new values need to be estimated by estimation (resampling) of values from past and future time points (Fig. 2.12). The most often used interpolation methods are linear and sinc interpolation. Note that the time points of slice scanning depend on the acquisition order specified at the scanner console. Besides an ascending or descending order, slices are often scanned interleaved, i.e. the odd slice numbers are recorded first followed by the even slice numbers. After appropriate temporal resampling, all slices within a functional volume of the new data set represent the same time point (Fig. 2.12).

2.3.2.2.3

Removal of Drifts and

Temporal Smoothing of Voxel Time Series

Due to physical and physiological noise, voxel time courses are often non-stationary exhibiting signal drifts. If the signal rises or falls with a constant slope from beginning to end, the drift is called a

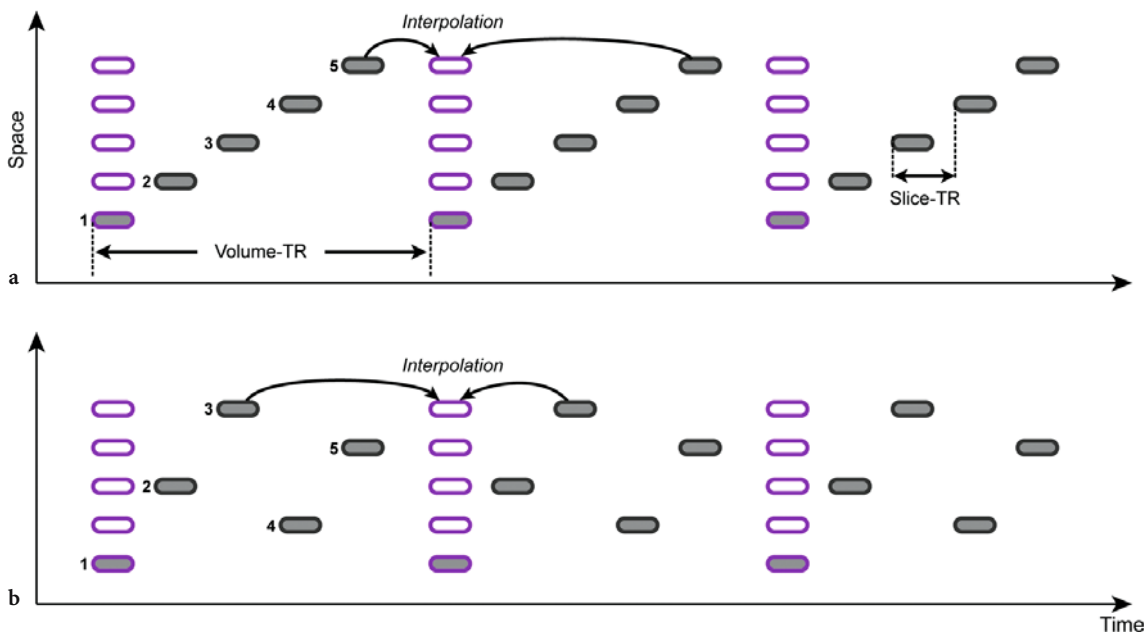


Fig. 2.12a,b. During slice scan time correction, slices within each functional volume (*black rectangles*) are “shifted in time” resulting in a new time series (*violet rectangles*) in which all slices of a functional volume are virtually measured at the same moment in time. To calculate intensity values at time points falling in-between measured time points, past and future values have to be integrated typically using sinc or linear interpolation. For correct interpolation, the volume TR, slice TR and slice scanning order must be known. **a** Five slices are scanned in ascending order. **b** Five slices are scanned in interleaved order.

linear trend. If the signal level slowly varies over time with a non-constant slope, the drift is called a non-linear trend. Since drifts describe slow signal changes they can be removed by Fourier analysis using a temporal high-pass filter. The original signal in the time domain is transformed in frequency space using the FT. In frequency space drifts can be easily removed because low frequency components, underlying drifts, are isolated from higher frequency components underlying task-related signal changes. The filtered frequency representation is then transformed back into the time domain by the inverse FT (Fig. 2.13). Removal of trends is very important for subsequent statistical data analysis

expecting stationary time courses. As an alternative to the removal of drifts during preprocessing, it is also possible to remove low-frequency components during statistical analysis (for details, see Sect. 2.3.2).

Another temporal preprocessing step consists in temporal smoothing of voxel time courses removing high-frequency signal fluctuations, which are considered as noise. While this step increases the signal-to-noise ratio, temporal smoothing is not recommended when analyzing event-related designs since it may distort estimates of temporally relevant parameters, such as the onset or width of average event-related responses.

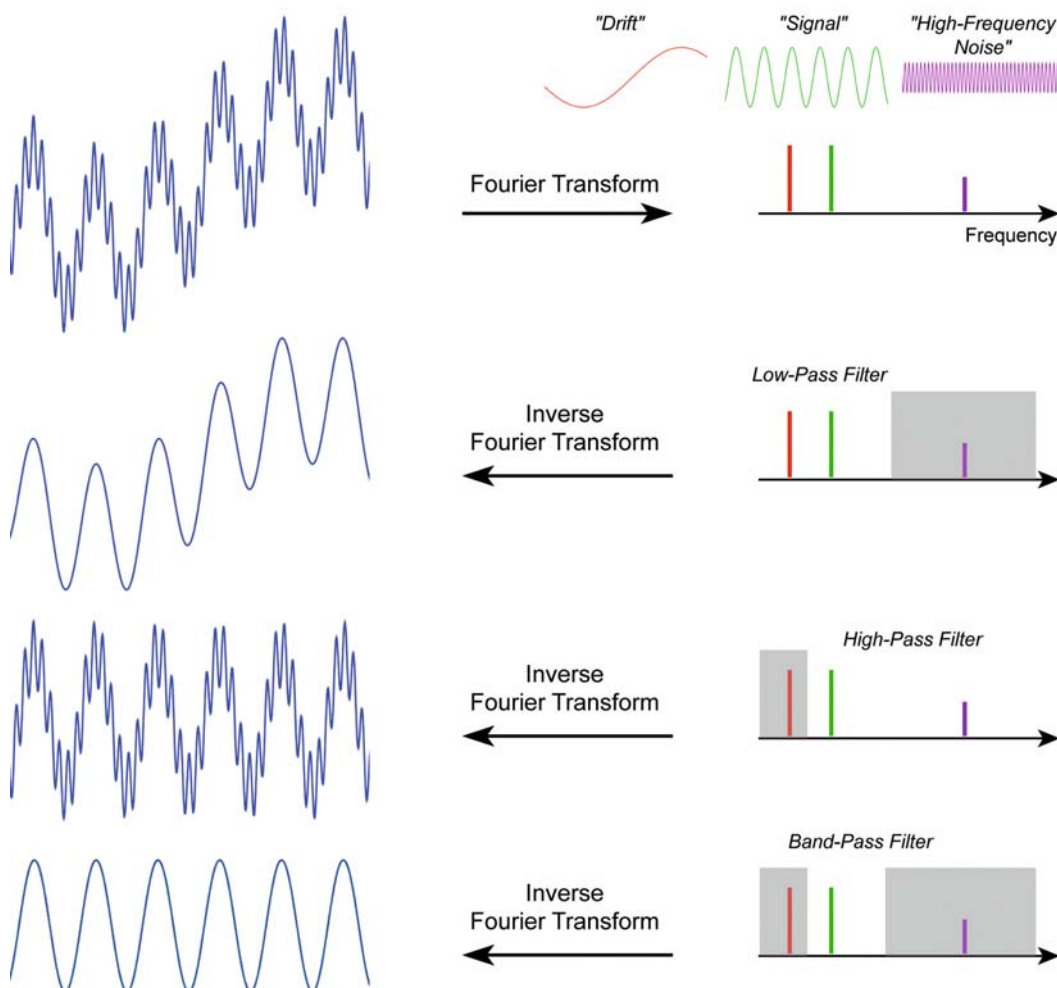


Fig. 2.13. Principle of temporal filtering using Fourier analysis. The time-domain signal can be converted in an equivalent frequency-domain signal using the Fourier transform (*upper row*). In this simplified example, the composite signal (*upper row, left*) consists only of three frequencies representing a drift, signal and high-frequency noise component (*upper row, right*). In the frequency domain, frequencies can be filtered to remove unwanted signal components. The filtered signal can then be converted back into the time domain using the inverse Fourier transform. In the *second row*, a low-pass filter is applied, in the *third row* a high-pass filter, and in the *fourth row* a bandpass filter.

2.3.2.2.4

Spatial Smoothing

To further enhance the signal-to-noise ratio, the data is often spatially smoothed by convolution with a 3D Gaussian kernel. In this process, each voxel is replaced by a weighted average value calculated across neighboring voxels. The shape and width of the Gaussian kernel determines the weights used to include surrounding voxels in the average. Note that smoothing reduces the spatial resolution of the data and should be therefore applied with care. Many studies, however, aim to detect regions larger than a few voxels, i.e. brain areas in the order of 1 cm³ or larger. Under these conditions, spatial smoothing with an appropriate kernel width of 4–8 mm is very useful since it suppresses noise and enhances the task-related signal. Furthermore, spatial smoothing increases the extent of activated brain regions, which is exploited in the context of group analyses (see Sect. 2.3.5) facilitating the integration of signals from corresponding but not perfectly coregistered brain regions.

From the description and discussion of standard preprocessing steps it should have become clear that there are no universally correct criteria to choose preprocessing steps and parameters because choices depend to some extent on the goal of data analysis. Some steps depend also on the experimental design of a study. If, for example, a high-pass temporal filter is used with an overly high cut-off point, task-related signal fluctuations could easily be removed from the data.

Besides the described core preprocessing steps, additional procedures may be applied. The next sections will describe three additional preprocessing steps.

2.3.2.2.5

Mean Intensity Adjustment

Besides drifts in individual voxel time courses, the mean intensity level averaged across all voxels might exhibit drifts over time. These global drifts can be corrected by scaling the intensity values of a functional volume in such a way that the new mean value is identical to the mean intensity value of a reference volume. Mean intensity adjustment is not strictly necessary since modern scanners keep a rather constant mean signal level over time. Under this condition, mean intensity adjustment may even produce a negative effect by

reducing true activation effects. If, for example, large parts of the brain activate during a main condition as compared to a rest condition, the mean signal level is higher during active periods and a mean intensity adjustment step will “correct” this. A plot of the mean signal level over time might be helpful, however, to identify problems of scanning quality, especially “spikes”, which are strong signal decreases (or increases) at isolated time points.

2.3.2.2.6

Motion Correction Within and Across Runs

A scanning session typically consists of a series of runs. In such a situation, head movements may not only occur within runs but also between runs. A simple approach to align all functional volumes of all runs of a scanning session with each other consists in specifying the same reference volume for all runs. If a session consists, for example, of three runs, all functional volumes could be aligned to the middle volume of the second run. Since functional data is often aligned with a 3D anatomical data set recorded in the same session, it is recommended to choose that functional volume as a reference, which is recorded just before (or after) the anatomical data set. Note, however, that the described across run motion correction works only if the slice positions are identically specified in all runs.

2.3.2.2.7

Distortion Correction of Functional Images

The BOLD-sensitive GE-EPI sequence is used for most fMRI studies because of its speed but it has the disadvantage that images suffer from signal drop outs and geometric distortions, especially in brain regions close to other tissue types such as air and liquor (susceptibility artifacts). These artifacts can be reduced substantially by using optimized EPI sequence parameters (e.g. WEISKOPF et al., in press) and parallel imaging techniques (see Sect. 2.4.1). A complete removal of drop-outs and geometric distortions is, however, not possible. Further improvements may be obtained by distortion correction routines, which may benefit from special scans measuring magnetic field distortions (e.g. field maps). The distortion corrected images may improve coregistration results between functional and anatomical data sets enabling a more precise localization of brain function.

2.3.3

Statistical Analysis of Functional Data

Statistical data analysis aims at identifying those brain regions exhibiting increased or decreased responses in specific experimental conditions as compared to other (e.g. control) conditions. Due to the presence of physiological and physical noise fluctuations, observed differences between conditions might occur simply by chance. It is the task of statistical data analysis to explicitly assess the effect of measurement variability (noise fluctuations) on estimated condition differences: If it is very unlikely that an observed effect is solely the result of noise fluctuations, we tend to accept that the observed effect reflects a true difference between conditions. In standard fMRI analyses, this assessment is performed independently for the time course of each voxel. The obtained statistical values, one for each voxel, form a three-dimensional statistical map. In more complex analyses, each voxel will contain several statistical values reflecting estimated effects of multiple conditions.

2.3.3.1

From Image Subtraction to Statistical Comparison

Figure 2.14 shows two fMRI time courses obtained from two different brain areas of an experiment with two conditions, a control condition (“Rest”) and a main condition (“Stim”). Each condition has been measured several times. Note that in a real experiment, one would not just present once the control and main condition as in Fig. 2.14, but one would design several “on-off” cycles in order to be able

to separate task-related responses from potential low-frequency drifts (see Sect. 2.3.2.2). How can we assess whether the response values are higher in the main condition than in the control condition? One approach consists in subtracting the mean value of the “Rest” condition, $\bar{X}_1$, from the mean value of the “Stim” condition, $\bar{X}_2$: $d = \bar{X}_2 - \bar{X}_1$. Note that one would obtain the same mean values and, thus, the same difference in cases (a) and (b). Despite the fact that the means are identical in both cases, the difference in case (b) seems to be more “trustworthy” than the difference in case (a) because the measured values vary less in case (b) than in case (a). Statistical data analysis goes beyond simple subtraction by taking into account the amount of variability of the measured data points. Statistical analysis essentially asks how likely it is to obtain a certain effect if there would be only noise fluctuations. This is formalized by the null hypothesis stating that there is no effect, i.e. no difference between conditions. In the case of comparing the means, μ_1 and μ_2 , the null hypothesis can be formulated as: $H_0: \mu_1 = \mu_2$. Assuming the null hypothesis, it can be calculated how likely it is that an observed effect would have occurred simply by chance. This requires knowledge about the amount of noise fluctuations which can be estimated from the data. By incorporating the variability of measurements, statistical data analysis allows to estimate the uncertainty of effects (e.g. mean differences) in data samples. If an effect is so large that it is very unlikely that it has occurred simply by chance (e.g. the probability is less than $p = 0.05$), one rejects the null hypothesis and accepts the alternative hypothesis stating that there exists a true effect. Note that the decision to accept or reject

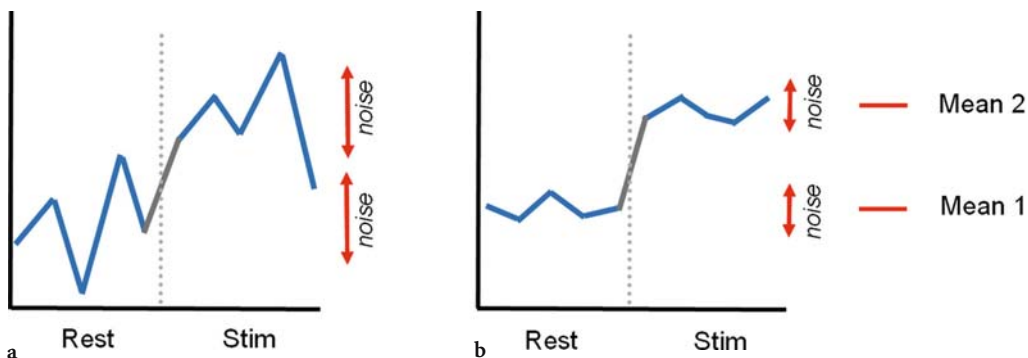


Fig. 2.14a,b. Principle of statistical data analysis. An experiment with two conditions (“Stim” and “Rest”) has been performed. **a** Time course obtained in area 1. **b** Time course obtained in area 2. Calculation and subtraction of Mean 1 (“Rest” condition) from Mean 2 (“Stim” condition) leads to the same result in (a) and (b). In a statistical analysis, the estimated effect (mean difference) is related to its uncertainty, which is estimated by the variability of the measured values within conditions. Since the variance within the two conditions is smaller in (b) than in (a), the estimated effect is more likely to correspond to a true difference in (b) than in (a).

the null hypothesis is based on a probability value which has been accepted by the scientific community ($p < 0.05$). A statistical analysis, thus, does not prove the existence of an effect, it only suggests “to believe in an effect” if it is very unlikely that the observed effect has occurred by chance. Note that a probability of $p = 0.05$ means that if we would repeat the experiment 100 times we would accept the alternative hypothesis in about five cases although there would be no real effect. Since the chosen probability value thus reflects the likelihood of wrongly rejecting the null hypothesis, it is also called error probability.

The uncertainty of an effect is estimated by calculating the variance of the noise fluctuations from the data. For the case of comparing two mean values, the observed difference of the means is related to the variability of that difference resulting in a t statistic:

$$t = \frac{\bar{X}_2 - \bar{X}_1}{\hat{\sigma}_{\bar{X}_2 - \bar{X}_1}}$$

The numerator contains the calculated mean difference while the denominator contains the estimate of the expected variability, the standard error of the mean difference. Estimation of the standard error $\hat{\sigma}_{\bar{X}_2 - \bar{X}_1}$ involves pooling of the variances obtained within both conditions. Since we observe a high variability in case (a) in the example data (Fig. 2.14), we will obtain a small t value. Due to the small variability of the data points in (b), we will obtain a larger t value in this case (Fig. 2.14). The higher the t value, the less likely it is that the observed mean difference is just the result of noise fluctuations. It is obvious that measurement of many data points allows a more robust estimation of this probability than the measurement of only a few data points. The error probability p can be calculated exactly from the obtained t value using the incomplete beta function $I_x(a,b)$ and the number of measured data points N :

$$p = I_{\frac{N-2}{N-2+t^2}}\left(\frac{N-2}{2}, \frac{1}{2}\right)$$

If the computed error probability falls below the standard value ($p < 0.05$), the alternative hypothesis is accepted stating that the observed mean difference exists in the population from which the data points have been drawn (i.e. measured). In that case, one also says that the two means differ significantly. Assuming that in our example the obtained p value falls below 0.05 in case (b) but not in case (a), we

would only infer for brain area 2 that the “Stim” condition differs significantly from the “Rest” condition.

2.3.3.2

Correlation Analysis

The described mean comparison method is not the ideal approach to compare responses between different conditions since this approach is unable to capture the gradual profile of fMRI responses. As long as the temporal resolution is low (volume-TR > 4 s), the mean of different conditions can be calculated easily because transitions of expected responses from different conditions occur within a single time point (Fig. 2.15). If the temporal resolution is high, the expected fMRI responses change gradually from one condition to the next due to the sluggishness of the hemodynamic response (Fig. 2.15, TR = 1 s). In this case, time points cannot be assigned easily to different conditions. Without special treatment, the mean response can no longer be easily computed for each condition. As a consequence, the statistical power to detect mean differences may be substantially reduced, especially for short blocks and events.

This problem does not occur when correlation analysis is used since this method enables explicit incorporation of the gradual increase and decrease of the expected BOLD signal. The predicted time courses in Fig. 2.15 can be used as the reference function in a correlation analysis. At each voxel, the time course of the reference function is compared with the time course of the measured data by calculation of a correlation coefficient r , indicating the strength of covariation:

$$r = \frac{\sum_{t=1}^N (X_t - \bar{X})(Y_t - \bar{Y})}{\sqrt{\sum_{t=1}^N (X_t - \bar{X})^2 \sum_{t=1}^N (Y_t - \bar{Y})^2}}$$

Index t runs over time points (t for “time”) identifying pairs of temporally corresponding values from the reference (X_t) and data (Y_t) time courses. In the numerator the mean of the reference and data time course is subtracted from the respective value of each data pair and the two differences are multiplied. The resulting value is the sum of these cross products, which will be high if the two time courses covary, i.e. if the values of a pair are both often above or below their respective mean. The term in

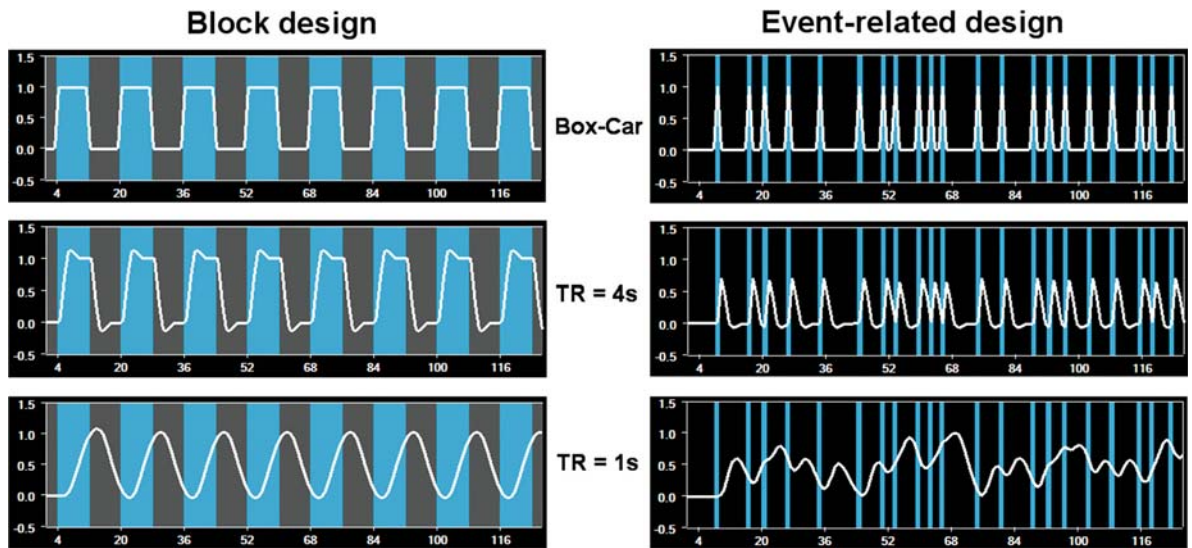


Fig. 2.15. Calculation of expected fMRI signals for a block and event-related design. The horizontal axis of each plot represents time (data points). The vertical axis represents the amplitude of the modelled fMRI response. The *blue* vertical segments correspond to intervals of a single main stimulation condition; the *grey* segments correspond to a control condition. *White* curves show predicted BOLD responses. The plots in the *upper* row depict time courses, which do not take into account the delayed hemodynamic response profile (“box-car”). The *white* curves in the other plots represent the expected time courses after application of a standard hemodynamic response function (two-gamma function) for a temporal resolution (volume-TR) of 4 s (*middle* row) and 1 s (*lower* row). Correlation analysis is able to capture the gradual increase and decrease of expected time courses for short TRs while it is impossible to unambiguously categorize time points as belonging to stimulation vs. baseline conditions in the context of a *t* test.

the denominator normalizes the covariation term in the numerator so that the correlation coefficient lies in a range of -1 and $+1$. A value of $+1$ indicates that the reference time course and the data time course go up and down in exactly the same way, while a value of -1 indicates that the two time courses run in opposite direction. A correlation value close to 0 indicates that the two time courses do not covary, i.e. the value in one time course cannot be used to predict the corresponding value in the other time course.

While the statistical principles are the same in correlation analysis as described for mean comparisons, the null hypothesis now corresponds to the statement that the population correlation coefficient ρ equals zero ($H^0: \rho = 0$). By including the number of data points N , the error probability can be computed assessing how likely it is that an observed correlation coefficient would occur solely due to noise fluctuations in the signal time course. If this probability falls below 0.05 , the alternative hypothesis is accepted stating that there is indeed significant covariation between the reference function and the data time course. Since the reference function is the result of a model assuming different response strengths in the

two conditions (e.g. “Rest” and “Stim”), a significant correlation coefficient indicates that the two conditions lead indeed to different mean activation levels in the respective voxel or brain area. The statistical assessment can be performed also by converting an observed r value into a corresponding t value, $t = r\sqrt{N-2} / \sqrt{1-r^2}$.

2.3.3.3

The General Linear Model

The described *t* test for assessing the difference of two mean values is a special case of an analysis of a qualitative (categorical) independent variable. A qualitative variable is defined by discrete levels, e.g. “stimulus off” vs. “stimulus on”. If a design contains more than two levels and multiple factors, an analysis of variance (ANOVA) can be performed, which can be considered as an extension of the *t* test. The described correlation coefficient on the other hand is suited for the analysis of quantitative independent variables. A quantitative variable may be defined by any gradual time course. If more than one reference time course has to be considered, multiple regression analysis can be performed, which can be considered as an extension

sion of the simple linear correlation analysis. The GLM is mathematically identical to a multiple regression analysis but stresses its suitability for both multiple qualitative and multiple quantitative variables. The GLM is suited to implement any parametric statistical test with one dependent variable, including any factorial ANOVA design as well as designs with a mixture of qualitative and quantitative variables (covariance analysis, ANCOVA). Because of its flexibility to incorporate multiple quantitative and qualitative independent variables, the GLM has become the core tool for fMRI data analysis after its introduction into the neuroimaging community by FRISTON and colleagues (1994, 1995). The following sections briefly describe the mathematical background of the GLM in the context of fMRI data analysis; a comprehensive treatment of the GLM can be found in the standard statistical literature, e.g. DRAPER and SMITH (1998) and KUTNER et al. (2005). Note that in the fMRI literature, the term “General Linear Model” refers to its univariate version. The term “univariate” here does not refer to the number of independent variables, but to the number of dependent variables. As mentioned earlier, a separate statistical analysis is performed for each voxel time series (dependent variable). In its general form, the GLM has been defined for multiple dependent variables, i.e. it encompasses tests as general as multivariate covariance analysis (MANCOVA).

From the perspective of multiple regression analysis, the GLM aims to “explain” or “predict” the variation of a dependent variable in terms of a linear combination (weighted sum) of several reference functions. The dependent variable corresponds to the observed fMRI time course of a voxel and the reference functions correspond to time courses of expected (idealized) fMRI responses for different conditions of the experimental paradigm. The reference functions are also called predictors, regressors, explanatory variables, covariates or basis functions. A set of specified predictors forms the design matrix, also called the model. A predictor time course is typically obtained by convolution of a condition box-car time course with a standard hemodynamic response function (Figs. 2.8, 2.15). A condition box-car time course may be defined by setting values to 1 at time points at which the modeled condition is defined (“on”) and 0 at all other time points. Each predictor time course X gets an associated coefficient or beta weight b , quantifying its potential contribution in explaining the voxel time course y . The voxel time course y is modeled as the sum of the defined

predictors, each multiplied with the associated beta weight b . Since this linear combination will not perfectly explain the data due to noise fluctuations, an error value e is added to the GLM system of equations with n data points and p predictors:

$$\begin{aligned} y_1 &= b_0 + b_1 X_{11} + \cdots \cdots \cdots + b_p X_{1p} + e_1 \\ y_2 &= b_0 + b_1 X_{21} + \cdots \cdots \cdots + b_p X_{2p} + e_2 \\ y_3 &= b_0 + b_1 X_{31} + \cdots \cdots \cdots + b_p X_{3p} + e_3 \\ &\vdots \qquad \qquad \qquad \vdots \qquad \qquad \qquad \vdots \qquad \qquad \qquad \vdots \\ y_n &= b_0 + b_1 X_{n1} + \cdots \cdots \cdots + b_p X_{np} + e_n \end{aligned}$$

The y variable on the left side corresponds to the data, i.e. the measured time course of a single voxel. Time runs from top to bottom, i.e. y_1 is the measured value at time point 1, y_2 the measured value at time point 2 and so on. The voxel time course (left column) is “explained” by the terms on the right side. The first column on the right side corresponds to the first beta weight b_0 . The corresponding predictor time course X_0 has a value of 1 for each time point and is, thus, also called “constant”. Since multiplication with 1 does not alter the value of b_0 , this predictor time course (X_0) does not explicitly appear in the equation. After estimation (see below), the value of b_0 typically represents the signal level of the baseline condition and is also called intercept. While its absolute value is not informative, it is important to include the constant predictor in a design matrix since it allows the other predictors to model small condition-related fluctuations as increases or decreases relative to the baseline signal level. The other predictors on the right side model the expected time courses of different conditions. For multi-factorial designs, predictors may be defined coding combinations of condition levels in order to estimate main and interaction effects. The beta weight of a condition predictor quantifies the contribution of its time course in explaining the voxel time course. While the exact interpretation of beta values depends on the details of the design matrix, a large positive (negative) beta weight typically indicates that the voxel exhibits strong activation (deactivation) during the modeled experimental condition relative to baseline. All beta values together characterize a voxel’s “preference profile” for one or more experimental conditions. The last column in the system of equations contains error values, also called residuals, prediction errors or noise. These error values quantify the deviation of the measured voxel time course from the predicted time course, the linear combination of predictors.

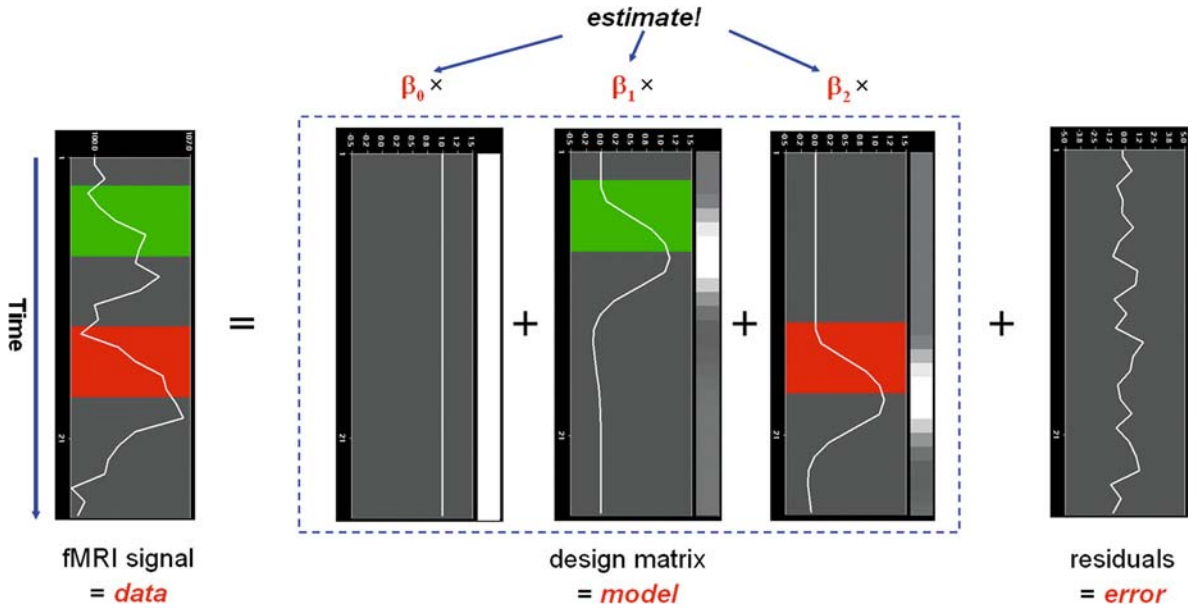


Fig. 2.16. Graphical display of a GLM. Time is running from *top* to *bottom*. *Left side* shows observed voxel time course (data). In this example the model (design matrix) consists of three predictors, the constant and two main predictors (*middle part*). Filled green and red rectangles depict stimulation time while the white curves depict expected BOLD responses. Expected responses are also shown in graphical view using a black-to-white colour range (*right side of each predictor plot*). Beta values have to be estimated (*top*) to scale the expected responses (predictors) in such a way that their weighted sum predicts the data values as good as possible (in the least squares sense, see text). Unexplained fluctuations (residuals, error) are shown on the *right side*.

The GLM system of equations may be expressed elegantly using matrix notation. For this purpose, we represent the voxel time course, the beta values and the residuals as vectors, and the set of predictors as a matrix:

$$\begin{bmatrix} y_1 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} 1 & X_{11} & \cdots & \cdots & X_{1p} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 1 & X_{n1} & \cdots & \cdots & X_{np} \end{bmatrix} \begin{bmatrix} b_0 \\ \vdots \\ b_p \end{bmatrix} + \begin{bmatrix} e_1 \\ \vdots \\ e_n \end{bmatrix}$$

Representing the indicated vectors and matrix with single letters, we obtain this simple form of the GLM system of equations:

$$\mathbf{y} = \mathbf{X}\mathbf{b} + \mathbf{e}$$

In this notation, the matrix $\mathbf{X}$ represents the design matrix containing the predictor time courses as column vectors. The beta values now appear in a separate vector $\mathbf{b}$. The term $\mathbf{X}\mathbf{b}$ indicates matrix-vector multiplication. Figure 2.16 shows a graphical representation of a GLM. Time courses of the signal, predictors and residuals have been arranged in column form with time running from top to bottom as in the system of equations.

Given the data $\mathbf{y}$ and the design matrix $\mathbf{X}$, the GLM fitting procedure has to find a set of beta values explaining the data as good as possible. The time course values $\hat{\mathbf{y}}$ predicted by the model are obtained by the linear combination of the predictors:

$$\hat{\mathbf{y}} = \mathbf{X}\mathbf{b}$$

A good fit would be achieved with beta values leading to predicted values $\hat{\mathbf{y}}$ which are as close as possible to the measured values $\mathbf{y}$. By rearranging the system of equations, it is evident that a good prediction of the data implies small error values:

$$\begin{aligned} \mathbf{e} &= \mathbf{y} - \mathbf{X}\mathbf{b} \\ &= \mathbf{y} - \hat{\mathbf{y}} \end{aligned}$$

An intuitive idea would be to find those beta values minimizing the sum of error values. Since the error values contain both positive and negative values (and because of additional statistical considerations), the GLM procedure does not estimate beta values minimizing the sum of error values, but finds those beta values minimizing the sum of squared error values:

$$\mathbf{e}'\mathbf{e} = (\mathbf{y} - \mathbf{X}\mathbf{b})'(\mathbf{y} - \mathbf{X}\mathbf{b}) \rightarrow \min$$

The term $\mathbf{e}'\mathbf{e}$ is the vector notation for the sum of squares ($\sum_{i=1}^N e_i^2$). The apostrophe symbol denotes transposition of a vector or matrix. The optimal beta weights minimizing the squared error values (the “least squares estimates”) are obtained non-iteratively by the following equation:

$$\mathbf{b} = (\mathbf{X}'\mathbf{X})^{-1} \mathbf{X}'\mathbf{y}$$

The term in brackets contains a matrix-matrix multiplication of the transposed, $\mathbf{X}'$, and non-transposed, $\mathbf{X}$, design matrix. This term results in a square matrix with a number of rows and columns corresponding to the number of predictors. Each cell of the $\mathbf{X}'\mathbf{X}$ matrix contains the scalar product of two predictor vectors. The scalar product is obtained by summing all products of corresponding entries of two vectors (“sum of squares”). In case that the predictors are normalized to possess zero means, the $\mathbf{X}'\mathbf{X}$ matrix corresponds to the predictor variance-covariance matrix.

The $\mathbf{X}'\mathbf{X}$ matrix is inverted as denoted by the “-1” symbol. The resulting matrix $(\mathbf{X}'\mathbf{X})^{-1}$ plays an essential role not only for the calculation of beta values but also for testing the significance of contrasts (see below). The remaining term on the right side, $\mathbf{X}'\mathbf{y}$, evaluates to a vector containing as many elements as predictors. Each element of this vector is the scalar product (covariance) of a predictor time course with the observed voxel time course.

An interesting property of the least squares estimation method is that the variance of the measured time course can be decomposed into the sum of the variance of the predicted values (model-related variance) and the variance of the residuals:

$$Var(\mathbf{y}) = Var(\hat{\mathbf{y}}) + Var(\mathbf{e})$$

Since the variance of the voxel time course is fixed, minimizing the error variance by least squares corresponds to maximizing the variance of the values explained by the model. The square of the multiple correlation coefficient R provides a measure of the proportion of the variance of the data which can be explained by the model:

$$R^2 = \frac{Var(\hat{\mathbf{y}})}{Var(\mathbf{y})} = \frac{Var(\hat{\mathbf{y}})}{Var(\hat{\mathbf{y}}) + Var(\mathbf{e})}$$

The values of the multiple correlation coefficient vary between 0 (no variance explained) to 1 (all variance explained by the model). A coefficient of $R = 0.7$, for example, corresponds to an explained variance

of 49% (0.7×0.7). An alternative way to calculate the multiple correlation coefficient consists in computing a standard correlation coefficient between the predicted values and the observed values: $R = r_{\hat{\mathbf{y}}\mathbf{y}}$. This equation offers another view on the meaning of the multiple correlation coefficient quantifying the interrelationship (correlation) of the combined set of predictor variables with the observed time course.

2.3.3.3.1

GLM Diagnostics

Note that if the design matrix (model) does not contain all relevant predictors, condition-related increases or decreases in the voxel time course will be “explained” by the error values instead of the model (Fig. 2.17). It is, therefore, important that the design matrix is constructed with all expected effects, which may also include reference functions not related to experimental conditions, for example, estimated motion parameters or drift predictors if not removed during preprocessing. In cases where all expected effects are properly modeled, the residuals should reflect only noise fluctuations. If some effects are not (correctly) modeled, a plot of the residuals will show low frequency fluctuations instead of a stationary noisy time course. A visualization of the residuals is, thus, a good diagnostic tool to assess whether the design matrix has been defined properly.

2.3.3.3.2

GLM Significance Tests

The multiple correlation coefficient is an important measure of the “goodness of fit” of a GLM. In order to test whether a specified model significantly explains variance in a voxel time course, the R value can be transformed into an F statistic with $p-1$ and $n-p$ degrees of freedom:

$$F_{p-1, n-p} = \frac{R^2 (n-p)}{(1-R^2) (p-1)}$$

With the known degrees of freedom in an error probability value p can be calculated for an obtained F value. A high F value (low p value) indicates that one or more experimental conditions substantially modulate the data time course.

While the overall F statistic may tell us whether the specified model significantly explains a voxel’s time course, it does not allow assessment of which individual conditions differ significantly from each

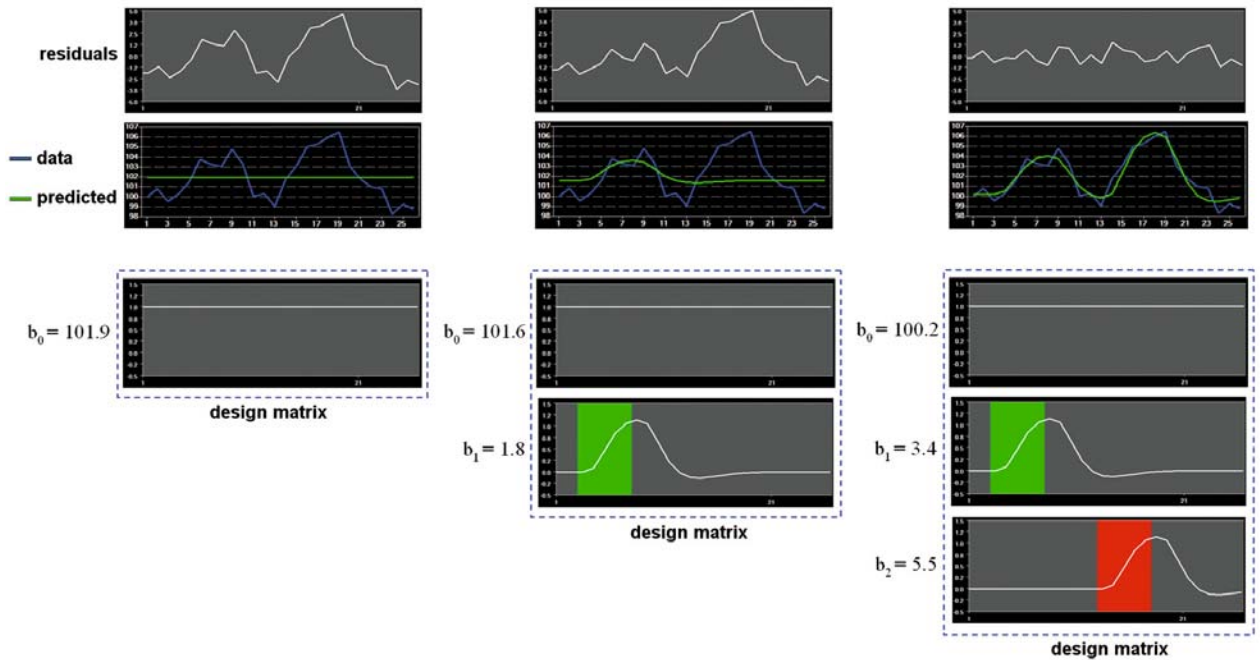


Fig. 2.17. Three GLMs fitting the same data with different design matrices. *Top row* shows residuals, *second row* predicted (*green*) and observed (*blue*) voxel time course. The design matrix on the *left* contains only one predictor, the constant term. The estimated beta weight (b_0) scales the constant term to the mean signal level. The design matrix in the *middle* adds a predictor for “*green*” main condition. The estimated beta weights (b_0, b_1) scale the predictors and the weighted sum explains more variance than the first model, but residual variance is still high. The third model (*right*) adds a predictor for “*red*” main condition. The estimated beta weights (b_0, b_1, b_2) scale the predictors and the weighted sum now explains all task-related signal fluctuations. The residuals reflect now only pure noise. The example highlights the importance of modelling all known effects in the design matrix.

other. Comparisons between conditions can be formulated as contrasts, which are linear combinations of beta values corresponding to null hypotheses. To test, for example, whether activation in a single condition deviates significantly from baseline, the null hypothesis would be $H_0: b_1 = 0$. To test whether activation in condition 1 is significantly different from activation in condition 2, the null hypothesis would state that the beta values of the two conditions would not differ, $H_0: b_1 = b_2$ or $H_0: (+1)b_1 + (-1)b_2 = 0$. To test whether the mean of condition 1 and condition 2 differs from condition 3, the following contrast could be specified: $H_0: (b_1 + b_2)/2 = b_3$ or $H_0: (+1)b_1 + (+1)b_2 + (-2)b_3 = 0$. The values used to multiply the respective beta values are often written as a *contrast vector* $\mathbf{c}$. In the latter example, the contrast vector would be written as $\mathbf{c} = [+1+1-2]$. Note that the constant term is treated as a confound and it is not included in contrast vectors, i.e. it is implicitly assumed that b_0 is multiplied by 0 in all contrasts. To include the constant explicitly, each contrast vector must be expanded by one entry at the beginning or end. Using matrix notation, the linear combination

defining a contrast can be written as the scalar product of contrast vector $\mathbf{c}$ and beta vector $\mathbf{b}$. The null hypothesis can then be simply described as $\mathbf{c}'\mathbf{b} = 0$. For any number of predictors k , such a contrast can be tested with the following t statistic with $n - p$ degrees of freedom:

$$t = \frac{\mathbf{c}'\mathbf{b}}{\sqrt{\text{Var}(\mathbf{e}) \mathbf{c}'(\mathbf{X}'\mathbf{X})^{-1}\mathbf{c}}}$$

The numerator of this equation contains the described scalar product of the contrast and beta vector. The denominator defines the standard error of $\mathbf{c}'\mathbf{b}$, i.e. the variability of the estimate due solely to noise fluctuations. The standard error depends on the variance of the residuals $\text{Var}(\mathbf{e})$ as well as on the design matrix $\mathbf{X}$, but not on the data time course $\mathbf{y}$. With the known degrees of freedom, a t value for a specific contrast can be converted in an error probability value p using the equation shown earlier. Note that the null hypotheses above were formulated as $\mathbf{c}'\mathbf{b} = 0$ implying a two-sided alternative hypothesis, i.e. $H_a: \mathbf{c}'\mathbf{b} \neq 0$. For one-sided alternative hypotheses, e.g. $H_a: b_1 > b_2$, the obtained p value from a two-

sided test can be simply divided by 2 to get the p value for the one-sided test. If this p value is smaller than 0.05 and if the t value is positive, the alternative hypothesis may be concluded.

2.3.3.3.3

Conjunction Analysis

Experimental research questions often lead to specific hypotheses, which can best be tested by the conjunction of two or more contrasts. As an example, it might be interesting to test with contrast c_1 whether condition 2 leads to significantly higher activity than condition 1 and with contrast c_2 whether condition 3 leads to significantly higher activity than condition 2. This question could be tested with the following conjunction contrast: $c_1 \wedge c_2 = [-1 \ 1 \ 0] \wedge [0 \ -1 \ 1]$. Note that a logical “and” operation is defined for Boolean values (true/false) but that t values associated with individual contrasts can assume any real value. An appropriate way to implement a logical “and” operation for conjunctions of contrasts with continuous statistical values is to use a minimum operation, i.e. the significance level of the conjunction contrast is set to the significance level of the contrast with the smallest t value: $t_{c_1 \wedge c_2} = \min(t_{c_1}, t_{c_2})$.

2.3.3.3.4

Multicollinear Design Matrices

Multicollinearity exists when predictors of the design matrix are highly intercorrelated. To assess multicollinearity, pairwise correlations between predictors are not sufficient. A better way to detect multicollinearity is to regress each predictor variable on all the other predictor variables and examine the resulting R^2 values. Perfect or total multicollinearity occurs when a predictor of the design matrix is a linear function of one or more other predictors, i.e. when predictors are linearly dependent on each other. While in this case solutions for the GLM system of equations still exist, there is no unique solution for the beta values. From a mathematical perspective of the GLM, the square matrix $X'X$ becomes singular, i.e. it loses (at least) one dimension, and is no longer invertible in case X exhibits perfect multicollinearity. Matrix inversion is required to calculate the essential term $(X'X)^{-1}$ used for computing beta values and standard error values (see above). Fortunately, special methods, including singular value decomposition (SVD), make it possible to obtain (pseudo-) inverses for singular (rank defi-

cient) matrices. Note, however, that in this case the absolute values of beta weights are not interpretable and statistical hypothesis tests must meet special restrictions.

In fMRI design matrices, multicollinearity occurs if all conditions are modeled as predictors in the design matrix including the baseline (rest, control) condition. Without the baseline condition, multicollinearity is avoided and beta weights are obtained which are easily interpretable. As an example consider the case of two main conditions and a rest condition. If we did not include the rest condition (recommended), the design matrix would not be multicollinear and the two beta weights b_1 and b_2 would be interpretable as increase or decrease of activity relative to the baseline signal level modeled by the constant term (Fig. 2.17, right). Contrasts could be specified to test single beta weights, e.g. the contrast $c = [1 \ 0]$ would test whether condition 1 leads to significant (de)activation. Furthermore, the two main conditions could be compared with the contrast $c = [-1 \ 1]$, which would test whether condition 2 leads to significantly more (or less) activation than condition 1. If we created the design matrix including a predictor for the rest condition, we would obtain perfect multicollinearity and the matrix $X'X$ would be singular. Using a pseudo-inverse or SVD approach, we would now obtain three beta values (plus the constant), one for the rest condition, one for main condition 1 and one for main condition 2. While the values of beta weights might not be interpretable, correct inferences of contrasts can be obtained if an additional restriction is met, typically that the sum of the contrast coefficients equals 0. To test whether main condition 1 differs significantly from the rest condition, the contrast $c = [-1 \ 1 \ 0]$ would now be used. The contrast $c = [0 \ -1 \ 1]$ would be used to test whether condition 2 leads to more (or less) activation than condition 1.

2.3.3.3.5

GLM Assumptions

Given a correct model, the estimation routine (ordinary least squares, OLS) of the GLM operates correctly only under the following assumptions. The population error values ε must have an expected value of zero at each time point, i.e. $E[\varepsilon_i] = 0$, and constant variance, i.e. $\text{Var}[\varepsilon_i] = \sigma^2$. Furthermore, the error values are assumed to be uncorrelated, i.e. $\text{Cov}(\varepsilon_i, \varepsilon_j) = 0$ for all $i \neq j$. To justify the use of t and F distributions in hypothesis tests, errors are further

assumed to be normally distributed, i.e. $\varepsilon_i \sim N(0, \sigma^2)$. In summary, errors are assumed to be normal, independent and identically distributed (abbreviated as “normal i.i.d.”). Under these conditions, the solution obtained by the least squares method is optimal in the sense that it provides the most efficient unbiased estimation of the beta values. While robust to small violations, assumptions should be checked using sample data. For fMRI measurements, the assumption of uncorrelated error values requires special attention.

2.3.3.3.6

Correction for Serial Correlations

In fMRI data, one typically observes serial correlations, i.e. high values are followed more likely by high values than low values and vice versa. Assessment of serial correlations is not performed on the original voxel time course but on the time course of the residuals since serial correlations in the signal are expected due to task-related fluctuations. Serial correlations most likely occur because data points are measured in rapid succession occurring also when phantoms are scanned. Serial correlations violate the assumption of uncorrelated errors (see above). Fortunately the beta values estimated by the GLM are correct estimates (unbiased) even in the presence of serial correlations. The standard errors of the betas are biased, however, leading to “inflated” test statistics, i.e. t or F values are higher than they should be. It is, thus, recommended to correct for serial correlations, which can be performed with several approaches. In pre-whitening approaches, autocorrelation is estimated and removed from the data and the model, and the GLM is re-fitted. In pre-colouring approaches, a known (strong) autocorrelation structure is imposed on the data, which is then properly handled by a more complex estimation procedure (generalized least squares). As an example, an often used pre-whitening method (COCHRANE-ORCUTT 1949; BULLMORE et al. 1996) is presented assuming the errors follow a first-order autoregressive, or $AR(1)$, process. After calculation of a GLM as usual, the amount of serial correlation r is estimated using pairs of successive residual values (e_t, e_{t+1}), i.e. the residual time course is correlated with itself shifted by one time point (lag = 1). In the second step, the estimated serial correlation is removed from the measured voxel time course by calculating the transformed time course $y_t^n = y_{t+1} - r \cdot y_t$. The superscript ‘ n ’ indicates the

values of the new, adjusted time course. The same calculation is also applied to each predictor time course resulting in an adjusted design matrix $\mathbf{X}^n$. In the third step, the GLM is recomputed using the corrected voxel time course and corrected design matrix resulting finally in correct standard errors for beta estimates and to correct significance levels for contrasts. If autocorrelation is not sufficiently reduced in the new residuals, the procedure can be repeated.

2.3.3.4

Creation of Statistical Maps

The statistical analysis steps were described for a single voxel’s time course since standard statistical methods are performed independently for each voxel. Since a typical fMRI data set contains about 100,000 voxels, a statistical analysis is performed 100,000 times. Running a GLM, for example, results in a set of estimated beta values attached to each voxel. A specified contrast $\mathbf{c}'\mathbf{b}_v$ will be performed using the same contrast own vector $\mathbf{c}$ for each voxel v , but it will use a voxel’s vector of beta values $\mathbf{b}_v$ to obtain a voxel-specific t and p value. Statistical test results for individual voxels are accumulated in a 3D data set called a statistical map. To visualize a statistical map, the obtained values, e.g. t values, can be shown at the respective positions of the voxels in the data set, which will replace the original intensity values (showing anatomical information). A more useful approach displays the statistical values only for those voxels exceeding a specified statistical threshold. This allows visualizing anatomical information in large parts of the brain while statistical information is shown only in those regions exhibiting significant signal modulations. While anatomical information is normally visualized using a range of grey values, supra-threshold statistical test values are typically visualized using multiple colours, for example, a red-to-yellow range for positive values and a green-to-blue range for negative values. With these colours, a positive (negative) t value just passing a specified threshold would be colored in red (green), while a very high positive (negative) t value would be colored in yellow (blue) (Fig. 2.18).

2.3.3.5

The Multiple Comparison Problem

An important issue in fMRI data analysis is the specification of an appropriate threshold for statistical

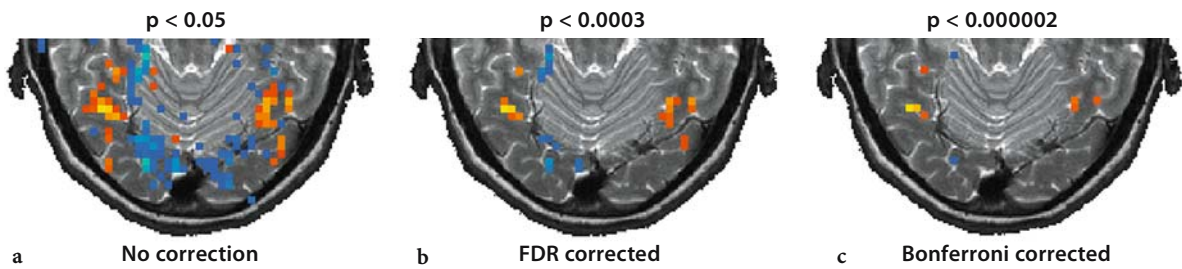


Fig. 2.18a–c. Comparison of two methods used to solve the multiple comparisons problem. A statistical map has been computed comparing responses to faces and houses. *Red/yellow* depict regions with larger responses to faces than to houses, while *blue* regions indicate areas with larger responses to houses than to faces. **a** No correction for multiple comparisons has been performed. **b** Thresholding result when using the false discovery rate approach (FDR). **c** Thresholding result when using the Bonferroni method. The p values shown on top of each panel have been used to threshold the map as provided by the respective method. The FDR method shows more voxels as significant because it is less conservative than the Bonferroni method.

maps. If there were only a single voxel's data, a conventional threshold of $p < 0.05$ (or $p < 0.01$) could be used, which would indicate the probability of obtaining the observed effect, quantified by an R , t or F statistic, solely due to noise fluctuations. Running the statistical analysis separately for each voxel creates, however, a massive multiple comparison problem. If a single test is performed, the conventional threshold protects us with a probability of $p < 0.05$ from wrongly declaring a voxel as significantly modulated when there is no effect (α error). Note that an error probability of $p = 0.05$ means that if we repeated the same test 100 times and assume that there is no effect (null hypothesis), we would wrongly reject (accept) the null (alternative) hypothesis on average in five cases (*false positive*, α error). If we assume that there is no real effect in any voxel time course, running a statistical test spatially in parallel is statistically identical to repeating the test 100,000 times for a single voxel. It is evident that this would lead to about 5000 false positives, i.e. about 5000 voxels would be labeled “significant” although they would surpass the 0.05 threshold purely due to chance.

The Bonferroni correction method is a simple multiple comparison correction approach adjusting the single-voxel threshold in such a way that we retain an error probability of 0.05 at the global level. With N independent tests, this is achieved by using a statistical significance level which is N times smaller than usual. The Bonferroni correction can be derived mathematically as follows: Under the assumption of independent tests, the probability that all of N performed tests lead to a sub-threshold result is $(1-p)^N$ and the probability to obtain one or more false positive results is $1-(1-p)^N$. In order to guarantee a global or family-wise error (FWE) probability of $p_{\text{FWE}} = 1-(1-p)^N$, the threshold for a single

test, p , has to be adjusted as follows: $p = 1-(1-p_{\text{FWE}})^{1/N}$. For small p_{FWE} values (e.g. 0.05), this equation can be approximated by $p = p_{\text{FWE}} / N$. This means that to obtain a global error probability of $p_{\text{FWE}} < 0.05$, the significance level for a single test is obtained by dividing the family-wise error probability by the number of independent tests. Given 100,000 voxels, we would obtain an adjusted single-voxel threshold of $p_v = p_{\text{FWE}} / N = 0.05/100000 = 0.0000005$. The Bonferroni correction method guarantees that we accept even a single voxel wrongly as significant with an error probability of only 0.05. The method, thus, controls the α error *across all voxels*, and it is therefore called a family-wise correction approach. For fMRI data, the Bonferroni method would be a valid approach to correct the α error if the data at neighboring voxels would be truly independent from each other. Neighboring voxels, however, show similar response patterns within functionally defined brain regions, such as the fusiform face area (FFA). In the presence of such spatial correlations, the Bonferroni correction method operates too conservatively, i.e. it corrects more strictly than necessary. As a result of an overly strict control of the α error, the sensitivity (power) to detect truly active voxels is reduced: Many voxels will be labeled as “not significant” although they would reflect true effects. Wrongly accepting (rejecting) a null (alternative) hypothesis is called β error.

WORSLEY et al. (1992) suggested a less conservative approach to correct for multiple comparisons taking the observation explicitly into account that neighboring voxels are not activated independently from each other but are more likely to activate together in clusters. In order to incorporate spatial neighborhood relationships in the calculation of global error probabilities, the method describes a statistical map

as a “Gaussian random field” (for details, see WORSLEY et al. 1992). Unfortunately, application of this correction method requires that the fMRI data are spatially smoothed, substantially reducing one of its most attractive properties, namely its high spatial resolution.

Another correction method incorporating the observation that neighboring voxels often activate in clusters is based on Monte Carlo simulations calculating the likelihood to obtain clusters of different sizes (FORMAN et al. 1995). In combination with relaxed single-voxel thresholds, calculated cluster extent thresholds are applied to the statistical map ensuring that a global error probability of $p < 0.05$ is met. This approach does not require spatial smoothing and appears highly appropriate for fMRI data. The only disadvantage is that the method is quite computer intensive.

While the described multiple comparison correction methods aim to control the family-wise error rate, the false discovery rate (FDR) approach (BENJAMINI and HOCHBERG 1995) uses a different statistical logic, and has been proposed for fMRI analysis by GENOVESE and colleagues (2002). In this approach, not the overall number of false positive voxels is controlled but the number of false positive voxels among the subset of voxels labeled as significant. Supra-threshold voxels given a specific threshold value are called “discovered” voxels or “voxels declared as active”. With a false discovery rate of $q < 0.05$ one would accept that 5% of the discovered (supra-threshold) voxels would be false positives. Given a desired false discovery rate, the FDR algorithm calculates a single-voxel threshold, which ensures that the voxels beyond that threshold contain not more than the specified proportion of false positives. With a q value of 0.05 this also means that one can “trust” 95% of the supra-threshold (color-coded) voxels since the null hypothesis has been rejected correctly. Since the FDR logic relates the number of false positives to the amount of truly active voxels, the FDR method adapts to the amount of activity in the data: The method is very strict if there is not much activity in the data, but assumes less conservative thresholds if larger regions of the brain show task-related effects. In the extreme case that not a single voxel is truly active, the calculated single-voxel threshold is identical to the one computed with the Bonferroni method. The FDR method appears ideal for fMRI data because it does not require spatial smoothing and it detects voxels with a high sensi-

tivity (low β error) if there are true effects in the data.

Another simple approach to the multiple comparisons problem is to reduce the number of tests by using anatomical information. Most correction methods, including Bonferroni and FDR, can be combined with this approach since a smaller number of tests leads to a less strict control of the α error and thus a smaller β error is made as compared to inclusion of all voxels. In a simple version of an anatomical constraint, an intensity threshold for the basic signal level can be used to remove voxels outside the head. The number of voxels can be further reduced by masking the brain, e.g. after performing a brain segmentation step. These simple steps typically reduce the number of voxels from about 100,000 to about 50,000 voxels. In a more advanced version, statistical data analysis may be restricted to grey matter voxels, which may be identified by standard cortex segmentation procedures (e.g. KRIEGESKORTE and GOEBEL 2001). This approach not only removes voxels outside the brain but also excludes voxels in white matter and ventricles. Note that anatomically informed correction methods do not require spatial smoothing of the data and not only reduce the multiple comparisons problem, but also reduce computation time since fewer tests (e.g. GLM calculations) have to be performed.

2.3.3.6

Event-Related Averaging

Event-related designs can not only be used to detect activation effects but also to estimate the time course of task-related responses. Estimation of mean response profiles can be achieved by averaging all responses of the same condition across corresponding time points with respect to stimulus onset (Fig. 2.19). Averaged (or even single trial) responses can be used to characterize the temporal dynamics of brain activity within and across brain areas by comparing estimated features such as response latency, duration and amplitude (e.g. KRUGGEL and VON CRAMON 1999; FORMISANO and GOEBEL 2003). In more complex, temporally extended tasks, responses to sub-processes may be identified. In working memory paradigms, for example, encoding, delay and response phases may be separated. Note that event-related selective averaging works well only for slow event-related designs. In rapid event-related designs, responses from different conditions may overlap substantially and event-related aver-

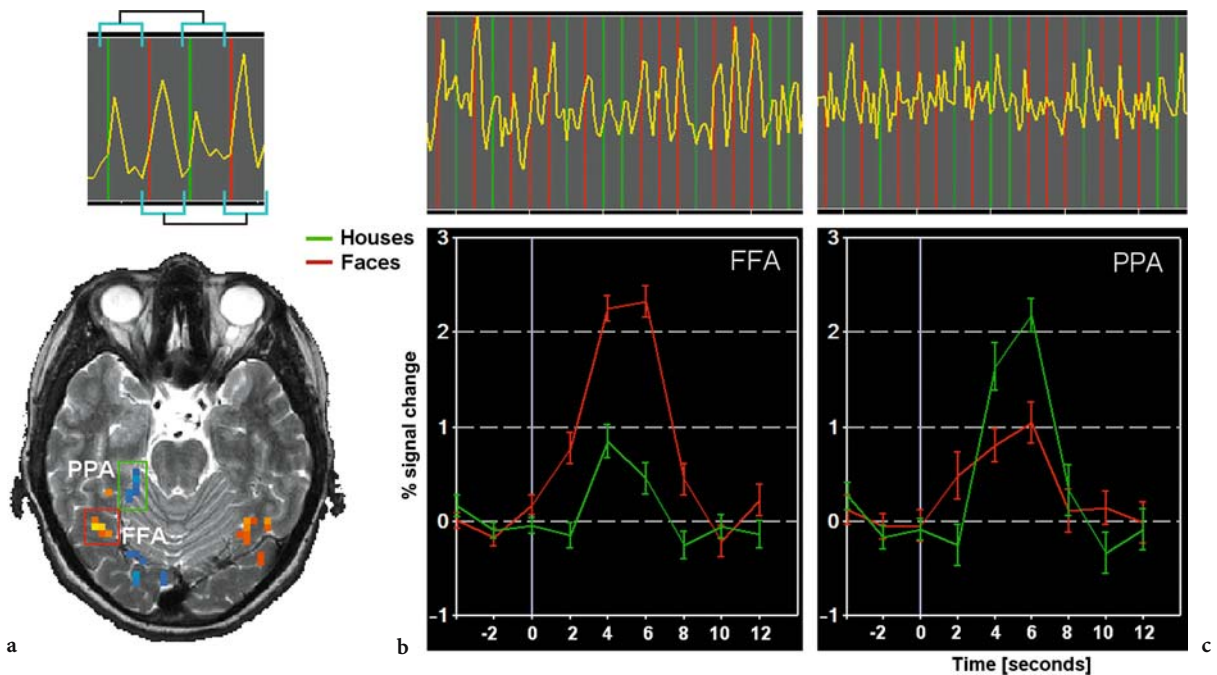


Fig. 2.19a–c. Principle of event-related averaging and event-related averaging plots from a slow event-related design. **a** The thresholded statistical map shows in *red/yellow* brain regions responding more to faces than to houses and in *blue* brain regions responding more to houses than to faces. The areas demarcated with *red* and *green* rectangles in the *lower panel* correspond well to fusiform face area (FFA) and parahippocampal place area (PPA), respectively (O’CRIVEN and KANWISHER 2000). **b** Time course from FFA (*upper panel*) and event-related averaging plot (*lower panel*) obtained by selectively averaging all responses belonging to the same condition. **c** Time course (*upper panel*) and event-related averaging plot (*lower panel*) from PPA.

ages are often meaningless. If the stimulus design, however, takes sufficient care of the expected overlap by ensuring that each condition occurs equally often before each event type, event-related averaging may be used successfully because response overlap cancels out. If a rest condition is included in such a fully counterbalanced design, its averaged response can be subtracted from the responses of the main conditions; otherwise averaged time courses show only differences between conditions.

2.3.3.7

Deconvolution Analysis

While standard design matrix construction (convolution of box-car with two-gamma function) can be used to estimate condition amplitudes (beta values) in rapid event related designs, results critically depend on the appropriateness of the assumed standard BOLD response shape: Due to variability in different brain areas within and across subjects, a *static* model of the response shape might lead to non-optimal fits. To model the shape of the hemo-

dynamic response more flexibly, additional basis functions (predictors) may be defined for each condition. Two often used additional basis functions are derivatives of the two-gamma function with respect to two of its parameters, delay and dispersion. If added to the design matrix for each condition, these basis functions make it possible to capture small variations in response latency and width. Other sets of basis functions (i.e. Gamma basis set, Fourier basis set) are much more flexible but obtained results are rather difficult to interpret. Deconvolution analysis is a general approach to estimate condition-related response profiles using a flexible and interpretable set of basis functions. It can be easily implemented as a GLM by defining an appropriate design matrix (Fig. 2.20) modelling each bin after stimulus onset by its own predictor (delta or “stick” functions). This is also called a finite impulse response (FIR) model because it allows estimating any response shape after a short stimulus (impulse). In order to capture the BOLD response for short events, 20 s are typically modeled after stimulus onset. This would require, for each condition, 20 predictors in case of a TR of 1 s, or

10 predictors in case of a TR of 2 s (Fig. 2.20). Despite overlapping responses, fitting such a GLM “recovers” the underlying condition-specific response profiles in a series of beta values, which appear in plots as if event-related averages have been computed in a slow event-related design (Fig. 2.20). Note, however, that the deconvolution analysis assumes a linear time invariant system (see Sect. 2.3.1). In order to uniquely estimate the large amount of beta values from overlapping responses, variable ITIs must be used in the experimental design (see Sect. 2.3.1). The deconvolution model is very flexible allowing any response shape to be captured. This implies, however, that nonsensical event-related time courses will also be detected easily. It might thus be more appropriate to apply the deconvolution model to a set of regions-of-interest (ROIs) identified on statistical maps obtained with a standard design matrix in a separate localizer experiment.

2.3.4

Integration of Anatomical and Functional Data

While fMRI measures brain activity an exact localization of the neural correlates of sensory, motor and cognitive functions requires a precise relationship of voxels in calculated statistical maps with voxels in high-resolution anatomical data sets. This is especially important in single subject analyses and, thus, for presurgical mapping. Functional data sets do not contain sufficient anatomical detail to specify the precise location of an active cluster in a subject’s brain. 3D renderings of high-resolution anatomical data sets may greatly aid in visualizing activated brain regions. Advanced visualization requires that a high-resolution 3D data set is recorded for a subject and that the functional data is coregistered to the 3D data set as precisely as possible. Anatomical data sets are also important for brain normalization, which is

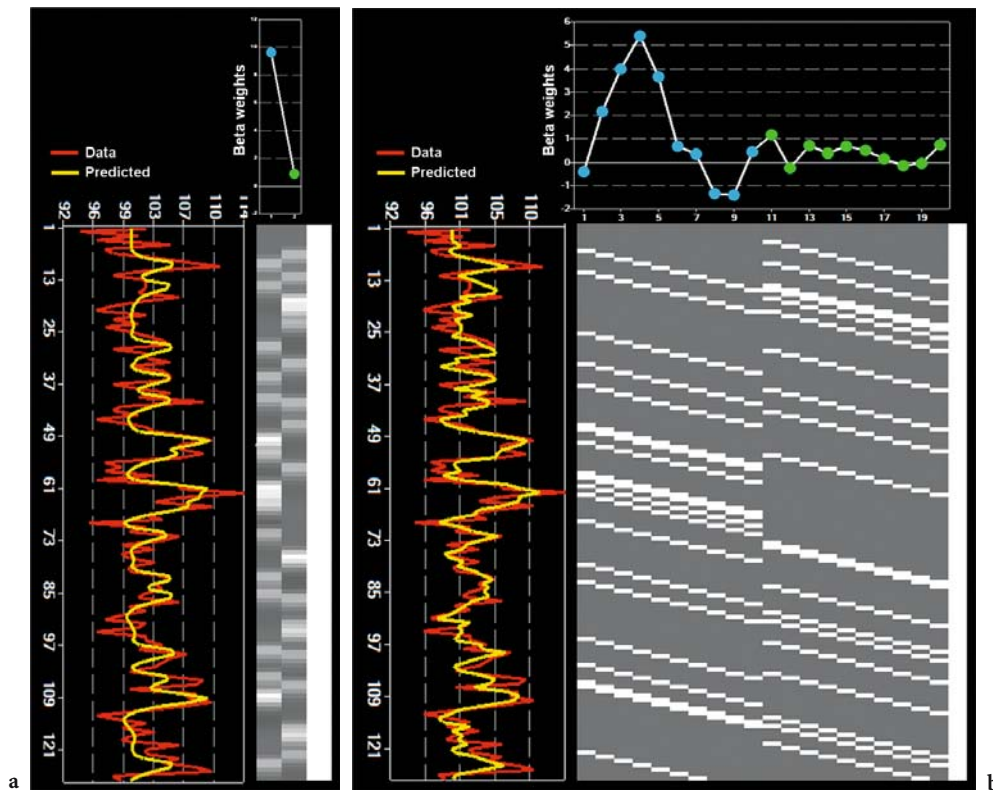


Fig. 2.20a,b. Deconvolution analysis of a rapid event-related design. Time runs from *top* to *bottom*, design matrix depicted in graphical view. Beta values are plotted horizontally at positions corresponding to the respective predictor. **a** Standard analysis with two main predictors obtained by convolution of stimulus times with standard hemodynamic response model (2-gamma function). Beta values can be compared with a standard contrast. **b** Deconvolution analysis fitting the same data. Each condition is modeled with 10 “stick” predictors making it possible to estimate the time course of condition-related responses as if stimuli were presented in a slow event-related design. Beta values may be compared within and across conditions.

a prerequisite of group studies. Anatomical data sets are typically recorded with slow, high-resolution, T_1 -weighted MRI sequences. A typical structural scan covering the whole brain with a resolution of 1 mm in all three dimensions (e.g. 180 sagittal slices) lasts between 5 and 20 min on current 1.5- and 3.0-Tesla scanners.

2.3.4.1

Visualizing Statistical Maps on Anatomical Images

Having identified a statistically significant region in the functional data set does not easily allow a precise statement about its location in the brain of the subject since the T_2^* -weighted functional data itself does often not contain enough anatomical details. Note that the richest anatomical detail because it is also T_1 -weighted. Unfortunately, this data set is often thrown away either by the scanner directly or by transfer of the data to the researcher. We recommend keeping the first functional volume and using it for visualization and coregistration due to its relative wealth of anatomical details. If anatomical, co-planar images are available, it is already helpful to overlay the functional results (thresholded statistical maps) on these “in-plane” images. Figure 2.19a shows, for example, a statistical map on a high-resolution, co-planar, T_2 weighted image. While high-resolution, co-planar images improve localization within the recording plane, the direction along slices is sampled with low resolution due to typical distances between slices of 3–5 mm (slice distance = slice thickness + slice gap). Identification of the anatomical substrate of an activated cluster is greatly assisted by visualizing functional data within isotropic, high-resolution 3D data sets. Overlaying or fusing images from functional data (MRI, PET, SPECT) with high-resolution anatomical MRI data sets is a common visualization method in functional imaging. In order to correctly fuse functional and anatomical data sets, appropriate coregistration transformations have to be performed.

2.3.4.2

Coregistration of Functional and Anatomical Data Sets

If functional images are superimposed on coplanar images, spatial transformations (translations and rotations) to align the two data sets are not necessary besides correction of small head movements), since the respective slices are measured at the same

3D positions. Since the co-planar anatomical images are recorded with a higher resolution (typically with a 256×256 matrix) than the functional images (typically 64×64 or 128×128 matrices), only a scaling operation for the two in-plane dimensions has to be applied. To allow high-quality visualization of the functional data in arbitrary anatomical cut planes, the functional data must be coregistered with high-resolution 3D data sets. These data sets are recorded with a different slice orientation and the coregistration step requires typically translations, rotations and scaling. These three elementary spatial transformations can be integrated in a single transformation step expressed in a standard 4×4 spatial transformation matrix. If the high-resolution 3D data set has been recorded in the same scanning session as the functional data, coregistration can be performed using the scanning parameters (slice positions, pixel resolution, slice thickness) from both recordings. Such a mathematical alignment would be perfect if there would be no head movement between the anatomical and functional images. To further improve coregistration results, an additional intensity-driven alignment step is often performed after the initial (mathematical) alignment. While this step operates similarly to that described for motion correction, it is not possible to align the two data sets perfectly well in all regions of the brain due to signal drop-outs and distortions in the functional EPI images. For neurosurgical purposes, it is important to ensure that at least the relevant regions of the brain do not suffer from EPI distortions and that they are perfectly coregistered with the anatomical data. EPI distortions and signal dropouts can be corrected to some extent with special MRI sequence modifications as well as with image processing software (WEISSKOPF et al. 2006). Using appropriate visualization tools, it is also possible to manually align a functional volume with an anatomical 3D data set. The precision of manual alignment, however, depends strongly on acquired expertise.

2.3.4.3

Visualizing Statistical Maps on Reconstructed Cortex Representations

High-resolution anatomical data sets can be used to create 3D volume or surface renderings of the brain, which allow additional helpful visualizations of functional data on a subject's brain (Fig. 2.21). These visualizations require segmentation of the

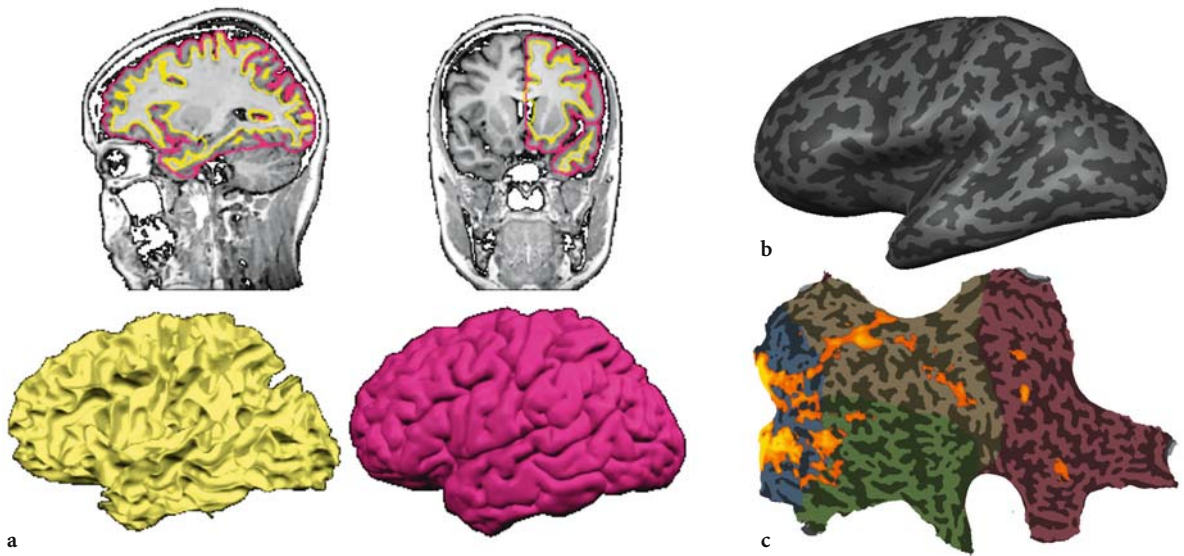


Fig. 2.21a–c. Cortex representations used for advanced visualization. **a** Segmentation and surface reconstruction of the inner (whitelgrey matter, yellow) and outer (grey matter/CSF, magenta) boundary of grey matter. **b** “Inflated” cortex representation of the left hemisphere obtained by iterative morphing process. **c** “Flat map” of the right cortical hemisphere with superimposed functional data.

brain, which can be performed automatically with most available software packages. For more advanced visualizations, segmentation of cortical voxels enable construction of topologically correct mesh representations of the cortical sheet, one for the left and one for the right hemisphere (KRIEGESKORTE and GOEBEL 2001). The obtained meshes (Fig. 2.21a) may be further transformed into inflated (Fig. 2.21b) and flattened (Fig. 2.21c) cortex representations. Functional data can then be superimposed on folded, inflated and flattened representations (Fig. 2.21c), which is particularly useful for topologically organized functional information, for example, in the context of retinotopic mapping experiments. To help in orientation, inflated and flattened cortex representations indicate gyral and sulcal regions by colour-coding local curvature; concave regions, indicating sulci, are depicted with a dark grey colour in Fig. 2.21 while convex regions, indicating gyri, are depicted with a light grey colour. A general advantage of visualizing functional data on flat maps is that all cortical activation foci can be visualized at once at their correct anatomical location. In contrast, visualizing several activated regions using a multi-slice representation depends on the chosen slice orientation and number of slices. Note that anatomical data is not only important to visualize functional data. Anatomical information may also be used to constrain statistical data analysis as has been described in Sect. 2.3.3.5.

Furthermore, the explicit segmentation of cortical voxels is also the prerequisite for advanced anatomical analyses, including cortical morphometry.

2.3.5

Group Analysis of Functional Data Sets

Presurgical neuroimaging requires detailed single subject analyses, which can be performed with the methods described in the previous sections. A standardized routine for analyzing (clinical) fMRI data in individuals is given in Chap. 4. If, however, characterization and statistical assessment of general brain patterns is desired, multiple subjects have to be integrated in groups. Such group studies make it possible to generalize findings from a sample of subjects to the population from which the patients or healthy subjects have been drawn. Group analysis of functional data sets is of clinical relevance when the effects of various brain pathologies or different therapies (e.g. pharmacological effects) on brain function are subject to study.

The integration of fMRI data from multiple subjects is challenging because of the *spatial correspondence problem*. This problem of “matching” homologue regions across brains manifests itself already at a purely anatomical level, but presents a fundamental problem of neuroscience when consid-

ered as a question of the consistency of structure–function relationships. At the anatomical level, the correspondence problem refers to the differences in brain shape and, more specifically, to differences in the gyral and sulcal pattern varying substantially across subjects. At this macroanatomical level, the correspondence problem would be solved if brains could be matched in such a way that for each macroanatomical structure in one brain, the corresponding region in the other brain would be known. In neuroimaging, the matching of brains is usually performed by a process called *brain normalization*, which involves warping each brain into a common space. After brain normalization, a point in the common space identified by its x , y , z coordinates is assumed to refer to a similar region in any normalized brain. The most commonly used target space for normalization is the Talairach space (see Sect. 2.3.5.1) and the closely related MNI template space. Unfortunately, warping brains in a common space does not solve the anatomical correspondence problem very well, i.e. macroanatomical structures, such as banks of prominent sulci, are often still misaligned with deviations in the order of 1 cm. In order to increase the chance that homologue regions overlap, functional data is therefore often smoothed with a Gaussian kernel with a width of about 1 cm. More advanced anatomical matching schemes attempt to directly align macroanatomical structures such as gyri and sulci (see Sect. 2.3.5.3).

The deeper version of the correspondence problem addresses the fundamental question of the existence of

an identical relationship between certain brain functions and neuroanatomical structures across subjects. While neuroimaging has successfully demonstrated that there is a common structure–function relationship across brains, a high level of variability has also been observed, especially for higher cognitive functions. A more satisfying answer to this fundamental question might only emerge after much more careful investigations, e.g. by letting the same subjects perform a large battery of tasks. An interesting approach to the functional correspondence problem has been proposed by simply averaging data from those brain regions, which are activated for the same task across subjects.

2.3.5.1

Talairach Transformation

The most frequently used standard space for brain normalization is the Talairach space (TALAIRACH and TOURNOUX 1988). A brain can be transformed into this space by applying a Talairach transformation procedure. A Talairach transformation is controlled either by the specification of a few prominent landmarks or by an intensity-driven match of a subject's brain to an “average brain” (typically the MNI template brain) located in Talairach space. In the explicit approach (TALAIRACH and TOURNOUX 1988), the midpoint of the anterior commissure (AC) is located first, serving as the origin of Talairach space. The brain is then rotated around the new origin (AC) so that the posterior commissure (PC)

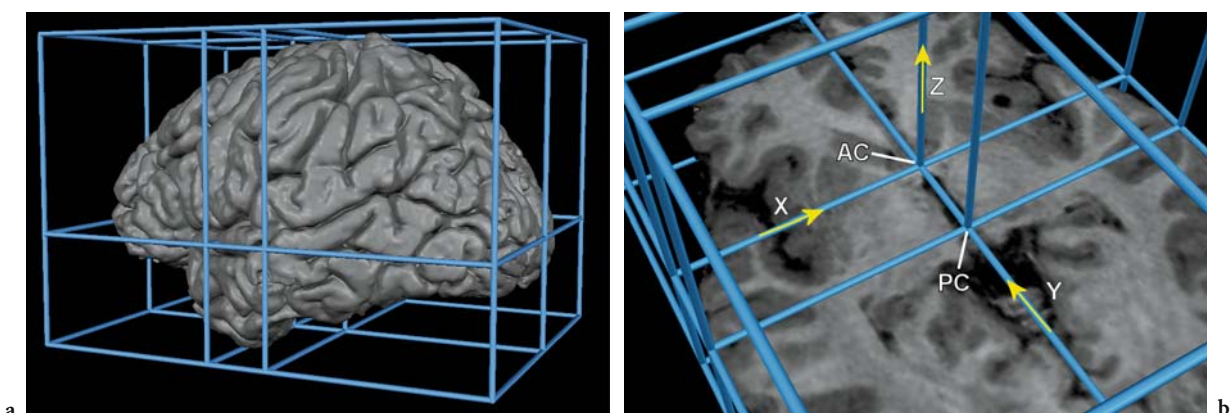


Fig. 2.22a,b. Definition of Talairach space. **a** View from *left*. **b** View from *top*. Talairach space is defined by three orthogonal axes pointing from *left* to *right* (x -axis), *posterior* to *anterior* (y -axis) and *inferior* to *superior* (z -axis). The origin of the coordinate system is defined by the anterior commissure (AC). Coordinates are in millimeters. The posterior commissure (PC) is located on the y -axis ($y = -23$ mm). The borders of the Talairach grid (**a**) correspond to the borders of the cerebrum. The most right point of the brain corresponds to $x = 68$ mm, the most left one to $x = -68$ mm, the most anterior one to $y = 70$, the most posterior one to $y = -102$, the most upper one to $z = 74$, and the most lower one to $z = -42$.

appears in the same axial plane as the anterior commissure (Fig. 2.22). The connection of AC and PC in the middle of the brain forms the y-axis of the Talairach coordinate system. The x-axis runs from the left to the right hemisphere through AC. The z-axis runs from the inferior part of the brain to the superior part through AC. In order to further specify the x- and z-axes, the y-z plane is rotated around the y (AC-PC)-axis until it separates the left and right hemisphere (mid-sagittal plane). After these steps the brain can be brought into AC-PC space, which is attractive for individual clinical applications, especially presurgical mapping and neuronavigation since it keeps the original size of the subject's brain intact while providing a common orientation for each brain. For a full Talairach transformation, a cuboid is defined running parallel to the three axes enclosing precisely the cortex. This cuboid or bounding box requires specification of additional landmarks specifying the borders of the cerebrum. The bounding box is sub-divided by several sub-planes. The midsagittal y-z plane separates two sub-cuboids containing the left and right hemisphere, respectively. An axial (x-y) plane through the origin separates two sub-cuboids containing the space below and above the AC-PC plane. Two coronal (x-z) planes, one running through AC and one running through PC, separate three sub-cuboids; the first contains the anterior portion of the brain anterior to the AC, the second contains the space between AC and PC and the third contains the space posterior to PC. These planes separate 12 sub-cuboids. In a final Talairach transformation step, each of the 12 sub-cuboids is expanded or shrunk linearly to match the size of the corresponding sub-cuboid of the standard Talairach brain. To reference any point in the brain, x, y, z coordinates are specified in millimeters of Talairach space. TALAIRACH and TOURNOUX (1988) also defined the "proportional grid", to reference points within the defined cuboids.

In summary, Talairach normalization ensures that the anterior and posterior commissures obtain the same coordinates in each brain and that the sub-cuboids defined by the AC, PC points and the borders of the cortex will have the same size. Note that the specific distances between landmarks in the original post-mortem brain are not important for establishing the described spatial relationship between brains. The important aspect of Talairach transformation is that correspondence is established across brains by linearly interpolating the space between important landmarks.

While Talairach transformation provides a recipe to normalize brains, regions at the same coordinates in different individuals do not necessarily point to homologous brain areas. This holds especially true for cortical regions. For subcortical structures around the AC, PC landmarks, however, the established correspondence is remarkably good.

As an alternative to specify crucial landmarks, the direct approach of stereotactic normalization (e.g. ASHBURNER and FRISTON 1999) attempts to align each individual brain as well as possible to an average target brain, called template brain. The most frequently used template brain is provided by the Montréal Neurological Institute (MNI) and has been created by averaging 152 single brains after manual Talairach transformation. Although automatic alignment to a template brain promises a better correspondence between brain regions, comparisons have shown that the achieved results are not substantially improved as compared to the explicit landmark specification approach, even when using non-linear spatial transformation techniques. This can be explained by noting that the template brain has lost anatomical details due to extensive averaging.

In order to bring functional data of a subject into Talairach space, the obtained spatial transformation for the anatomical data may be applied to the functional data if it has been coregistered with the unnormalized anatomical data set. Using the intensity-driven matching approach, functional data sets may also be directly normalized because versions of the MNI template brain for functional (EPI) scans are also available. If possible, it is, however, recommended to apply the Talairach transformation obtained for the anatomical data also to the functional data because this approach guarantees that the precision of functional-anatomical alignment achieved during coregistration is not changed during the normalization step.

2.3.5.2 Correspondence Based on Functional Localizer Experiments

An interesting approach to establish correspondence between brains is to use functional information directly. Using standardized stimuli, a specific region-of-interest (ROI) may be functionally identified in each subject. The ROIs identified in such functional localizer experiments are then used to extract time courses in subsequent main experi-

ments. The extracted time courses of individual subjects are then integrated in group analyses. If the assumption is correct that localizer experiments reveal homologue brain regions in different subjects, the approach provides an optimal solution to the correspondence problem and will allow detection of subtle differences in fMRI responses at the group level with high statistical power. Statistical sensitivity is further enhanced by avoiding the massive multiple comparison correction problem. Instead of about 100,000 tests, only a few tests need to be performed in parallel, one for each ROI. The approach is statistically sound because the considered regions have been determined independently from the data of the main experiment in previous localizer runs. It is also possible to use the same functional data for both localizer and main experiment as long as the contrast to localize ROIs is orthogonal to any contrast used to test more subtle differences. The localizer approach has been applied successfully in many experiments, most notably in studies of the ventral visual cortex (e.g. O'CRIVEN and KANWISHER 2000).

Unfortunately, it is often difficult to define experiments localizing the same pattern of activated brain areas in all subjects, especially in studies of higher cognitive functions, such as attention, mental imagery, working memory and planning. If at all possible, the selection of homologue functional brain areas in these experiments is very difficult and depends on the investigator's choice of thresholding statistical maps and often on additional decisions such as grouping sub-clusters to obtain the same number of major clusters for each subject. Note that the observed variability in more complex experiments could be explained by at least two factors. On the one hand the location of functionally homologue brain regions may vary substantially across subjects with respect to aligned macroanatomical structures. On the other hand, subjects may engage in different cognitive strategies to solve the same task leading to a partially different set of activated brain areas. Most likely, the observed variability is caused by a mixture of both sources of variability. Another problem of the localizer approach is the tendency to focus only on a few brain areas, namely those which can be mapped consistently in different subjects. This tendency bears the danger to overlook other important brain regions. At a more philosophical level, the localizer approach might suggest an overly simplistic view of the brain as consisting of a set of universal, highly specialized modules.

2.3.5.3

Cortex-Based Normalization

In recent years, more advanced, purely anatomical, brain normalization techniques have been proposed going beyond Talairach space alignment. A particularly interesting approach attempts to explicitly align the cortices of subjects (FISCHL et al. 1999; GOEBEL et al. 2004, 2006) starting with topologically correct cortex mesh representations (see Sect. 2.3.4.3). More specifically, this approach aligns cortices by increasing the overlap of curvature information. Since the curvature of the cortex reflects the gyral/sulcal folding pattern of the brain, this brain matching approach essentially aligns corresponding gyri and sulci across subject's brains. It has been shown that cortex-based alignment substantially increases the statistical power and spatial specificity of group analyses (e.g. VAN ATTEVELDT et al. 2004).

2.3.5.4

Statistical Analysis of Group Data

After brain normalization, the data from multiple subjects can be statistically analyzed simply by "concatenating" them over corresponding points. Corresponding points may be voxel coordinates in Talairach space, vertex coordinates in cortex space or identified ROIs in the localizer approach. Note that the power of statistical analysis depends on the achieved alignment of homologue functional brain areas. If the alignment is poor, suboptimal group results may be obtained since active voxels of some subjects will be averaged with non-active voxels of other subjects. In order to increase the overlap of activated brain areas across subjects, the functional data of each subject is often extensively smoothed, typically with a Gaussian filter with a full width of half maximum (FWHM) of 8–12 mm. While such an extensive spatial smoothing increases the overlap of active regions, it introduces other problems including potential averaging of non-homologous functional areas within and across brains and the suppression of small functional clusters.

After concatenating the data, the statistical analysis described earlier can then be applied to the concatenated time courses. In the context of the GLM, the multi-subject voxel time courses as well as the multi-subject predictors may be obtained by concatenation. After estimating the beta values, contrasts can be tested in the same way as described for single subject data. While the described concatenation

approach leads to a high statistical power due to the large number of blocks or events, the obtained results can not be generalized to the population level since the data is analyzed as if it stems from a single subject. Significant findings only indicate that the results are replicable for the same “subject” (group of subjects). In order to test whether the obtained results are valid at the population level, the statistical procedure must assess the variability of observed effects across subjects (random effects analysis) as opposed to the variability across individual measurement time points as performed in the concatenation approach (fixed effects analysis). There are many statistical methods to assess the variability across subjects for the purpose of proper population inferences. A simple and elegant method is provided by multi-level summary statistics approach (e.g. KIRBY 1993). In a first level, mean effects (summary statistics) are estimated for each subject (level 1). The estimated effects at the first level per subject enter the second level as the dependent variable and are analyzed for significant effects. Since the summarized data at the second level explicitly models the variability of the estimated effects across subjects, the obtained results can be generalized to the population from which the subjects (sample) were drawn. To summarize the data at the first level, a standard GLM may be used to estimate effects – beta values – separately for each subject. Instead of one set of beta values in fixed effects analysis, this step will provide a separate set of beta values for each subject. The obtained beta values can be analyzed at the second level using a standard ANOVA with one or more within-subject factors categorizing the beta values. If the data represent multiple groups of subjects, a between factor for group comparisons can be added.

These short explanations indicate that the statistical analysis at the second level does not differ from the usual statistical approach in medical studies. The only major difference to standard statistics is that the analysis is performed separately for each voxel (or vertex) requiring methods to correct for a massive multiple comparison problem as has been described above. Note that in addition to the estimated subject-specific effects of the fMRI design (beta values of first level analysis), additional external variables (e.g. an IQ value for each subject) may be incorporated as covariates at the second level.

2.4

Recent Developments and Future Trends

The described analysis steps for single subjects and for group comparisons represent essential components of a standard fMRI analysis, which are performed in a similar way for most fMRI studies. A standard analysis involves proper preprocessing, including drift removal and 3D motion correction, coregistration of functional and anatomical data, brain normalization, and a thorough statistical analysis usually based on the GLM. As a result, statistical maps localize regions showing differential responses with respect to specified experimental hypotheses. Random effect group analyses allow generalization of observed findings from a sample of subjects to the population level. Event-related averages of active brain regions or pre-specified ROIs can be used to compare estimated condition time courses within and across brain areas, often revealing additional interesting insights. The following sections describe recent technical developments and analysis methods, which may further improve fMRI data recording and analysis.

2.4.1

Improvements in Data Acquisition

2.4.1.1

Parallel Imaging

In recent years, parallel imaging techniques (e.g. PRUESSMANN et al. 1999) have been developed and dubbed e.g. “SENSE”, “IPAT” and “SMASH” by scanner manufacturers. The basic idea of parallel imaging is the simultaneous acquisition of MRI data with two or more receiver coils, each having a different spatial sensitivity. During image reconstruction, complementary information from the different receiver coils can be combined to fill k space reducing the number of time-consuming phase encoding steps. Besides appropriate coils (called “phased array coils”), parallel imaging requires that MRI scanners are equipped with multiple processing channels operating in parallel. Note that parallel imaging may be used either to increase temporal resolution using a standard matrix size or to increase spatial resolution using a conventional image acquisition time. Using parallel imaging to reduce scan time without sacrificing image quality is especially relevant

for patient scans. Furthermore, parallel imaging may also reduce GE-EPI imaging artifacts because it allows images to be acquired with shorter echo times. Note that typical EPI artifacts, such as signal dropouts in regions of neighboring tissue types and geometrical distortions, increase with increasing echo times.

2.4.1.2

Spatial Resolution

The ultimate spatial and temporal resolution of fMRI is not primarily limited by technical constraints but by properties of the vascular system. The spatial resolution of the vascular system, and hence fMRI, seems to be in the order of 1 mm since relevant blood vessels run vertically through cortex in a distance of about 1 mm (DUVERNOY et al. 1981). An achievable resolution of about 1 mm might be just enough to resolve *cortical columns*. A cortical column contains thousands of neurons possessing similar response specificity. A conventional brain area, such as the fusiform face area, could contain a set of cortical columns, each coding a different basic (e.g. face) feature. Cortical columns could, thus, form the basic building blocks (“alphabet”) of complex representations (FUJITA et al. 1992). Since neurons within a column code for roughly the same feature, measuring the brain at the level of cortical columns promises to provide a relevant level for describing brain functioning. In cat visual cortex, for example, orientation columns could be measured with fMRI at ultra-high magnetic fields (4 and 9 Tesla; KIM et al. 2000). The observed pattern of active orientation columns systematically changed when showing cat gratings of different orientations. Using high magnetic fields (3–7 Tesla), columnar resolution appears to also be within reach for human brain imaging (e.g. CHENG et al. 2001). Even if clear cortical columns are not directly visible, recent work has shown the possibility of revealing the detailed functional organization of small brain areas in the human brain. As an example, a recent 7-Tesla study showed tonotopic, mirror-symmetric maps within early human auditory cortex (FORMISANO et al. 2003). The described tonotopic maps were much smaller than the large retinotopic maps in human visual cortex, which had therefore already been observed 10 years earlier with 1.5-Tesla scanners (SERENO et al. 1995).

2.4.1.3

Temporal Resolution

Despite the sluggishness of the fMRI signal, it has been shown that the obtained responses may reflect timing information with very high temporal precision. The signal of the left and right visual cortex, for example, reliably reflects temporal differences between stimulation of the left and right visual field as short as 100 ms (MENON 1999). When properly taking care of different hemodynamic delays in different brain areas, the analysis of BOLD onset latencies may also be very useful in revealing the sequential order of activity across brain areas within trials of complex cognitive tasks (fMRI mental chronometry, e.g. FORMISANO and GOEBEL 2003). In order to measure the brain with a temporal resolution in the order of milliseconds, other methods such as electroencephalography (EEG) and magnetoencephalography (MEG) must be used. If one succeeds in performing a proper combined analysis of EEG/MEG and fMRI data (DALE and HALGREN 2001; BLEDOWSKI et al. 2006), it becomes possible to describe brain function both with respect to its topographic distribution as well as with respect to its precise timing. While EEG/MEG data and fMRI data are conventionally obtained in different sessions, it has recently become possible to measure EEG data directly during fMRI recording sessions (e.g. MULERT et al. 2004).

2.4.2

Selected Advanced Data Analysis Methods

In the following sections, a selected list of analysis methods is shortly described aiming at improving or extending the standard analysis procedure.

2.4.2.1

Nonparametric Statistical Approaches

As stated in Sect. 2.3.3.3.5, GLM hypothesis testing requires normally distributed residuals with equal variance. Fortunately, the GLM is robust with respect to minor violations of the normality assumption. To avoid, however, wrong inferences due to non-normal distributions, non-parametric methods may be used, especially when analyzing small data samples.

2.4.2.2

Bayesian Statistics

The use of Bayesian statistics has recently been proposed because it provides an elegant framework for multi-level analyses (FRISTON et al. 2002). In the Bayesian approach, the data of a single experiment (or the data of a single subject) is not considered in isolation, but in the light of available a priori knowledge. This a priori knowledge is formalized with prior probabilities $p(H_i)$ for relevant initial hypotheses H_i . Obtained new data D modifies the a priori knowledge resulting in posterior conditional probabilities $p(H_i|D)$, which are updated probabilities of the initial hypotheses given the new data. To calculate these probabilities, the inverse conditional probabilities $p(D|H_i)$ must be known describing the probability to obtain certain observations given that the hypotheses H_i are true. In the context of the empirical Bayes approach, these conditional probabilities can be estimated from the data. The empirical Bayes approach is appropriate for the analysis of fMRI data, since it allows an elegant formulation of hierarchical random effects analyses. It is, for example, possible to enter estimated parameters at a lower level as prior probabilities at the next higher level. Furthermore, the approach allows integrating correction for multiple comparisons resulting in thresholding values similar to the ones obtained with the false discovery rate approach.

2.4.2.3

Brain Normalization

As described earlier, brain normalization methods have an important influence on the quality of group analyses, since optimization of the standard analysis does not lead to substantial improvements if voxel time courses are concatenated from non-matching brain regions. The described cortex-based normalization technique may substantially improve the alignment of homologue brain regions across subjects. For more complex tasks, different, non-matching activity patterns might reflect different cognitive strategies used by subjects. To cope with this situation, it would be desirable to use methods allowing automatic estimation of the similarity of activity patterns across subjects. Such methods could suggest splitting a group in sub-groups with different statistical maps corresponding to the neural correlate of different cognitive strategies. Such a clustering approach has recently been implemented

in the context of group-level ICA analyses (ESPOSITO et al. 2005).

2.4.2.4

Data-Driven Analysis Methods

When considering the richness of fMRI data, it may be useful to apply data-driven analysis methods, which aim at discovering interesting spatio-temporal relationships in the data, which would be eventually overlooked with a purely hypothesis-driven approach. Data-driven methods, such as independent component analysis (ICA, e.g. McKEOWN et al. 1998; FORMISANO et al. 2002) do not require a specification of expected, stimulus-related responses since they are able to extract interesting information automatically (“blindly”) from the data. It is, thus, not necessary to specify an explicit statistical model (design matrix). This is particularly interesting with respect to paradigms for which the exact specification of event onsets is difficult or impossible. Spatial ICA of fMRI data has been successfully applied in many tasks including the automatic detection of active networks during perceptual switches of ambiguous stimuli (CASTELO-BRANCO et al. 2002) and the automatic detection of spontaneous hallucinatory episodes in schizophrenic patients (VAN DE VEN et al. 2005). Data-driven methods are exploratory in nature, and should not be viewed as replacements, but as complementary tools for hypothesis-driven methods: If interesting, unexpected events have been discovered with a data-driven method, one should test these observations in subsequent studies with a hypothesis-driven standard statistical analysis.

2.4.2.5

Effective Connectivity

In contrast to the standard statistical analysis analyzing data voxel-wise, data driven methods process fMRI data in a global, multivariate approach. This multivariate approach allows these methods to detect functionally connected networks of brain areas. Global, multivariate methods may, thus, reveal the functional integration of brain areas, whereas the classical voxel-wise statistical approach is suited to reveal the functional segregation (functional specialization) of brain regions. Besides data-driven methods such as ICA, many approaches have been used to model the interaction between spatially remote brain regions more explicitly. In the simplest case, one cor-

relates the time courses from two regions resulting in a measure (e.g. linear correlation coefficient) of functional connectivity. Functional connectivity can be calculated separately for different experimental conditions, which makes it possible to assess whether two brain areas change their functional coupling in different cognitive contexts (BÜCHEL et al. 1999). In conditions of attention, for example, two remote areas might work more closely with each other than in conditions of no attention.

Models of effective connectivity go beyond simple pair-wise correlation analysis and assess the validity of models containing directed interactions between brain areas. These directed effective connections are often symbolized by arrows connecting boxes each representing a different brain area. Structural equation models (SEM, e.g. MCINTOSH and GONZALEZ-LIMA 1994), and more recently, dynamic causal modeling (DCM, e.g. PENNY et al. 2004) is used to test effective connectivity models. An interesting data-driven approach to effective connectivity modeling is provided by methods based on the concept of Granger causality. This approach does not require specification of connectivity models but enables automatic detection of effective connections from the data by mapping Granger causality in the whole brain for any selected reference voxel or region of interest (GOEBEL et al. 2003; ROEBROECK et al. 2005).

2.4.2.6

Multivariate Analysis of Distributed Activity Patterns

While standard analyses process the time course of each voxel independently and data-driven methods search for patterns in the whole four-dimensional data set, several new analysis approaches focus on more local, multi-variate pattern analyses (e.g. HAXBY et al. 2001; KRIEGESKORTE et al. 2006). In these approaches, time courses from voxels within a region are jointly analyzed; distributed activity patterns corresponding to different conditions are statistically compared using multivariate approaches (e.g. MANOVA). By moving across the brain including a neighborhood of a certain extent (e.g. 1 cm), this local multivariate matching approach offers the possibility of localizing spatially distributed effects, which would be potentially too weak to be discovered by single voxel analysis. This approach does not require that voxels within a region behave in the same way, since it extracts the amount of informa-

tion within the multivariate signal in a given region. If, for example, some voxel time courses in a local neighborhood show a weak increase and other voxel time courses show a weak decrease, these effects would potentially cancel out in an ROI average, but could well contribute to a measure of multivariate information. Local, multivariate approaches are especially well suited to investigate distributed, overlapping representations in the brain (HAXBY et al. 2001).

2.4.2.7

Real-Time Analysis of fMRI Data

The described steps and techniques to analyze fMRI data are very computation intensive and are, thus, performed in most cases hours or days after data acquisition has been completed. There are many scenarios that would benefit greatly from a real-time analysis of fMRI data, especially when studying single subjects as in presurgical mapping. Using appropriately modified analysis tools and state-of-the-art computer hardware, it is possible nowadays to perform real-time fMRI analysis during an ongoing experiment, including 3D motion correction and incremental GLM statistics of whole-brain recordings. It is even possible to run some data-driven tools, including ICA, in real-time (ESPOSITO et al. 2003). One obvious benefit of real-time fMRI analysis is quality assurance. If, for example, one observes during an ongoing measurement that a patient moves too much, or that the (absence of) activity patterns indicates that the task was not correctly understood, the running measurement may be stopped and repeated after giving the subject further instructions. If the ongoing statistical analysis, on the other hand, indicates that expected effects have reached a desired significance level earlier than expected, one could save scanning time by stopping the measurement ahead of schedule. Real-time fMRI also offers the possibility to plan optimal slice positioning for subsequent runs based on the results obtained of an initial run. Based on the results of a first run, it would be, for example, possible to position a small slab of slices at an identified functional region for subsequent high-resolution spatial and/or temporal scanning. More advanced applications of real-time fMRI include neurosurgical monitoring and neurofeedback (WEISKOPF et al. 2003). In fMRI neurofeedback studies, subjects learn to voluntarily control the level of activity in circumscribed brain areas using mental strategies such as visual or auditory imagery.

References

- Ashburner J, Friston KJ (1999) Nonlinear spatial normalization using basis functions. *Hum Brain Mapp* 7:254–266
- Bandettini PA, Birn RM, Donahue KM (2000) Functional MRI: background, methodology, limits, and implementation. In: JT Cacioppo, LG Tassinari, GG Berntson (eds) *Handbook of psychophysiology*. Cambridge University Press, New York, pp 978–1014
- Bandettini PA, Cox RW (2000) Event-related fMRI contrast when using constant interstimulus interval: theory and experiment. *Magn Reson Med* 43:540–548
- Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B* 57:289–300
- Blamire AM, Ogawa S, Ugurbil K et al. (1992) Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging. *Proc Natl Acad Sci USA* 89:11096–11073
- Bledowski C, Cohen Kadosh K, Wibral M, Rahm B, Bittner RA, Hoechstetter K, Scherg M, Maurer K, Goebel R, Linden DE (2006) Mental chronometry of working memory retrieval: a combined functional magnetic resonance imaging and event-related potentials approach. *J Neurosci* 26:821–829
- Boynton GM, Engel SA, Glover GH, Heeger DJ (1996) Linear systems analysis of functional magnetic resonance imaging in human V1. *J Neurosci* 16:4207–4221
- Brown MA, Semelka RC (1999) MRI – basic principles and applications. New York, Wiley-Liss
- Büchel C, Coull JT, Friston KJ (1999) The predictive value of changes in effective connectivity for human learning. *Science* 283:1538–1541
- Buckner RL, Bandettini PA, O'Craven KM, Savoy RL, Petersen SE, Raichle ME, Rosen BR (1996) Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proc Natl Acad Sci USA* 93:14878–14883
- Bullmore E, Brammer M, Williams SC et al. (1996) Statistical methods of estimation and inference for functional MR image analysis. *Magn Reson Med* 35:261–277
- Buxton RB, Wong EC, Frank LR (1998) Dynamics of blood flow and oxygen metabolism during brain activation: The balloon model. *Magn Reson Med* 39:855–864
- Buxton RB, Uludag K, Dubowitz DJ, Liu TT (2004) Modeling the hemodynamic response to brain activation. *Neuroimage* 23:S220–S233
- Carman GJ, Drury HA, Van Essen D (1995) Computational methods for reconstructing and unfolding the cerebral cortex. *Cereb Cortex* 5:506–517
- Castelo-Branco M, Formisano E, Backes W, Zanella F, Neuenschwander S, Singer W, Goebel R (2002) Activity patterns in human motion-sensitive areas depend on the interpretation of global motion. *Proc Natl Acad Sci USA* 99:13914–13919
- Cheng K, Waggoner AK, Tanaka K (2001) Human ocular dominance columns as revealed by high-field functional magnetic resonance imaging. *Neuron* 32:359–374
- Cochrane D, Orcutt GH (1949) Application of least squares regression to relationships containing autocorrelated error terms. *J Am Stat Assoc* 44:32–61
- Dale AM, Buckner RL (1997) Selective averaging of rapidly presented individual trials using fMRI. *Hum Brain Mapp* 5:329–340
- Dale AM, Halgren E (2001) Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. *Curr Opin Neurobiol* 11:202–208
- Draper NR, Smith H (1998) *Applied regression analysis*, 3rd edition. John Wiley & Sons, New York
- Duvernoy HM, Delon S, Vannson JL (1981) Cortical blood vessels of the human brain. *Brain Res Bull* 7:519–579
- Esposito F, Seifritz E, Formisano E, Morrone R, Scarabino T, Tedeschi G, Cirillo S, Goebel R, Di Salle F (2003) Real-time independent component analysis of fMRI time-series. *Neuroimage* 20:2209–2224
- Esposito F, Scarabino T, Hyvarinen A, Himberg J, Formisano E, Comani S, Tedeschi G, Goebel R, Seifritz E, Di Salle F (2005) Independent component analysis of fMRI group studies by self-organizing clustering. *Neuroimage* 25:193–205
- Fischl B, Sereno MI, Tootell RBH, Dale AM (1999) High-resolution inter-subject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* 8:272–284
- Formisano E, Goebel R (2003) Tracking cognitive processes with functional MRI mental chronometry. *Current Opinion in Neurobiology* 13:174–181
- Formisano E, Esposito F, Kriegeskorte N, Tedeschi G, Di Salle F, Goebel R (2002) Spatial independent component analysis of functional magnetic resonance imaging time-series: characterization of the cortical components. *Neurocomputing* 49:241–254
- Formisano E, Kim DS, Di Salle F, van de Moortele PF, Ugurbil K, Goebel R (2003) Mirror-symmetric tonotopic maps in human primary auditory cortex. *Neuron* 40:859–869
- Fox PT, Raichle ME, Mintun MA, Dence C (1988) Nonoxidative glucose consumption during focal physiological neural activity. *Science* 241:462–464
- Friston KJ, Jezzard P, Turner R (1994) The analysis of functional MRI time-series. *Hum Brain Mapp* 1:153–171
- Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ (1995) Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp* 2:189–210
- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998) Event-related fMRI: characterizing differential responses. *Neuroimage* 7:30–40
- Friston KJ, Penny W, Phillips C, Kiebel S, Hinton G, Ashburner J (2002) Classical and Bayesian inference in neuroimaging: theory. *Neuroimage* 16:465–483
- Fujita I, Tanaka K, Ito M, Cheng K (1992) Columns for visual features of objects in monkey inferotemporal cortex. *Nature* 360:343–346
- Genovese CR, Lazar NA, Nichols T (2002) Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 15:870–878
- Goebel R, Singer W (1999) Cortical surface-based statistical analysis of functional magnetic resonance imaging data. *Neuroimage, Supplement*
- Goebel R, Roebroeck A, Kim DS, Formisano E (2003) Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. *Magn Reson Imaging* 21:1251–1261
- Goebel R, Hasson U, Lefi I, Malach R (2004) Statistical analyses across aligned cortical hemispheres reveal high-resolution

- lution population maps of human visual cortex. *Neuroimage* 22, Supplement 2
- Goebel R, Esposito F, Formisano E (2006) Analysis of functional image analysis contest (FIAC) data with BrainVoyager QX: from single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Hum Brain Mapp* 27:392–401
- Haxby JV, Gobbini MI, Furey ML, Ishai A, Schouten JL, Pietrini P (2001) Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* 293:2425–2430
- Huettel SA, Song AW, McCarthy G (2004) Functional magnetic resonance imaging. Sinauer Associates, Sunderland, MA USA
- Kim DS, Duong TQ, Kim SG (2000) High-resolution mapping of iso-orientation columns by fMRI. *Nat Neurosci* 3:164–169
- Kirby KN (1993) Advanced data analysis with SYSTAT. Van Nostrand Reinhold, New York
- Kriegeskorte N, Goebel R (2001) An efficient algorithm for topologically correct segmentation of the cortical sheet in anatomical MR volumes. *Neuroimage* 14:329–346
- Kriegeskorte N, Goebel R, Bandettini P (2006) Information-based functional brain mapping. *Proc Natl Acad Sci USA* 103:3863–3868
- Kruggel F, von Cramon DY (1999) Temporal properties of the hemodynamic response in functional MRI. *Hum Brain Mapp* 8:259–271
- Kutner MH, Nachtsheim CJ, Neter J, Li W (2005) Applied linear statistical models, 5th edn. McGraw-Hill, Boston
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150–157
- Logothetis NK, Wandell B (2004) Interpreting the BOLD signal. *Annu Rev Physiol* 66:735–769
- Magistretti PJ, Pellerin L, Rothman DL, Shulman RG (1999) Energy on demand. *Science* 283:496–497
- Mathiesen C, Caesar K, Lauritzen M (2000) Temporal coupling between neuronal activity and blood flow in rat cerebellar cortex as indicated by field potential analysis. *J Physiol* 523:235–246
- McIntosh AR, Gonzalez-Lima F (1994) Structural equation modeling and its application to network analysis in functional brain imaging. *Hum Brain Mapp* 2:2–22
- McKeown M, Makeig S, Brown S, Jung TP, Kindermann S, Bell A, Iragui V, Sejnowski T (1998) Blind separation of functional magnetic resonance imaging (fMRI) data. *Hum Brain Mapp* 6:368–372
- Menon RS, Kim SG (1999) Spatial and temporal limits in cognitive neuroimaging with fMRI. *Trends Cogn Sci* 3:207–216
- Mulert C, Jäger L, Schmitt R, Bussfeld P, Pogarell O, Möller HJ, Juckel G, Hegerl U (2004) Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. *Neuroimage* 22:83–94
- NessAiver M (1997) All you really need to know about MRI physics. Simply Physics, Baltimore
- O'Craven KM, Kanwisher N (2000) Mental imagery of faces and places activates corresponding stimulus-specific brain regions. *J Cogn Neurosci* 12:1013–1023
- Ogawa S, Lee TM, Kay AR, Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA* 87:9868–9872
- Penny WD, Stephan KE, Mechelli A, Friston KJ (2004) Comparing dynamic causal models. *Neuroimage* 22:1157–1172
- Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P (1999) SENSE: sensitivity encoding for fast MRI. *Magn Reson Med* 42:952–962
- Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ (2000) Positron emission tomography in the study of emotion, anxiety, and anxiety disorders. In: Cacioppo JT, Tassinary LG, Berntson GG (eds) *Handbook of psychophysiology*. Oxford University Press, New York, pp 389–406
- Robson MD, Dorosz JL, Gore JC (1998) Measurements of the temporal fMRI response of the human auditory cortex to trains of tones. *Neuroimage* 7:185–198
- Roebroeck A, Formisano E, Goebel R (2005) Mapping directed influence over the brain using Granger causality and fMRI. *Neuroimage* 25:230–242
- Scherg M, Linden DEJ, Muckli L, Roth R, Drüen K, Ille N, Zanella FE, Singer W, Goebel R (1999) Combining MEG with fMRI in studies of the human visual system. In: Yoshimoto T, Kotani M, Karibe H, Nakasato N (eds) *Recent advances in biomagnetism*. Tohoku University Press, Sendai
- Schild HH (1990) MRI made easy. Schering AG, Berlin
- Sereno MI, Dale AM, Reppas JB, Kwong KK, Belliveau JW, Brady TJ, Rosen BR, Tootell RB (1995) Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science* 268:889–893
- Talairach G, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Thieme, New York
- Van Atteveldt N, Formisano E, Goebel R, Blomert L (2004) Integration of letters and speech sounds in the human brain. *Neuron* 43:271–282
- Van de Ven VG, Formisano E, Roder CH, Prvulovic D, Bittner RA, Dietz MG, Hubl D, Dierks T, Federspiel A, Esposito F, Di Salle F, Jansma B, Goebel R, Linden DE (2005) The spatiotemporal pattern of auditory cortical responses during verbal hallucinations. *Neuroimage* 27:644–655
- Wager TD, Nichols TE (2003) Optimization of experimental design in fMRI: a general framework using a genetic algorithm. *Neuroimage* 18:293–309
- Weiskopf N, Veit R, Erb M, Mathiak K, Grodd W, Goebel R, Birbaumer N (2003) Physiological self-regulation of regional brain activity using real-time functional magnetic resonance imaging (fMRI): methodology and exemplary data. *Neuroimage* 19:577–586
- Weiskopf N, Hutton C, Josephs O, Deichmann R (2006) Optimal EPI parameters for reduction of susceptibility-induced BOLD sensitivity losses: a whole-brain analysis at 3 T and 1.5 T. *Neuroimage* 32:493–504
- Worsley KJ, Marrett S, Neelin P, Evans AC (1992) A three-dimensional statistical analysis for CBF activation studies in human brain. *J Cereb Blood Flow Metab* 12:900–918

Functional Neuroanatomy

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KEY POINTS

We present the surface anatomy of the brain describing in detail the typical configuration of the sulci and gyri and their most frequent variations. After describing the borders of the lobes we give guidance on the methods of localising functionally important atomic structures such as the pericentral cortex, Heschl's gyrus and the calcarine sulcus.

On the basis of the surface anatomy and the cytoarchitectonic subdivision of the cortex we describe the function of selected areas related to the motor system and to speech.

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Introduction

Modern neurophysiology and fMRI have refined our concepts of cerebral organization. This section presents the surface anatomy of the brain and begins to address the functional interrelationships among the cortical areas.

3.1

Surface Anatomy

3.1.1

Convexity Surface

3.1.1.1

Sylvian Fissure

The convexity face of the Sylvian fissure displays five major arms (rami) that help to define the surface anatomy of the convexity (Fig. 3.1). The long nearly horizontal portion of the sylvian fissure is the

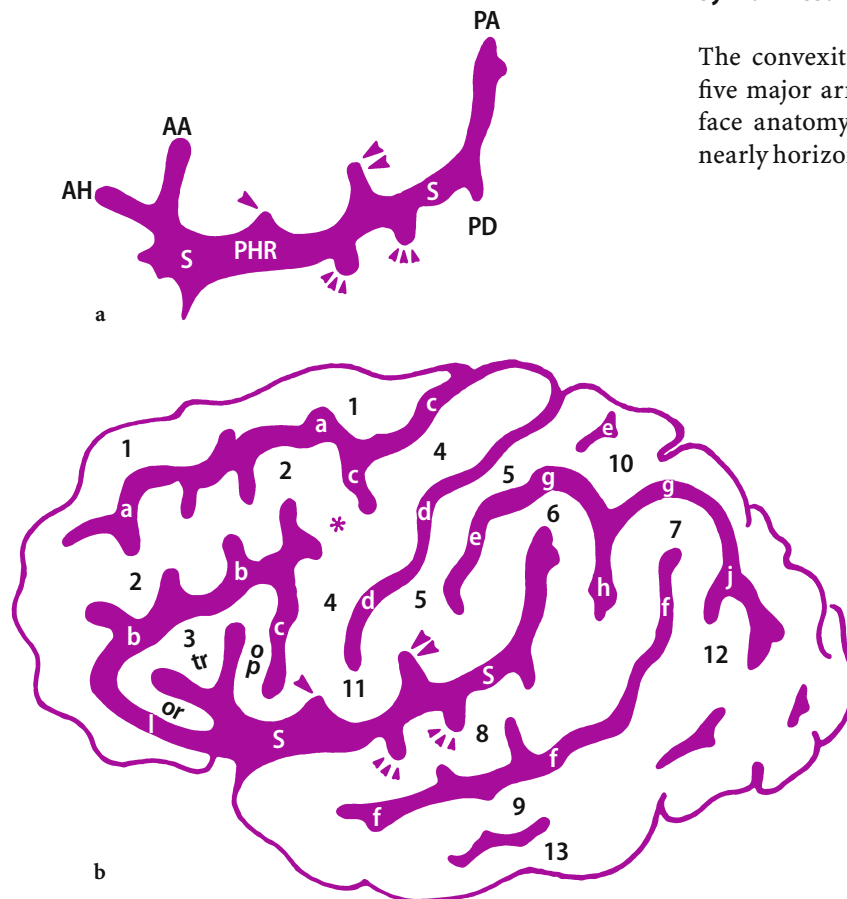


Fig. 3.1a,b. Surface anatomy of the convexity. **a** Sylvian fissure (dark area). The margins of the frontal, parietal, and temporal opercula are defined by the configuration of the sylvian fissure (S), its five major rami (the anterior horizontal ramus [AH],

anterior ascending ramus [AA], posterior horizontal ramus [PHR], posterior ascending ramus [PA], and posterior descending ramus, [PD], and its minor arms, the anterior subcentral sulcus (single arrowhead), posterior subcentral sulcus (double arrowheads), and transverse temporal sulci (triple arrowheads). **b** Cerebral convexity. The configuration of the sylvian fissure then permits identification of the adjoining gyri and sulci. GYRI: 1 = superior frontal gyrus (SFG); 2 = middle frontal gyrus (MFG); 3 = inferior frontal gyrus (or: pars orbitalis; tr: pars triangularis; op: pars opercularis); 4 = precentral gyrus (preCG); 5 = postcentral gyrus (post CG); 6 = supramarginal gyrus (SMG); 7 = angular gyrus (AG); 8 = superior temporal gyrus (STG); 9 = middle temporal gyrus (MTG); 10 = superior parietal lobule (SPL); 11 = subcentral gyrus; 12 = temporooccipital arcus; 13 = inferior temporal gyrus; * = union of the MFG (2) with the preCG (4). SULCI: a = superior frontal sulcus (SFS); b = inferior frontal sulcus (IFS); c = precentral sulcus (preCS); d = central sulcus (CS); e = postcentral sulcus (post CS); f = superior temporal sulcus (STS); g = intraparietal sulcus (IPS); h = primary intermediate sulcus; j = secondary intermediate sulcus; k = accessory intermediate sulcus (not shown in this image); S = Sylvian fissure; single black arrowhead = anterior subcentral sulcus; double black arrowheads = posterior subcentral sulcus; triple black arrowheads = transverse temporal sulci. Note specifically how the anterior horizontal and anterior ascending rami of the sylvian fissure divide the inferior frontal gyrus into the three partes orbitalis (or), triangularis (tr), and opercularis (op). The lateral orbital sulcus (l) separates the pars orbitalis from the lateral orbital gyrus. (From Naidich TP, Valavanis AG, Kubik S: Anatomic relationships along the low-middle convexity: Part 1-normal specimens and magnetic resonance imaging. *Neurosurgery* 36:517-532, 1995; with permission)

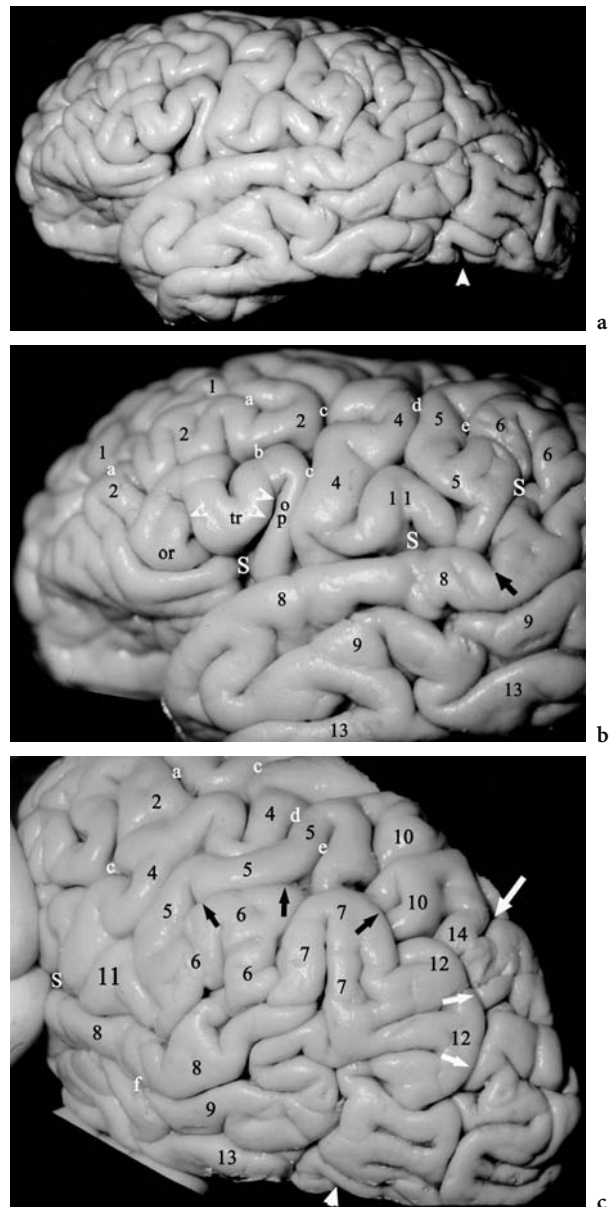
posterior horizontal ramus. At its anterior end, the anterior horizontal ramus and the anterior ascending ramus arise together in a “V” or “Y” configuration. At its posterior end, the prominent posterior ascending ramus and the small posterior descending ramus branch outward in a “T” or “fishtail” configuration. The anterior subcentral sulcus and the posterior subcentral sulcus form two minor arms that extend superiorly into the frontoparietal operculum to delimit the subcentral gyrus. One or multiple transverse temporal sulci extend inferiorly into the temporal lobe in relation to the transverse temporal gyrus of Heschl.

3.1.1.2

Frontal Lobe

The convexity surface of the frontal lobe is formed by four gyri and three sulci (Fig. 3.2). The superior frontal gyrus (SFG) is a horizontally oriented, roughly rectangular bar of tissue that forms the uppermost margin of the frontal lobe. The middle frontal gyrus (MFG) is a horizontally oriented, undulant length of tissue that zig-zags posteriorly to merge with the anterior face of the precentral gyrus. The inferior frontal gyrus (IFG) is a triangular gyrus that nestles inferiorly against the anteriormost portion

Fig. 3.2a–c. Normal cerebral convexity. **a** Anatomic specimen full surface. **b** Magnified view of the low-middle convexity. **c** Magnified oblique view of the parietal lobe. The surface vessels and the pia-arachnoid have been removed to expose the gyri and sulci more clearly (labels as in Fig. 3.1.). In **a**, the single large white arrowhead = preoccipital notch. In **b**, the portions of the sylvian fissure (S) are indicated: first white S = vallecule leading to the anterior horizontal ramus (single white arrow) and the anterior ascending ramus (double white arrow); second white S = posterior horizontal ramus; third white S = posterior ascending ramus; short black arrow = posterior descending ramus of the sylvian fissure. In **c**, the anterior border of the occipital lobe extends from the lateral end of the parietooccipital sulcus (large white arrow) above to the preoccipital notch (large white arrowhead) below. The intraparietal sulcus (multiple large black arrows) crosses the theoretical lobar border to become the intraoccipital sulcus (multiple large white arrows). The inferior parietal lobule is composed of the SMG (6), the AG (7), and the temporooccipital arcus (second pli de passage of Gratiolet) (12). The superior parietal lobule merges into the superior occipital gyrus across the parietooccipital border through the parietooccipital arcus (first pli de passage of Gratiolet) (14). (a and b from Naidich TP, Valavanis AG, Kubic S, et al.: Anatomic relationships along the low-middle convexity: Part II: Lesion localisation. *Internat J Neuroradiol* 3:393–409, 1997; c from Naidich TP, Brightbill TC: The intraparietal sulcus. A landmark for localization of pathology on axial CT scans. *Internat J Neuroradiol* 1:3–16; with permission)



of the Sylvian fissure. The precentral gyrus (preCG) is a nearly vertical gyrus that forms the posterior border of the frontal lobe, behind the SFG, MFG and IFG. The superior frontal sulcus (SFS) separates the SFG from the MFG. At its posterior end, the SFS bifurcates to form the superior precentral sulcus. The inferior frontal sulcus (IFS) separates the MFG from the IFG. At its posterior end, the IFS bifurcates to form the inferior precentral sulcus. Together, the superior and inferior portions of the preCS delimit the anterior face of the precentral gyrus, except where the MFG merges with the preCG between the superior and inferior precentral sulci.

The frontal gyri display characteristic configurations (Fig. 3.1) and variations (ALBANESE et al. 1989; NAIDICH et al. 1995, 1997). The IFG has an overall triangular configuration (hence its synonym: triangular gyrus). The IFS courses above the IFG, bifurcates into the inferior preCS, and thereby separates the triangular IFG from the MFG above and from the preCG behind. The anterior horizontal and anterior ascending rami of the sylvian fissure extend upward into the triangular IFG, partially subdividing it into

three portions: the *pars orbitalis*, which abuts the orbital gyri of the frontal lobe; the *pars triangularis* in the centre; and the *pars opercularis*, which forms the anteriormost portion of the frontal operculum. Together, the three parts of the IFG resemble an oblique letter “M” (Figs. 3.1–3.4). Because the anterior ascending ramus of the Sylvian fissure cuts through the full thickness of the IFG to reach the insula, the cortex of the *pars opercularis* presents both a superficial cortex visible on the surface and a deep cortex within the depths of the fissure (NAIDICH et al. 2001a).

3.1.1.3

Temporal Lobe

The convexity surface of the temporal lobe is formed by three horizontal gyri: the superior temporal gyrus (STG), the middle temporal gyrus (MTG) and the inferior temporal gyrus (ITG), separated by the superior temporal sulcus (STS) and the inferior temporal sulcus (ITS) (Fig. 3.5). The superior and middle temporal gyri extend posteriorly, and then



Fig. 3.3a,b. Normal variations in convexity anatomy. **a** Convexity surface of a prepared left hemisphere. **b** Sagittal section of a prepared left hemisphere. A vertically oriented connecting gyrus (*short black arrow*) crosses the inferior frontal sulcus (IFS) (*b*) to unite the pars triangularis (*tr*) with the middle frontal gyrus (MFG) (2). A sulcus triangularis (between the *t* and the *r*) deeply notches the superior surface of the pars triangularis making it appear bifid. The precentral gyrus (4) and the postcentral gyrus (5) unite beneath the central sulcus to form the subcentral gyrus (11), which is delimited by a shallow anterior subcentral sulcus (*single black arrowhead*) and a deep posterior subcentral sulcus (*double black arrowheads*). The inferior portion of the postcentral sulcus (*e*) forms the initial upswing of the arcuate intraparietal sulcus (IPS) (*g*). The posterior ascending ramus of the sylvian fissure (*S*) indents the inferior parietal lobule (IPL) to form the supramarginal gyrus (SMG) (6). The superior temporal sulcus (STS) (*f*) indents the posterior portion of the IPL to form the angular gyrus (AG) (7). The entire STS parallels the sylvian fissure, hence its synonym: parallel sulcus. The distal end of the STS within the AG may be designated the angular sulcus. In this specimen an intercalated accessory preangular gyrus (A2) separates the SMG from the AG. Note the relationships of the IPS (*g*), the SMG (6), the AG (7), and the accessory preangular gyrus (A2) with the primary intermediate sulcus (*h*), the secondary intermediate sulcus (*j*) and the accessory intermediate sulcus (*k*). In **b**, the sagittal section exposes the characteristic appearance of the transverse temporal gyrus of Heschl (*H*) on the superior surface of the temporal lobe. (From Naidich TP, Valavanis AG, Kubik S: Anatomic relationships along the low-middle convexity: Part 1—normal specimens and magnetic resonance imaging. *Neurosurgery* 36:517–532. 1995; with permission)

Fig. 3.4. Sagittal T1 weighted MR imaging of the language-related areas of the normal cerebral convexity. T1-weighted image of a 78-year-old man. Labels as in Figures 3.1 and 3.2. (From Naidich TP, Valavanis AG, Kubik S, Taber KH, Yasargil MG: Anatomic relationships along the low-middle convexity: Part II—lesion localisation. *Internat J Neuroradiol* 3:393–409. 1997; with permission)

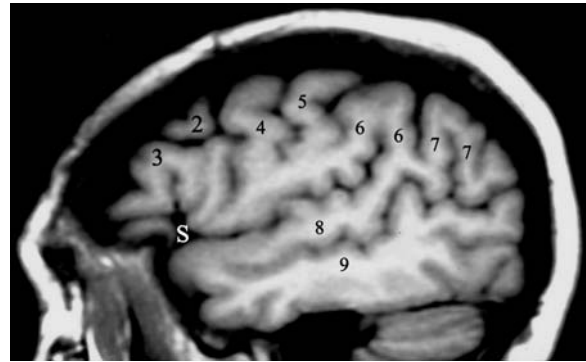
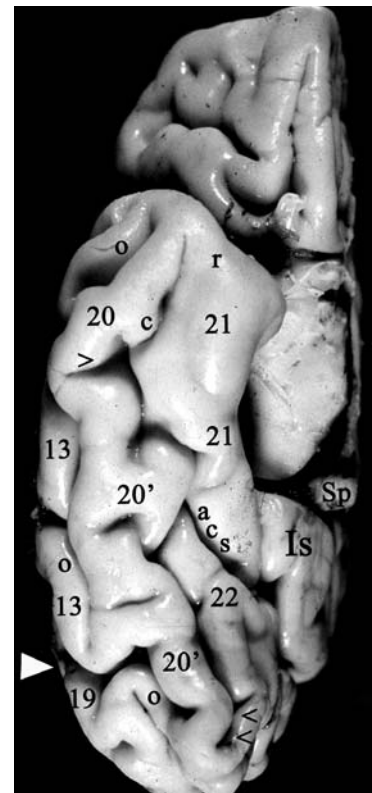
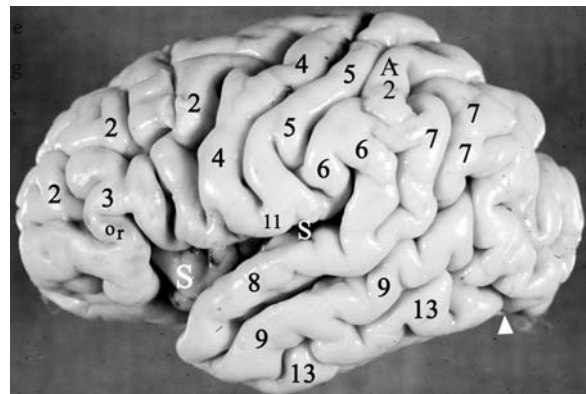


Fig. 3.5a,b. The temporal lobe. Prepared anatomic specimen of the right hemisphere from a 1-day-old girl. **a** Convexity (reversed to match the other lateral views). The simplified gyral and sulcal pattern reflects the young age. The inferior temporal gyrus (13) extends posteriorly to the pre-occipital notch (*large white arrowhead*). An accessory preangular gyrus (A2) is situated superior to the SMG (6) and anterior to the AG (7). Labels as in Figs. 3.1 and 3.2. **b** Inferior surface. The brainstem and the inferior thalamus have been removed to reveal the medial surface more clearly. The inferior temporal gyrus (13) and the inferior occipital gyrus (19) form the inferior margin of the hemisphere, separated by the preoccipital notch (*large white arrowhead*). The lateral occipitotemporal sulcus (*o*) delineates their medial border and separates them from the lateral occipitotemporal gyrus (LOTG) (20) further medially. The medial occipitotemporal sulcus (synonym: collateral sulcus) (*c*) delimits the medial border of the LOTG over its full length. Anteriorly, the collateral sulcus approximates the rhinal sulcus (*r*), and may run into it, or may parallel it. The parahippocampal gyrus (PHG) (21) forms the medial surface of the temporal lobe over its full length and extends posteriorly to become the isthmus (*Is*) of the cingulate gyrus inferior to the splenium (*Sp*). In the anterior half of the temporal lobe the collateral sulcus (*c*) separates the LOTG (20) from the PHG (21). In the posterior half, the medial occipitotemporal gyrus (MOTG) (lingual gyrus) (22) intercalates itself between the LOTG and the PHG. The collateral sulcus stays with the medial border of the LOTG, so the collateral sulcus (*c*) separates the LOTG (20) from the MOTG (22), while the anterior calcarine sulcus (*acs*) separates the MOTG (22) from the PHG (21). The anterior and posterior transverse collateral sulci (*single and double black arrowheads*) delimit a midportion of the LOTG (20') that has been designated by Duvernoy (DUVERNOY 1991) as the fusiform gyrus. (From Daniels OL, Haughton VM, Naidich TP: *Cranial and Spinal Magnetic Resonance Imaging. An Atlas and Guide*. New York, Raven Press, 1987; with permission)



swing upward to join with the parietal lobe. The inferior temporal gyrus forms the inferior edge of the convexity surface of temporal lobe and curves onto the inferior surface of the temporal lobe. It is delimited posteriorly by a small notch, the pre-occipital notch (synonyms: temporo-occipital notch or incisura), which separates the inferior temporal gyrus anteriorly from the inferior occipital gyrus posteriorly. The STS courses parallel to the posterior horizontal and the posterior ascending rami of the sylvian fissure (hence its synonym, parallel sulcus). The posterior portion of the STS is directed superiorly, and is sometimes designated the angular sulcus. The ITS courses approximately parallel to the inferior margin of the convexity and may become continuous posteriorly with the inferior occipital sulcus.

3.1.1.4

Parietal Lobe

The convexity surface of the parietal lobe is formed by three portions: the vertically oriented postcentral gyrus (post CG) anteriorly, and the two superior parietal (SPL) and inferior parietal (IPL) lobules posteriorly (Figs. 3.1–3.4). The postCG courses vertically just posterior and parallel to the preCG. The postCG is separated from the preCG by the intervening central sulcus (CS) over most of its length. However, inferiorly, the postCG merges with the preCG inferior to the CS along the subcentral gyrus (subCG) just above the sylvian fissure. Superiorly, the postCG merges with the preCG superior the CS along the paracentral lobule (paraCL) on the medial surface of the hemisphere. Thus the precentral and postcentral gyri actually form a continuous band of tissue that circles around the central sulcus from the precentral gyrus through the subcentral gyrus, into the postcentral gyrus and the paracentral lobule, returning into the precentral gyrus.

The posterior border of the post CG is delimited by the superior and inferior postcentral sulci. The superior postCS separates the upper postCG from the superior parietal lobule. The inferior postCS separates the postCG from the inferior parietal lobule. The inferior postCS may be considered the upswing of a long, deep, arcuate intraparietal sulcus (IPS) that ascends behind the lower postCG and then slashes posteriorly across the convexity surface of the parietal lobe, dividing it into the SPL situated superomedial to the IPS and the IPL situated inferolateral to the IPS. The posterior downswing

of the arcuate IPS then crosses the theoretical border between the parietal and occipital lobes, and continues into the occipital lobe, where it is designated the intraoccipital sulcus (IOS) (synonym: superior occipital sulcus, SOS) (Figs. 3.1–3.4). Posteriorly, the SPL becomes continuous with the superior occipital gyrus (SOG) behind it through a narrow band of tissue designated the arcus parieto-occipitalis (first *pli de passage* of Gratiolet) (Fig. 3.2) (DUVERNOY 1991).

Within the inferior parietal lobule, the posterior ascending ramus of the sylvian fissure swings upward into the anterior portion of the IPL and is capped by a horseshoe-shaped gyrus designated the supramarginal gyrus (SMG). In parallel fashion, the distal STS swings upward into the posterior portion of the IPL where it is capped by a second horseshoe-shaped gyrus designated the angular gyrus (AG). The AG usually lies just posterior to the SMG, but may be displaced from that position by variant accessory gyri (Figs. 3.1–3.4) (NAIDICH et al. 1995, 1997). Together the SMG and the AG constitute most of the IPL. An additional small horseshoe of tissue, designated the second parieto-occipital arcus (second *pli de passage* of Gratiolet), connects the AG with the middle OG posterior to it, completing the IPL (Fig. 3.2) (DUVERNOY 1991). A small primary intermediate sulcus descends from the IPS to separate the SMG from the AG. A small secondary intermediate sulcus descends from the IPS to define the posterior border of the AG, separating the AG from the rest of the IPL posterior to it (NAIDICH et al. 2001a).

3.1.1.5

Occipital Lobe

The convexity surface of the occipital lobe has also been divided into three horizontal gyri: the superior occipital gyrus (SOG), the middle occipital gyrus (MOG), and the inferior occipital gyrus (IOG). These are separated by the superior and inferior occipital sulci (SOS and inferior OS). The SOS (synonym: intraoccipital sulcus) is the direct continuation of the IPS (Figs. 3.1–3.4). The inferior OS is usually co-extensive with the inferior temporal sulcus. Therefore, the MOG lies just posterior to the confluence of the temporal and parietal lobes at the SMG, the AG, the STG and the MTG. The MOG is the largest portion of the occipital lobe on the convexity. It is usually subdivided into a superior and an inferior portion by a horizontally-oriented middle OS (synonym: lateral OS).

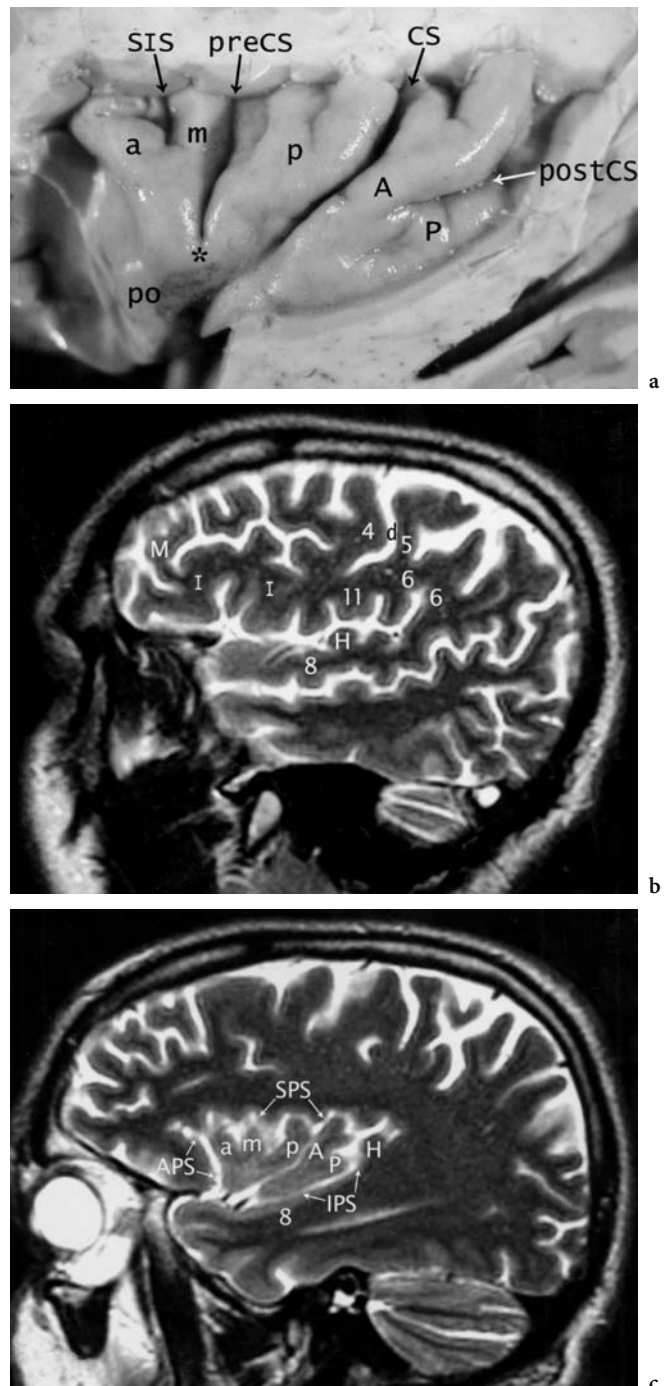
3.1.1.6

Insula

Separating the superior and inferior covers (opercula) of the sylvian fissure discloses the Island of Reil (insula). The insula is delimited circumferentially by the peri-insular sulcus (synonym: circular sulcus), composed of the anterior, superior and infe-

rior perisylvian sulci (Türe et al. 1999). The central sulcus of the convexity extends over the insula as the central sulcus of the insula, dividing the insula into a larger anterior and a smaller posterior lobule (Fig. 3.6) (Naidich et al. 2004; Nieuwenhuys et al. 1988; Türe et al. 1999). The anterior lobule typically has three vertically-oriented short insular gyri designated the anterior short, middle short and poste-

Fig. 3.6a–c. Insula. **a** Prepared anatomic specimen of the convexity surface of the insula, after removal of the overhanging opercula. A 71-year-old man. The central sulcus (CS) extends across the triangular insula like a “hockey stick,” dividing it into a larger anterior lobule and a smaller posterior lobule. The anterior lobule typically displays three gyri, the anterior short (*a*), middle short (*m*) and posterior short (*p*) insular gyri, separated by the short insular sulcus (SIS) and the precentral sulcus (*preCS*). These three characteristically converge inferiorly to form the apex (*) of the insula. The posterior insular lobule typically displays two gyri, the anterior long (*A*) and the posterior long (*P*) insular gyri, separated by the postcentral sulcus (*postCS*). These too often merge together, anteriorly, just behind the central sulcus. Just inferomedial to the apex (*), the pole of the insula (*po*) forms the most anteroinferomedial portion of the insula. The central sulcus courses under the apex and the pole, and then abruptly swings medially toward the suprasellar cistern. **b,c** Normal sagittal T2-weighted MRI. A 51-year-old man. Laterally (**b**), the convexity gyri form two opercula that cover the insula. Superiorly, the inferior frontal gyrus (*I*), the inferior ends of the precentral (*4*) and postcentral (*5*) gyri, the subcentral gyrus (*11*), and the supramarginal gyrus (*6*) form the frontoparietal operculum. The superior temporal gyrus (*8*) and Heschl’s gyrus (*H*) form the temporal operculum. *M* = middle frontal gyrus. Medially (**c**), the insula is delimited by the peri-insular sulcus, composed of three segments: the anterior (APS), superior (SPS) and inferior (IPS) peri-insular sulci. The anterior (*a*), middle (*m*) and posterior (*p*) short insular gyri constitute the larger anterior lobule, while the anterior (*A*) and posterior (*P*) long insular gyri form the smaller posterior lobule. The central sulcus courses between the two lobules. Heschl’s gyrus (*H*) snugs up against the posteromedial portion of the posterior long insular gyrus. *8* = superior temporal gyrus. (From Naidich TP, Kang E, Fatterpekar GM, Delman BN, Gultekin SH, Wolfe D, Ortiz O, Yousry I, Weisman M, Yousry TA: The Insula: Anatomic Study and MR Imaging Display at 1.5 T. *AJNR Am J Neuroradiol* 25:222–232. 2004 with permission)



rior short insular gyri. These three converge antero-infero-laterally to form the apex of the insula. The posterior lobule of the insula typically displays two oblique gyri: the anterior and posterior long insular gyri. The anterior insula is connected exclusively to the frontal lobe, whereas the posterior insula is connected to both the temporal and the parietal lobes (NAIDICH et al. 2004; TURE et al. 1999).

3.1.2

Inferior Surface

3.1.2.1

The Frontal Lobe

The inferior (orbital) surface of the frontal lobe is formed by the gyrus rectus medially and four orbital gyri laterally, separated by the olfactory and orbital sulci. The gyrus rectus forms the medial margin of the orbital surface of frontal lobe for the full length of the frontal lobe. The lateral border of the gyrus rectus is delimited by the olfactory sulcus (Fig. 3.7). The orbital gyri are arranged around an “H-shaped” orbital sulcus as the medial orbital, lateral orbital, anterior orbital and posterior orbital gyri.

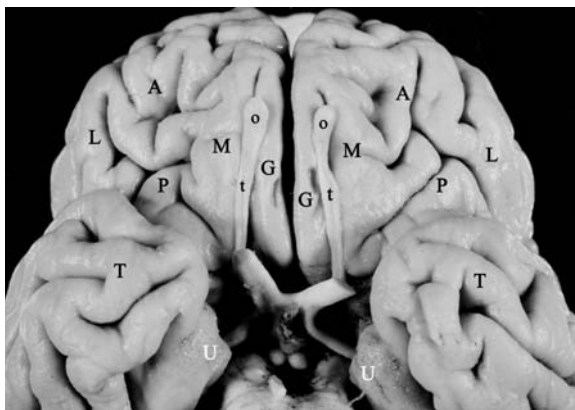


Fig. 3.7. Inferior surface of frontal lobe. Prepared anatomic specimen of the inferior surfaces of the anterior brain. The inferior surface of the frontal lobes is divided into two portions. The paired paramedian linear gyri recti (G) flank the interhemispheric fissure and are delimited laterally by the olfactory sulci, largely obscured here by the olfactory bulbs (o) and tracts (t). Lateral to the olfactory sulci, the orbital gyri of the frontal lobe are arranged around approximately H-shaped orbital sulci as the paired medial (M), lateral (L), anterior (A), and posterior (P) orbital gyri. In true base view, the anterior temporal lobes (T) overlap the posterior orbital gyri. Note the paired uncus (U)

3.1.2.2

The Temporo-occipital Lobes

The inferior surface of the temporo-occipital lobe is formed by the inferior temporal gyrus, the lateral occipitotemporal gyrus (LOTG), the medial occipitotemporal gyrus (MOTG) (synonym: lingual gyrus) and the parahippocampal gyrus (PHG), separated by the lateral occipitotemporal sulcus, the collateral sulcus and the anterior calcarine sulcus (Fig. 3.5). Medially, the parahippocampal gyrus forms the medial border of the temporal lobe for the full length of the temporal lobe, from just posterior to the temporal pole to the level of the splenium. Posterior to the splenium, the medial occipitotemporal gyrus forms the medial border of the occipital lobe. Laterally, along the full length of the temporo-occipital lobes, the inferior temporal gyrus and the inferior occipital gyrus curve medially, form the inferior cerebral margin, and pass onto the inferior surface, where they constitute the lateralmost portion of the inferior surface of the temporo-occipital lobes. Only the small pre-occipital notch delimits the inferior temporal gyrus from the inferior occipital gyrus. Centrally, the LOTG runs the full length of the temporo-occipital lobes from the temporal pole to the occipital pole. Throughout its length, the LOTG remains just medial to the ITG and the IOG, and is separated from them by the lateral occipitotemporal sulcus. Medially, the medial occipitotemporal sulcus (synonym: collateral sulcus) runs the full length of the LOTG (Fig. 3.5b). In the anterior half of the temporal lobe, the lateral occipitotemporal sulcus separates the LOTG from the parahippocampal gyrus. In the posterior half of the temporal lobe, the medial occipitotemporal gyrus intercalates itself between the LOTG and the parahippocampal gyrus. Therefore, in the posterior half of the temporal lobe, the lateral occipitotemporal sulcus separates the LOTG from the MOTG, while the anterior calcarine sulcus separates the MOTG from the PHG.

Two synonyms are commonly used for temporo-occipital gyri. The term *lingual gyrus* usually refers to the MOTG (DUVERNOY 1991; ONO et al. 1990). The term *fusiform gyrus* is most often used to designate either the LOTG (ONO et al. 1990) or a large middle portion of the LOTG that crosses the arbitrary border of the temporal and the occipital lobes between the anterior and the posterior transverse collateral sulci (DUVERNOY 1991). However, in another usage WILLIAMS et al. 1989 group the MOTG and the LOTG

together as the fusiform gyrus. In most brains the fusiform gyrus is larger on the left (KOPP et al. 1977; NAIDICH et al. 2001a).

3.1.3

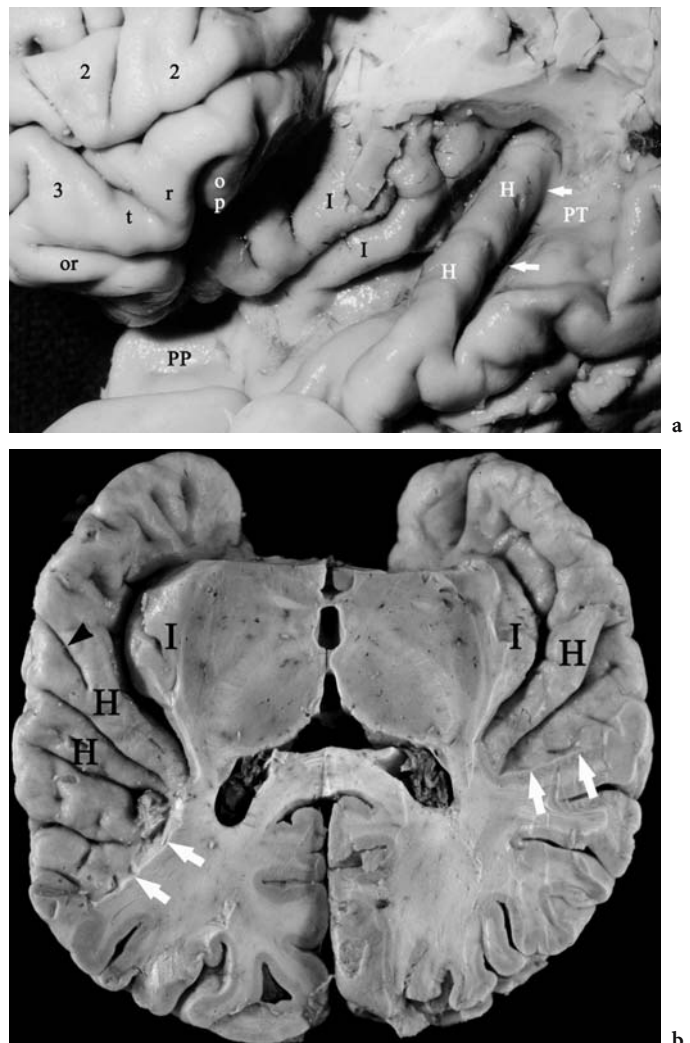
Superior Surface of the Temporal Lobe

Opening the margins of the sylvian fissure, or resecting the overlying superior operculum, displays the superior surface of the temporal lobe, designated the superior temporal plane. The prominent feature(s) of this plane are one or more transverse temporal gyri (of Heschl) (Fig. 3.8). Heschl's gyrus or gyri (HG) arise just posteromedial to the insula and course obliquely across the superior temporal surface from posteromedial to anterolateral and may be visible at the external surface of the sylvian fissure.

The presence of a HG is constant. The number of HG on each side and their symmetry are highly variable. Heschl's gyri may be single (66–75%), double (25–33%), or triple (1%), both unilaterally and bilaterally (YOSHIURA et al. 2000; YOUSRY et al. 1997a). Heschl's gyrus is often larger and longer on the left side than the right, but there is no constant relationship between HG and the side of handedness, or cerebral dominance. (CARPENTER and SUTIN 1983; YOUSRY et al. 1997a). A shallow longitudinal sulcus (of Beck) may groove the superior surface of HG, especially laterally, giving it a partially bifid appearance. A deep transverse temporal sulcus (Heschl's sulcus [HS]) typically defines the posterior border of HG.

The oblique Heschl's gyrus divides the superior surface of the temporal lobe into three parts. (1) The flat superior surface of the temporal lobe anterior to

Fig. 3.8a,b. The superior surface of the temporal lobe from prepared anatomic specimens. **a** Anatomy of Heschl's gyrus in relation to the insula. Resection of the frontal and parietal opercula exposes the middle frontal gyrus (2); the pars orbitalis (*or*) triangularis (*tr*), and the residual portion of the opercularis (*op*) of the inferior frontal gyrus (3); the oblique long gyri (*black I*) of the posterior insula; the length of a single Heschl gyrus (*H*) which courses obliquely across the superior surface of the temporal lobe from just posterior to the insula (posteromedially) toward the convexity surface of the superior temporal gyrus (anterolaterally); Heschl's sulcus (*white arrows*) immediately posterior to Heschl's gyrus; the planum polare (*PP*) anterior to the HG; and the planum temporale (*PT*) posterior to HG. (From Naidich TP, Matthews VP; integrating neuroanatomy and functional MR imaging; language lateralisation. ASNR AM Society Neuroradiol 75–83, 2000 with permission). **b** Exposure of the superior surfaces of both temporal lobes by resection of the overlying frontal and parietal opercula. Right is to the reader's right. The single right and the dual left Heschl's gyri (*H*) course obliquely across the upper surface of the temporal lobe from just posterior to the insulae (*I*) (posteromedially) to the convexity surface (anterolaterally). A shallow Beck's sulcus (*small black arrowhead*) grooves the left HG laterally. Heschl's sulcus delimits the posterior border of HG. The planum polare extends from the temporal pole to the anterior aspect of HG. The planum temporale extends between Heschl's sulcus and the posterior limit of the sylvian fissure (*white arrows*), and is substantially larger on the left



HG is designated the planum polare. (2) From HS at the posterior border of HG to the posterior end of the sylvian fissure, the flat superior surface of the temporal lobe is designated the planum temporale. (3) The posterosuperior extension of the planum temporale along the posterior bank of the posterior ascending ramus of the sylvian fissure may be designated the planum parietale. The planum temporale is triangular. It is typically asymmetric on the two sides, and most often is larger on the left in humans, chimpanzees and other great apes (Fig. 3.8) (GANNON et al. 1998). The size of the planum temporale seems to correlate with the side of language dominance (and perhaps with right or left handedness, gender or both (GALABURDA and SANIDES 1980; GALABURDA et al. 1998; GESCHWIND 1965a, b, 1970; GESCHWIND and LEVITSKY 1968; PIENIADZ and NAESER 1984; STEINMETZ et al. 1989b, 1990a, b, 1991; STEINMETZ and SEITZ 1991). Most of the variation in the sizes of the planum temporale may be ascribed to differing sizes of a cytoarchitectonic zone designated area Tpt (GALABURDA and SANIDES 1980). Area Tpt has a homologue in nonhuman primates that shows significant asymmetry (left>right) at the cellular level (GANNON et al. 1998).

3.1.4

Medial Surface

The medial surface of the cerebrum is arranged as a radial array of gyri and sulci that are oriented either co-curvilnear with the corpus callosum or perpendicular to it (Fig. 3.9). The major gyri of the medial surface are the cingulate gyrus (CingG), the superior frontal gyrus (SFG) (whose medial surface may also be designated the medial frontal gyrus), the paracentral lobule (ParaCL), the precuneus (PreCu), the cuneus (Cu), and the medial occipitotemporal gyrus (MOTG) (synonym: lingual gyrus). The major sulci are the callosal sulcus (CaS), the cingulate sulcus (CingS), the paracentral sulcus (ParaCS), the subparietal sulcus (SubPS), the parieto-occipital sulcus (POS), the calcarine sulcus (CaS), and the anterior calcarine sulcus (AntCaS). The cingulate gyrus encircles the corpus callosum. It is delimited from the corpus callosum centrally by the callosal sulcus and from the superior frontal gyrus and paracentral lobule superficially by the cingulate sulcus.

The gyri that form the medial surface of the brain peripheral to the cingulate gyrus and sulcus are nothing more than the medial aspects of the gyri

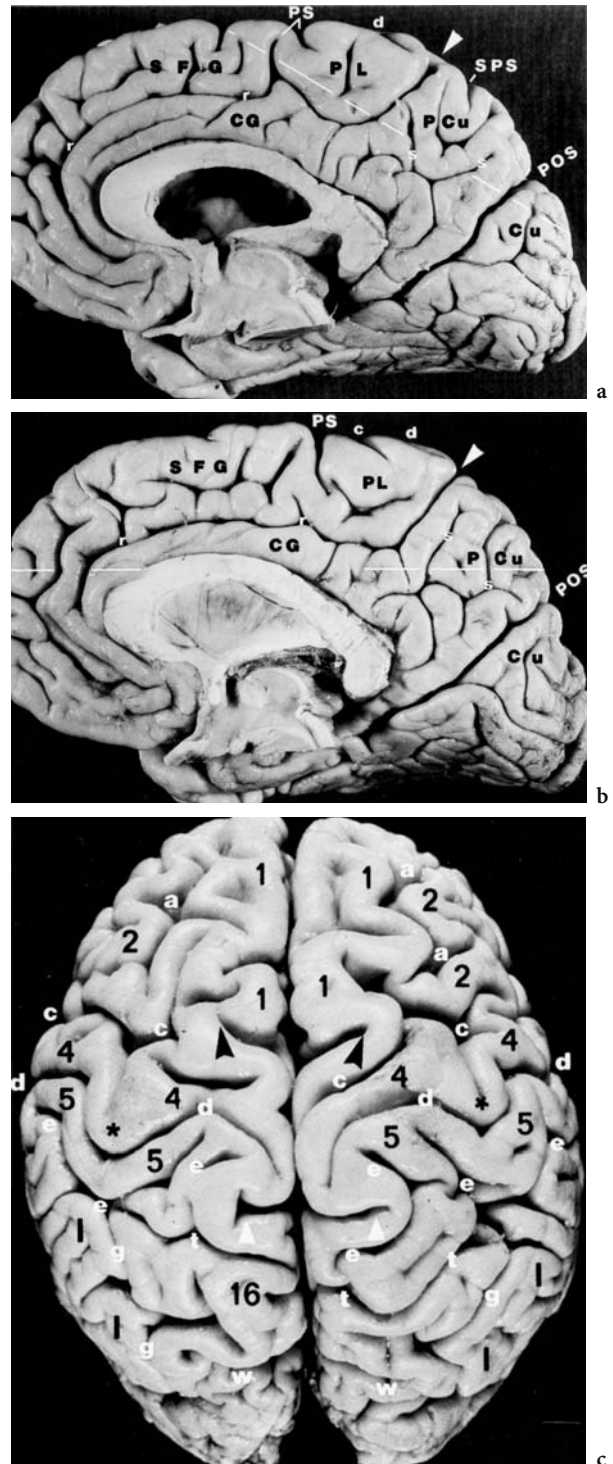
that constitute the high convexity of the brain. The superior frontal gyrus of the convexity curves over the cerebral margin onto the medial surface to form a broad arc of tissue designated the SFG or medial frontal gyrus. The precentral gyrus and the postcentral gyrus curve over the cerebral margin from the convexity onto the medial surface, and join together to form the paracentral lobule. The superior parietal lobule curves over the cerebral margin onto the medial surface to form the precuneus. The superior occipital gyrus curves over the cerebral margin onto the medial surface to form the cuneus. The SFG is separated from the paracentral lobule posterior to it by the paracentral sulcus. The posterior end of the cingulate sulcus sweeps upward to reach the cerebral margin. This radially-oriented distal portion of the cingulate sulcus is the pars marginalis (pM). The pars marginalis separates the paracentral lobule anteriorly from the precuneus posteriorly. The upper end of the central sulcus typically curves over the margin onto the medial surface of the hemisphere just anterior to the pars marginalis. This medial portion of the CS courses posteriorly nearly perpendicular to the pars marginalis. The "H"-shaped subparietal sulcus lies posterior to the pars marginalis and separates the inferior end of the precuneus from the cingulate gyrus deep to it. The parieto-occipital sulcus courses parallel to the pars marginalis, joins with the anterior end of the calcarine sulcus, and continues anteriorly as the anterior calcarine sulcus. The POS separates the precuneus anteriorly from the cuneus posteriorly. The calcarine sulcus separates the cuneus superiorly from the MOTG (lingual gyrus) inferiorly. The anterior calcarine sulcus separates the cingulate gyrus anteriorly from the MOTG posteriorly. The calcarine sulcus may remain entirely on the medial surface of the hemisphere, extend posteriorly to reach the occipital pole, or extend beyond medial surface onto either the convexity or inferior surfaces of the occipital lobe.

3.2

Lobar Borders

The precise borders of the temporal, parietal and occipital lobes on the convexity are highly arbitrary. Published diagrams from different authors indicate substantially different criteria for partitioning the

Fig. 3.9a–c. Medial and superior surfaces of both hemispheres. Prepared anatomic specimens. **a, b** Medial surfaces. The major sulci subdivide the medial surface of each cerebral hemisphere into the cingulate gyrus (CG), medial surface of the superior frontal gyrus (SFG), paracentral lobule (PL), precuneus (PCu) and cuneus (Cu). The posterior end of the cingulate sulcus sweeps sharply upward toward the superior cerebral margin as the marginal portion of the cingulate sulcus (pars marginalis, *white arrowhead*), which separates the paracentral lobule anteriorly from the precuneus posteriorly. Anterior to the pars marginalis, the paracentral sulcus (PS) arises from the cingulate sulcus and/or from the cerebral margin to separate the superior frontal gyrus from the paracentral lobule. The vertical and horizontal arms of the “H-shaped” subparietal sulcus (s) groove the medial surface of the precuneus and delimit it from the cingulate gyrus inferior to it. The superior ends of the vertical arms of the subparietal sulcus may reach to and notch the superior margin. The superior medial end of the central sulcus (d) usually crosses over the cerebral margin onto the medial surface and then recurves sharply posteriorly to course nearly perpendicular to the pars marginalis, just millimeters in front of the pars marginalis. As a consequence the most superior medial portion of the precentral gyrus (4) merges with the most superior medial portion of the postcentral gyrus (5) around the uppermost end of the central sulcus, to form the paracentral lobule anterior to the pars marginalis. A posterior portion of the postcentral gyrus passes posterior to the pars marginalis to merge with the precuneus. The prominent parieto-occipital sulcus (POS) courses approximately parallel to the pars marginalis, but posterior to the splenium, and delimits the parietal lobe plus cingulate gyrus anterosuperiorly from the occipital plus temporal lobes posteroinferiorly. **c** Superior surface of the two hemispheres. The two cerebral hemispheres border the interhemispheric fissure (IHF). Multiple sulci oriented at right angles to the IHF form a series of transverse grooves or “crossbars” across the IHF. The paired partes marginales (*white arrowheads*) are often the most prominent of these grooves and extend laterally into the hemispheres for a substantial distance. At the vertex, the lateral edges of the two partes marginales often curve anteriorly to form a bracket, open anteriorly. The paired central sulci (d) undulate across the cerebral convexity between the precentral gyri (4) and the postcentral gyri (5). They typically hook sharply posteriorly (*) as they circumscribe the hand motor region of the precentral gyrus (*), and then reverse curvature, become concave posteriorly, and converge toward the IHF just anterior to the partes marginales. The two central sulci (d) characteristically (but not invariably) pass anterior to and medial to the lateral edges of the partes marginales (“enter the bracket”) and reach to or cross the superior margins of the hemispheres. The postcentral gyri course superiorly, behind the precentral gyri, toward or to the cerebral margins. The medial ends of the postcentral sulci (e) usually bifurcate around the partes marginales to form a prominent “parenthesis” configuration (e, e in the right hemisphere). The interlocking curves of the precentral gyri (d), postcentral gyri (e) and the partes marginales (*white arrowheads*) form a characteristic set of interlocking curves that usually identifies these sulci and the adjacent gyri. Other labels: 1. superior frontal gyrus; 2. middle



frontal gyrus; 4. precentral gyrus; 5. postcentral gyrus; 16. precuneus; a. superior frontal sulcus; c. precentral sulcus; d. central sulcus; e. postcentral sulcus; g. intraparietal sulcus; r. cingulate sulcus; s. subparietal sulcus; t. superior parietal sulcus; and w. parieto-occipital sulcus. (From Naidich TP, Brightbill TC. The pars marginalis: Part I. A “bracket” sign for the central sulcus in axial plane CT and MRI. *Internat J Neuroradiology* 2:3–19. 1996; with permission)

TPO lobes along the convexity (YOUSRY 1998). The very definitions of these borders and their lobes have evolved substantially over the years (YOUSRY 1998). In one common system of nomenclature, one identifies the lobes by first finding the lateral end of the deep parieto-occipital sulcus near the superior margin of the hemisphere. Then one identifies the inconstant pre-occipital notch in the inferior margin of the hemisphere (Fig. 3.10). The arbitrary anterior border of the occipital lobe is then defined by the drawing the "lateral parietotemporal line"

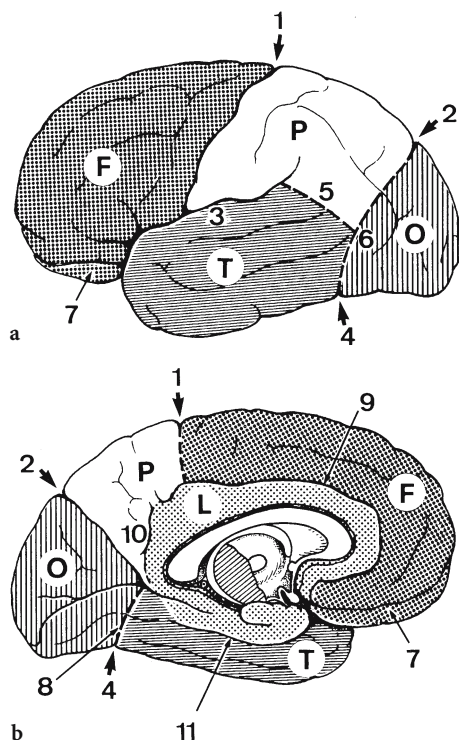


Fig. 3.10a,b. Lobar borders according to Ono, Kubik, and Abernathy. **a** Convexity. **b** Medial surface. The anterior border of the occipital lobe is delimited by the lateral parietotemporal line (6) drawn between the parieto-occipital sulcus and the preoccipital notch. On the convexity, the temporal lobe is separated from the parietal lobe by the temporo-occipital line (5) drawn from the sylvian fissure to the middle of the anterior border of the occipital lobe. On the basal surface, the temporal lobe is separated from the occipital lobe by the basal parietotemporal line (8) drawn from the preoccipital notch to the union of the parieto-occipital sulcus with the calcarine sulcus (unlabelled). F = frontal lobe, O = occipital lobe; P = parietal lobe; T = temporal lobe., 1 = central sulcus; 2 = parieto-occipital sulcus, 3 = sylvian fissure; 4 = preoccipital notch; 5 = temporo-occipital line; 6 = lateral parietotemporal line; 7 = orbital surface; 8 = basal parietotemporal line; 9 = cingulate sulcus; 10 = subparietal sulcus; 11 = collateral sulcus. (From Ono M, Kubik S, Abernathy CD: *Atlas of the Cerebral Sulci*. New York, Thieme Medical publishers, 1990, p 9; with permission)

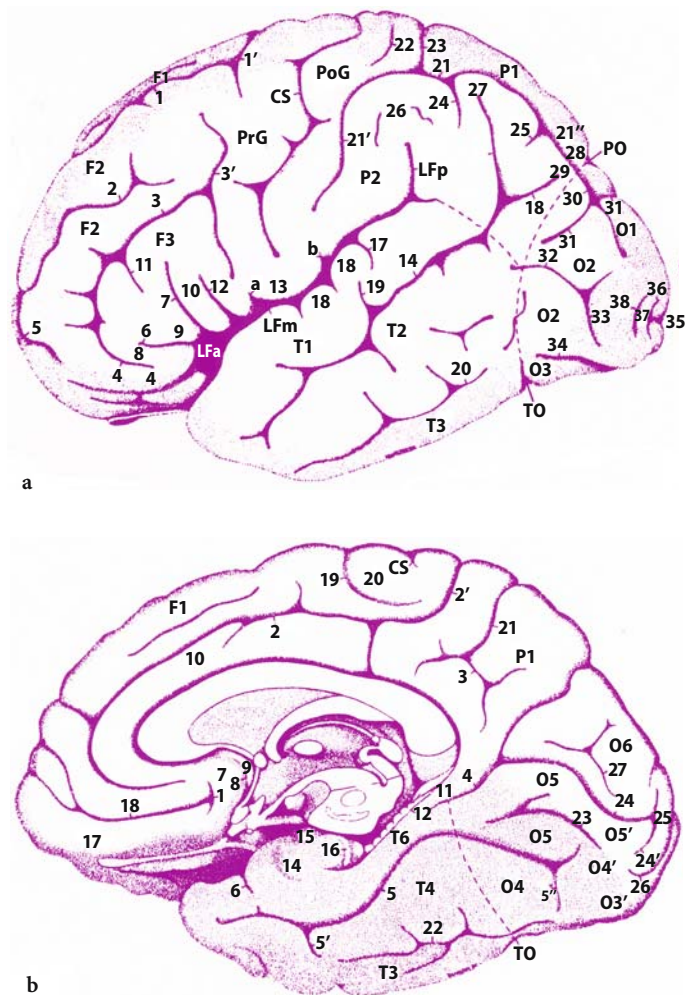
along the convexity from the lateral end of the parieto-occipital sulcus above to the preoccipital notch inferiorly.

Next one demarcates the borders of the temporal and parietal lobes that abut onto the occipital lobe. To do this, one draws the "temporo-occipital line", defined variably, as (1) an arc from the distal end of the posterior descending ramus of the sylvian fissure to the midpoint of the anterior border of the occipital lobe (ONO et al. 1990), (2) an arc from the posterior descending ramus of the sylvian fissure to the anterior border of the occipital lobe, taking care to make sure that the arc is cocurvilinear with the IPS above (DUVERNOY 1991; SCHWALBE 1881; YOUSRY 1998), (3) an arc from the posterior descending ramus of the sylvian fissure to the anterior border of the occipital lobe at the preoccipital notch (JENSEN 1871; YOUSRY 1998), or (4) a straight linear extension from the distal end of the posterior horizontal ramus of the sylvian fissure to the anterior border of the occipital lobe (DEJERINE 1895; TALAIRACH and TOURNOUX 1988; YOUSRY 1998).

On the medial surface, the deep parieto-occipital sulcus clearly divides the parietal lobe from the occipital lobe and is the landmark used to define the anterior border of the medial occipital lobe in all systems of nomenclature. On the inferior surface, the demarcation of the lobes again becomes arbitrary. On the inferomedial surface one may delineate the temporal lobe from the occipital lobe by drawing a basal parietotemporal line from the preoccipital notch to, variably, (1) the inferior end of the parieto-occipital sulcus where it joins the calcarine sulcus (Fig. 3.10) (ONO et al. 1990), (2) the anterior calcarine sulcus beneath the splenium (Fig. 3.11) (DUVERNOY 1991), or (3) the anterior end of the anterior calcarine sulcus (JENSEN 1871; YOUSRY 1998).

Because the patterns of sulcal branching, the gyral configurations, and the very definitions of the lobes used for anatomic description are so highly variable in this region, it may ultimately prove more accurate to designate the entire region as the TPO confluence. One could then choose to divide the convexity surface of the TPO confluence along the line of the multimodal association cortex from the lateral end of the parieto-occipital sulcus downward to, and then along, the superior temporal sulcus to define three functional compartments; a temporoparietal lobe rostral to the multimodal area (for somatosensory and auditory processing), a temporo-occipital lobe caudal to the multimodal area (for visual processing), and a TPO multimodal association lobe (for

Fig. 3.11a,b. Lobar borders according to Duvernoy. **a** Convexity. **b** Inferomedial surface. The anterior border of the occipital lobe is delimited by the same lateral parietotemporal line drawn between the parietooccipital sulcus and the preoccipital notch. On the convexity, the temporal lobe is separated from the parietal lobe by a temporo-occipital line drawn concurvilinear with the intraparietal sulcus from the posterior descending ramus of the sylvian fissure to the anterior border of the occipital lobe. On the basal surface, the temporal lobe is separated from the occipital lobe by a basal parietotemporal line drawn from the pre-occipital notch to the anterior calcarine sulcus inferior to the splenium. The posterior end of the superior temporal sulcus bifurcates as it extends into the inferior parietal lobule, making a large angular gyrus (a common variation). The fusiform gyrus is formed from portions of the temporal lobe (*T4*) and the occipital lobe (*O4*) that occupy the mid portion of the lateral occipitotemporal gyrus between the anterior (*5'*) and posterior (*5''*) transverse collateral sulci. Convexity surface (**a**): *LFa*, *LFm*, and *LFp* = lateral fissure (anterior, middle and posterior segments); *CS* = central sulcus; *PO* = parieto-occipital fissure; *TO* = temporo-occipital incisure; *F1*, *F2*, and *F3* = superior, middle, and inferior frontal gyri; *PrG* = precentral gyrus; *T1*, *T2*, and *T3* = superior, middle and inferior temporal gyri; *P1* = superior parietal gyrus (lobule); *P2* = inferior parietal gyrus (lobule); *PoG* = postcentral gyrus; *O1*, *O2*, and *O3* = superior, middle (synonym: lateral), and inferior occipital gyri; *21*, *21'*, and *21''* = intraparietal sulcus; *33* = sulcus lunatus. Inferomedial surface (**b**): *P1* = precuneus; *T3* = inferior temporal gyrus; *T4* = temporal portion of the fusiform gyrus; *T5* = parahippocampal gyrus; *TO* = temporo-occipital incisure; *O3* = inferior occipital gyrus; *O4* = occipital portion of the fusiform gyrus; *O5* = lingual gyrus; *O6* = cuneus; *2* = cingulate sulcus; *2'* = marginal segment of the cingulate sulcus (pars marginalis); *3* = subparietal sulcus; *4* = anterior calcarine sulcus; *22* = lateral occipitotemporal sulcus; *24* = calcarine sulcus. The caudal portions of *O3*, *O4* and *O5* merge together at the inferior aspect of the occipital lobe. (From Duvernoy H: *The Human Brain: Surface, Three-Dimensional Sectional Anatomy and MRI*. New York, Springer-Verlag, Vienna, 1991, pp 5–9; with permission)



integrating the diverse modalities). On the medial surface, one could similarly use the multimodal association cortex that extends along the parieto-occipital sulcus and the anterior calcarine sulcus to divide the medial surface of the hemisphere into a medial parietal region rostral to the multimodal cortex (for somatosensory processing), a caudal temporo-occipital lobe (for visual processing), and the interposed multimodal lobe (for integration) (NAIDICH et al. 2001a).

The term limbic lobe signifies a broad band of tissue on the medial surfaces of the two hemispheres that, considered together, encircle the brainstem, creating a limb about the stem. Specifically, the

limbic lobe includes the subcallosal area, the cingulate gyrus, the isthmus of the cingulate gyrus, the parahippocampal gyrus, and the piriform lobe, which according to Duvernoy corresponds to the anterior parahippocampal gyrus (DUVERNOY 1991).

Recently, Yasargil emphasized the arbitrary and uncertain borders between the lobes and proposed a new lobar classification in which the continuous circle of tissue formed by the precentral gyrus, subcentral gyrus, postcentral gyrus and paracentral gyrus was considered to be a separate, distinct *central* lobe. Thus the Yasargil classification would include seven lobes, the frontal central, parietal, occipital, temporal, insular and limbic lobes (YASARGIL 1994).

3.3

Localizing Anatomic Sites Independent of Lobar Anatomy

Several attempts have been made to identify functionally relevant anatomic sites, *independent of* the variable lobar and sulcal borders. These systems depend on first establishing reference planes that are based upon a very limited number of deep anatomic structures, then designating all locations in space in terms of coordinates based upon those limited reference planes, and finally identifying all other anatomic features in terms of these coordinates. These attempts may be extended to “correct for” differences in overall head and brain shape by “morphing” the anatomy of any individual brain to superimpose its gross contours on those of a single standard anatomic reference brain. Applied to groups of patients, such systems may detect commonalities otherwise obscured by individual variation, but at the costs of (1) information specific to each individual and (2) understanding of the range of normal variation.

3.3.1

Talairach-Tournoux Coordinate System and “Talairach Space”

Talairach and Tournoux took a horizontal plane that extended through the brain along a line drawn from the top of the anterior commissure (AC) to the bottom of the posterior commissure (PC). The line is the AC-PC line. The horizontal plane through the anterior and posterior commissures is the Talairach-Tournoux baseline. From this baseline a vertical plane is raised perpendicular to the baseline at the top of the anterior commissure. This is the VAC (vertical at the anterior commissure). A second similar vertical plane is raised perpendicular to the baseline at the bottom of the posterior commissure. This is the VPC (vertical at the posterior commissure). These planes define the coronal position. The third orthogonal plane is taken as the midline vertical plane through the AC-PC line. All anatomic positions are then defined by their coordinates in the vertical direction (designated from superior to inferior as 1–12), anteroposterior direction (A to I), and transverse direction (designated from the midline to lateral as a–d). Thus, the central sulcus is found in “a,1–2, F” of the left or right

hemisphere. These coordinates are considered to exist in “Talairach space” independent of any sulcal or lobar borders.

3.4

Identification of Specific Anatomic Structures

3.4.1

The Pericentral Cortex

The pericentral region consists of two parallel gyri, the precentral and postcentral gyri, separated by the CS. Superiorly, the CS nearly always reaches the cerebral margin and may extend onto the medial interhemispheric surface of the brain. In this location, the precentral and postcentral gyri fuse to each other to form the paracentral lobule around the upper end of the CS. Inferiorly, the CS rarely reaches the sylvian fissure. Instead, the preCG and postCG fuse together to form the subcentral gyrus between the inferior end of the CS and the sylvian fissure. This is partially delimited anteriorly and posteriorly by the anterior and posterior subcentral sulci (Fig. 3.9). Functional and anatomical MRI have both been used to define significant regions along the preCG (primary motor cortex) and the postCG (primary sensory cortex).

3.4.1.1

Functional Methods

Functional MRI (fMRI) shows that the motor hand area is located at the middle genu of the CS in a portion of the preCG that displays a characteristic omega or epsilon shaped “knob” or “knuckle” (NAIDICH and BRIGHTBILL 1996b; YOUSRY et al. 1997b). Using MEG (magnetoencephalography) it is possible to identify the postCG reliably (SOBEL et al. 1993). Using PET (positron emission tomography), it can be shown that the cortical representation of the sensory hand area is located along the anterior bank of the postCG at a characteristic curve of the CS immediately posterior to the motor hand area (RUMEAU et al. 1994). On fMRI, detection of an “activated” vein can assist in the identification of the CS, especially in patients with tumors distorting the cortical anatomy (YOUSRY et al. 1996). Currently fMRI is increasingly used to define the central region preoperatively.

3.4.1.2

Anatomical Methods

CT has shown that the marked normal variability of the cortical anatomy can limit the use of standard systems for localizing anatomy, such as the Talairach space (STEINMETZ et al. 1989a). Therefore, specific signs have been developed to help to identify the individual portions of the pericentral region more directly (IWASAKI et al. 1991; NAIDICH and BRIGHTBILL 1995, 1996a, b; NAIDICH et al. 1995; YOUSRY et al. 1995, 1997b). The sensitivity and specificity of these signs have been evaluated and the multiple signs combined into a system for localizing the CS and related gyri (NAIDICH and BRIGHTBILL 1996b). Three axial and three sagittal signs are most important. These signs should always be used together, systematically, so that the failure of any one sign is corrected by the concordance of localization given by the other signs (NAIDICH and BRIGHTBILL 1996b).

● Axial Plane Images

The precentral knob: a focal, posteriorly-directed protrusion of the posterior surface of the preCG, designated the precentral knob, has been shown by fMRI to be the site of the hand motor area. This focal motor region is seen on axial CT and MRI images as an inverted omega (90%) or as a horizontal epsilon (10%) in all cases (Fig. 3.12). This sign has a high inter-rater reproducibility (YOUSRY et al. 1997b) as well as high “applicability” (NAIDICH and BRIGHTBILL 1996b).

The pars bracket sign: in axial plane CT and MRI, the pars marginalis of the cingulate sulcus of the left and the right cerebral hemispheres appear together as a horizontal bracket. The medial end of the CS enters the pars bracket immediately anterior to the pars marginalis in 94%–96% of cases (Fig. 3.12), whereas the postcentral sulcus enters the pars bracket in only 3%. Thus, the relationship of a sulcus to the pars bracket permits accurate identification of the CS (the “bracket sign”). This sign is also characterized by a high applicability (NAIDICH and BRIGHTBILL 1996a, 1996b).

Thickness of the pre- and postcentral gyri: the full sagittal dimension of the preCG is thicker than that of the postCG (Fig. 3.12) (NAIDICH and BRIGHTBILL 1996b; NAIDICH et al. 1995). Further, the posterior *cortex* of the preCG is also thicker than the anterior cortex of the postCG at the cor-

responding site on the other side of the central sulcus (MEYER et al. 1996). Using T1-weighted turbo inversion recovery sequences the mean cortical thicknesses of the anterior (preCG) and posterior (postCG) banks of the CS were found to be 2.70 and 1.76 mm for both hemispheres with a mean cortical thickness ratio of 1.54 (Fig. 3.12) (MEYER et al. 1996). The difference in cortical thickness is based on and explained by cytoarchitectonic studies (BRODMANN 1909; NAIDICH and BRIGHTBILL 1996b; VON ECONOMO and KOSKINAS 1925). These three signs are the most important and most reliable for attempting to localize the CS in the axial plane (NAIDICH and BRIGHTBILL 1996b).

● Sagittal Plane Images

Lateral sagittal plane. The “M” shape of the inferior frontal gyrus. The anterior horizontal and anterior ascending rami of the sylvian fissure extend upward into the IFG, giving it the shape of a letter “M”. The first vertical line of the “M” represents the pars orbitalis. The middle “v” of the “M” represents the pars triangularis. The posterior vertical line of the “M” represents the pars opercularis of the IFG. Identification of the “M” provides the starting point for subsequent, sequential identification of the preCS, preCG, CS and postCG (Fig. 3.13) (NAIDICH et al. 1995, 1997; STEINMETZ et al. 1990a).

Middle sagittal plane: the precentral knob. The posteriorly directed expansion of the preCG at the hand motor area may be identified at the level of the insula as a posteriorly directed hook, which fits neatly into the concavity of the hand sensory region of the postcentral gyrus. This configuration defines the position of the preCG, the CS and the postCG in 92% of cases (Fig. 3.13) (YOUSRY et al. 1997b).

Medial sagittal plane: the pars marginalis. The posterior portion of the cingulate sulcus, which sweeps upward to reach the cerebral margin, is the pars marginalis. The CS lies millimeters anterior to the pars marginalis. Characteristically the portion of the CS that lies on the medial surface of the brain curves posteriorly to course nearly perpendicular to the pars marginalis (Fig. 3.13) (NAIDICH and BRIGHTBILL 1996b).

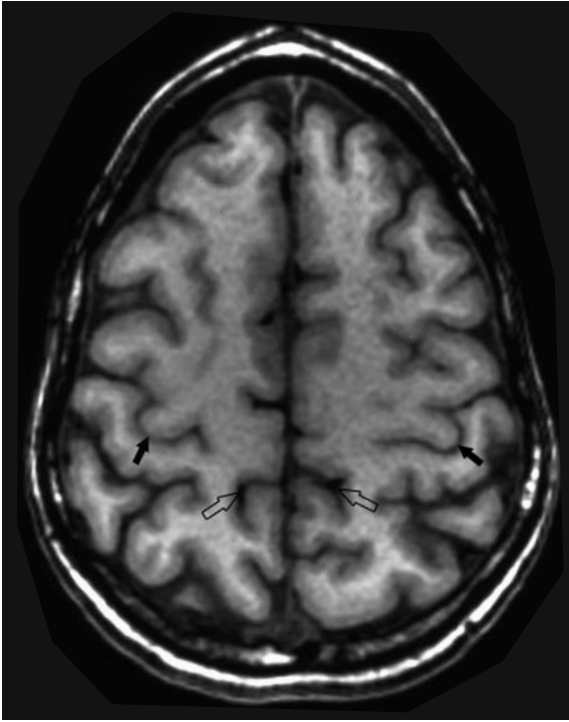
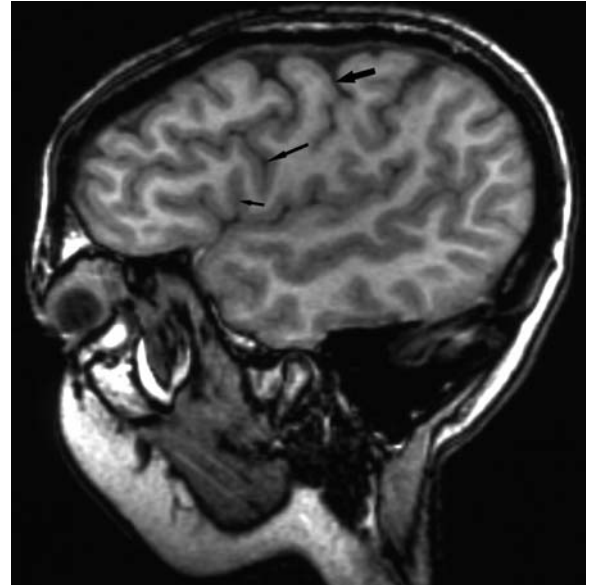
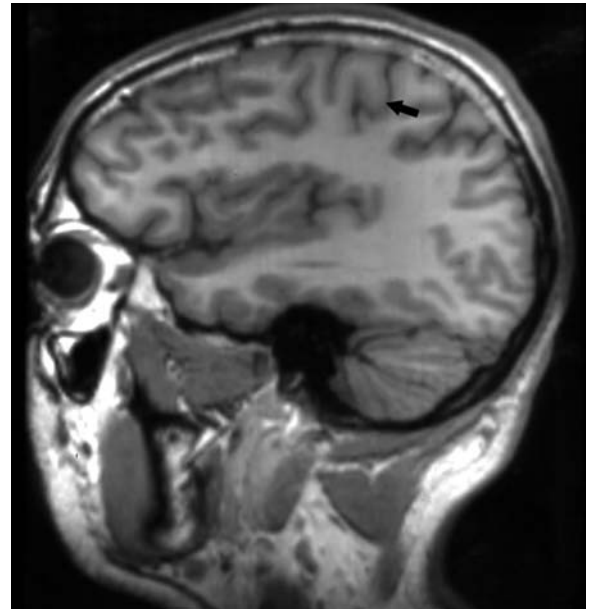


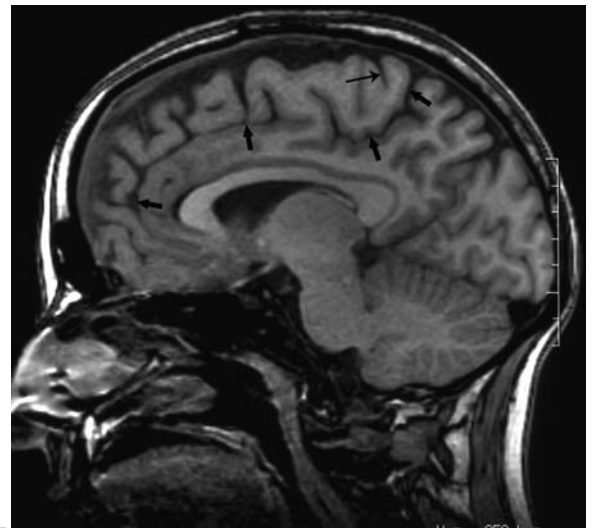
Fig. 3.12. Pericentral region. Axial landmarks. In the axial plane (T1-weighted MPRAGE sequence), the Ω -shaped knob of the precentral gyrus is easily identified (*arrows*). The pars marginalis of the cingulate sulcus of both hemispheres appears as a horizontal bracket (*open arrows*). The medial end of the central sulcus enters the pars bracket immediately anterior to the pars. The full sagittal dimension of the precentral gyrus is thicker than that of the postcentral gyrus. The cortex of the precentral gyrus is thicker than the cortex of the postcentral gyrus



a



b



c

Fig. 3.13a–c. Pericentral region. Sagittal landmarks (T1-weighted MPRAGE sequence). **a** In the sagittal plane the anterior horizontal ramus (unlabeled anteriorly) and anterior ascending ramus (*short thin arrow more posteriorly*) of the sylvian fissure are first identified on the lateral sections, and used to identify the M Shape of the inferior frontal gyrus. Posterior to this gyrus, in order, lie the precentral gyrus (*long thin arrow*), the subcallosal gyrus, the central sulcus (*short thick arrow*) and the postcentral gyrus. **b** At the level of the insula, the posteriorly directed hook (*arrow*) of the motor hand area defines the precentral gyrus. **c** The cingulate sulcus and its ramus marginalis (*arrows*) are first identified. The central sulcus (*thin arrow*) lies immediately anterior to the pars marginalis and is oriented such that it curves posteriorly, to course nearly perpendicular to the ramus marginalis

3.4.2

The Superior Temporal Plane

The transverse temporal gyrus of Heschl courses anterolaterally over the superior surface of the temporal lobe from the posterior border of the insula medially to the convexity surface of the temporal lobe laterally. HG corresponds to Brodmann area 41 (BRODMANN 1909), the primary auditory cortex (A1). Usually, only a restricted posteromedial portion of HG can be considered the true site of A1 (LIEGEOIS-CHAUVEL et al. 1991). A second HG may

be present posterior and parallel to the first and may occasionally be functionally included in A1 (LIEGEOIS-CHAUVEL et al. 1995).

Using MRI, HG may be identified accurately in the axial, sagittal and coronal planes. In the *sagittal plane*, HG has a characteristic shape easily identified on the supratemporal surface just lateral to the insula. Depending on the number of HG present, HG may assume the form of a single “omega”, a “mushroom”, a “heart” or a double Ω (Fig. 3.14) (YOUSRY et al. 1997a). In the *coronal plane* perpendicular to the Talairach-Tournoux baseline, HG is



Fig. 3.14a–c. Heschl's gyrus. Landmarks in three planes (T1-weighted MPRAGE sequence). **a** In the sagittal plane just lateral to the insula, the shape of HG (arrow) is so characteristic that it can easily be identified directly on the supratemporal surface without need for additional landmarks. Depending on the presence and extent of any intermediate sulcus, HG may appear Ω -shaped, on medial sections of the temporal lobe and insula. **b** In a coronal plane perpendicular to the bicommissural plane, the section on which HG (arrows) is identified best is characterized by (1) a tent-like shape formed as the two fornices converge to join with each other and (2) the presence of the VIIIth cranial nerves. **c** In the axial plane HG (arrows) is identified by its temporal location and its characteristic anterolateral course on the section in which the adhesion interthalamica (massa intermedia) can be identified

found best in the section that displays the (tentlike) convergence of the two fornix and the VIIIth cranial nerves (Fig. 3.14) (YOUSRY et al. 1997a). In the *axial plane*, HG is found most easily in the section which displays the massa intermedia of the thalamus (Fig. 3.14) (YOUSRY et al. 1997a).

3.4.3

The Occipital Lobe

The occipital lobe is important for the visual areas (V1–V3, Brodmann areas 17–19) it contains. The primary visual area (V1, Brodmann area 17) is located in the striate cortex. Most of the striate cortex extends along the calcarine sulcus (KOROGI et al. 1996). However, the precise site of the striate cortex is variable. The striate cortex may be exposed on the medial surface of the occipital lobe, lie hidden within the depths of the calcarine sulcus, extend into the parieto-occipital or anterior calcarine sulci, and/or lie on the tentorial surface of the occipital lobe (KOROGI et al. 1996). The precise configuration of the calcarine sulcus also varies (Fig. 3.15). Korogi et al. found that the sulcus could be a single continuous sulcus without major branches (50%), could give off major branches (26%), and could even show significant disruptions (24%) (KOROGI et al. 1996).

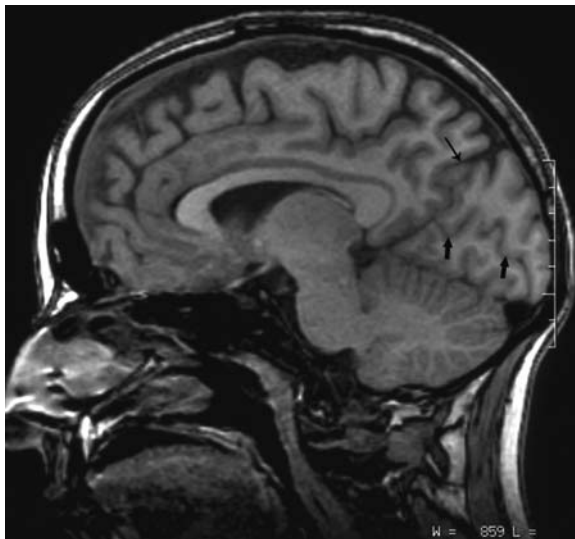


Fig. 3.15. Occipital lobe (T1-weighted MPRAGE sequence). The calcarine sulcus (arrows) runs obliquely in an antero-superior direction from the occipital pole to its junction with the parieto-occipital sulcus (*thin arrow*) to form the anterior calcarine sulcus. The calcarine sulci show a gradual posterior declination

In the coronal plane, the calcarine sulci and parieto-occipital sulci were symmetric in only 60% of cases. One calcarine sulcus was significantly lower than the other in 24% (by more than 10 mm in 12% of cases) (KOROGI et al. 1996). The calcarine and the parieto-occipital sulci formed a “V” in 16% (KOROGI et al. 1996). The exact positions and (a)symmetries of the calcarine and parieto-occipital sulci are also influenced by the magnitude of any occipital petalia. These variations complicate the identification of the calcarine sulcus (YOUSRY et al. 2001).

3.5

Cortical Architecture

3.5.1

Cytoarchitectonics

The neocortex exhibits six cell layers characterized by differing proportions of cell types, cell densities, and myelination of fibers. From superficial to deep, the six neocortical layers are designated by Roman numerals: I. Molecular layer; II. External granule cell layer; III. External pyramidal cell layer; IV. Internal granule cell layer; V. Internal pyramidal cell layer; and VI. Multiform layer. Further variations within each layer may lead to subdivisions such as layers IVA and IVB. In general, afferent fibers to the cortex synapse in layers I–IV. Afferents from specific thalamic nuclei end predominantly in layer IV. Efferents from the cortex arise in Layers V and VI. Those efferents directed to the brainstem and spinal cord arise mainly in layer V (CARPENTER and SUTIN 1983; GILMAN and NEWMAN 1996).

Granule cells are small polymorphic (stellate, tufted, or bipolar) cells that form the major component of the external and internal granule cell layers (II and IV). These are mainly γ -aminobutyric acid-(GABA)-ergic inhibitory neurons. Pyramidal cells are pyramid-shaped cells with their apical dendrites directed superficially to layer I. The basal dendrites span outward laterally. The major axon arises from the base of each pyramidal cell to pass to its target. Small pyramidal cells found in layers II, III, and IV project to intracortical regions (GILMAN and NEWMAN 1996). Large pyramidal cells in layer V project to the brainstem and the spinal cord (GILMAN and NEWMAN 1996). Giant pyramidal cells with direct corticomotoneuronal connections to the (alpha)

motoneurons of the brainstem and the spinal cord are designated Betz's cells. In humans, Betz's cells are found exclusively in the primary motor cortex (M1).

Throughout the cortex, the cell layers differ in their total thickness, the thickness of each layer, the concentrations of cells within each layer, the conspicuity of each layer, the degree of myelination of the fibers within the layer, and the presence or absence of special cells, like the Betz cells. These variations give each region a specific cytoarchitecture that subserves the function of that region. The cytoarchitectonic variations in the cortex lead to classifications of cortical regions by their cytoarchitecture. If the six-layered neocortical organization is readily discernable, the cortex is designated homotypical. If focal specialization of the cytoarchitecture partly obscures these layers, the cortex is designated heterotypical (VON ECONOMO and KOSKINAS 1925). VON ECONOMO and KOSKINAS (1925) grouped the cortical regions into five types (Fig. 3.16). Three types were considered homotypical: frontal cortex, parietal cortex, and polar cortex. Two were considered heterotypical cortices: the agranular cortex (specialized for motor function) and the koniocortex (specialized for sensory function). BRODMANN (1909) recognized additional variations in cortical architecture, subdivided the cortex into approximately 40 distinct cytoarchitectonic areas, and tried to relate the cortical architecture to function. These regions are now designated the Brodmann areas (BA) (Fig. 3.17).

In humans, the motor cortex is formed of three major cortical types:

- The heterotypical agranular isocortex is characterized by increased overall thickness, significantly reduced to absent granule cells in layer IV, and thick well-developed layers of large pyramidal cells in layers III and V (ZILLES et al. 1996). In this agranular cortex, even the small cells in layers II (and the region of IV) are predominantly pyramidal in shape. Type (a) corresponds predominantly to BA 4, 6, 8, 24, 44, and 45, and is found in the posterior half of the precentral gyrus, the anterior half of the cingulate gyrus, the anterior portion of the insula, and in a narrow strip which extends from the retrosplenial portion of the cingulate gyrus into the parahippocampal gyrus (Figs. 3.16 and 3.17). Within these areas, the primary motor cortex, designated M1 (Brodmann's area 4), is characterized by the presence of giant Betz's cells in

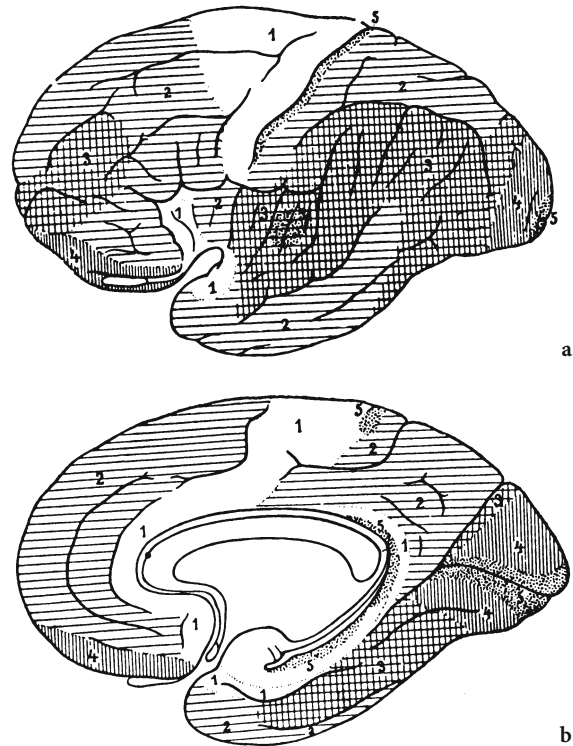


Fig. 3.16a,b. The five types of cerebral isocortex are distributed over the convexity (a) and medial surface (b) of the cerebral hemisphere. Cortex Type 1 = agranular (motor) heterotypical; 2 = frontal homotypical; 3 = parietal homotypical; 4 = polar homotypical; 5 = granular (sensory) heterotypical (koniocortex). Note that the words frontal and parietal used in this way signify types of isocortex and not anatomic locations or lobes. (From von Economo C, Koskinas GN; *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*. Wien, Springer Verlag, 1925; with permission)

- lower layer V (ZILLES et al. 1996). The motor speech areas, BA 44 and BA 45, are found in the inferior frontal gyrus.
- The homotypical frontal cortex is characterized by narrow granule cell layers composed of loosely arrayed small granule cells and by prominent small and medium-sized pyramidal cells in layers III and V (CARPENTER and SUTIN 1983). Giant Betz's cells are absent. This frontal cortex corresponds to BA 9, 10, 11, 46, and 47, and is found along the convexity and the anteriormost medial surfaces of the superior and middle frontal gyri.
- The homotypical polar cortex is characterized by overall cortical thinness, well-developed granule cell layers, and a comparative wealth of cells (CARPENTER and SUTIN 1983; NAIDICH et al. 2001b). It corresponds to BA 10.

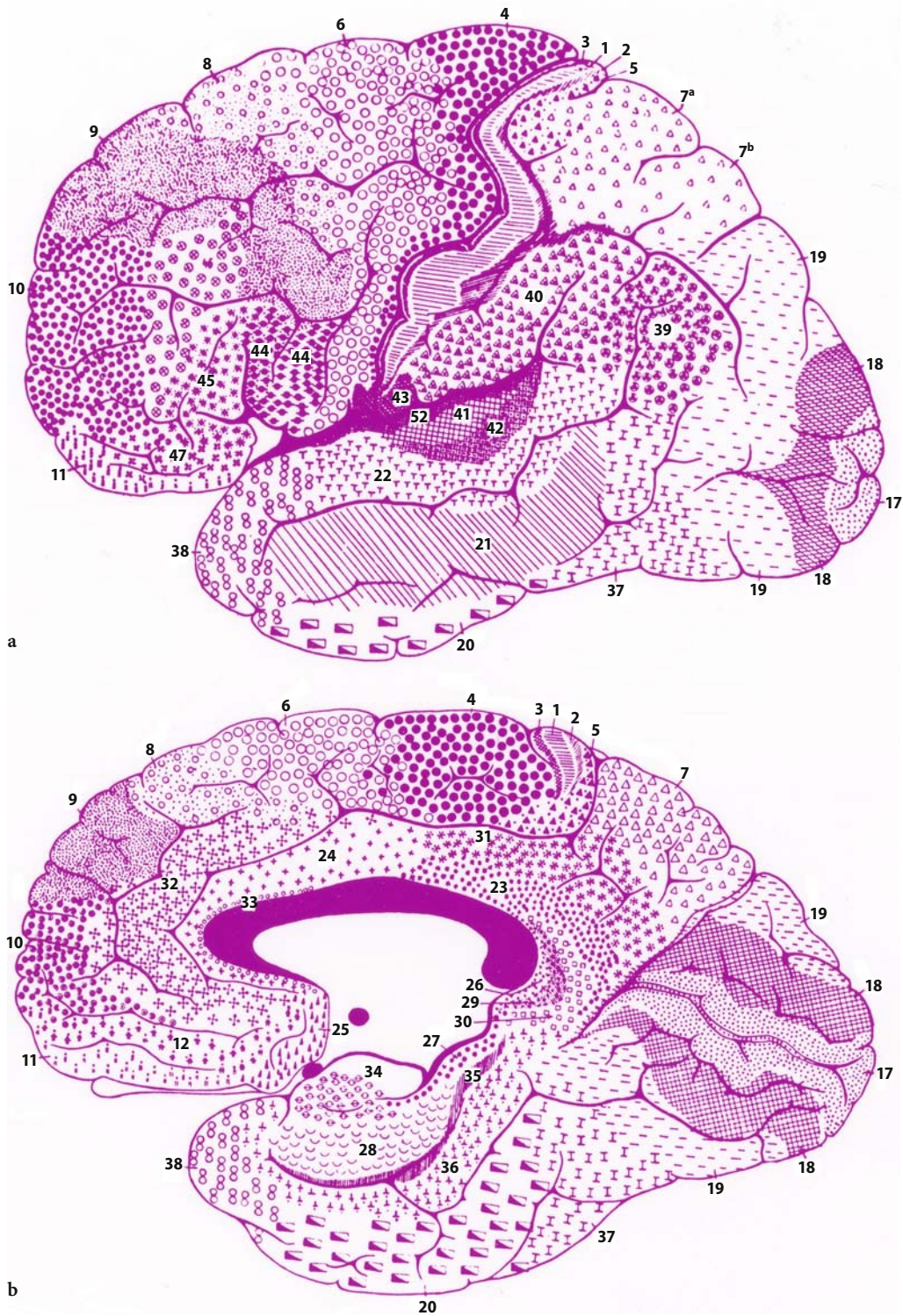


Fig. 3.17a,b. Cytoarchitecture of the human cortex. Convexity (a) and medial (b) surface views of Brodmann's areas. Symbols indicate Brodmann's parcellation of the cortex into the cytoarchitectonic areas that are designated by the Brodmann area (BA) numbers assigned. Compare with Fig. 1 (Parts a and b from Carpenter MB, Sutin J (eds): Human Neuroanatomy, edn 8. 1983, chap 19; with permission)

3.5.2 Somatotopy

The term somatotopy refers to the topographic organization of function along the cortex. It is a map of the sites at which smaller or larger regions of cortex form functional units that correspond to body parts or to motions across a joint. In specific regions like the primary auditory cortex, the somatotopy may be described by a more specific word such as tonotopy. For white matter, the preferred term is myelotopy. The presence of somatotopy signifies that the functional activity of the cortex is organized topographically along the cortex. Absence of somatotopy signifies that medicine has failed, thus far, to appreciate any topographic organization of that cortex. Somatotopy may be fine, as in the primary motor cortex (BA 4), where relatively restricted zones of cortex correspond to defined manipulation units (Fig. 3.18). It may be very fine, as in the hand motor area along the precentral gyrus, where there may be representation for the motion of each individual digit. Alternatively, somatotopy may be very crude, as in the SMA, the pre-SMA, and the cingulate motor cortex (CMC), where cortical zones seem to correspond to broad regions, such as head, trunk, upper and lower extremities, rather than to individual motion units (Fig. 3.19). Using PET to measure regional cerebral blood flow (rCBF), GRAFTON et al. (1993) have shown within-arm somatotopy of the primary motor cortex,

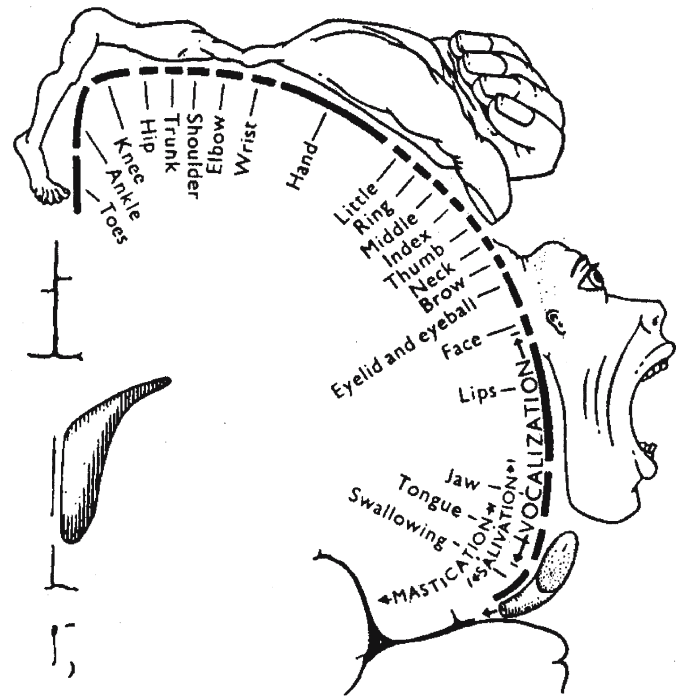


Fig. 3.18. Somatotopy of the primary motor cortex (M1): the motor homunculus, as described by Penfield and Jasper. (From Williams PL, Warwick R, Dyson M, et al. (eds): *Gray's Anatomy*, edn 37. Edinburgh, Churchill Livingstone, 1989, pp 1047–1063; with permission)

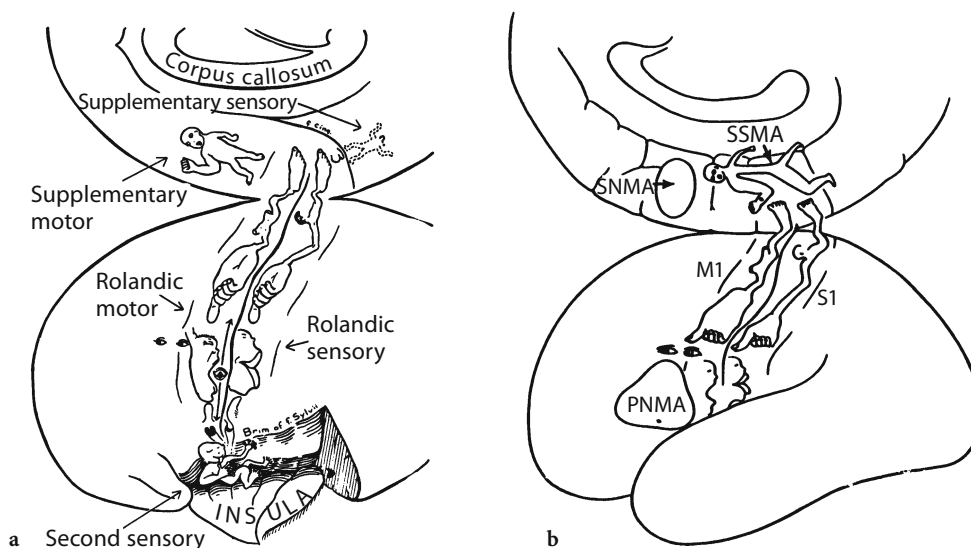


Fig. 3.19. **a** Somatotopy of the supplementary motor areas (SMA) as represented by Penfield and Jasper. **b** Somatotopy of the pre-SMA (the supplementary negative motor area [SNMA]) and the relation of the pre-SMA to the SMA, simplified from Penfield and Jasper. M1 = primary motor cortex; PNMA = primary negative motor cortex; S1 = primary sensory cortex; SSMA = supplementary somatosensory cortex. (a from Luders HO: The supplementary sensorimotor area. An overview. *Advances in Neurology* 70:1–16, 1996; b from Freund H–J: Historical overview. *Adv Neurology* 70:17–27, 1996; with permission)

the SMA, and the CMA. KLEINSCHMIDT et al. (1997) used fMRI to show somatotopy for digits in the human hand motor area and concluded that "... somatotopy within the hand area of the primary motor cortex does not present as qualitative functional segregation but as quantitative predominance of certain movement or digit representation embedded in an overall joint hand area" (NAIDICH et al. 2001b).

3.5.3

Selected Areas Involved in Motor and Speech Function

3.5.3.1

Primary Motor Cortex (M1)

The primary motor cortex is designated M1 and corresponds to BA 4. M1 extends from the anterior part of the paracentral lobule on the medial surface, over the cerebral margin, and down the convexity along the crown and posterior face of the precentral gyrus (Figs. 3.3 and 3.17). Its anteroposterior extent is broader superiorly and on the medial surface. From there, BA 4 tapers progressively downward toward the sylvian fissure. Just above the sylvian fissure and behind the inferior frontal gyrus, BA 4 becomes restricted to a narrow strip along the posterior face of the precentral gyrus, within the central sulcus (Fig. 3.17).

M1 is heterotypical agranular isocortex characterized by significant overall cortical thickness, reduced to absent granule cells in layer IV, prominent pyramidal cells in layers III and V, and prominent giant Betz cells in lower layer V (ZILLES et al. 1996). The individual Betz's cells are largest in size superomedially at the paracentral lobule, and smallest inferolaterally at the operculum (CARPENTER and SUTIN 1983). Classically, the somatotopy of M1 is given by the motor homunculus (Fig. 3.18). Each functional zone was considered to be responsible for directing the action of a group of muscles that effects motion across a joint. Individual neurons within this group innervate different muscles, so that individual muscles are innervated repeatedly in different combinations by multiple different cell clusters to effect action across different joints. In the classic concept, therefore, the motor map represents motion of the joint, rather than any single body part. More recently, GRAZIANO et al. (2002) have shown that the motor homunculus may better be considered a map of final body postures.

M1 activates anterior horn cells within the spinal cord to generate specific patterns of movement

(MARSDEN et al. 1996). It serves to execute voluntary activity of the limbs, head, face and larynx, both contralaterally and ipsilaterally. Contralaterally, M1 excites all muscle groups of the extremity. Ipsilaterally, M1 excites the proximal musculature most strongly, especially the shoulder. By direct stimulation of neurons in monkeys, TANJI et al. (1987, 1988) found that 77.2% of movement-related M1 neurons are contralateral motor neurons, affecting action of the contralateral side, 8.2% are ipsilateral motor neurons, responsible for action on the ipsilateral side, and 4.5% are bilateral motor neurons. Stimulation of M1 produces simple motions, such as flexion and extension at one or more joints, and not skilled movements. Regions of M1 exhibit different thresholds for inciting action. These thresholds are lowest for the thumb and highest for the face.

Activation studies confirm activation of the ipsilateral hemisphere by sensorimotor tasks (LI et al. 1996). The ipsilateral activation is greater for motor than for sensory tasks and is greater for the nondominant hand than for the dominant hand (LI et al. 1996). The left and the right primary motor cortices show reciprocal actions. Transcranial magnetic stimulation of the motor cortex may inhibit the contralateral cortex (ALLISON et al. 2000). Direct focal stimulation of M1 causes excitation of a homologous area in the contralateral M1, surrounded by a zone of inhibition (ALLISON et al. 2000; ASANUMA and OKUDA 1962). In fMRI studies, unilateral finger movements activate M1 ipsilaterally. The same movements may also deactivate portions of M1 ipsilaterally (ALLISON et al. 2000).

3.5.3.2

Supplementary Motor Area (SMA)

The SMA (Figs. 3.18 and 3.19) (PENFIELD and WELCH 1951) is also known by a large number of synonyms, including: the SMA proper, caudal SMA, posterior SMA, the supplementary sensorimotor area, M2, and BA 6a α (medial) (OLIVIER 1996; RIZZOLATTI et al. 1996; SEITZ et al. 1996). In this chapter, the term SMA refers to the SMA proper, distinct from the more anteriorly situated pre-SMA. Anatomically, the SMA proper corresponds to BA 6a α (medial) situated along the medial cerebral cortex in the paracentral lobule and posterior portion of the superior (medial) frontal gyrus. Its specific site varies among individuals, but it is typically found in relation to the medial precentral sulcus (ZILLES et al. 1996). ZILLES et al. (1996) report that the SMA is located between the VAC and the VPC (Fig. 3.20).

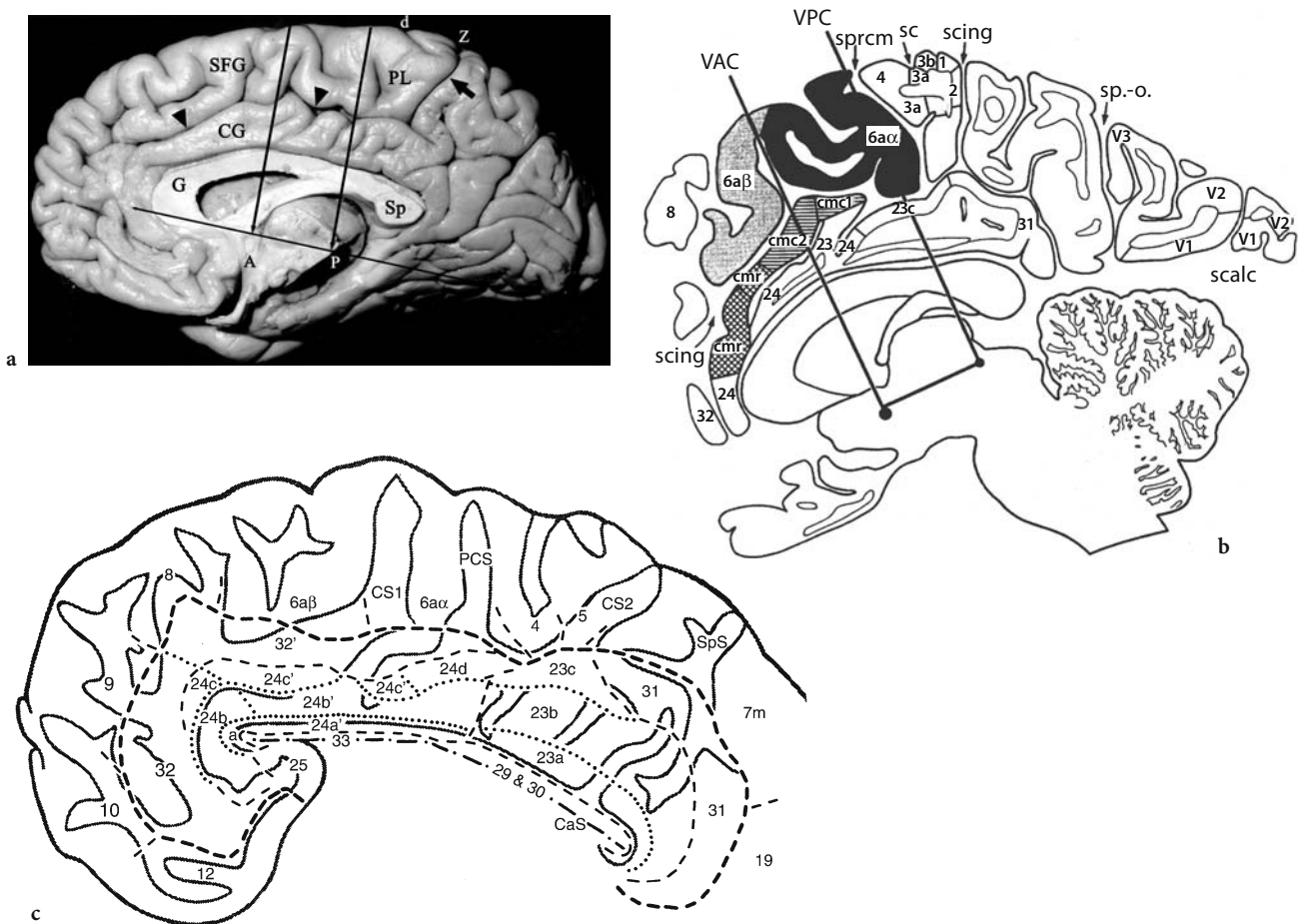


Fig. 3.20a–c. Mesial motor areas: SMA, pre-SMA, and CMA. **a** Gross anatomy of the medial surface of the hemisphere. Prepared specimen, oriented with anterior to the reader's left. This hemisphere displays the co-curvilinearity of the fornix (F), the genu (G) and splenium (Sp) of the corpus callosum; the callosal sulcus (not labeled), the cingulate gyrus (CG); the single cingulate sulcus (arrowheads); the superior frontal gyrus (SFG); and the paracentral lobule (PL). The pars marginalis (arrow, z) of the cingulate sulcus sweeps upward to the cerebral margin to define the posterior aspect of the paracentral lobule. The central sulcus (d) cuts the cerebral margin just anterior to the pars marginalis, and then courses a short (and variable) distance down the medial face of the paracentral lobule, almost perpendicular to the pars marginalis. To illustrate the anatomic relationships, the AC-PC line has been drawn from the superior surface of the anterior commissure (AC, here labeled A) to the inferior surface of the posterior commissure (PC, here labeled P), and the perpendiculars erected to this line at the AC and the PC. The AC-PC line is the baseline for the Talairach-Tournoux coordinate system (TALAIRACH and TOURNOUX 1988). **b** The medial parasagittal plane, oriented with anterior to the readers' left. CC = corpus callosum; AC = anterior commissure; PC = posterior commissure. The VAC and VPC are the vertical lines erected perpendicular to the AC-PC line at AC (VAC) and PC (VPC). The cytoarchitectonic areas are numbered after Brodmann and the Vogts. *Black areas* show the position of the SMA on the medial surface of the hemisphere. *Solid gray* shows the position of the pre-SMA. *Cross hatching* indicates the rostral portion of the cingulate motor area (cmr), whereas the *horizontal lines* show the caudal portion of the cingulate motor area (cmc), itself divided into parts one and two. scing = cingulate sulcus; sc = central sulcus. V1–V3 are the visual cortical areas. **c** Flat map of the cytoarchitectonic areas of the human cingulate cortex and the locations of adjacent areas. The cingulate sulcus is shown with two separate segments (CS1, CS2). *Thick lines* = outline of the cingulate areas; *thin lines* divide each major cingulate area; *stippling* = borders of each sulcus; *dotted lines* = the subdivisions of each area; *dot-dash line* = the fundus of the callosal sulcus; the fundi of the other sulci are not marked for simplicity. PCS = paracentral sulcus. (a from Naidich TP, Hof PR, Yousry TA et al.: The motor cortex: anatomic substrates of function. *Neuroimaging Clinics of North America* 11:171–193, 2001; b from Zilles K, Schlaug G, Geyer S et al.: Anatomy and transmitter receptors of the supplementary motor areas in the human and non human primate brain. *Adv Neurol* 70:29–43, 1996 and Vogt BA, Bogt LT, Nimchinsky EA et al.: Primate cingulate cortex chemoarchitecture and its disruption in Alzheimer's disease: In: FE Bloom, A Bjorklund, T Hokfelt (eds): *Handbook of chemical neuroanatomy*, vol 13. The primate nervous system, Part I. Amsterdam, Elsevier Science BV, 1997; c adapted from Vogt BA, Minchinsky EA, Vogt LJ et al: Human cingulate cortex: Surface features, flat maps, and cytoarchitecture. *J Comp Neurol* 359: 490–506, 1995; with permission)

The SMA is bordered anteriorly by the pre-SMA, posteriorly by the primary motor cortex, laterally by the premotor cortex on the convexity, and ventrally (inferiorly) by the posterior CMA (FRIED 1996; ZILLES et al. 1996).

The SMA is a heterotypical agranular isocortex characterized by reduced to absent granule cell layers and by absence of Betz cells in pyramidal cell layer V. The SMA (BA 6a α on the medial surface) can be distinguished from the laterally adjacent premotor area (BA 6a α on the convexity), because the SMA has increased cell density in the lower part of layer III and in layer Va (ZILLES et al. 1996). The SMA can be distinguished from the pre-SMA, because the SMA shows poorer delineation of the laminae and poorer distinction of layer III from layer V (ZILLES et al. 1996).

The SMA exhibits crude somatotopy. From anterior to posterior, one finds representations of the head, trunk, and upper and lower extremities (FRIED et al. 1991). In humans, one stimulation study with subdural electrode grids placed along the mesial cortex elicited a finer somatotopy (FRIED et al. 1991). In order from anterior to posterior, these authors found face, neck, distal upper extremity, proximal upper extremity, proximal lower extremity, and distal lower extremity. The SMA clearly shows greater representation of the contralateral side than the ipsilateral side. The dominant SMA exerts more control than the nondominant SMA, both contralaterally and ipsilaterally. The supplementary eye fields lie in relation to the head portion of the SMA, but are distinct from the SMA (LIM et al. 1996; TANJI 1994).

The SMA appears to act in several different ways:

- *Connections to the Cervical Motor Neurons.* The SMA has tight, probably monosynaptic, connections to the cervical motoneurons (94% contralateral, 6% ipsilateral). SMA activity in one hemisphere is associated with movement of either arm, especially whole-arm prehension involving the shoulder and trunk muscles. Stimulation of the SMA causes a characteristic posture with raising of the opposite arm (abduction and external rotation at the shoulder with flexion at the elbow) and turning of the head and eyes to gaze at the elevated hand (CARPENTER and SUTIN 1983; CHAUVEL et al. 1996; FREUND 1996a, b). The trunk and lower extremities show bilateral synergic contractions (CARPENTER and SUTIN 1983). Distal hand muscles are weakly represented in the SMA. Isolated finger movements, easily elicited by stimulation of MI, are rarely elicited by stimulating SMA. The SMA appears less involved with distal grasping.
- *Posture.* The SMA plays a role in posture, especially in anticipating and correcting posture during motor tasks, so that the final position or task is performed successfully. In normal subjects, when a heavy object is lifted from one hand by the other, there is anticipatory adjustment of the posture of the forearm flexors, so position is maintained despite the unloading (BRUST 1996; VIALLET et al. 1992).
- *Action.* Stimulation of the SMA leads to an urge to act and an anticipation of action (FRIED et al. 1991). In monkeys, TANJI et al. (1987, 1988) used intracellular recording to demonstrate that 38% of SMA cells fire before any action is performed. At least some SMA neurons fire before M1 neurons.
- *Laterality.* The SMA is involved with selecting the laterality of the task. In monkeys, 27% of motor-related SMA neurons only fire before deciding on which side to perform an action (TANJI et al. 1987, 1988). Considering SMA neurons and premotor neurons together as one group of non M1 neurons, TANJI et al. (1987, 1988) showed that when choosing which upper extremity to use for a job, 16% of non-M1 cells fire before deciding right, not both; 20% fire before deciding left, not both; 20% fire before deciding either, not both; and 40% fire before deciding both, not either.
- *Coordination and Cooperation.* The SMA serves to assist bimanual coordination and cooperation between the paired upper and the paired lower extremities, especially for self-initiated action. The SMA appears to be required for independent control of the contralateral hand.
- *Sequences of Action.* The SMA is heavily involved in learning and generating sequences of actions and with executing multiple actions involving both sides of the body (GILMAN and NEWMAN 1996; PASSINGHAM 1996; SHIBASAKI et al. 1993). It may serve in selecting a specific action from among a group of remembered tasks. In monkeys, TANJI and SHIMA (1994) found one group of SMA cells that were preferentially activated in relation to a particular order of forthcoming movements, guided by memory. A second group of SMA cells became active after the performance of one particular movement and then remained active during the waiting period before performing a second specific movement.

These cells were not active if the preceding or subsequent movement was different. Thus, these cells seem to signal a temporal linkage combining two specific movements (TANJI and SHIMA 1994). Single unit discharges were also observed in the SMA before the performance of the remembered sequence of movements (preparatory sequencing of neurons) and in the midst of the sequence of movements (tonic sequencing of neurons) (TANJI 1994; TANJI et al. 1987, 1988; TANJI and SHIMA 1994). Similarly, rCBF in the SMA increases with ideation about sequential motor tasks (e.g., when subjects plan but do not execute fast, isolated finger movements) (ROLAND 1999). When these tasks are actually executed, increased rCBF can be seen contralaterally in M1 and bilaterally in the SMA. From these data, the SMA seems to be crucial for learned, internally generated (i.e., self-initiated) voluntary motor behaviour (BURTON et al. 1996; FREUND 1996a, b; FREUND and HUMMELSHEIM 1985; RAO et al. 1993), especially in the preparation and initiation of such voluntary motor behavior (FREUND 1996b; LUDERS 1996). The SMA seems to be less related to performance of the movements themselves. Simple repetition of fast finger motion does not stimulate SMA (FREUND 1996b).

Stimulation studies also show a relation between the complexity of a task and the speed with which the action itself is performed. Simple tasks, like flexion of one joint, are commonly performed rapidly. More complex tasks involving multiple joints, multiple body regions, or both evolve more slowly. In some stimulations, the responses elicited were repeated several times until stimulation stopped (FRIED 1996).

- **Attention-Intention Network.** The SMA may form part of an attention-intention network. FRIED (1996) found that most ipsilateral and bilateral sequences can be elicited from the right, non-dominant SMA. The right hemisphere has an attention mechanism that spans both hemispheres, whereas the left hemisphere seems to mediate only contralateral attention (FRIED et al. 1991). Therefore, the lateralization of attention to the right hemisphere and the lateralization of motor intention to the right SMA may signify a right cerebral dominance for attention and motor intention directed at the external milieu in which the motor action takes place (FRIED 1996; FRIED et al. 1991; NAIDICH et al. 2001b).

3.5.3.3

Pre-supplementary Motor Area (pre-SMA)

The term pre-SMA signifies a motor area that has also been called rostral SMA, anterior SMA, BA 6a β (medial), and the supplementary negative motor area (Figs. 3.19 and 3.20). It corresponds to BA 6a β (medial) (SEITZ et al. 1996). The pre-SMA lies along the medial face of the superior (medial) frontal gyrus just anterior to the SMA. It shows individual variability. According to ZILLES et al. (1996), the pre-SMA lies predominantly anterior to VAC (Fig. 3.20). It borders posteriorly on the SMA, laterally on the anterior portion of the premotor cortex on the convexity, and ventrally (inferiorly), on the anterior cingulate motor area (ZILLES et al. 1996).

The pre-SMA is heterotypical agranular isocortex with no Betz cells. It can be distinguished from the SMA posterior to it because the pre-SMA has more pronounced lamination and clearer demarcation of layer III from layer V (ZILLES et al. 1996). The pre-SMA exhibits a somatotopy similar in form to the SMA, but even cruder in detail. From anterior to posterior, there are areas for head, upper, and lower extremities.

The pre-SMA seems to serve in sequencing and preparing complex tasks, especially internally generated, visually guided tasks. Stimulation of the pre-SMA may elicit negative motor activity for diverse tasks. FRIED (1996) found that pre-SMA stimulation causes slowing or arrest of the entire spectrum of motor activity tested, including speech. When a patient executes a repetitive task, such as rapid alternating movements of the hand, stimulation of the pre-SMA causes the movements to gradually slow down and come to a halt. Activation studies suggest that the pre-SMA is involved in the decision whether to act, whereas the SMA proper plays a similar role in directing motor action once the decision to act is made (HUMBERSTONE et al. 1997; NAIDICH et al. 2001b).

3.5.3.4

Cingulate Motor Area (CMA)

The CMA is composed of two portions (Fig. 3.20), which appear to correspond to the functionally defined anterior cingulate motor area (CMA rostral; cmr) and a posterior cingulate motor area (CMA caudal; cmc). The CMA corresponds to BA 24c and BA 24d (and perhaps the posterior portion of BA 32, BA 32' of Vogt) (VOGT C and VOGT 1919; VOGT O and

VOGT, 1926). It lies in the superior (dorsal) and inferior (ventral) banks of the cingulate sulcus and, in macaques, does not extend onto the medial surface of the cingulate gyrus (SHIMA et al. 1991). From the callosal sulcus (inferiorly) to the superior frontal gyrus (superiorly), the cerebral cortex undergoes transition from true allocortex (BA 33), through intermediate stages (lower and upper BA 24), to true isocortex (BA 32) (ZILLES et al. 1996). Intermediate area BA 24, therefore, is subdivided into three bands co-extensive with the cingulate gyrus and sulcus. These three bands are designated BA 24a (ventral band), 24b (intermediate band), and 24c and 24d (dorsal bands). BA 32 lies superior to BA 24c and BA 24d. Dorsal band BA 24c and 24d is then subdivided further into a rostral zone (cmr), conforming approximately to BA 24c, and a caudal zone (cmc) conforming approximately to BA 24d (VOGT BA et al. 1995, 1997; ZILLES et al. 1996). The cmr lies entirely rostral to VAC. The cmc flanks VAC, but lies entirely anterior to the VPC (Fig. 3.20).

BA 24c and 24d (cmr and cmc) are heterotypical agranular motor cortices (ZILLES et al. 1996). In fine detail, both cmr and cmc appear heterogeneous, leading to further subdivisions of their cytoarchitecture and nomenclature (ZILLES et al. 1996). Compared with BA 24c, BA 24d shows a thinner overall width of layer V, clearer borders between layers III and V, larger cells in layers III and VI, and, larger cells in layer V.

The CMA exhibits crude somatotopy with multiple representations of the body (FREUND 1996b). BA 24c includes representations of the head and the forelimbs (FREUND 1996b). Posterior to BA 24c, BA 24d has representations for the forelimbs and the hindlimbs, but with the forelimbs situated caudal to the hindlimbs (LUPPINO et al. 1991). Thus, the CMA (cmr and cmc) exhibits mixed somatotopy that is partially reversed from that seen in the SMA and in the pre-SMA (FREUND 1996b; LUPPINO et al. 1991; ZILLES et al. 1996).

The CMA projects directly to M1 with somatotopic organization (SHIMA et al. 1991). CMA fibres also project directly to the spinal cord (SHIMA et al. 1991). Stimulation of the CMA causes contralateral or bilateral movements of the lower and the upper extremities (FREUND 1996b). Single-cell studies in macaques show that more than 60% of CMA motoneurons fire before movement-related activity (SHIMA et al. 1991). Most are involved in simple movements of the distal forelimb. These cells may show either a short lead time or a long lead time between

firing and action. Long lead time cells (500 ms to 2 s) are more common in the anterior than the posterior cingulate area and show this long lead time in response to self-paced tasks, not stimulus-triggered tasks. Few CMA cells respond to visual, auditory, or tactile stimuli. Overall, the anterior CMA appears to be significant for self-paced internally guided tasks. According to PAUS et al. (1993), the anterior CMA participates in motor control by facilitating the execution of appropriate responses or by suppressing the execution of inappropriate responses.

The zone designated rostral CMA (cmr) is involved with autonomic function. Cells project to the hypothalamus and periaqueductal gray matter. Stimulation of cmr causes nonvolitional vocalization and fear reactions involving the heart, gut, bladder, and genitalia (JURGENS 1983; NIMCHINSKY et al. 1995, 1997; NAIDICH et al. 2001b; VOGT BA et al. 1995, 1997).

3.5.3.5

Premotor Area

The pre-motor area (pre-MA) may be designated M2. It extends along the frontal convexity to occupy contiguous portions of the superior frontal gyrus, the middle frontal gyrus, and the precentral gyrus (Figs. 3.19 and 3.20). The dorsal pre-MA lies within the posterior portions of the superior and middle frontal gyri. The ventral pre-MA occupies the anterior face and part of the crown of the precentral gyrus anterior to the primary motor area (M1). Like M1, the ventral portion of pre-MA progressively tapers inferiorly. An additional small area, BA 6b, lies further inferiorly, superior to the sylvian fissure and anterior to the motor face area. The pre-MA corresponds to BA 6a α (convexity), BA 6a β (convexity) and BA 6b (CARPENTER and SUTIN 1983).

The pre-MA is a heterotypical agranular isocortex with large, well-formed pyramidal cells in layers III and V. Betz's cells are absent. Large pyramidal cells that resemble Betz's cells are present in the border zone abutting onto BA 4 posteriorly, but these cannot be designated Betz's cells, by definition. Granule cell layer IV is thin and difficult to discern. The pre-MA exhibits somatotopy that is similar to, but cruder than, the motor homunculus of the primary motor cortex (M1; BA 4).

Stimulation of BA 6a α (convexity) causes responses similar to those elicited by stimulation of the primary motor cortex M1 (BA 4), but requires higher current to elicit the response. Stimulation of

BA 6a β (convexity) elicits more general movement patterns, characterized by abduction and elevation of the arm (frequently associated with rotation of the head, eyes, and trunk to the opposite side). Stimulation of the leg region causes synergic patterns of flexion and extension of the contralateral extremity (CARPENTER and SUTIN 1983; FREUND 1996a). These movements resemble the effect of stimulating the SMA (FREUND 1996a). Stimulation of BA 6b produces rhythmic, coordinated, complex movements of the face, masticatory, and laryngeal and pharyngeal musculature (CARPENTER and SUTIN 1983). Like the pre-SMA, the pre-MA contains cells that fire before a motion is initiated and that appear to determine the usage of the extremities: right, left, or both (TANJI et al. 1987, 1988). Intracellular recordings in monkeys indicate that 48% of motor-related pre-MA neurons fire before all types of motion. Of motor-related pre-MA neurons, 18% fire exclusively before decisions as to the laterality of subsequent activity, not in relation to the performance of the movement (TANJI et al. 1987, 1988). The pre-MA responds more to visual signals and is active in visually guided sequential movements. The pre-MA appears active (i) during mental preparation for a motor task directed by verbal instructions; (ii) when voluntary movements are performed under somatosensory, auditory, or visual guidance; and (iii) when sensory input is necessary to execute the task. The pre-MA appears especially active when a new motor program is established or an old motor program is modified on the basis of new sensory input (ROLAND et al. 1980a, b). In monkeys, some of the neurons seem to be stimulated both in performing a task and in observing a similar task being performed by the experimenter (especially when the monkey uses manual or oral "observation"). These neurons are designated mirror neurons (GALLESE et al. 1996; NAIDICH et al. 2001b).

3.5.3.6

Prefrontal Cortex (pre-FC)

The term prefrontal cortex designates the cortex that is situated anterior to the pre-MA, corresponding to BA 9, BA 10, and BA 46. It lies along the frontal convexity in the superior and middle frontal gyri and extends onto the medial surface of the frontal lobe along the superior (medial) frontal gyrus (Figs. 3.3, 3.16, and 3.17). The pre-FC is a homolateral frontal type of isocortex characterized by a more-or-less clearly recognizable granule cell layer IV and an

absence of Betz cells (ZILLES et al. 1996). No somatotopy is known.

The pre-FC is involved with executive functions, behaviour, and memory. Brodmann's area 46 on the dorsolateral pre-FC appears to be involved with the selection of items, whether selecting different items from an internal memory of possible tasks or selecting freely between movements needed to perform a voluntary action (ROWE et al. 2000). Right dorsolateral pre-FC (BA 9 and BA 46) is involved in decisions of what to do and when to do it (MARSDEN et al. 1996; PASSINGHAM 1996). Neurons of the pre-FC are involved with inhibitory responses to stimuli that require a delay in the motor responses (GILMAN and NEWMAN 1996). They are thought to integrate motivational elements with complex sensorimotor stimuli (GILMAN and NEWMAN 1996). HASEGAWA et al. (2000) have detected pre-FC neurons that appear to track long periods of time (as long as 30 s). Activity of these cells correlates with success of past or future performance of complex tasks, not the immediate activity. These cells may set the tone for general behaviour, in a fashion similar to that accomplished by stimulants, enthusiasm, arousal, or fatigue (HASEGAWA et al. 2000). Using PET measurement of rCBF during a simple motor task of sequential opposition of the thumb to each finger, KAWASHIMA et al. (1993) showed activation of the contralateral pre-FC for both right and left-handed tasks. Tasks performed with the nondominant hand, however, additionally activated the ipsilateral primary motor area and ipsilateral pre-FC. Thus, the pre-FC exhibits asymmetric activity with dominant or nondominant simple motor tasks (NAIDICH et al. 2001b).

3.5.3.7

Broca's Area

Broca's area is the motor speech area. It conforms to BA 44 and to the posterior portion of BA 45. Broca's area occupies the inferior frontal gyrus (*pars opercularis* and a small posterior portion of *pars triangularis*) in the dominant hemisphere. Some data indicate that many women, but not men, have motor speech areas in the inferior frontal gyri bilaterally (PUGH et al. 1996; SHAYWITZ et al. 1995). The motor speech area traditionally assigned to the inferior frontal gyrus has recently been suggested to lie instead in the anterior insula (PRICE 2000). Broca's area is a heterotypical agranular isocortex, characterized by reduced thickness of the granule cell layer IV and by the presence of large pyramidal

cells in layers III and V. Betz cells are absent. No somatotopy is known.

Broca's area is believed to generate the signals for the musculature to produce meaningful sound. It may also be involved in the initiation of speech (ALEXANDER et al. 1989; DEMONET et al. 1992), the organization of articulatory sequences (DEMONET et al. 1992), and in the covert formation of speech (inner speech). Lesions of Broca's area are associated with a form of aphasia termed, variably, motor aphasia, anterior aphasia, non-fluent aphasia, executive aphasia and Broca's aphasia. Patients who have this form of aphasia exhibit difficulty with the production of speech, and therefore, produce little speech. The speech produced is emitted slowly, with great effort and with poor articulation (GESCHWIND 1970). There are phonemic deficits. Small grammatical words and word endings are omitted (GESCHWIND 1970). There is a characteristic, comparable disorder in their written output. Surprisingly, these patients may retain musical ability and, despite severe motor aphasia, may sing melodies correctly and even elegantly (GESCHWIND 1970). Patients who have Broca's aphasia maintain good comprehension of the spoken and written language. Patients who have lesions restricted to the traditional Broca's area in the inferior frontal gyrus do not exhibit persisting speech apraxia (DRONKERS 1996). Recovery after Broca's aphasia appears to involve a transient shift of function to the right hemisphere, followed by a return to normal laterality (NEVILLE and BAVELIER 1998). A new capability for speech production has been observed to arise within the right hemisphere of an adult several years after corpus callosotomy (NEVILLE and BAVELIER 1998).

Broca's area and its right hemispheric homologue are also involved with auditory hallucinations (CLEGHORN et al. 1990; LENNOX et al. 2000; MCGUIRE et al. 1993). Schizophrenics experiencing auditory hallucinations show increased metabolism and activation in Broca's area, the left anterior cingulate region, and the left and right superior temporal regions, among other sites (CLEGHORN et al. 1990; LENNOX et al. 2000; MCGUIRE et al. 1993).

3.5.3.8

Dronkers' Area

Dronkers' area (DRONKERS 1996) has no other specific designation. Brodmann did not parcelate nor number the insular cortex in his final work. Dronkers' area occupies the precentral gyrus of

the anterior lobule of the insula. The cortex is a heterotypical agranular isocortex, characterized by a poorly defined layer IV and medium-sized pyramids in layers III and V. No somatotopy has yet been established.

Electrocortical stimulation of the insula during epilepsy surgery has been reported to cause word finding difficulties, but the specific site on the insula was not specified (OJEMANN and WHITAKER 1978). The anterior insula has been suggested to be the true site of the function that Broca ascribed to the inferior frontal gyrus (PRICE 2000). Lesions of the precentral gyrus of the insula are associated with speech apraxia (Fig. 3.21). This is a disorder of the motor planning of speech, i.e., a disorder in programming the speech musculature to produce correct sounds in the correct order with the correct timing (DRONKERS 1996). Such patients exhibit inconsistent articulatory errors that approximate the target word. They grope toward the desired word with disruption of prosody and rate (DRONKERS 1996). These patients maintain good perception of language and can perceive and recognize speech sounds, including their own articulatory errors.

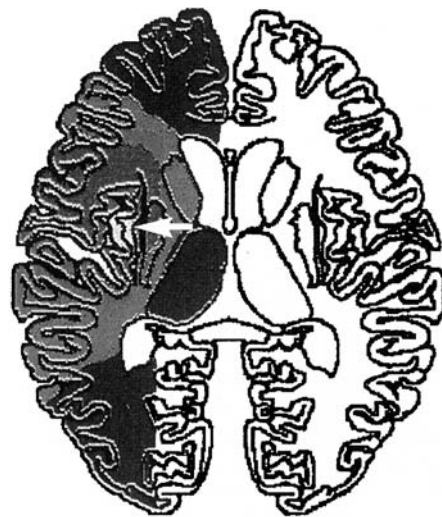


Fig. 3.21. Speech apraxia. Complete double dissociation in Dronkers' area. Pooled data from 25 patients with speech apraxia show that the only region of involvement common to all cases is the precentral gyrus (white arrow) of the insula. Pooled data from 19 other patients with similar infarctions but no speech apraxia showed no involvement in this same area. (From Dronkers NF: A new brain region for coordinating speech articulation. *Nature* 384:159–161, 1996; with permission)

An alternate conception of speech apraxia is that it represents a disorder in temporal co-ordination that disrupts the timing or the integration of movements between two independent articulators. Speech apraxia is distinct from oral apraxia. Oral apraxia is a defect in planning and performing voluntary oral movements with the muscles of the larynx, pharynx, lips and cheeks, although automatic movements of the same muscles are preserved (TOGNOLA and VIGNOLO 1980). Oral apraxia often co-exists with speech apraxia and has been related to lesions in the left frontal and central opercula, in the anterior insula, and in a small area of the STG (DRONKERS 1996; TOGNOLA and VIGNOLO 1980). The insula has also been reported to be involved in conductive aphasia and Broca's aphasia, where articulatory errors are prominent (DRONKERS 1996).

3.5.3.9

Sensory Appreciation of Speech

The sensory speech area may be designated Wernicke's area (WA). The site(s) of Wernicke's area are very poorly defined (ROLAND 1999). Most of WA appears to lie along the most caudal part of BA 22 in the STG and the planum temporale (area tpt of Galaburda and Sanides (GALABURDA and SANIDES 1980) or TA 1 of VON ECONOMO and KOSKINAS (1925). Wernicke's area also includes part of the multimodal belt in the STS (NIEUWENHUYNS 1994; NIEUWENHUYNS et al. 1988). Thus, one may also include in WA BA 40, BA 39, BA 22 and BA 37. Anatomically, WA is the

least well-defined area, largely due to the significant variation in gyral and sulcal anatomy of this region of the brain (VON ECONOMO and KOSKINAS 1925). In most individuals, WA involves parts of the dominant hemisphere around the posterior sylvian fissure, i.e., the SMG, the angular gyrus, the bases of the STG and the MTG and the planum temporale. Price reports that the role ascribed by Wernicke to WA is actually found along the posterior superior TS (PRICE 2000). Cytoarchitectonically, Wernicke's area is a homotypical granular cortex.

Wernicke's area serves to recognize speech relayed to it from the left HG. Direct cortical stimulation of WA intraoperatively causes impairment of language (OJEMANN et al. 1989; OJEMANN 1983; OJEMANN and WHITAKER 1978). Patients who have lesions in WA exhibit a form of aphasia designated, variably, sensory aphasia, fluent aphasia, posterior aphasia and Wernicke's aphasia. These patients produce speech fluently, effortlessly and rapidly, often too rapidly. The output has the rhythm and melody of normal speech, but is remarkably empty of content. These patients show poor comprehension of language and poor ability to repeat language. They use poor grammar and exhibit many errors in word usage (termed *paraphrasias*), including well-articulated replacements of simple sounds, such as spoot for spoon (GESCHWIND 1970). Patients who have Wernicke's aphasia show the same errors in written output. Recovery of function after Wernicke's aphasia appears to involve a long lasting shift of function to the right hemisphere (NAIDICH et al. 2001a).

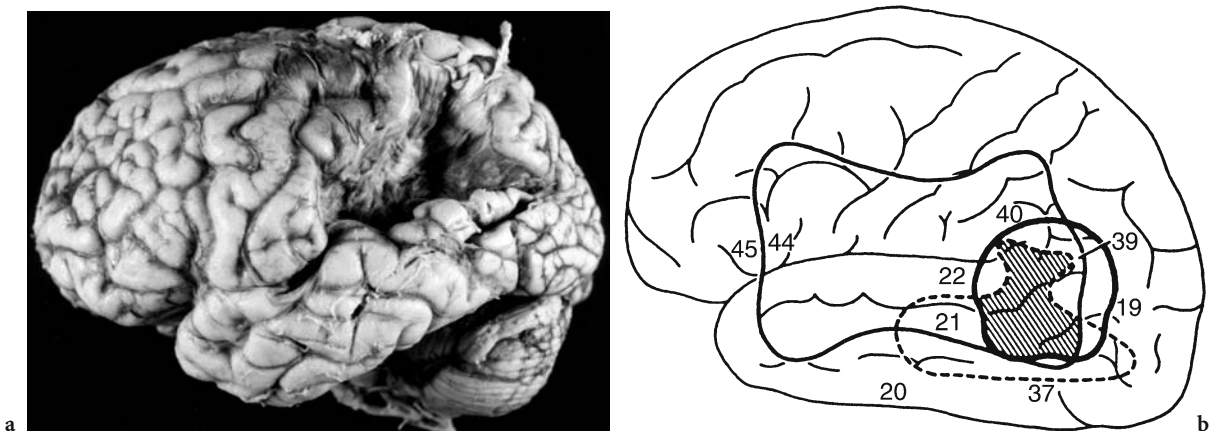


Fig. 3.22a,b. Lesions of the posterior language area. **a** Large depressed area representing an old infarction of the temporo-parietal language area in the dominant left hemisphere. **b** Site of pure semantic deficit for single word comprehension. Area of *broken line* indicates the cortical projection of an extensive subcortical hematoma cavity. (From Hart J Jr, Gordon B: Delineation of single-word semantic comprehension deficits in aphasia, with anatomical correlation. *Ann Neurol* 27:226–231, 1990; with permission)



Fig. 3.23. The arcuate fasciculus interconnects the language areas. Immediately deep to the gyri and sulci of the language areas lie interconnecting fiber tracts, specifically: the arcuate fasciculus (1), extreme capsule (2), inferior longitudinal fasciculus (5), short association fibers (6), superior longitudinal fasciculus (7), and uncinate fasciculus (9); 8 = temporal pole. (From England MA, Wakely J. Color atlas of the brain and spinal cord. St Louis, Mosby Year Book 1991, p 95, with permission)

3.5.3.10

Interconnection of Speech Areas: Arcuate Fasciculus

The term *arcuate fasciculus* signifies a broad bundle of fibers that interconnects WA with Broca's area. The arcuate fasciculus may also be designated the anterior limb of the superior longitudinal fasciculus (NIEUWENHUYSES et al. 1988). It extends between BA 22 and BA 44. The arcuate fasciculus courses from the posterior temporal lobe around the posterior edge of the sylvian fissure to the inferior parietal lobule deep to the SMG and then forward deep to the insula to reach the inferior frontal gyrus. More rostral parts of the STG are also connected with successively more rostral parts of the prefrontal cortex (NIEUWENHUYSES et al. 1988). The temporal pole is connected with the medial frontal and orbitofrontal cortices through the uncinate fasciculus (NIEUWENHUYSES et al. 1988). The auditory association areas, particularly the rostral areas, establish connections with the paralimbic cortex of the cingulate gyrus and the PHG (NIEUWENHUYSES et al. 1988). No myelotopy has yet been determined.

Lesions of the arcuate fasciculus disconnect Wernicke's area from Broca's area, causing a conduction aphasia (Figs. 3.22 and 3.23). Patients who have conduction aphasia exhibit good comprehension of the spoken language (WA intact) and fluency of speech (Broca's area intact), but have phonetic errors and

poor ability to repeat language. The patient has fluent paraphasic speech and writing with good comprehension of spoken and written language (GESCHWIND 1970). The inability to repeat speech indicates disruption of the arcuate fasciculus. The disorder in repetition is greatest for the small grammatical words (the, if, is). Repetition of numbers is relatively preserved (NAIDICH et al. 2001a).

3.6

Conclusion

Understanding of the structure and function of the brain depends, in part, on an understanding of the basic anatomic structure of the parts, the cytoarchitecture of the cortex, the functional somatotopy, and the interconnections and dominances among the diverse regions. This chapter has tried to present some of the relevant data and to provide a guide to our current, necessarily limited, understanding of brain function. It is hoped that it may serve as one foundation for advances in understanding the brain.

References

- Albanese E, Merlo A, Albanese A, Gomez E (1989) Anterior speech region. Asymmetry and weight-surface correlation. *Arch Neurol* 46:307–310
- Alexander MP, Hiltbrunner B, Fischer RS (1989) Distributed anatomy of transcortical sensory aphasia. *Arch Neurol* 46:885–892
- Allison JD, Meador KJ, Loring DW, Figueroa RE, Wright JC (2000) Functional MRI cerebral activation and deactivation during finger movement. *Neurology* 54:135–142
- Asanuma H, Okuda O (1962) Effects of transcallosal volleys on pyramidal tract cell activity of cat. *J Neurophysiol* 25:198–208
- Brodmann K (1909) *Vergleichende Lokalisationlehre der Grosshirnrinde*. Verlag von Johann Ambrosius Barth, Leipzig
- Brust JC (1996) Lesions of the supplementary motor area. *Adv Neurol* 70:237–248
- Burton DB, Chelune GJ, Naugle RI, Bleasel A (1996) Neurocognitive studies in patients with supplementary sensorimotor area lesions. *Adv Neurol* 70:249–261
- Carpenter MB, Sutin J (1983) Human neuroanatomy. In the cerebral cortex. Williams and Wilkins, Baltimore, pp 643–705
- Chauvel PY, Rey M, Buser P, Bancaud J (1996) What stimulation of the supplementary motor area in humans tells

- about its functional organization. *Adv Neurol* 70:199–209
- Cleghorn JM, Garnett ES, Nahmias C, Brown GM, Kaplan RD, Szechtman H et al. (1990) Regional brain metabolism during auditory hallucinations in chronic schizophrenia. *Br J Psychiatry* 157:562–570
- Dejerine J (1895) *Anatomie des centres nerveux*. Rueff et Cie, Paris
- Demonet JF, Chollet F, Ramsay S, Cardebat D, Nespoulous JL, Wise R et al. (1992) The anatomy of phonological and semantic processing in normal subjects. *Brain* 115:1753–1768
- Dronkers NF (1996) A new brain region for coordinating speech articulation. *Nature* 384:159–161
- Duvernoy H (1991) *The human brain: surface. Three-dimensional sectional anatomy and MRI*. Springer, Berlin Heidelberg New York
- Freund HJ (1996a) Functional organization of the human supplementary motor area and dorsolateral premotor cortex. *Adv Neurol* 70:263–269
- Freund HJ (1996b) Historical overview. *Adv Neurol* 70:17–27
- Freund HJ, Hummelsheim H (1985) Lesions of premotor cortex in man. *Brain* 108:697–733
- Fried I (1996) Electrical stimulation of the supplementary sensorimotor area. *Adv Neurol* 70:177–185
- Fried I, Katz A, McCarthy G, Sass KJ, Williamson P, Spencer SS et al. (1991) Functional organization of human supplementary motor cortex studied by electrical stimulation. *J Neurosci* 11:3656–3666
- Galaburda A, Sanides F (1980) Cytoarchitectonic organization of the human auditory cortex. *J Comp Neurol* 190:597–610
- Galaburda AM, LeMay M, Kemper TL (1998) Right- left asymmetries in the brain. Structural differences between the hemispheres may underlie cerebral dominance. *Science* 199:852–856
- Gallese V, Fadiga L, Fogassi L, Rizzolatti G (1996) Action recognition in the premotor cortex. *Brain* 119:593–609
- Gannon PJ, Holloway RL, Broadfield DC, Braun AR (1998) Asymmetry of chimpanzee planum temporale: human-like pattern of Wernicke's brain language area homolog. *Science* 279:220–222
- Geschwind N (1965a) Disconnexion syndromes in animals and man. I. *Brain* 88:237–294
- Geschwind N (1965b) Disconnexion syndromes in animals and man. II. *Brain* 88:585–644
- Geschwind N (1970) The organization of language and the brain. Language disorders after brain damage help in elucidating the neural basis of verbal behavior. *Science* 170:940–944
- Geschwind N, Levitsky W (1968) Human brain: left-right asymmetries in temporal speech region. *Science* 161:186–187
- Gilman S, Newman SW (1996) Manter and Gatz's essentials of clinical neuroanatomy and neurophysiology. In: *The cerebral cortex*. FA Davis, Philadelphia
- Grafton ST, Woods RP, Mazziotta JC (1993) Within-arm somatotopy in human motor areas determined by positron emission tomography imaging of cerebral blood flow. *Exp Brain Res* 95:172–176
- Graziano M, Taylor CS, Moore T (2002) Complex movements evoked by microstimulation of precentral cortex. *Neuron* 34:841–851
- Hasegawa RP, Blitz AM, Geller NL, Goldberg ME (2000) Neurons in monkey prefrontal cortex that track past or predict future performance. *Science* 290:1786–1789
- Humberstone M, Sawle GV, Clare S, Hykin J, Coxon R, Bowtell R et al. (1997) Functional magnetic resonance imaging of single motor events reveals human presupplementary motor area. *Ann Neurol* 42:632–637
- Iwasaki S, Nakagawa H, Fukusumi A, Kichikawa K, Kitamura K, Otsuji H et al. (1991) Identification of pre- and postcentral gyri on CT and MR images on the basis of the medullary pattern of cerebral white matter. *Radiology* 179:207–213
- Jensen J (1871) Die Furchen und Windungen der menschlichen Großhirnhemisphären. *Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin* 27:465–473
- Jurgens U (1983) Afferent fibers to the cingular vocalization region in the squirrel monkey. *Exp Neurol* 80:395–409
- Kawashima R, Yamada K, Kinomura S, Yamaguchi T, Matsui H, Yoshioka S et al. (1993) Regional cerebral blood flow changes of cortical motor areas and prefrontal areas in humans related to ipsilateral and contralateral hand movement. *Brain Res* 623:33–40
- Kleinschmidt A, Nitschke MF, Frahm J (1997) Somatotopy in the human motor cortex hand area. A high-resolution functional MRI study. *Eur J Neurosci* 9:2178–2186
- Kopp N, Michel F, Carrier H (1977) Etude de certaines asymétries hémisphériques du cerveau humain. *J Neurol Sci* 34:349–363
- Korogi Y, Takahashi M, Okuda T, Ikeda S, Kitajima M, Yoshizumi K et al. (1996) MR topography of the striate cortex: correlation with anatomic sections. *Int J Neuroradiol* 2:534–540
- Lennox BR, Park SB, Medley I, Morris PG, Jones PB (2000) The functional anatomy of auditory hallucinations in schizophrenia. *Psychiatry Res* 100:13–20
- Li A, Yetkin FZ, Cox R, Houghton VM (1996) Ipsilateral hemisphere activation during motor and sensory tasks. *AJNR Am J Neuroradiol* 17:651–655
- Liegeois-Chauvel C, Musolino A, Chauvel P (1991) Localization of the primary auditory area in man. *Brain* 114:139–151
- Liegeois-Chauvel C, Laguitton V, Badier JM, Schwartz D, Chauvel P (1995) [Cortical mechanisms of auditive perception in man: contribution of cerebral potentials and evoked magnetic fields by auditive stimulations]. *Rev Neurol (Paris)* 151:495–504
- Lim SH, Dinner DS, Luders HO (1996) Cortical stimulation of the supplementary sensorimotor area. *Adv Neurol* 70:187–197
- Luders HO (1996) The supplementary sensorimotor area. An overview. *Adv Neurol* 70:1–16
- Luppino G, Matelli M, Camarda RM, Gallese V, Rizzolatti G (1991) Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study in the macaque monkey. *J Comp Neurol* 311:463–482
- Marsden CD, Deecke L, Freund HJ, Hallett M, Passingham RE, Shibasaki H et al. (1996) The functions of the supplementary motor area. Summary of a workshop. *Adv Neurol* 70:477–487
- McGuire PK, Shah GM, Murray RM (1993) Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *Lancet* 342:703–706

- Meyer JR, Roychowdhury S, Russell EJ, Callahan C, Gitelman D, Mesulam MM (1996) Location of the central sulcus via cortical thickness of the precentral and postcentral gyri on MR. *AJNR Am J Neuroradiol* 17:1699–1706
- Naidich TP, Brightbill TC (1995) The intraparietal sulcus. A landmark for localization of pathology on axial CT-scans. *Int J Neuroradiol* 1:3–16
- Naidich TP, Brightbill TC (1996a) The pars marginalis: Part 1. A „bracket“ sign for the central sulcus in axial plane CT and MRI. *Int J Neuroradiol* 2:3–19
- Naidich TP, Brightbill TC (1996b) Systems for localizing fronto-parietal gyri and sulci on axial CT and MRI. *Int J Neuroradiol* 2:313–338
- Naidich TP, Valavanis AG, Kubik S (1995) Anatomic relationships along the low-middle convexity: Part I – Normal specimens and magnetic resonance imaging. *Neurosurgery* 36:517–532
- Naidich TP, Valavanis AG, Kubik S (1997) Anatomic relationships along the low-middle convexity: Part II – Lesion localization. *Int J Neuroradiol* 3:393–409
- Naidich TP, Hof PR, Gannon PJ, Yousry TA, Yousry I (2001a) Anatomic substrates of language. *Neuroimaging Clin N Am* 11:305–341
- Naidich TP, Hof PR, Yousry TA, Yousry I (2001b) The motor cortex: anatomic substrates of function. *Neuroimaging Clin N Am* 11:171–193
- Naidich TP, Kang E, Fatterpekar GM, Delman BN, Gultekin SH, Wolfe D et al. (2004) The insula: anatomic study and MR imaging display at 1.5 T. *AJNR Am J Neuroradiol* 25:222–232
- Neville HJ, Bavelier D (1998) Neural organization and plasticity of language. *Curr Opin Neurobiol* 8:254–258
- Nieuwenhuys R (1994) The human brain: an introductory survey. *MedicaMundi* 39:64–79
- Nieuwenhuys R, Voogd J, van Huijzen C (1988) The human central nervous system. A synopsis and atlas. Springer, Berlin Heidelberg New York, pp 247–292
- Nimchinsky EA, Vogt BA, Morrison JH, Hof PR (1995) Spindle neurons of the human anterior cingulate cortex. *J Comp Neurol* 355:27–37
- Nimchinsky EA, Vogt BA, Morrison JH, Hof PR (1997) Neurofilament and calcium-binding proteins in the human cingulate cortex. *J Comp Neurol* 384:597–620
- Ojemann GA (1983) Brain organization for language from the perspective of electrical stimulation mapping. *Behav Brain Sci* 6:189–230
- Ojemann GA, Whitaker HA (1978) Language localization and variability. *Brain Lang* 6:239–260
- Ojemann G, Ojemann J, Lettich E, Berger M (1989) Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg* 71:316–326
- Olivier A (1996) Surgical strategies for patients with supplementary sensorimotor area epilepsy. The Montreal experience. *Adv Neurol* 70:429–443
- Ono O, Kubik S, Abernathy CD (1990) Atlas of the cerebral sulci. Atlas of the cerebral sulci. Thieme, New York
- Passingham RE (1996) Functional specialization of the supplementary motor area in monkeys and humans. *Adv Neurol* 70:105–116
- Paus T, Petrides M, Evans AC, Meyer E (1993) Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J Neurophysiol* 70:453–469
- Penfield W, Welch K (1951) The supplementary motor area of the cerebral cortex; a clinical and experimental study. *AMA Arch Neurol Psychiatry* 66:289–317
- Pieniadz JM, Naeser MA (1984) Computed tomographic scan cerebral asymmetries and morphologic brain asymmetries. Correlation in the same cases post mortem. *Arch Neurol* 41:403–409
- Price CJ (2000) The anatomy of language: contributions from functional neuroimaging. *J Anat* 197:335–359
- Pugh KR, Shaywitz BA, Shaywitz SE, Constable RT, Skudlarski P, Fulbright RK et al. (1996) Cerebral organization of component processes in reading. *Brain* 119:1221–1238
- Rao SM, Binder JR, Bandettini PA, Hammeke TA, Yetkin FZ, Jesmanowicz A et al. (1993) Functional magnetic resonance imaging of complex human movements. *Neurology* 43:2311–2318
- Rizzolatti G, Luppino G, Matelli M (1996) The classic supplementary motor area is formed by two independent areas. *Adv Neurol* 70:45–56
- Roland PE (1999) Brain activation. In: Motor functions. Language. Wiley, New York, pp 269–290
- Roland PE, Larsen B, Lassen NA, Skinhoj E (1980a) Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J Neurophysiol* 43:118–136
- Roland PE, Skinhoj E, Lassen NA, Larsen B (1980b) Different cortical areas in man in organization of voluntary movements in extrapersonal space. *J Neurophysiol* 43:137–150
- Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE (2000) The prefrontal cortex: response selection or maintenance within working memory? *Science* 288:1656–1660
- Rumeau C, Tzourio N, Murayama N, Peretti-Viton P, Levrier O, Joliot M et al. (1994) Location of hand function in the sensorimotor cortex: MR and functional correlation. *AJNR Am J Neuroradiol* 15:567–572
- Schwalbe G (1881) Lehrbuch der neurologie. Verlag von Eduard Besold, Erlangen
- Seitz RJ, Schlaug G, Knorr U, Steinmetz H, Tellmann L, Herzog H (1996) Neurophysiology of the human supplementary motor area. Positron emission tomography. *Adv Neurol* 70:167–175
- Shaywitz BA, Shaywitz SE, Pugh KR, Constable RT, Skudlarski P, Fulbright RK et al. (1995) Sex differences in the functional organization of the brain for language. *Nature* 373:607–609
- Shibasaki H, Sadato N, Lyshkow H, Yonekura Y, Honda M, Nagamine T et al. (1993) Both primary motor cortex and supplementary motor area play an important role in complex finger movement. *Brain* 116:1387–1398
- Shima K, Aya K, Mushiake H, Inase M, Aizawa H, Tanji J (1991) Two movement-related foci in the primate cingulate cortex observed in signal-triggered and self-paced forelimb movements. *J Neurophysiol* 65:188–202
- Sobel DF, Gallen CC, Schwartz BJ, Waltz TA, Copeland B, Yamada S et al. (1993) Locating the central sulcus: comparison of MR anatomic and magnetoencephalographic functional methods. *AJNR Am J Neuroradiol* 14:915–925
- Steinmetz H, Seitz RJ (1991) Functional anatomy of language processing: neuroimaging and the problem of individual variability. *Neuropsychologia* 29:1149–1161
- Steinmetz H, Furst G, Freund HJ (1989a) Cerebral cortical localization: application and validation of the proportional grid system in MR imaging. *J Comput Assist Tomogr* 13:10–19

- Steinmetz H, Rademacher J, Huang YX, Heftner H, Zilles K, Thron A et al. (1989b) Cerebral asymmetry: MR planimetry of the human planum temporale. *J Comput Assist Tomogr* 13:996–1005
- Steinmetz H, Ebeling U, Huang YX, Kahn T (1990a) Sulcus topography of the parietal opercular region: an anatomic and MR study. *Brain Lang* 38:515–533
- Steinmetz H, Rademacher J, Jancke L, Huang YX, Thron A, Zilles K (1990b) Total surface of temporoparietal intrasylvian cortex: diverging left-right asymmetries. *Brain Lang* 39:357–372
- Steinmetz H, Volkman J, Jancke L, Freund HJ (1991) Anatomical left-right asymmetry of language-related temporal cortex is different in left- and right-handers. *Ann Neurol* 29:315–319
- Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. 3-Dimensional proportional system. An approach to cerebral imaging. Thieme, New York
- Tanji J (1994) The supplementary motor area in the cerebral cortex. *Neurosci Res* 19:251–268
- Tanji J, Shima K (1994) Role for supplementary motor area cells in planning several movements ahead. *Nature* 371:413–416
- Tanji J, Okano K, Sato KC (1987) Relation of neurons in the nonprimary motor cortex to bilateral hand movement. *Nature* 327:618–620
- Tanji J, Okano K, Sato KC (1988) Neuronal activity in cortical motor areas related to ipsilateral, contralateral, and bilateral digit movements of the monkey. *J Neurophysiol* 60:325–343
- Tognola G, Vignolo LA (1980) Brain lesions associated with oral apraxia in stroke patients: a clinico-neuroradiological investigation with the CT scan. *Neuropsychologia* 18:257–272
- Ture U, Yasargil MG, Al-Mefty O, Yasargil MG (1999) Topographic anatomy of the insular region. *J Neurosurg* 90:720–733
- Viallet F, Massion J, Massarino R, Khalil R (1992) Coordination between posture and movement in a bimanual load lifting task: putative role of a medial frontal region including the supplementary motor area. *Exp Brain Res* 88:674–684
- Vogt BA, Nimchinsky EA, Vogt LJ, Hof PR (1995) Human cingulate cortex: surface features, flat maps, and cytoarchitecture. *J Comp Neurol* 359:490–506
- Vogt BA, Vogt LJ, Nimchinsky EA (1997) Primate cingulate cortex chemoarchitecture and its disruption in Alzheimer's disease. In: Bloom FE, Bjorklund A, Hokfelt T (eds) *Handbook of chemical neuroanatomy*. Vol 13. Elsevier Science, Amsterdam, pp 455–528
- Vogt C, Vogt O (1919) Allgemeinere ergebnisse unserer hirnforschung. *J Psychol Neurol* 25:279–461
- Vogt O, Vogt C (1926) Die vergleichend-architektonische und vergleichend-reizphysiologische feldung der grobhirnrinde unter besonderer berücksichtigung der menschlichen. *Naturwissenschaften* 14:1190–1194
- von Economo C, Koskinas GN (1925) *Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen*. Springer, Berlin Heidelberg New York
- Williams PL, Warwick R, Dyson M (1989) *Grays anatomy*. Churchill Livingstone, New York
- Yasargil MG (1994) *Microneurosurgery*. Thieme, Stuttgart
- Yoshiura T, Higano S, Rubio A, Shrier DA, Kwok WE, Iwanaga S et al. (2000) Heschl and superior temporal gyri: low signal intensity of the cortex on T2-weighted MR images of the normal brain. *Radiology* 214:217–221
- Yousry TA (1998) Historical perspective: The cerebral lobes and their boundaries. *Int J Neuroradiol* 4:342–348
- Yousry TA, Schmid UD, Jassoy AG, Schmidt D, Eisner WE, Reulen HJ et al. (1995) Topography of the cortical motor hand area: prospective study with functional MR imaging and direct motor mapping at surgery. *Radiology* 195:23–29
- Yousry TA, Schmid UD, Schmidt D, Hagen T, Jassoy A, Reiser MF (1996) The central sulcal vein: a landmark for identification of the central sulcus using functional magnetic resonance imaging. *J Neurosurg* 85:608–617
- Yousry TA, Fesl G, Buttner A (1997a) Heschl's Gyrus: anatomic description and methods of identification on magnetic resonance imaging. *Int J Neuroradiol* 3:2–12
- Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A et al. (1997b) Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain* 120:141–157
- Yousry TA, Yousry I, Naidich TP (2001) Progress in neuroanatomy. In: Demaerel P (ed) *Recent advances in diagnostic neuroradiology*. Springer, Berlin Heidelberg New York
- Zilles K, Schlaug G, Geyer S, Luppino G, Matelli M, Qu M et al. (1996) Anatomy and transmitter receptors of the supplementary motor areas in the human and nonhuman primate brain. *Adv Neurol* 70:29–43

Presurgical Functional MRI in Patients with Brain Tumors

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KEY POINTS

Neurosurgery in functionally important brain sites carries a high risk for surgery induced neurological deficits. In patients with brain tumors fMRI facilitates the selection of a safe treatment and to plan and perform function preserving surgery. However, fMRI has not yet reached the status of an established and standardized diagnostic neuroimaging procedure and still needs to be performed in clinical research trials. Preoperative fMRI is performed exclusively in individual patients and therefore differs fundamentally from research applications in the neurosciences.

Besides reviews of the current literature optimized presurgical fMRI protocols for motor, somatosensory and language function are presented, along with a standardized data evaluation routine using a dynamic statistical threshold. Examples of physiological brain activation are given. Criteria for selecting candidates for presurgical fMRI are proposed. Illustrative cases demonstrate typical and atypical presurgical fMRI findings. Important diagnostic capabilities and limitations of presurgical fMRI are discussed.

In conclusion fMRI is feasible for clinical routine neuroimaging and provides important diagnostic information noninvasively that is otherwise unavailable. Preoperative fMRI is valid and reasonably accurate to localize the different representations of the human body in the primary motor and somatosensory cortex prior to brain tumor surgery, which in general holds also true for language localization and lateralization. The number of studies on presurgical language fMRI is still limited, however, and the results are more heterogeneous. Here fMRI has at least potential to help reducing the number of invasive diagnostic measures needed. If, and to what extent, intraoperative electrocorticography or Wada-test can be replaced is not yet clear.

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4.1

Brain Tumors and Brain Tumor Surgery

The incidence of brain tumors has been estimated at 7–10 persons per 100,000 inhabitants (PARKIN and MUIR 1992). Roughly 80% of the patients with malignant brain tumors die from the disease (LANDIS et al. 1999) and only half of the patients survive longer than one year (DAVIS et al. 1998; DAVIS, MCCARTHY and JUKICH 1999; DAVIS et al. 1999). By means of histology, brain tumors can be classified as “primary” arising from the brain and its linings or as “secondary” metastatic disease affecting the CNS predominantly from lung, breast, kidney, gastrointestinal and skin cancer. In adults, primary and secondary brain tumors can be approximated equiprevalent, whereas in children metastatic disease is rare.

Extraaxial tumors are typically noninvasive and affect the brain by displacement or compression. Clinical symptoms may also be related to occlusive hydrocephalus caused by impaired circulation of cerebrospinal fluid (CSF) due to compression of ventricles or connecting foramina. The primary goal of treatment is complete removal. Intraaxial tumors grow inside the brains parenchyma. The spectrum of appearance is wide – from focal and well defined masses to diffusely infiltrating processes. Clinical signs and symptoms depend mainly on location and mass effect. According to protocols of the World Health Organization (WHO) brain tumors are classified based on the cells of origin – nine basic groups have been defined (OSBORN 2004). About half of the primary brain tumors are of glial origin – a four tiered grading system has been established based on pleomorphism, mitotic activity, endothelial proliferation and necrosis. Most gliomas are infiltrative and have ill defined margins making a complete surgical removal often impossible. Patients with low grade gliomas have a median survival of 6–10 years, but these tumors tend to a malignant transformation. The average survival of patients with glioblastoma multiforme is in the range of several months, comparable to primary CNS lymphoma or metastatic disease where prolonged survival is rather exceptional.

The treatment of brain tumors and metastases is traditionally based on surgery, radiation oncology and chemotherapy or a combination of these treatments, tailored to target location and pathology. More recently cellular and molecular biology has entered the field to open up new diagnostic and ther-

apeutic options. Modern neuroimaging – based on morphological, metabolic and functional measures – provides very detailed diagnostic information on intracranial pathologies and has helped to guide and refine treatment and to estimate procedural risks and prognosis (JACOBS et al. 2005). Reduction of morbidity associated with treatment is of utmost importance, which holds true especially for patients where complete removal of the pathology is impossible and cure cannot be achieved. Here neurosurgery aims to eliminate as much of the tumor as safely possible by maintaining important functions of the brain. To achieve this, cutting edge technology is applied for image guided neurosurgery and functional neuronavigation (NIMSKY et al. 2006).

4.2

Presurgical Functional Neuroimaging – Rationale and Diagnostic Aims

Neurosurgical procedures in or next to functionally relevant brain structures invariably carry the risk of surgery-induced post-operative neurological deficits. Although undoubtedly all brain areas are in some way of functional importance, in clinical practice the term of “functionally relevant” or “eloquent” brain region refers to those brain structures where damage can result in severe neurological symptoms and consequently in a significant reduction of the patient’s life quality. Resection of the so called “rolandic” or “central” brain tumors, for example, can lead to injury of the primary motor and somatosensory cortices and therefore cause permanent movement and sensibility impairments. Patients with frontal or temporal lesions of the left hemisphere are particularly prone to suffer from post-operative motor or sensory language deficits, while mesiotemporal interventions can entrain memory dysfunction. Therefore, the indication for neurosurgery in such patients has to be put restrictively and other, less invasive, therapeutic options like radiotherapy or neuroradiological intervention – as in the case of vascular malformations – have to be taken into consideration. This holds true especially in patients where curative treatment is not possible. Here the preservation of brain function and the reduction of morbidity associated with the treatment are crucial. Prudent individual choice of optimal surgical access and resection borders for

each patient can be of utmost importance to avoid damage to functionally relevant brain structures (DUFFAU 2006). Similar to brain tumor surgery, epilepsy surgery aims at complete removal of epileptogenic zones with minimized damage to eloquent brain areas (see Chap. 5). Thus, depending on the location of the pathology, the determination of hemispheric dominance and precise spatial relationship between brain tumor/epileptogenic zone and functionally relevant brain area can be mandatory for selection of the appropriate therapeutic modality and for the planning and implementation of function-preserving neurosurgical interventions. Ideally, this information should be available before therapy, which would help to reduce neurosurgical morbidity and to shorten post-operative hospitalization. In this view, functional neuroimaging not only offers a variety of novel options for clinical diagnostics and research, but also opens up a new diagnostic field of neuroradiology, with a shift from strictly morphological imaging to measurement and visualization of brain function (STIPPICH et al. 2002).

The reference procedure for mapping human brain function intraoperatively is electrocorticography (ECoG) (PENFIELD W 1937; PENFIELD W 1950; WOOLSEY, ERICKSON and GILSON 1979; OJEMANN et al. 1989; OJEMANN 1991; CEDZICH et al. 1996; DUFFAU et al. 1999), consisting of electrophysiological recordings from the cerebral cortex with surface electrodes, which is a demanding technique offered only by specialized centers. Application of ECoG considerably increases surgery duration and involves distressing awake craniotomy, since mapping of language and memory related brain structures requires active collaboration of the patient. A particular disadvantage of ECoG is the fact that it is applied during surgery and thus, the results obtained cannot be incorporated in the pre-operative process of therapy selection and planning. Presurgical determination of hemispheric dominance is traditionally achieved by the invasive WADA-test (WADA and RASMUSSEN 1960; RAUSCH et al. 1993), where language and memory functions are assessed neuro-psychologically during intra-arterial injection of barbiturates. This method bears all risks of cerebral angiography, is disagreeable for the patient and goes along with several days of hospitalization. Frequently used electrophysiological methods measuring directly neuronal activity via detection of electromagnetic fields with excellent temporal resolution (ms range), are electroencephalography (EEG) (BERGER 1929; GEVINS 1995; GEVINS et al. 1995) and magnetoen-

cephalography (MEG) (HARI and ILMONIEMI 1986). However, localization of electromagnetic sources requires complicated mathematical modeling and calculations (based on single- or multipole models and various spherical head models) and is therefore limited in precision and accuracy (HÄMÄLÄINEN et al. 1993). EEG is considered the reference procedure for the delineation of epileptic activity.

The diagnostic potential of routine presurgical morphological imaging is limited with respect to localizing functionally relevant brain structures. Magnetic resonance imaging (MRI) permits detailed images of brain parenchyma and intracranial pathologies (OSBORN 2004), but no assessment of brain function. Anatomically identifiable landmarks for specific functions could be described solely for the central region (see chapter 3), and even there reliability reaches a maximum of approximately 95% in healthy volunteers (Fig. 4.1). In the presence of anatomical variants, malformations of the brain, or patients with large or vastly infiltrating tumors, these morphological landmarks are not consistently identifiable. Pathological signal changes involving the pre- or postcentral gyrus further complicate presurgical diagnostics. A trustworthy attribution of a functional representation to a defined anatomical landmark is – even with intact rolandic anatomy – only feasible for the hand motor area, showing as a correlate a characteristic dorsally oriented convexity in the precentral gyrus, the so-called “hand-knob” (YOUSRY et al. 1997). However, motor activity can also be detectable outside of typical landmarks and the pattern of motor cortex activation is modulated by different physiological factors (YOUSRY, NAIDICH and YOUSRY 2001). Other representations of the human body in the pre- or postcentral gyrus lack any reliable morphological correlate (FESL et al. 2003). Their localization can be merely estimated knowing the somatotopic organization of the rolandic cortex in motor and somatosensory homunculi (PENFIELD W 1937), (PENFIELD 1950)). Moreover, the localization and extent of activated brain sites can vary under pathological conditions as well as the pattern of brain activation. Besides local mass effects and hemodynamic alterations brain tumors and arterio-venous malformations (AVM) may also induce neuroplastic changes – a phenomenon also observed in patients with epilepsy (WUNDERLICH et al. 1998; FANDINO et al. 1999; HOLODNY et al. 1999; ALKADHI et al. 2000; BITTAR et al. 2000; DUFFAU, SICHEZ and LEHERICY 2000; HOLODNY et al. 2000; LEHERICY et al. 2000; ROUX et al. 2000; CARPENTIER et al. 2001; DUFFAU

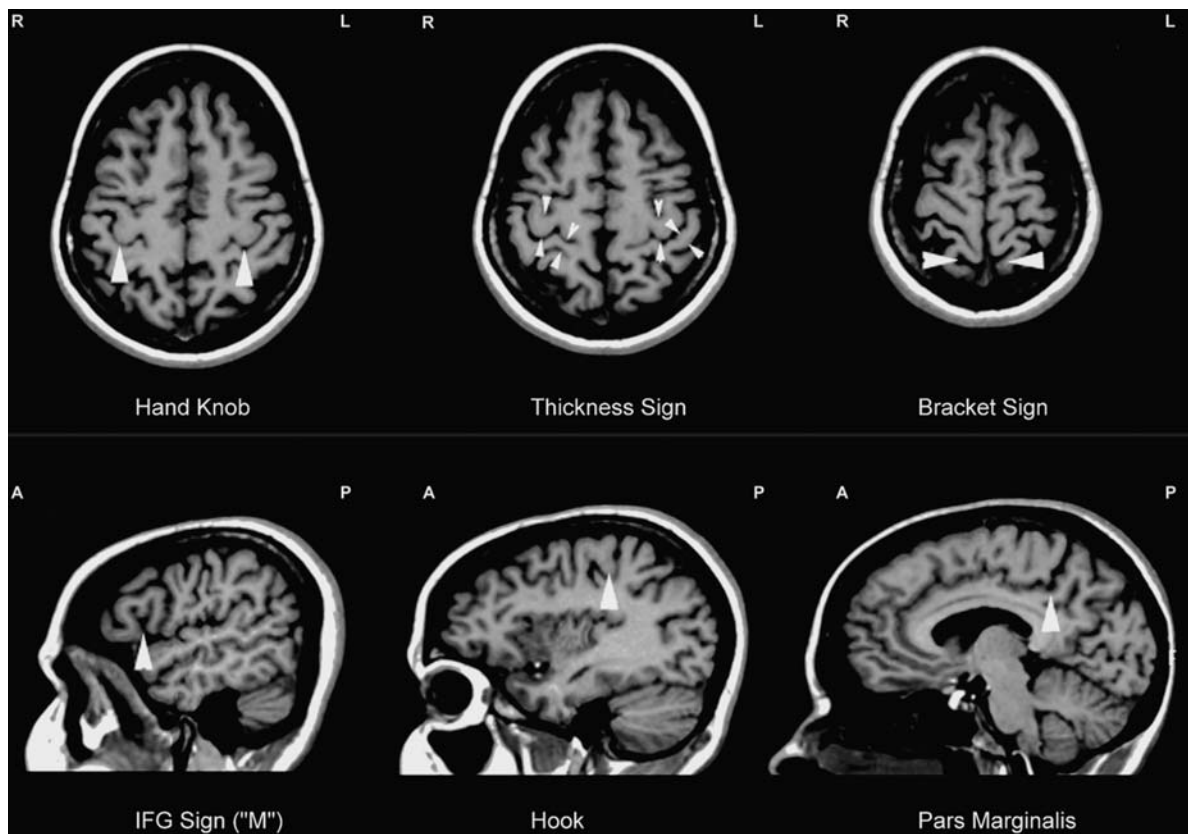


Fig. 4.1. Anatomical landmarks on morphological MRI according to Naidich and Yousry in transverse (*upper row*) and sagittal (*lower row*) views. *White arrows* indicate the relevant anatomical structures. The “hand knob” and “hook” are synonyms for the “precentral knob” (see Chap. 3). Modified from STIPPICH, KRESS et al. 2003 with permission

2001; KRINGS et al. 2002; RUTTEN et al. 2002; BACIU et al. 2003). This further holds true for language-associated brain structures (DUFFAU et al. 2001) (LAZAR et al. 1997; SPRINGER et al. 1999; SPREER et al. 2001; DUFFAU et al. 2002; DUFFAU, DENVIL and CAPELLE 2002; HERTZ-PANNIER et al. 2002; HOLODNY et al. 2002; LEHERICY et al. 2002; PETROVICH et al. 2004) which, other than motor cortex representations, display a marked anatomical variability even in the healthy subject (BOGEN JE 1976; PRICE 2000; NAIDICH et al. 2001). Additionally, many cognitive brain functions are under the influence of individual factors, such as handedness (SZAFLARSKI et al. 2002), multilinguality (BELLO et al. 2006) (HASEGAWA, CARPENTER and JUST 2002) (HERNANDEZ et al. 2001) (ILLES et al. 1999) (KIM et al. 1997) (KLEIN et al. 1995) (ROUX and TREMOULET 2002), age (GAILLARD et al. 2000; GAILLARD et al. 2001; SCHLAGGAR et al. 2002) or gender (SHAYWITZ et al. 1995; FROST et al. 1999). That variability suggests the need for functional localization tailored to the individual patient.

The use of functional neuroimaging methods is especially valuable prior to neurosurgery in rolandic (JACK et al. 1994; BAUMANN et al. 1995; YOUSRY et al. 1995; ATLAS et al. 1996; MUELLER et al. 1996; PUJOL et al. 1996; YOUSRY et al. 1996; KRINGS et al. 1997; ROUX et al. 1997; SCHLOSSER et al. 1997; STAPLETON et al. 1997; YETKIN et al. 1997; DYMARKOWSKI et al. 1998; KRINGS et al. 1998; LEE, JACK and RIEDERER 1998; NITSCHKE et al. 1998; PUJOL et al. 1998; SCHULDER et al. 1998; ACHTEN et al. 1999; LEE et al. 1999; ROUX et al. 1999; ROUX et al. 1999; HIRSCH et al. 2000; LEHERICY, DUFFAU et al. 2000; KOBER et al. 2001; KRINGS et al. 2001; OZDOBA et al. 2002; LIU, HALL and TRUWIT 2003; SCHIFFBAUER et al. 2003; STIPPICH et al. 2003; TOWLE et al. 2003; KRISHNAN et al. 2004; PARMAR, SITO and YEO 2004; REINGES et al. 2004; MAJOS et al. 2005; ROESSLER et al. 2005; VAN WESTEN et al. 2005; NIMSKY, GANSLANDT et al. 2006), frontal or temporo-parietal (DESMOND et al. 1995; BINDER et al. 1996; BAHN et al. 1997; FITZGERALD et al. 1997; HERHOLZ et al. 1997; HERTZ-PANNIER et al. 1997; WORTHINGTON

et al. 1997; VAN DER KALLEN et al. 1998; YETKIN et al. 1998; BENSON et al. 1999; BITTAR et al. 1999; BITTAR et al. 1999; KILLGORE et al. 1999; RUGE et al. 1999; RUTTEN et al. 1999; SPRINGER, BINDER et al. 1999; BAZIN et al. 2000; GRABOWSKI TJ 2000; HIRSCH, RUGE et al. 2000; LEHERICY et al. 2000; LURITO et al. 2000; GAILLARD et al. 2002; POURATIAN et al. 2002; RUTTEN et al. 2002; RUTTEN et al. 2002; ROUX et al. 2003; VAN WESTEN, SKAGERBERG et al. 2005; GRUMMICH et al. 2006; STIPPICH 2006) and mesiotemporal (DEBLAERE et al. 2002; AVILA et al. 2006) brain areas for the individual functional localization of motor, somatosensory, language- and memory-related brain activation as well as for the determination of hemispheric dominance and of epileptogenic zones. At present, functional magnetic resonance imaging (fMRI) is the most widely used method of functional neuroimaging. This modern imaging technique measures brain function indirectly (KWONG et al. 1992) with high spatial accuracy, but lower temporal resolution than EEG (GEVINS, LEONG et al. 1995) or MEG (HÄMÄLÄINEN M 1993). Advantages of fMRI over positron emission tomography (PET) (FOX et al. 1986) (MAZZIOTTA et al. 1982; RAICHLE 1983) or single-photon emission computer tomography (SPECT) (HOLMAN and DEVOUS 1992) – other methods measuring brain activity indirectly, albeit with lower spatial/temporal resolution (glucose- or oxygen-metabolism, blood flow/perfusion changes) – are its non-invasiveness, lack of radiation, repeatability and broad availability of clinical scanners.

fMRI assesses brain activity indirectly via detection of local hemodynamic changes in capillaries (MENON et al. 1995) and draining veins (FRAHM et al. 1994) of functional areas. The blood-oxygen-level-dependent (BOLD) technique makes use of blood as an intrinsic contrast agent (OGAWA et al. 1990; OGAWA et al. 1990; OGAWA et al. 1992). BOLD-signals have been shown to reflect actual neuronal activity with high spatial accuracy (LOGOTHETIS et al. 2001; LOGOTHETIS 2002; LOGOTHETIS 2003; LOGOTHETIS and PFEUFFER 2004; LOGOTHETIS and WANDELL 2004). For details please refer to Chap. 2 giving information about the physiological bases and methodological-technical aspects of fMRI also in the context of clinical applications. While fMRI was quickly established in basic neuroscience research, it is so far rarely used in clinical diagnostics and research mostly due to its higher technical and methodological requirements as compared to morphological MRI. Nowadays though, new high performance gradient systems and the development

of ultrafast MR-sequences enable examination of the entire brain in clinically apposite time. Better functionality of data processing and immediate data analysis (so-called “real time fMRI”) (WEISKOPF et al. 2003; WEISKOPF et al. 2004) facilitate the use of fMRI under clinical conditions (FERNANDEZ et al. 2001; MOLLER et al. 2005). Clinical fMRI is always done in individual patients with the goal of a “functional” diagnosis and thereby differs fundamentally from the experiments in basic neuroscience research. General instructions for clinical fMRI have been published in the “current protocols in magnetic resonance imaging” (THULBORN 2006). However, until recommendations or guidelines of the responsible medical associations are released, clinical fMRI needs to be performed in the framework of research trials (see Sect. 4.3.2).

Presurgical diagnostics in patients with brain tumors and epilepsy are to date the most commonly established clinical applications of fMRI. Historically, due to its good spatial resolution and direct correlation to surface anatomy BOLD-fMRI was used shortly after its first description (BANDETTINI et al. 1992) (KWONG, BELLIVEAU et al. 1992) (OGAWA, TANK et al. 1992) for presurgical localization of the primary sensorimotor cortex in patients with rolandic brain tumors (JACK, THOMPSON et al. 1994), (see Sect. 4.4), and soon after for determination of the language dominant hemisphere in patients with left frontal or temporo-parietal tumors (DESMOND, SUM et al. 1995) as well as for the localization of Broca and Wernicke language areas (FITZGERALD, COSGROVE et al. 1997), (see Sect. 4.5). There is substantial evidence from validation studies with established reference procedures (see Chap. 7) and from multimodal investigations comparing fMRI with other methods of functional neuroimaging (see Chap. 8), suggesting good reliability of fMRI in the (presurgical) localization of functional areas and – not unisono however – in determination of hemispheric language dominance, given that indications and limits of the method are considered.

The predominant diagnostic aims of presurgical functional neuroimaging are:

- Localization of eloquent brain areas with respect to the envisaged site of surgery
- Determination of the dominant hemisphere for specific brain functions
- Localization of epileptic zones and lateralization of epileptic activity
- Delineation of neuroplastic changes in brain activity

4.3

Presurgical fMRI: Practical, Technical and Methodological Considerations

4.3.1

Practical Issues

In contrast to experimental applications of fMRI in research laboratories where permanent test setups can be installed, generally healthy subjects are examined and where the measured results do not need necessarily to be immediately available, the clinical application of fMRI in a hospital setting presents particular challenges. Technically and methodologically custom-tailored developments including hardware, software, imaging protocols and data evaluation routines (see Sects. 4.3.3 and 4.3.4) are required in order to allow successful examination of patients with existing deficits, uncooperative or sedated patients and children (HAJNAL et al. 1994; BAUDENDISTEL et al. 1996; BUCKNER et al. 1996; COX 1996; FRISTON 1996; LEE et al. 1996; GOLD et al. 1998; LEE et al. 1998; LEE et al. 1998; STIPPICH et al. 1999; THULBORN and SHEN 1999; BOOKHEIMER 2000; HAMMEKE, BELLGOWAN and BINDER 2000; HIRSCH, RUGE et al. 2000; GAILLARD, GRANDIN and XU 2001; HSU, WU and LEE 2001; ROUX et al. 2001; HOELLER et al. 2002; RUTTEN, RAMSEY et al. 2002; STIPPICH, HEILAND et al. 2002; ROBERTS TP 2003; STEGER and JACKSON 2004; HULVERSHORN et al. 2005; HULVERSHORN et al. 2005; WEISKOPF et

al. 2005; LIU and OGAWA 2006; PRIEST et al. 2006; WIENBRUCH et al. 2006). Instructions for dealing with sources of error and solving specific problems arising in clinical fMRI are given in Chapter 10.

Any clinical application of fMRI involves a “paradigm” (a defined functional measurement including stimulation) adjusted to the relevant problem and an fMRI protocol (comprising several different paradigms plus at least one morphological 3D data set for overlay procedures) optimized for clinically acceptable examination times, low susceptibility to artifacts, good signal yield and reliable localization of functional brain areas. For clinical purposes block designed paradigms, with cyclically alternating stimulation and baseline conditions, are usually more feasible than the methodologically more demanding event-related paradigms (Fig. 4.2). Ideally, it should be possible to use clinical fMRI protocols even in patients with existing neurological and cognitive deficits. Thus, particularly when creating complex protocols, such as for language or other cognitive brain functions, close cooperation with neuropsychological experts is strongly advisable. Prior to any clinical fMRI examination, accurate documentation of relevant neurological / neuropsychological deficits must be available in order to avoid erroneous data interpretation. Individual training and stimulation adjustment according to patient ability is also indispensable. The time required for this generally exceeds the actual measurement time and can vary in own experience between 20 min and 3 h according to patient ability (STIPPICH, HEILAND

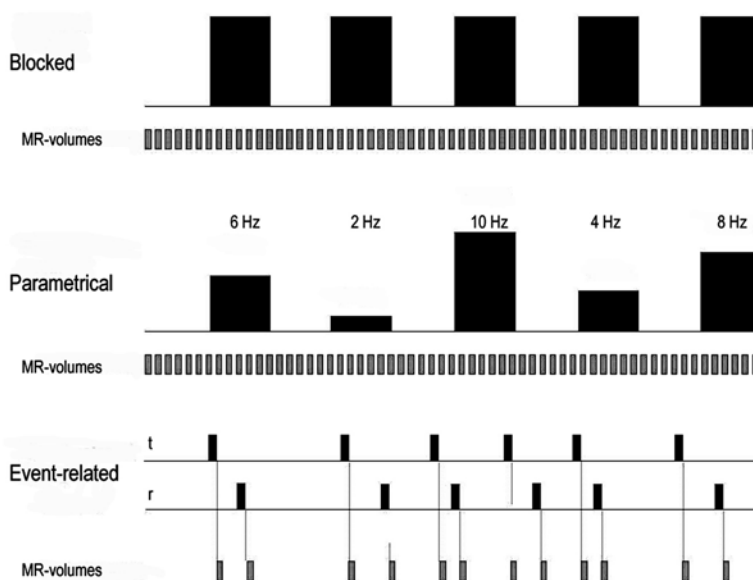


Fig. 4.2. Schematic illustration of different paradigm designs used for fMRI studies. Conventional “blocked design” consists of different stimulation periods that repeatedly alternate over time, while images are acquired continuously (MR-volumes). Usually a series of identical stimuli (or tasks) is applied during each period. “Parametrical design” is a modification of blocked design with a systematic variation of the applied stimulation between periods (e.g. trigger frequency). “Event-related” design requires triggering and enables to measure BOLD-responses to single events (e.g. a single finger movement) with improved temporal resolution. Images can be acquired continuously or discontinuously (shown). To achieve higher SNR averaging of a larger number of events needs to be performed (for details see Chap. 2). Modified from STIPPICH, HEILAND et al. 2002 with permission

et al. 2002). By using optimized and standardized protocols, fMRI examinations can be integrated in clinical routine MR imaging without major problems. To investigate motor function, self-triggered movements are most commonly used (see Sect. 4.4.3), and non-standardized tactile stimuli (e.g. manual stroking of the hand by the examiner) to measure somatosensory function (HAMMEKE et al. 1994). Language functions are examined using various paradigms involving acoustic or visual stimulation (see Sect. 4.5.3). In studies on preoperative fMRI published to date, required measurement times per paradigm show a high variability between 1 min (STIPPICH et al. 2004) and over 20 min (RUTTEN, RAMSEY et al. 2002); technical and methodological differences are also significant. To make “getting started” in preoperative fMRI easier, sample established protocols* are presented in Sects. 4.4.4, 4.4.5 and 4.5.4. In our experience, these protocols ensure robust functional localization at 1.5 T and sufficient BOLD signals (measured parameters: (1) r = correlation of the measured BOLD signals to the applied hemodynamic reference function, (2) $\Delta S\%$ = relative BOLD signal change). Scan times per paradigm are

66 s or 105 s (fully automatic somatosensory stimulation) (STIPPICH, ROMANOWSKI et al. 2004) (STIPPICH et al. 2005), 140 s (motor) (STIPPICH, OCHMANN and SARTOR 2002), and 234 s (language) (STIPPICH C, MOHAMMED J et al. 2003). Reproducibility of functional localizations and BOLD signals during one MR session, as well as on different examination days, is high. However, due to the persisting lack of consensus on the performance of clinical fMRI examinations, it is not yet possible to make definitive recommendations on how these should be carried out – thus we refer the reader also to the large body of data available (see Sects. 4.4.1 and 4.5.1).

Examination times in clinical routine neuroimaging are in general limited and rarely exceed 1 h. Within this time, the entire stimulation equipment needs to be set up at the scanner and subsequently dismantled (Fig. 4.3). Positioning of the pre-trained patient is more time-consuming than in routine morphological MR-imaging. Head fixation should be optimal to minimize motion artifacts and all stimulation devices must be installed and calibrated (Figs. 4.4 and 4.5). Once the measuring position is established a final performance test prior to the start

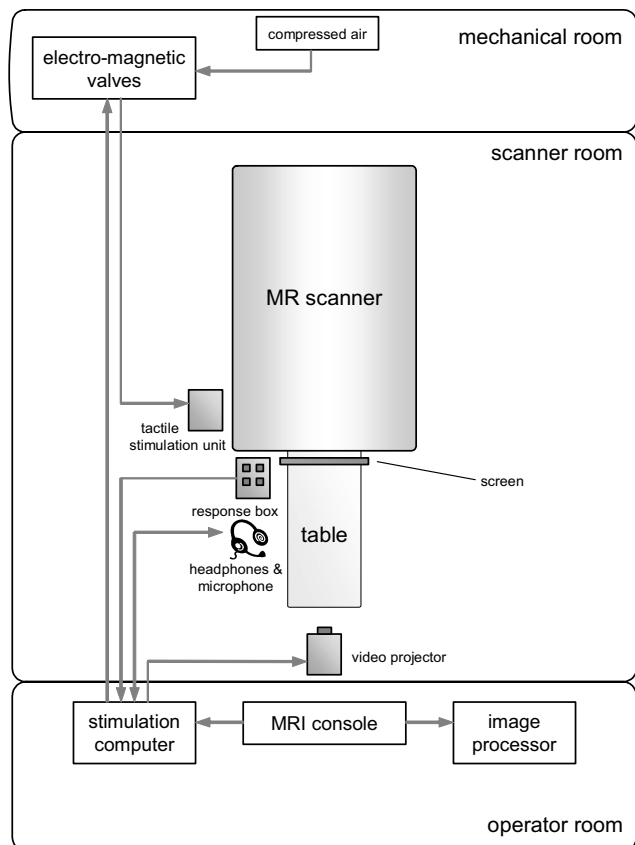


Fig. 4.3. Scheme of a typical fMRI setup. Electrical equipment placed inside the scanner room requires sufficient shielding. Test measurements should be performed to exclude imaging artifacts. For all electrical stimulation devices and critical metal implants safety measurements on phantoms are recommended (GEORGI et al. 2004; AKBAR, STIPPICH and ASCHOFF 2005)



Fig. 4.4a-c. Typical equipment for visual stimulation. **a** High resolution video beamer. As for all electronic devices, a placement outside the scanner room should be preferred to avoid imaging artifacts. **b** Semitransparent projection screen mounted to the scanner bore. **c** Commercial mirror system for back-projection mounted to the head-coil (Reprinted from Radiologie up2date 4/2005 317–336 with permission)



Fig. 4.5. Fully automated pneumatically driven tactile stimulation. Flexible membranes (4D Neuroimaging, Aachen, Germany) connected to pressure resistant pneumatic tubes transmit the stimuli to the lips, fingers or toes (not shown). *Upper left:* the 24-channel high precision electromagnetic valve system was designed to investigate somatosensory somatotopy (Reprinted from Radiologie up2date 4/2005 317–336 with permission)

of the fMRI examination is strongly recommended – i.e., each patient should shortly repeat the task inside the scanner under supervision of the investigator. In general all clinical fMRI measurements should be closely monitored by the investigator to document errors arising while paradigms are carried out. For this reason, our investigators remain in the scan room while motor paradigms are carried out by the patients. In language fMRI, the patients are asked directly after each measurement for correct task performance before the next scan is started. This is also advisable for clinical fMRI of other cognitive functions, such as memory. These brief post-scan interviews are also important to document incorrect task performance as a basis for the sometimes unavoidable and time-consuming manual post-processing of erroneous data from patients who are difficult to examine. However, erroneous measurements should be repeated immediately where possible.

The results of clinical fMRI measurements usually need to be available already on the examination day in order to ensure that fMRI data can be considered in the therapeutic decision-making process. Traditionally the processing of fMRI data takes place after the fMRI measurements (offline) using freely available or commercial software (Cox 1996; FRISTON 1996; GOLD, CHRISTIAN et al. 1998; ROBERTS 2003). Most clinical high-field MR-imagers today offer optional programs for processing fMRI data “online” (FERNANDEZ, DE GREIFF et al. 2001; MOLLER, FREUND et al. 2005). The functionality of the different “real-time fMRI” software packages is variable and the choice of appropriate programs is usually made on the basis of individual criteria. However, any data processing software for fMRI should at least offer image alignment, motion correction, temporal and spatial data smoothing and multiple statistical tests to assess functional activation (see Chap. 2). It is also important to note that tools for superimposing functional images on morphological images and for data export (e.g. neuronavigation) are essential in presurgical fMRI, where as capabilities for spatial normalization can be considered as optional.

Since no guidelines or recommendations for the evaluation and interpretation of clinical fMRI are to date available, appropriate routines and criteria for diagnostic interpretation need to be set by the individual institutions. Here the use of dynamic statistical thresholds helps to reliably localize functional brain areas and to provide defined

BOLD signal readings (see Sect. 4.3.4). Regardless of the software used for data processing and of the level of automation achieved, the superposition of the intrinsically distorted echo-planar MR-images (EPI) onto anatomical 3D data sets, as well as defining the appropriate display parameters for intraoperative representation of functional data, remain manual procedures. As with the medical evaluation and documentation of clinical fMRI findings, they require sufficient experience on the part of the investigator. These investigator-related factors in particular underline the need to establish standardized fMRI protocols, data processing and evaluation procedures to achieve consistent quality of clinical examinations.

4.3.2 Legal Aspects

fMRI is not yet a definitively established method of clinical diagnostic imaging. It should be explicitly pointed out that clinical fMRI should currently only be carried out in the framework of scientific studies until the hard- and software components for medical applications have been certified and until official recommendations or guidelines have been issued by the relevant medical associations. Until then, individual routines and standards need to be established for measuring techniques and examination protocols, data processing and evaluation, as well as for medical evaluation and documentation of clinical fMRI findings. Validation of preoperative fMRI using established reference procedures (e.g. ECoG, Wada test) by the operator is indispensable, even if the examination protocols suggested in this book are used. As a basic principle, clinical fMRI examinations should be performed, evaluated and interpreted by trained and experienced investigators with particular expertise in this area, since careless use of this very promising technique could endanger patients.

4.3.3 Evaluation of Presurgical fMRI Data

Presurgical fMRI examinations are always carried out in individual patients with the primary goal of an individual “functional” diagnosis. To achieve this, the surgically relevant brain areas need to be reliably localized and their spatial relation to brain

tumor or epileptogenic zones accurately identified. Precisely localizing the anatomical correlate of the center of gravity of a functional area (focus of activation) and correct naming of the corresponding anatomical structure (gyrus) is essential, as far as pathology allows. When determining hemisphere dominance important limitations of the method need to be considered (see Sect. 4.6).

In general, it is important to note that the *spatial extent* of a functional brain area cannot be reliably determined using BOLD fMRI, since this varies according to the statistical threshold chosen for data evaluation. Therefore, defining resection margins on the basis of BOLD activations is not safe and

should not be permitted until sufficient data from prospective clinical trials on this topic are available. In addition, the spatial coordinates of the focus of activation change with statistical threshold as well as with cluster size and BOLD signals (Fig. 4.6). When evaluating clinical fMRI data, the use of one or more predetermined (fixed) statistical thresholds – a common approach in research fMRI – does not solve the problem, since BOLD signal intensities and cluster sizes differ significantly from one patient to another and between different paradigms (e.g. foot movement, hand movement) even when examinations are carried out in a standardized way. The same holds true for different fMRI measurements carried out in

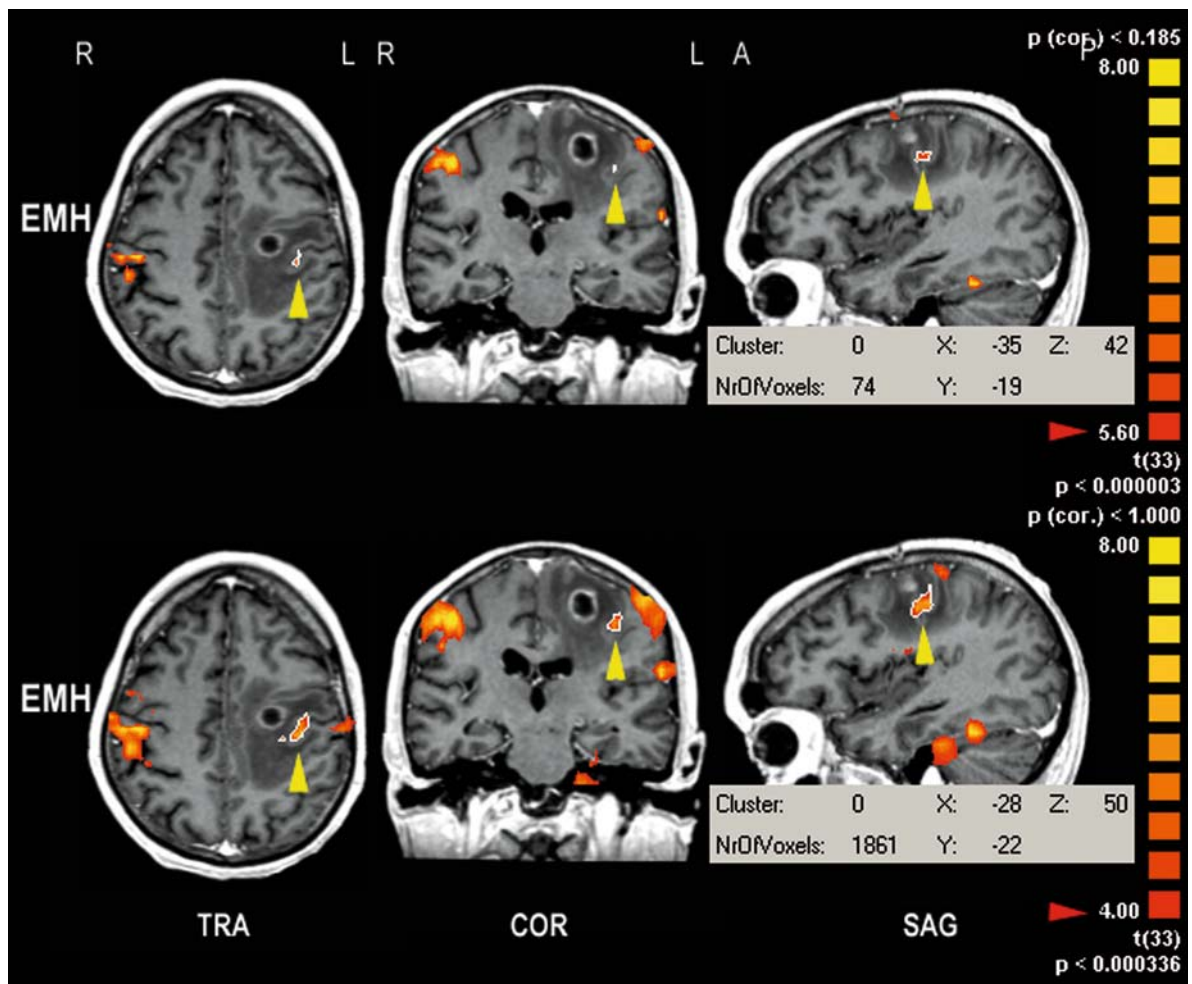


Fig. 4.6. Influence of the statistical threshold on spatial extent and localization of the center of gravity of BOLD-fMRI activation. With decreasing statistical threshold BOLD-clusters increase in size and show a marked shift of spatial coordinates (please compare *upper* and *lower* rows). Yellow arrowheads indicate primary sensorimotor activation obtained from contralateral finger opposition in a hemiparetic patient; red arrowheads indicate the statistical threshold used to display functional activation. Grey boxes: spatial coordinates (x, y, z) of the center of gravity of BOLD-clusters (cluster size in mm^3 , 1 voxel = 1 mm^3)

the same patient, regardless whether performed on different days or within the same scanning session. Even more importantly the arbitrary representation of the extent of functional brain areas may lead the neurosurgeon into a false sense of security, a security which is in reality unfounded and which could consequently lead to endangering the patient. One practical approach to solving this problem lies in adapting the evaluation of individual fMRI data on the basis of clearly defined criteria using dynamic statistical thresholding (Fig. 4.7), (see Sect. 4.3.4).

Determining hemisphere dominance with fMRI is at least equally challenging. Typically, activated voxels in defined target regions of both hemispheres

(e.g. Broca's and Wernicke's areas and their anatomically homologous areas in the right hemisphere) are counted at a particular statistical threshold, following which lateralization indices are calculated from quotients (STIPPICH, MOHAMMED et al. 2003). This procedure has intrinsic problems for several reasons. (1) The BOLD activation measured depends on the paradigm used, but batteries of different paradigms have proven to be more reliable to localize and lateralize language as compared to using one single paradigm alone (RAMSEY et al. 2001) (RUTTEN, RAMSEY et al. 2002). In addition, some linguistically different paradigms account better for the complexity of language in presurgical fMRI. The results of

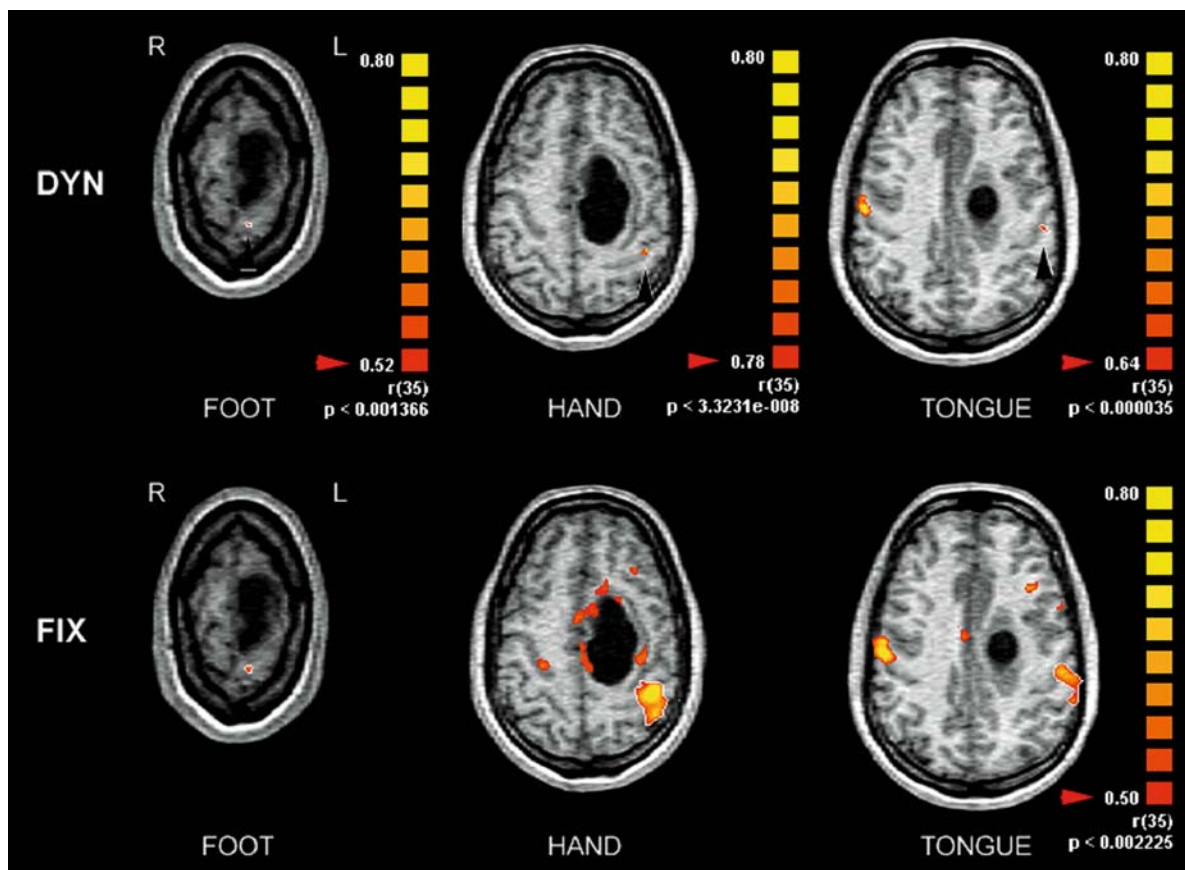


Fig. 4.7. Comparison of dynamic thresholding (DYN, upper row) and fixed thresholding (FIX, lower row) in somatotopic mapping of the left primary sensorimotor cortex. Dynamic thresholding enables to adapt the data evaluation to different fMRI measurements in a standardized way. Using the empirically proven cluster size of 36 mm^3 as the standard for data evaluation allows to achieve well outlined fMRI activations (black arrowheads) and enables to precisely assess their anatomical correlates and spatial coordinates as well as to measure BOLD-signals under defined conditions (r = correlation of the measured BOLD-signals to the hemodynamic reference function (hrf), ΔS = relative BOLD-signal change [%]). Fixed thresholding (here adapted to the “weakest” activation (foot)) results in BOLD-clusters of variable size and spatial coordinates precluding reliable assessment of their anatomical correlates as well as of BOLD-signal characteristics. In this patient, at low statistical threshold artificial activations occurred around the tumor, obscuring diagnostic information and potentially confusing the neurosurgeon (please compare Hand, upper and lower rows)

the various paradigms are rarely identical, but often congruent. There are, however, no scientific findings to indicate how conflicting results should be medically interpreted. (2) BOLD activation varies independently between hemispheres if the stimulus frequency is varied, even when the same paradigm is used (KONRAD et al. 2005). This means that the lateralization measured depends on both the statistical threshold chosen and the “cerebral workload” associated with the respective task. (3) MRI yields relative rather than absolute measurements, in contrast to imaging modalities based on ionizing radiation (e.g. CT). Thus, the results of BOLD fMRI are semiquantitative on account of the method.

In spite of the limitations mentioned, fMRI yields – in the vast majority of patients – important diagnostic information noninvasively which is otherwise unavailable. Functional landmarks facilitate the choice of the most sparing therapy on the basis of a careful consideration of the benefits and risks, as well as planning and execution of function-preserving interventions. At the same time, preoperative fMRI has the potential to reduce the number of invasive diagnostic procedures, such as the Wada test or ECoG, either before or during neurosurgery. However, at this stage fMRI cannot fully replace these invasive measures and should therefore be considered as a supportive diagnostic modality.

4.3.4

Analyzing fMRI Data in Individual Patients

Defining analysis routines is a significant prerequisite for medical interpretation of clinical fMRI data, alongside standardizing clinical examination protocols, setting reference values and automating data processing. The above are the minimum requirements if clinically diagnostic information from fMRI examinations is to be gleaned. Diagnostic evaluation of non-standardized fMRI examinations in “interesting” patients is highly inadvisable.

A number of freely available and commercial programs are available for fMRI data processing and evaluation (COX 1996; FRISTON 1996; GOLD, CHRISTIAN et al. 1998; ROBERTS 2003). Due to the diversity of these programs and the varying requirements and preferences of the individual user, we are unable to recommend any program in particular. The following three-step procedure using dynamic thresholding was developed for BrainVoyager on the basis of local factors, but is transferable to other programs.

Preprocessing (step 1, for details see Chap. 2): Any interpretation of clinical fMRI data should begin with processing the raw data, including at minimum image alignment, correction of motion artifacts and temporal-spatial smoothing. Generally, functional activation maps are then calculated on the basis of individual layers (2D fMRI maps), for which various statistical processes can alternatively be used [e.g., t-test, cross correlations, general linear model (GLM), etc.]. As a basic principle, a reference function corrected for delayed hemodynamic response should be used. A volume map of activations (3D fMRI maps) can be calculated following (manual) superposition of the EPI layers onto anatomical 3D data sets (Fig. 4.8). The minimum number of voxels a cluster must contain in order to be shown can be freely predetermined. On the basis of empirical experience we consider a cluster size of 36 mm^3 appropriate and define this as a standard parameter of all 3D analyses. On the one hand, randomly scattered activations are barely shown at this cluster size; on the other hand, clusters are not so large that small anatomic details are obscured. When defining own standards, it should be borne in mind that the representation of the cluster also depends on spatial smoothing.

Dynamic thresholding (step 2): This evaluation process for individual fMRI data typically begins at the maximal statistical threshold, so that no more activations are shown (empty map). By progressively lowering the statistical threshold, the activation which best correlates to the hemodynamic reference function (HRF) is initially shown. Much like the tip of an iceberg, this activation is small and well outlined, in such a way that the anatomic correlate of the activation focus and the spatial coordinates can be accurately determined. The associated correlation of the measured BOLD signal to the HRF (r), the relative BOLD signal changes ($\Delta S\%$) and the cluster size can be measured under defined conditions. By further reducing the statistical threshold activations in other functional areas appear, for which the measurements mentioned can be taken (STIPPICH, KAPFER et al. 2000; STIPPICH, MOHAMMED et al. 2003; STIPPICH, BLATOW et al. 2007; STIPPICH, RAPPS et al. 2007). Thus, for each fMRI data set there is an individual hierarchy of the various functional activations associated with the applied paradigm. Simultaneously, the size of clusters already shown on a higher statistical level increases with the decreasing threshold. This can be used to determine the dominant hemisphere by calculating a lateralization

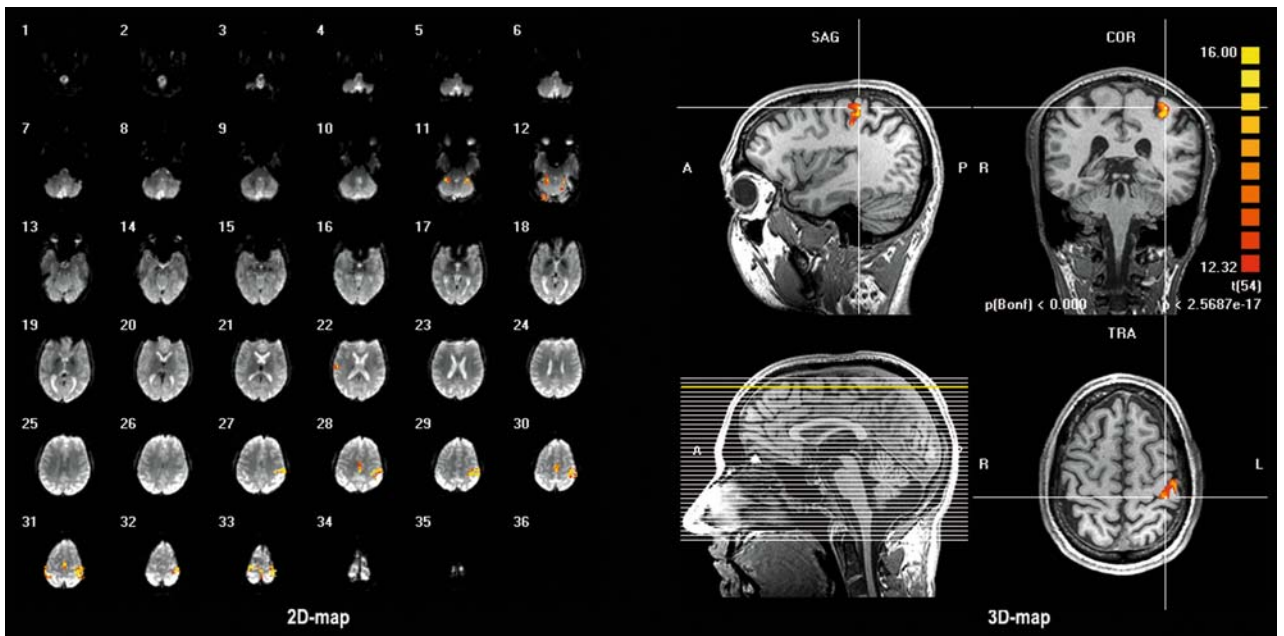


Fig. 4.8. Overlay of 2D-fMRI activation maps (*left*) on anatomical 3D-data sets (*right, bottom left*) results in 3D-fMRI activation maps (*right*) that are typically used for diagnostic presurgical fMRI. This is usually a manual procedure and requires sufficient experience of the examiner to cope with the distortions of the functional EPI-images and other imaging artifacts (movement artifacts, BOLD-signals of venous origin, etc.). The fit should be optimized to the different anatomical structures of interest in patients with rolandic, frontal or temporo-parietal brain tumors

index (LI) according to the established formula $LI = (LH - RH) : (LH + RH)$, where “LH” is the number of voxels in the left hemisphere and “RH” the number in the right hemisphere (STIPPICH, MOHAMMED et al. 2003). Due to the well outlined clusters separate lateralization indices can be calculated e.g. for the Broca and Wernicke speech areas, enabling a highly detailed analysis of atypical language activation as influenced by the presence of brain tumor (Fig. 4.9). In order to distinguish reliably the measured BOLD signals from noise, $r > 0.5$ for motor and language function or $r > 0.4$ for somatosensory brain activation have been proven empirically as appropriate lower thresholding limits, each with $p < 0.05$. Alternatively, or additionally, an error rate could be determined which should not be exceeded in order to evaluate a BOLD activation as “real”; e.g. a false discovery rate (FDR) < 0.001 (0.1%). Since this statistic has only been introduced in current BV software versions, we do not as yet have sufficient clinical experience to report.

Checking BOLD signal characteristics (step 3, for details see Chaps. 2 and 10): Measuring BOLD signals under defined conditions can help separate

real activations from artifacts. Both the correlation to HRF (r) and the signal intensity ($\Delta S\%$) should remain within the normal range (Fig. 4.10). Unphysiologically high signal intensity can arise due to a “venous” origin of the activation – this assumption is supported by a sulcal localization of the cluster focus – or by motion artifacts. In the latter case, the strongest, usually ring-shaped activations tend to occur in the frontal circumference of the brain opposite the supporting point of the head (occipital). Depending on the dominant motion components, other localizations are also possible. Here the onset of the measured signal time course corresponds better to the boxcar function of the block design than to the HRF (for details see Chap. 10).

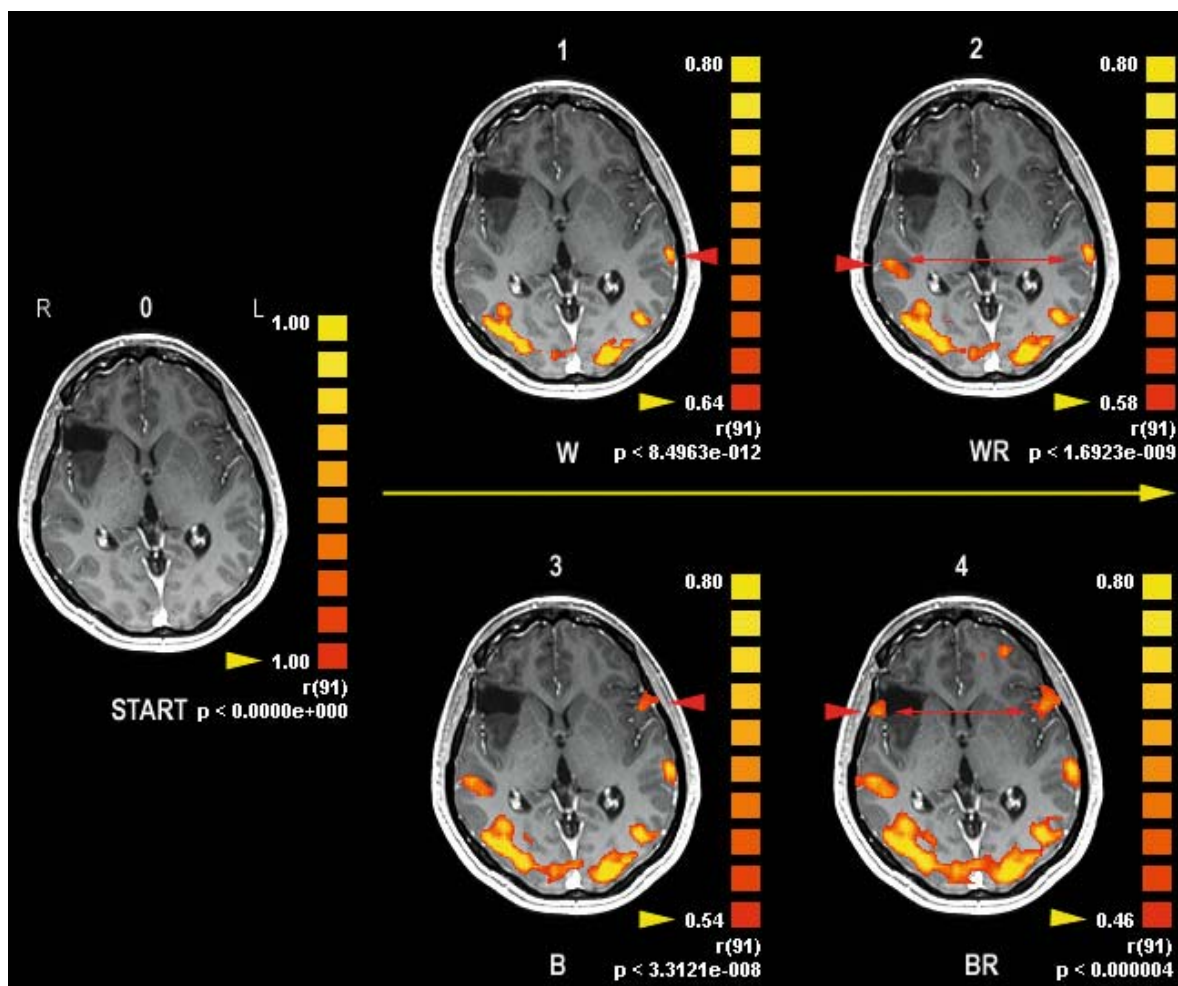


Fig. 4.9. Dynamic thresholding: Evaluation routine for individual clinical fMRI data. Continuous reduction of the statistical threshold (yellow arrowheads) results in a hierarchy of different functional activations (red arrowheads) associated with a given task (example: word generation). Starting point (0) is at the maximum statistical threshold ($r = 1.0$), no activation displayed. Wernicke activation (W) correlates best to the hrf (1, $r = 0.64$) followed by WR (2, $r = 0.58$), B (3, $r = 0.54$) and BR (4, $r = 0.46$). Regional lateralization indexes (LI) are calculated from BOLD-cluster sizes in corresponding functional brain areas in the left and right hemisphere (red double headed arrows). Empirically proven default parameters: Clustersize > 35 mm³, correlation to the hrf: $r > 0.4$ with $p < 0.05$.

4.4 Presurgical fMRI of Motor and Somatosensory Function

Surgery on rolandic brain tumors entails a high risk of motor and sensory deficits. FMRI of motor function is the most frequently used presurgical application, due to the comparatively low equipment requirements for this examination (no stimulation devices are necessary), the relative ease with which it is performed, and the generally stable functional

activation. The diagnostic aim is to localize the primary motor cortex in relation to rolandic tumors. On the basis of morphological MR imaging and clinical findings (motor and / or sensory deficit) the indication for presurgical fMRI should be assessed (see Sect. 4.4.2) and the appropriate examination protocol individually determined (see Sects. 4.4.4–4.4.6). Even patients with tumor-associated pareses can be examined using special paradigms (see Sects. 4.4.5 and 4.4.6). According to the site and extent of the tumor, a single fMRI reading can suffice; however,

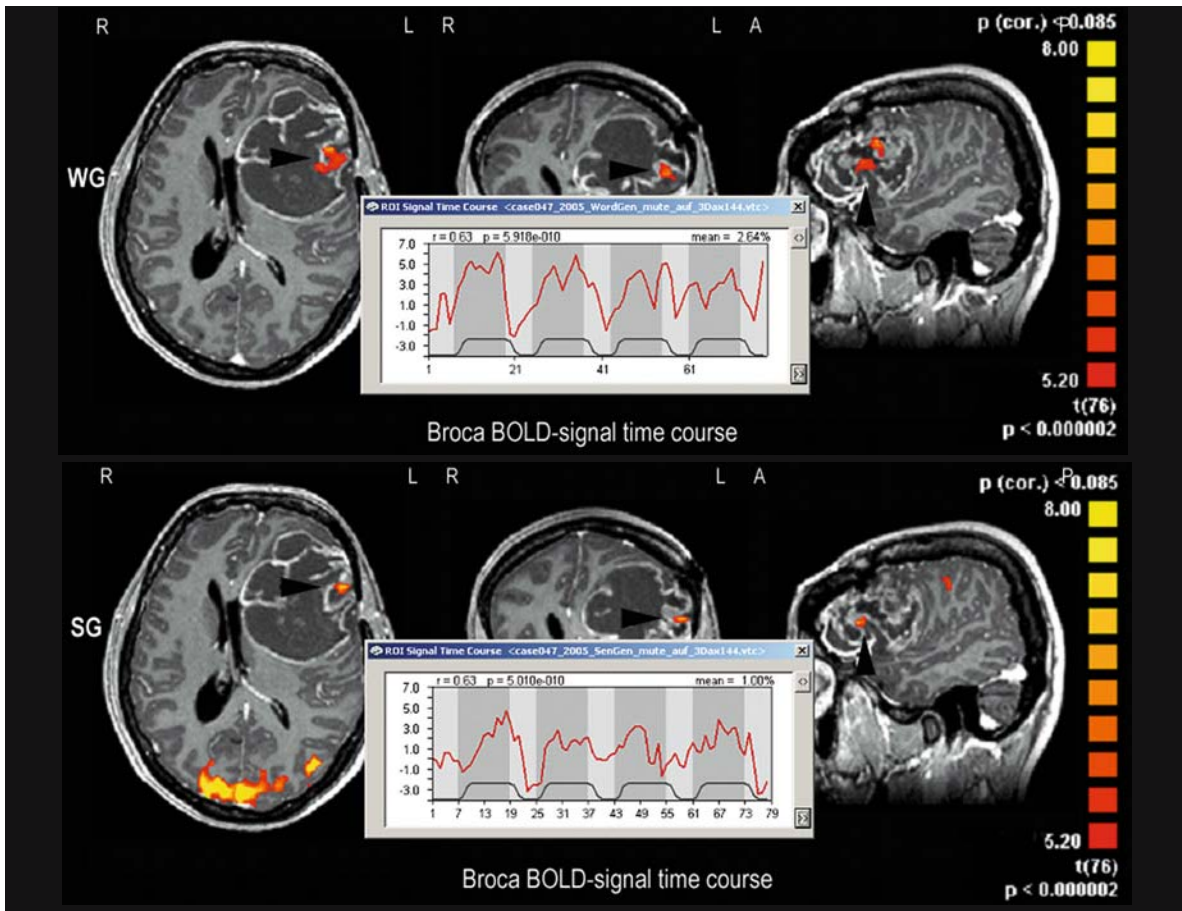


Fig. 4.10 Measuring BOLD-signals under defined conditions helps to distinguish between “true” activation and “artifacts”. In this left handed patient with a giant left frontal high grade glioma (WHO grade IV) presurgical fMRI was performed to assess language dominance. fMRI indicated left dominance and functional tissue directly adjacent to the malignancy. Good reproducibility of the functional localization of Broca’s area using two different paradigms (WG = word generation, SG = sentence generation) and “physiological” BOLD-signal parameters (WG: $r=0.63$, $\Delta S=2.64\%$, SG: $r=0.63$, $\Delta S=1.00\%$) made artifacts unlikely

it is often necessary to examine the entire motor and, where appropriate, somatosensory somatotopy. Today, presurgical localization of various body representations in the pre- and postcentral gyrus by fMRI can be considered reliable (see Chap. 7). Even neuroplastic changes can be examined, although in the presence of brain tumors both shifts in body representations in the pre- and postcentral gyrus, as well as abnormally strong activation in secondary cortical areas, can be observed (see Chap. 9).

4.4.1 Review of Literature

Shortly after the first reports on BOLD fMRI in healthy subjects (BELLIVEAU et al. 1991) (BANDETTINI,

WONG et al. 1992) (KWONG, BELLIVEAU et al. 1992) (OGAWA et al. 1993) the potential usefulness of functional imaging techniques in clinical context, and particularly in presurgical identification of motor and somatosensory cortices was postulated. The literature concerning functional imaging in patients with tumoral lesions in and adjacent to the central area will be reviewed here, while specific literature on patients with epilepsy or lesions near language related areas is discussed in Section 4.5.1 and in Chapter 5. The first description of presurgical fMRI as a clinically useful application dates from 1994, when Jack et al. provided proof of principle in two patients with brain tumors in the sensorimotor cortex, validating their preliminary results with established electrophysiological techniques (JACK, THOMPSON et al. 1994). Soon after, several case studies (BAUMANN, NOLL et al.

1995) (COSGROVE, BUCHBINDER and JIANG 1996) and reports with small numbers of patients (PUCE et al. 1995) (PUJOL, CONESA et al. 1996) (MUELLER, YETKIN et al. 1996) (KRINGS, REUL et al. 1998) harboring glial tumors or arteriovenous malformations (AVM) confirmed technical and practical feasibility of fMRI using motor and sensory tasks in the clinical context and stressed the high potential value of this new upcoming technique for preoperative risk assessment, therapeutic decision making and surgical planning.

During the following years investigations with larger numbers of tumor patients (up to 50) were carried out, claiming their results to represent an important factor for surgical decision (SCHLOSSER, MCCARTHY et al. 1997) (PUJOL, CONESA et al. 1998). Comparisons of presurgical fMRI data with the established reference procedure intracortical stimulation (ICS) were numerous and only those specifically dealing with brain tumor patients will be mentioned here, since a detailed description of validation studies is offered in Chapter 7. Virtually all studies report highly concordant data of presurgical fMRI and ICS in patients with lesions around the central sulcus (DYMAREKOWSKI, SUNAERT et al. 1998) (ACHTEN, JACKSON et al. 1999) (ROUX, BOULANOUAR et al. 1999) (ROUX, BOULANOUAR et al. 1999) with agreement between fMRI and ICS data ranging from 83% in 33 patients (MAJOS, TYBOR et al. 2005) to 92% in 60 patients (LEHERICY, DUFFAU et al. 2000). Task sensitivity for identification of the sensorimotor region estimated in large groups of tumor patients was 85% in 103 patients (KRINGS et al. 2001) or 97% in 125 patients (HIRSCH, RUGE et al. 2000). Furthermore, it should be briefly noted, that various groups focused on the correlation of fMRI results in patients with central lesions with those of other functional imaging procedures, e.g. PET (BITTAR, OLIVIER et al. 1999); for details please refer to Chapter 8 on multimodal functional imaging.

One of the first attempts to evaluate the impact of fMRI on neurosurgical planning was published by Lee et al. The authors applied preoperative fMRI sensorimotor mapping in 32 tumor patients and report that the results were used to determine feasibility of surgical resection in 55%, to aid in surgical planning in 22% and to select patients for invasive surgical functional mapping in 78%. Overall the fMRI results were useful in one or more of these surgical decision making categories in 89% of all examined tumor patients (LEE, WARD et al. 1999). A similar range was documented by Ternovoi et al., who found that presurgical fMRI results had an influence on therapeutic tactics in 69% of 16 tumor patients (TERNOVOI

et al. 2004). Other investigators tried to establish a functional risk predictor for postoperative clinical outcome. Haberg et al. examined 25 patients with primary brain tumors near sensorimotor regions. In 80% of the patients successful fMRI measurements were obtained, out of which 75% were used in preoperative planning. The risk of postoperative loss of function was significantly lower, when the distance between tumor periphery and BOLD activation was 10 mm or more (HABERG et al. 2004). Similarly, Krishnan et al. who evaluated BOLD activation in 54 patients, found that a lesion-to-activation distance of less than 5 mm and incomplete resection were predictors for new postoperative neurological deficits and recommended cortical stimulation within a 10 mm range (KRISHNAN, RAABE et al. 2004). In patients with medial frontal lesions, preoperative fMRI was used to establish the area at risk for resection of specific parts of the supplementary motor area associated with transient postoperative motor deficits and speech disorders (KRAINIK et al. 2001) (KRAINIK et al. 2003) (KRAINIK et al. 2004). In a recent study the authors used fMRI-guided resection in 16 patients with low grade gliomas. Since these tumors are generally not contrast enhancing, resection borders are particularly difficult to establish based on morphological imaging alone. Using fMRI for the determination of resection borders, no permanent neurological deficits and no radiographic tumor progression within a median follow-up time of 25 months were observed (HALL, LIU and TRUWIT 2005). However, the data available to quantify a safe distance between functional activation and resection borders with respect to surgically induced neurological deficits are still very limited and do not justify any general conclusion or recommendation.

Overall, although the above mentioned studies clearly demonstrated feasibility of presurgical fMRI in clinical environment and postulated a contribution of the obtained additional clinical information to pretherapeutic decision making, an effect on the decrease in posttherapeutic morbidity was not corroborated. In order to achieve this, controlled clinical trials using optimized and standardized protocols would be required. Although most investigators agree on the necessity of a standardized routine and several methodological studies presenting optimized protocols for clinical use were published (HIRSCH, RUGE et al. 2000) (RAMSEY, SOMMER et al. 2001) (RUTTEN, RAMSEY et al. 2002) (STIPPICH, HOFMANN et al. 1999) (STIPPICH et al. 2000) (STIPPICH, OCHMANN et al. 2002) (STIPPICH,

ROMANOWSKI et al. 2004) (STIPPICH, ROMANOWSKI et al. 2005), no large scale clinical trials addressing actual benefit for the patient, in terms of decrease in morbidity have been undertaken so far.

Although sensorimotor areas are identified with high success rates using fMRI in patients with central lesions by most investigators, a frequently encountered phenomenon is an altered pattern of activation as compared to the normal brain function, currently denominated as lesion-induced reorganization or plasticity. In an early study in seven patients with intracerebral gliomas of the primary sensorimotor cortex, activation was found to be displaced or reduced (ATLAS, HOWARD et al. 1996). Roux et al. correlated the type of activation with histologic tumor characteristics in 17 patients. In infiltrating tumors, intratumoral activation was detected, which was displaced and scattered correlated with the degree of infiltration, whereas in noninfiltrating tumors activation showed extra-tumoral shift. In tumors in distance from the motor cortex no intratumoral activation was measured (ROUX, RANJEVA et al. 1997). Likewise, a PET study with 51 patients describes that central lesions are more frequently associated with altered patterns of activation than lesions in noncentral locations (BITTAR, OLIVIER et al. 2000). Other studies found significant BOLD signal decrease in areas adjacent to tumor tissue in motor and sensory cortices as compared to the contralateral side. This effect was present in glial tumors, most pronounced in glioblastoma and presumably related to tumor induced changes in local cerebral hemodynamics (HOLODNY, SCHULDER et al. 1999) (HOLODNY, SCHULDER et al. 2000) (SCHREIBER et al. 2000) (KRINGS et al. 2002), while in non-glial tumors (metastasis, cavernoma, abscess, AVM, meningioma) no BOLD signal decrease was found (SCHREIBER, HUBBE et al. 2000). A recent report on 33 patients with different intra- and extra-axial tumors established the influence of tumor type and distance from eloquent cortex on activation volumes in fMRI (LIU et al. 2005). In addition to a displacement or a reduction of activation in the primary sensorimotor cortex harboring the tumor, other patterns of lesion-induced reorganization encompass activation of solely the contralesional cortex or an enhanced activation of non-primary sensorimotor areas with increasing degree of paresis (ALKADHI, KOLLIAS et al. 2000) (CARPENTIER, CONSTABLE et al. 2001) (KRINGS, TOPPER et al. 2002) (REINGES et al. 2005). Also in patients with prior surgery (KIM et al. 2005) or newly acquired central paresis after resection (REINGES, KRINGS et al. 2005) significant decreases

in BOLD activation are observed. One possible explanation for this tumor-induced BOLD signal loss was lately proposed by an fMRI study where tumor blood volume and perfusion were measured. The authors concluded that the BOLD amplitude correlates with total intratumoral blood volume and thus, reduced peritumoral perfusion due to a tumor aspirating perfusion (steal phenomenon) goes along with reduced BOLD activation (LUDEMANN et al. 2006). Of note is however, that resection of glioma with preoperative edema may cause transient increase of BOLD activation ipsilateral to the tumor, presumably by a decrease of pressure on the brain (KOKKONEN et al. 2005). Lesion-induced functional reorganization may reflect the recruitment of plastic neuronal networks to compensate for sensory or motor impairment. On the level of a functional diagnosis in presurgical fMRI these reorganization phenomena are of major clinical significance for the planning of resections, since they can potentially cause false negative results. For further information please refer to chapter 9 on brain plasticity.

During the past few years the use of combined presurgical fMRI and diffusion tensor imaging (DTI) techniques for tractography was suggested to provide a better estimate of proximity of tumor borders to eloquent cortex than fMRI measurements alone. In particular for space-occupying lesions affecting the central region, visualization of the origin, direction and functionality of large white matter tracts allowing imaging of functional connectivity was put forward to improve surgical outcome and to promise a decrease in patient morbidity (KRINGS et al. 2001) (PARMAR, SITO et al. 2004) (ULMER et al. 2004) (SHINOURA et al. 2005) (STIPPICH, KRESS et al. 2003) (HOLODNY et al. 2001).

Very recently, first reports on the application of real-time fMRI in clinical environment were published. This novel technique enables quick preliminary online analysis of fMRI data, which is particularly useful in surgical diagnostics, considering that fMRI data acquisition and processing are very time consuming. Möller et al. demonstrated technical feasibility of presurgical real-time fMRI examination of 10 patients with central area tumors immediately prior to surgery (MÖLLER, FREUND et al. 2005). In another study motor and language tasks were used for real-time fMRI in 11 tumor patients. The authors report satisfactory activation for hand motor tasks, weaker activation for foot motor tasks, and no useful activation for language tasks at the chosen threshold, concluding that the procedure

needed to be optimized, but was generally feasible in clinical routine (SCHWINDACK et al. 2005). Furthermore, Gasser et al. lately achieved the recording of intraoperative fMRI in 4 anesthetized patients with lesions in the vicinity of the central region. Using a passive stimulation paradigm and analyzing the data during acquisition by online statistical evaluation, they obtained intraoperative identification of eloquent brain areas taking into account brain shift (GASSER et al. 2005). For further details on intraoperative imaging techniques and the specific problems caused by brain shift, see Chap. 6.

Finally, with the introduction of higher magnetic field scanners to clinical diagnostics, practicability of presurgical fMRI at 3 Tesla was established in patients with brain tumors (ROESSLER, DONAT et al. 2005) (VAN WESTEN, SKAGERBERG et al. 2005). For a general review on the role of imaging in disease management and the development of improved image-guided therapies in neurooncology see also the latest article by Jacobs et al. (JACOBS, KRACHT et al. 2005).

4.4.2

Selection of Candidates for Presurgical Motor and Somatosensory fMRI

In patients with rolandic brain tumors, presurgical fMRI is usually performed when neurological symptoms indicate an involvement of the sensorimotor cortex, and when insufficient information is yielded by morphological imaging. Four scenarios can be distinguished:

- Due to tumor growth, MR-morphologic rolandic landmarks cannot be identified (see Fig. 4.15). In these patients it is neither possible to localize the pre- or postcentral gyrus on the basis of anatomic criteria alone, nor to reliably estimate putative surgery-related sensorimotor deficits. Here, fMRI offers somatotopic motor and somatosensory mapping of up to six functional landmarks in the pre- and postcentral cortical representations of the lower and upper extremities, as well as in the facial area. As patients with tumors invading the pre- or postcentral gyrus often present with contralateral motor and/or sensory deficits the application of dedicated paradigms may be required.
- Although the rolandic region is morphologically localizable, the "hand-knob" and/or precentral hook are no longer clearly identifiable because of shift or compression by the tumor. In this case the MR-morphologic reference of the motor hand

area as an orientation point for somatotopic mapping of the precentral gyrus is absent; surgery-related neurological deficits cannot be reliably estimated; planning and performing a low-risk intervention is problematic. Any presurgical fMRI should at minimum image the motor hand area, while somatotopic mapping can, with relatively little extra effort, increase the diagnostic value of the examination.

- The tumor lies directly above or below the identifiable motor hand area (see Figs. 4.16–4.18). In this case, somatotopic mapping is indicated in order to better estimate surgery-related neurological deficits in the lower extremities or facial area, as well as to provide the operator with extra functional landmarks.
- Presurgical fMRI can also be helpful when there is a discrepancy between morphological findings and the clinical status of the patient, e.g. little or no neurological deficits despite verifiable tumor growth into the central region. This and similar constellations should prompt a search for atypical brain activation as a result of tumor-associated cerebral plasticity and reorganization. The same holds true for patients with recurrent malignancies, where the functional system was already affected during former treatment (see Fig. 4.19). Whether damage to secondary areas during surgery in such patients actually leads to additional and lasting neurological deficits remains unclear.

We see no indication to answer the following question by presurgical fMRI: what is the risk for functional deficits after resection of the outlined contrast-enhancing areas in the pre- or postcentral gyrus? fMRI is not able to answer this question since defining resection margins using fMRI should still be considered non-reliable – as outlined earlier only very limited data are available on that topic (HABERG, KVISTAD et al. 2004) (KRISHNAN, RAABE et al. 2004) (HALL, LIU et al. 2005) that do not justify general conclusions on how to determine "safe" resection borders based on presurgical fMRI data (see Sect. 4.4.1). Such interventions are fundamentally hazardous, not least because of the risk of damage to important fiber bundles.

Note: the selection criteria mentioned here are meant as suggestions arising from typical morphological and clinical findings in patients with rolandic brain tumors. It is currently not possible to define a medical indication in a strict sense for fMRI. This is due to the lack of controlled prospective studies demonstrat-

ing the clinical benefit of presurgical fMRI in terms of reduced postoperative morbidity or mortality.

4.4.3

Motor and Somatosensory Paradigms for Presurgical fMRI

A complex neuronal network of functional areas in both hemispheres of the human brain is recruited for the planning and execution of arbitrary movements, whereby somatosensory impulses are processed and motor functions steered (see Chap. 3). Reliable localization of the various body representations in the primary motor and somatosensory cortex is essential in presurgical fMRI diagnostics, since permanent paralysis or sensory deficits can result from surgery-related injury. Neurological deficits resulting from injury to the secondary areas, however, are usually only temporary and can be fully compensated (ZENTNER et al. 1996). Nevertheless, the functional localization of pre-motor activations may be of clinical relevance in hemiplegic patients (STIPPICH, KAPFER et al. 2000) (see Sect. 4.4.6).

Most investigators use self-triggered movements to assess motor activation and sensorimotor somatotopy, e.g. various movements of the tongue or lips, the hand or fingers and the foot or toes (see Sect. 4.4.4). Some groups use mechanical aids to assess better movements or to measure various physical parameters (force, acceleration) (BAUDEN-DELSTEL, SCHAD et al. 1996). To ensure a successful examination in the clinical setting, it is essential that the paradigms are feasible, that motion artifacts are kept to a minimum and that examination time is short. Under these conditions, BOLD activations in the primary motor cortex are generally very reliable.

When defining motor paradigms in a block design it is of principal importance to establish whether only the primary motor cortex activation needs to be measured, or whether secondary areas should also be considered. In the case where only the primary motor cortex is the target, paradigms can also include movements in both sides of the body (e.g. right hand vs left hand). Since unilateral movements lead to activation of secondary areas in both hemispheres, secondary areas are active during alternating movements of the right and left body side throughout the entire measurement, but continuous activation is not shown in the statistical evaluation of fMRI data acquired using conventional block

designs, due to the lack of “contrast” between the various stimulation blocks. If information needs to be obtained regarding secondary motor activation, paradigms with strictly unilateral movements of a single body part should be applied, with “resting” as the control condition. Alternatively, three different stimulation conditions could be integrated in the paradigm, i.e., right movement – rest – left movement. However, the number of blocks per paradigm is then increased, and consequently also examination time and susceptibility to motion artifacts. In addition it should be borne in mind that – sensu strictu – information on brain activation in the tumor-unaffected hemisphere is largely insignificant for presurgical fMRI. Also paradigms enabling for the examination of several cortical body representations are problematic in brain tumor patients (e.g. foot – hand – face). Although scan time could be reduced compared to three individual measurements, the time needed is still substantially longer than for each individual measurement alone. Particularly in the case of agitated patients or patients with paresis, the likelihood of motion artifacts increases, subsequently affecting all functional localizations. Only secondary functional areas which are exclusive to the respective movement can be localized. All jointly recruited areas escape detection on diagnostic fMRI. In conclusion paradigms with movements of a single part of the body alternating with true rest that provide short scan times are most appropriate for presurgical fMRI of motor function (Fig. 4.11).

Clinical feasibility tests carried out on neurosurgical patients with and without tumor-related pareses or sensory disturbances showed that self-triggered movement tasks are better suited to presurgical fMRI than controlled paradigms, since only in this way each patient can perform within his or her ability. To keep the likelihood of motion artifacts to a minimum (HOELLER, KRINGS et al. 2002) (KRINGS, REINGES et al. 2001), the following movement tasks were chosen: repetitive tongue movements with closed mouth, opposition of fingers D2–D5 to D1 with free choice of sequence, repetitive flexion and extension of all five toes without moving the ankle. The prerequisite of this examination is again “resting” as a control condition (STIPPICH, OCHMANN et al. 2002) (Fig. 4.12). Alternatively, in the case of mild paresis of the upper extremity, fist clenching / releasing can be tested. Face, arm and leg movements, or movement of the feet, can often lead to poor diagnostic evaluation of data due to strong motion artifacts; therefore, they are not recom-

mended for clinical fMRI. A paradigm with block duration of 20 s and three repeat cycles, adding to an examination time of 140 s, is a suitable compromise between robust functional localization of the primary motor cortex, high BOLD signals and short scan time (Fig. 4.13).

Determination of motor function with presurgical fMRI is limited in patients with high-grade paresis (PUJOL, CONESA et al. 1998) (KRINGS, TOPPER et al. 2002). In the case where the fMRI protocol is based solely on self-triggered movements contralateral to the tumor, a reliable preoperative fMRI diagnosis

is not guaranteed – the pareses are result of insufficient residual function of the primary motor cortex, which can lead to weak, or even absent, BOLD signals. Nevertheless, many patients with tumor-related paresis can be successfully examined: (1) by activating the primary somatosensory lip, finger and toe representations of the postcentral gyrus (STIPPICH, HOFMANN et al. 1999). The somatosensory stimulation does not require patient cooperation, can also be applied in children, poorly cooperative or sedated patients and activates primary (STIPPICH, ROMANOWSKI et al. 2004) and secondary (STIPPICH,

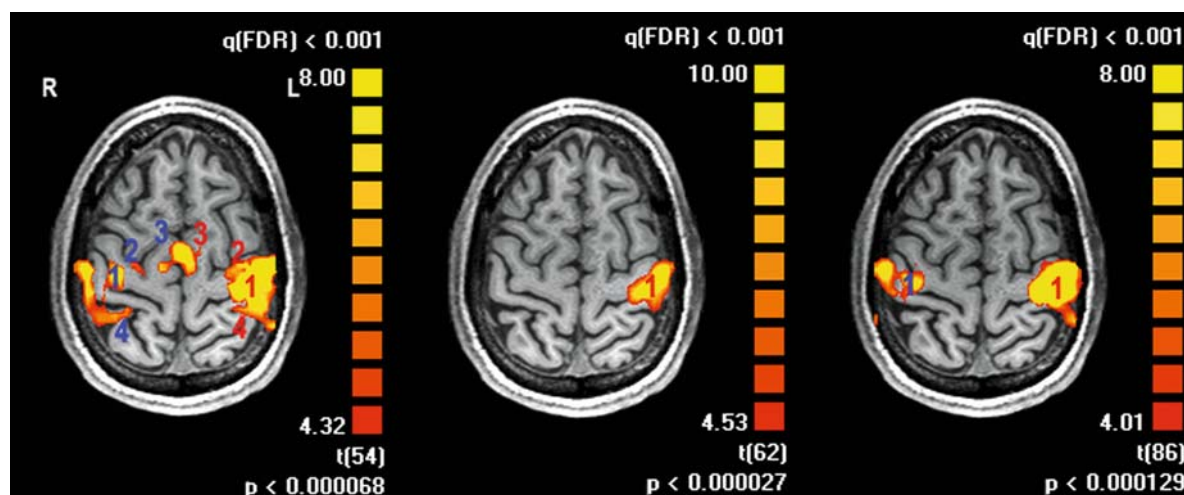


Fig. 4.11. Variation of paradigms to localize the motor hand area results in different activation patterns. *Left:* complex finger opposition of the right hand vs rest; strong activation of cortical motor network in both hemispheres. The large contralateral cluster (*left*) covers the primary sensorimotor cortex (1), premotor cortex (2) and parietal cortex (4). Bilateral supplementary motor activation (3, 3) is displayed in the midline, as well as ipsilateral (*right*) premotor activation (2), primary sensorimotor coactivation (1) and parietal activation (4). *Middle:* complex finger opposition of the right vs left hand; strong contralateral (*left*) primary sensorimotor activation (1), but no activation of secondary areas. *Right:* complex finger opposition of the right hand vs right toe movements and tongue movements; strong contralateral (*left*) primary sensorimotor activation (1) and ipsilateral primary sensorimotor coactivation (1), but no activation of secondary areas

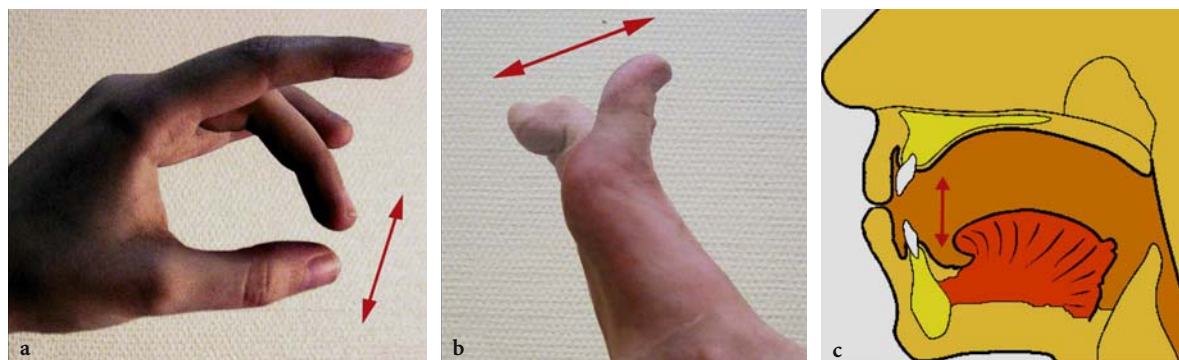


Fig. 4.12a–c. Recommended self-paced movements to investigate sensorimotor somatotopy in clinical fMRI. **a** Complex finger opposition of digits 2 to 5 against the thumb in a random order. Movement frequency ~ 3 Hz. **b** Toe up and down movements, frequency > 1 Hz. **c** Tongue up and down movements with the mouth closed. Movement frequency ~ 3 Hz (Reprinted from Radiologie up2date 4/2005 317–336 with permission)

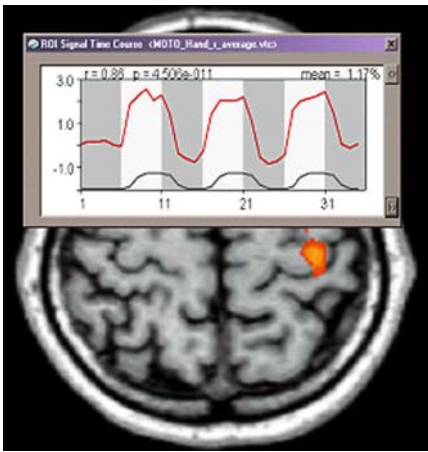


Fig. 4.13. Clinical standard protocol for motor paradigms. The block-designed paradigm consists of four rest periods (light grey) alternating with three stimulation periods (white), each 20 s in duration. The BOLD-signal time course of the motor hand area activation (red line) shows task related increases in regional hemodynamics. The black line indicates the hemodynamic reference function (hrf)

ROMANOWSKI et al. 2005) cortical areas. Even at 1.5 T fMRI sensitivity is sufficient to localize the cortical somatosensory representations in most patients. It is possible to distinguish various body representations in the postcentral gyrus (STIPPICH, HOFMANN et al. 1999) (see 4.5.5) and even individual finger representations (KURTH et al. 1998). While most published studies used non-standardized stimuli, such as manual hand stroking, automatic stimuli guarantee reproducible stimulation conditions. Electric (KURTH et al. 1998) (KAMPE, JONES and AUER 2000) (GOLASZEWSKI et al. 2004), tactile (STIPPICH, HOFMANN et al. 1999) (WIENBRUCH, CANDIA et al. 2006) or vibrotactile (GOLASZEWSKI et al. 2002) (GOLAS-

ZEWSKI et al. 2006) stimulators are the most commonly used. As a further adjunct, complex finger opposition of the non-paretic hand (ipsilateral to the brain tumor) can be used to elicit robust premotor activation as an additional functional landmark for the precentral gyrus on the tumors side (STIPPICH, KAPFER et al. 2000) (see 4.5.6, Fig. 4.22)

4.4.4

Presurgical Somatotopic Mapping of the Primary Motor Cortex

Somatotopic motor cortex mapping is the most frequently used presurgical fMRI protocol in patients with rolandic brain tumors (STIPPICH, OCHMANN et al. 2002). This standard protocol contains three different fMRI measurements. Paradigms should include tongue movements as well as finger and toe movements contralateral to the tumor to localize the motor homunculus in relation to the brain tumor (Fig. 4.14). Even in case of complete destruction of the rolandic anatomy fMRI provides diagnostic information that is relevant to confirm the indication to operate and to plan and implement safer surgery (Fig. 4.15). In patients with small tumors that are – by anatomical consideration – not critical for all body representations it seems appropriate to shorten the protocol by leaving the least relevant body representations unexamined (Figs. 4.16–4.18). However, the examination of a single body representation alone, e.g. the motor hand representation, is often not sufficient to provide the required diagnostic information. Somatotopic mapping enables also to assess plastic changes of cortical motor activation, e.g. in patients with recurrent malignancies prior to repeated surgical treatment (Fig. 4.19).

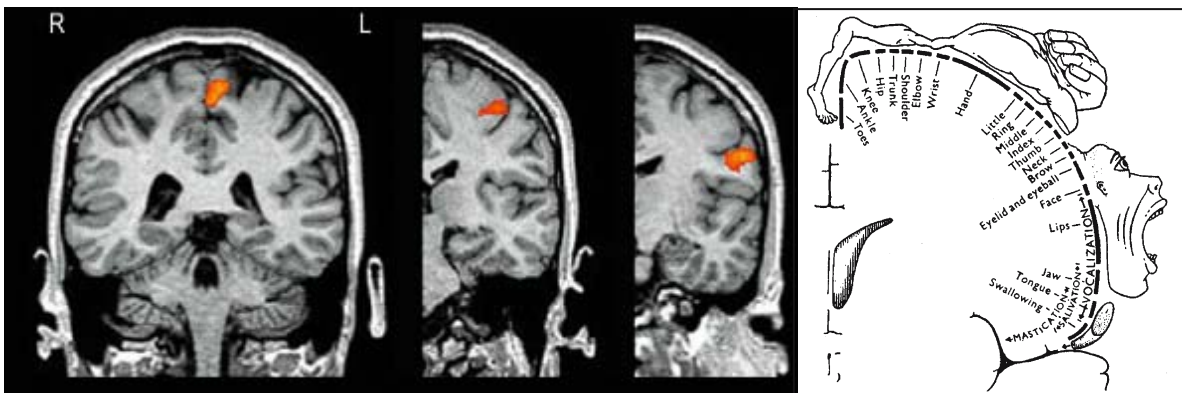


Fig. 4.14. fMRI motor cortex somatotopy. From left to right: foot, hand and tongue representations, drawing of the motor homunculus

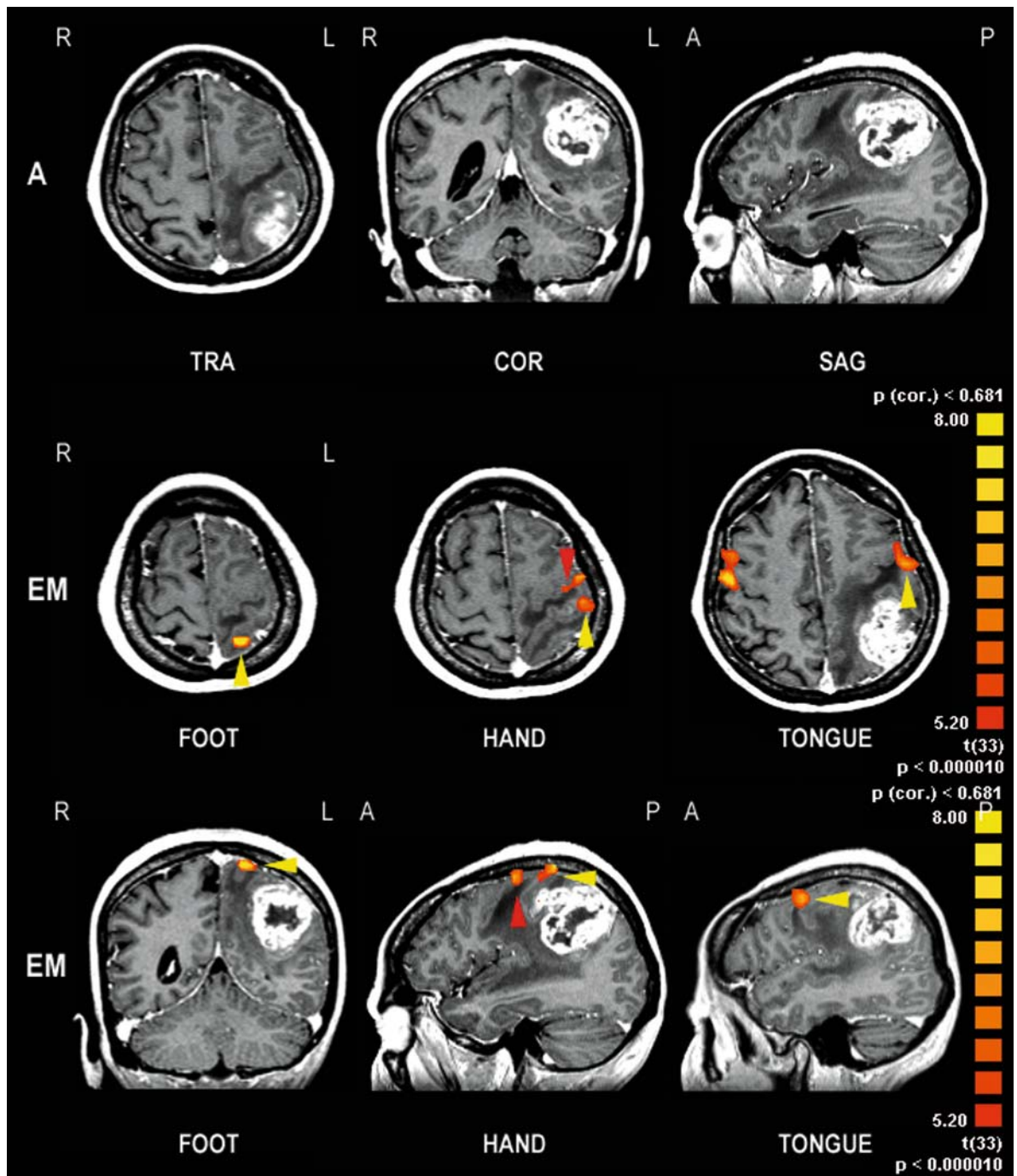


Fig. 4.15. Presurgical fMRI somatotopic mapping of the motor cortex. On morphological images no rolandic landmarks can be identified in the left hemisphere due to the mass effect of this large malignant glioma (upper row, A = anatomy). Foot, hand and tongue movements (EM = executed movement) revealed robust fMRI activation of the respective primary motor cortex body representations (yellow arrowheads). Using functional landmarks the rolandic anatomy (precentral gyrus, central sulcus, postcentral gyrus) can be easily identified in relation to the brain tumor. FMRI indicated a parietal localization of the contrast enhancing glioma. Note the additional premotor activation (red arrowhead) localizing the ventral wall of the precentral gyrus/precentral sulcus

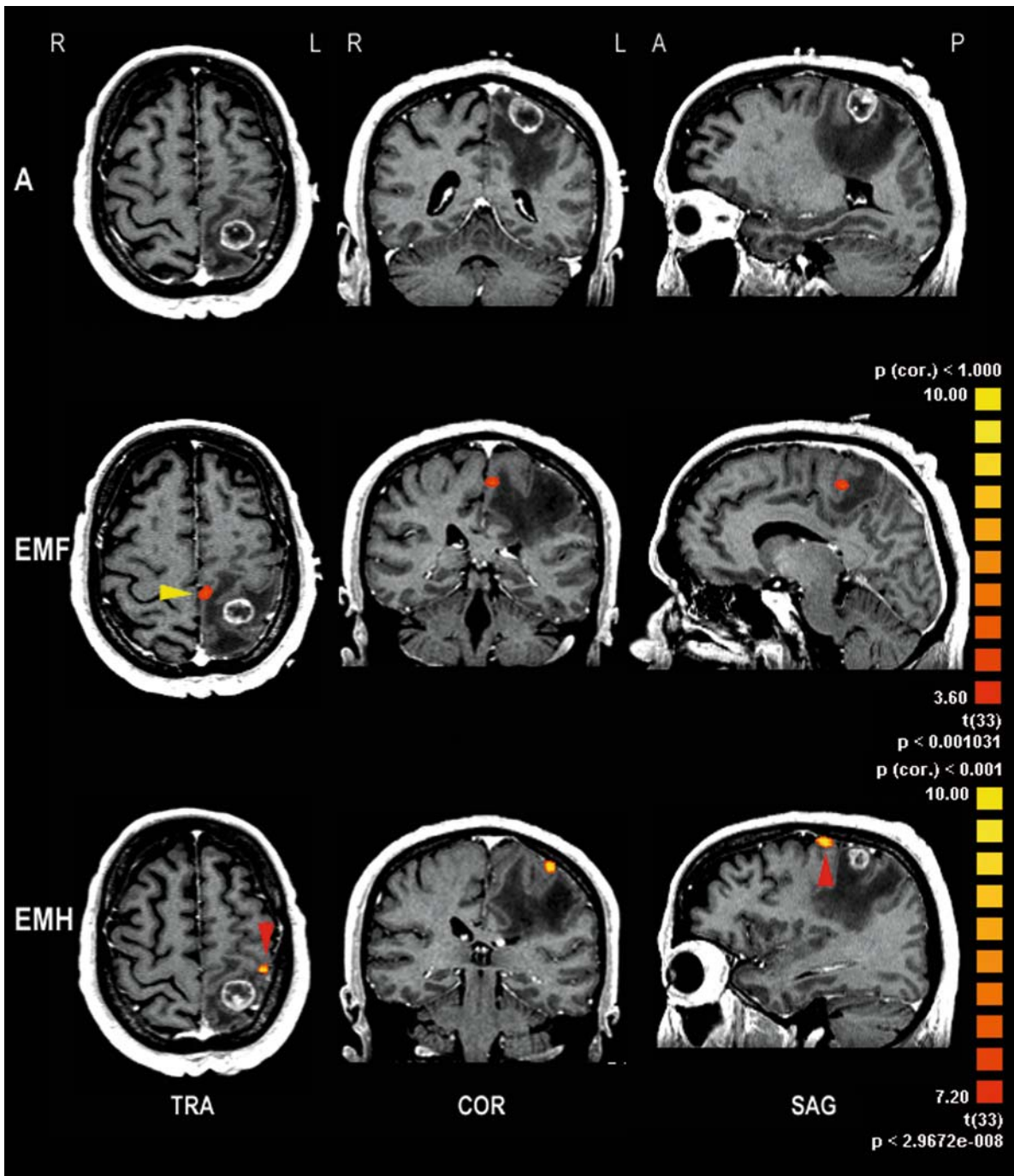


Fig. 4.16. Presurgical fMRI somatotopic mapping of the upper motor cortex in a left postcentral high grade glioma. On morphological images the compressed “precentral knob” can be identified in transverse and sagittal views. Foot (EMF) and hand (EMH) movements were associated with activation of the respective primary motor cortex representations, confirming the postcentral localization of the tumor

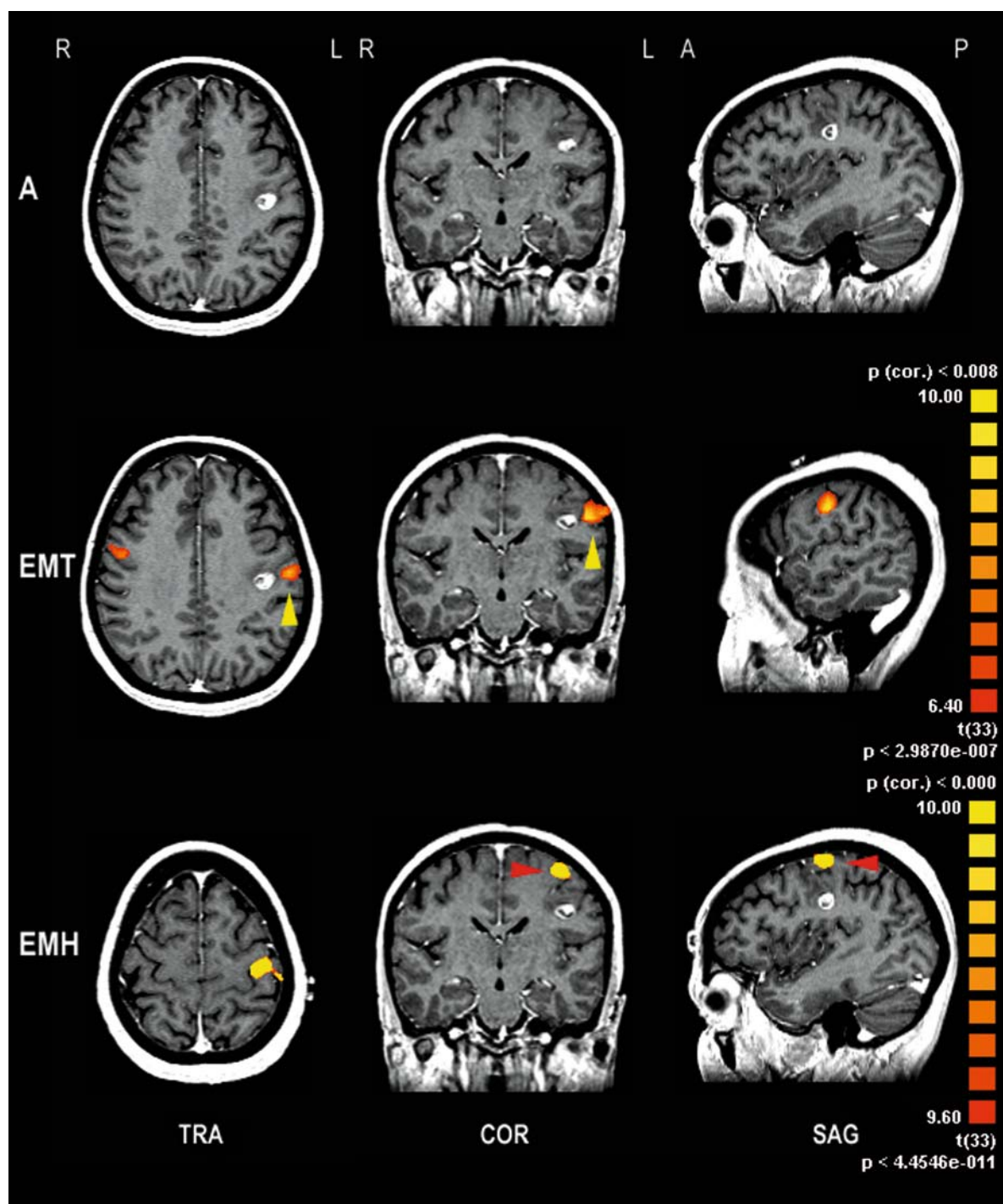


Fig. 4.17. Presurgical fMRI somatotopic mapping of the lower motor cortex in a left rolandic cavernoma. On morphological images the rolandic anatomy was intact. Tongue (MT) and hand (MH) movements were driven by activation of the respective primary motor cortex representations, confirming the central localization of the tumor and a close spatial relationship to the tongue representation

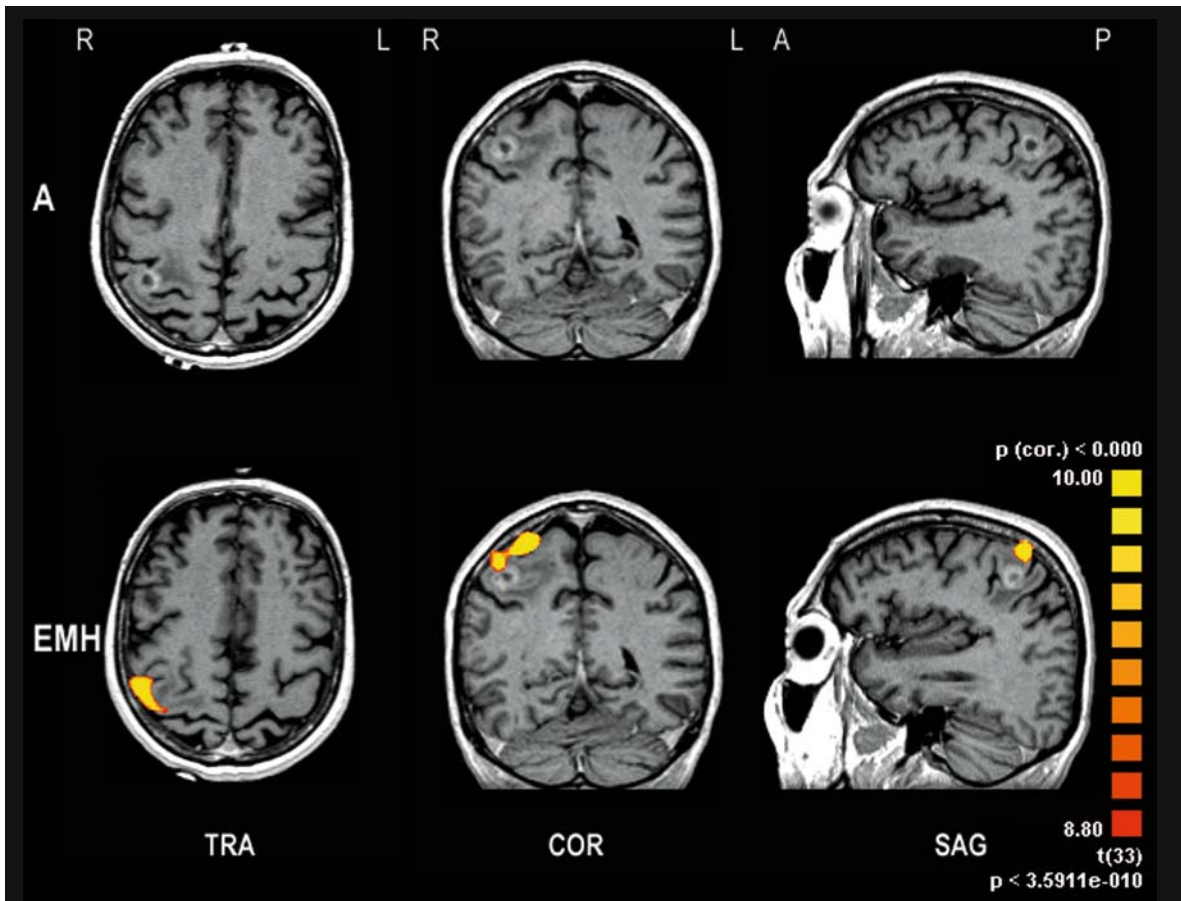


Fig. 4.18. Presurgical fMRI localization of the motor hand area. On morphological images a rolandic metastasis is visualized at the motor hand area bridging the central sulcus towards the postcentral gyrus. FMRI confirmed a close spatial relationship between the primary motor hand representation and the tumor. Interestingly the center of gravity of the BOLD-cluster was shifted upwards from the precentral knob towards the foot representation (see EMH, coronal view)

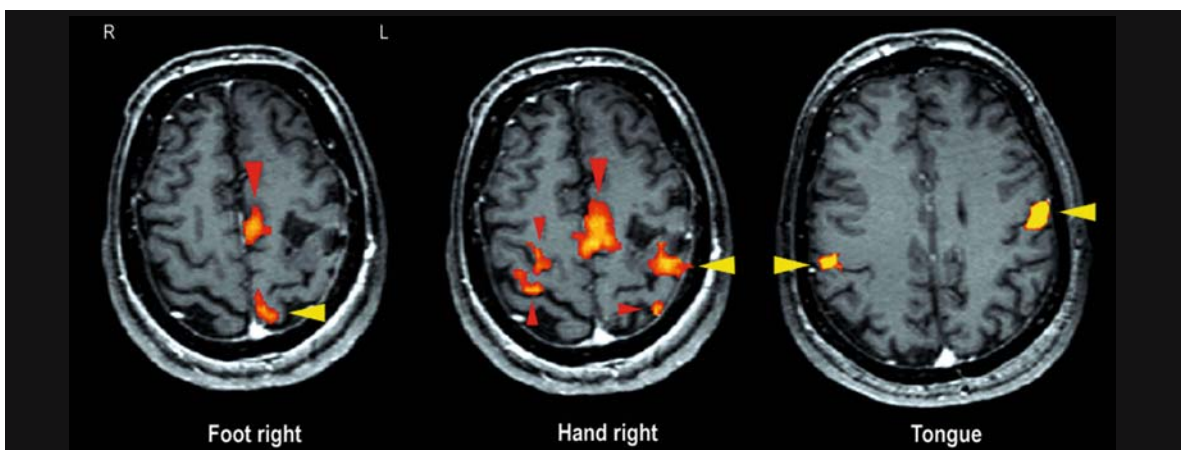


Fig. 4.19. Presurgical fMRI somatotopic mapping of the motor cortex in a hemiparetic patient with a recurrent left rolandic astrocytoma prior to repeated surgery. Foot, hand and tongue movements revealed robust fMRI activation of the respective primary motor cortex body representations (yellow arrowheads). Note the increased activation in secondary areas (red arrowheads): in the supplementary motor area during toe and finger movements and in the whole cortical motor network in both hemispheres during finger movements, respectively

4.4.5

Presurgical Somatotopic Mapping of the Primary Somatosensory Cortex

This fMRI protocol was designed to localize the different somatosensory body representations of the postcentral gyrus (STIPPICH, HOFMANN et al. 1999) (Fig. 4.20). In presurgical fMRI somatotopic mapping is mostly used as diagnostic adjunct, when motor paradigms are difficult to apply – e.g. in uncooperative, sedated or hemiparetic patients or in children, but there is also potential for standardized follow up measurements on neu-

roplastic changes of the somatosensory system. The fully automatic pneumatically driven 24-channel tactile stimulation used in our institution is artifact-free, produces reproducible stimuli and consistent examination conditions for comparative and outcome studies. The whole unit can be set up and removed within 5 min. Scan times per measurement are 66 s (STIPPICH, ROMANOWSKI et al. 2004) or 105 s respectively (STIPPICH, ROMANOWSKI et al. 2005). This presurgical fMRI protocol enables to assess the spatial relationship between brain tumors and the postcentral gyrus, facilitating the estimation of possible post-operative sensory deficits (Fig. 4.21).

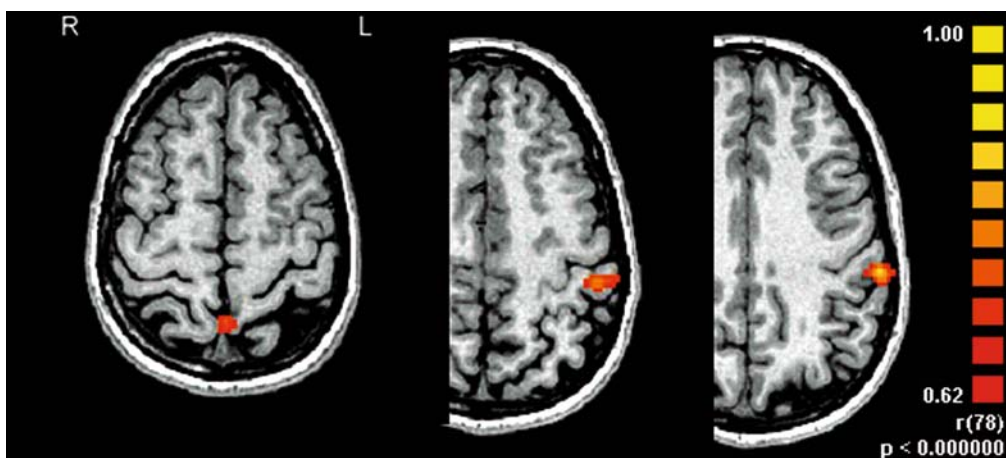


Fig. 4.20. fMRI primary somatosensory cortex somatotopy. *From left to right:* toe, finger and lip representations. Stimulation: D1 & D2 right foot and right hand, upper and lower lips to the right side; stimulus frequency = 4 Hz, air pressure = 3 bar. Clinical standard fMRI protocols for somatosensory stimulation, conventional block-design, stimulation vs rest. **a** Primary somatosensory cortex (S1), six periods of rest alternating with five periods of stimulation, each 6 s in duration (STIPPICH et al. 2004). **b** Secondary somatosensory cortex (S2), four periods of rest alternating with three periods of stimulation, each 15 s in duration (STIPPICH et al. 2005). Modified from Stippich et al. 1999 with permission

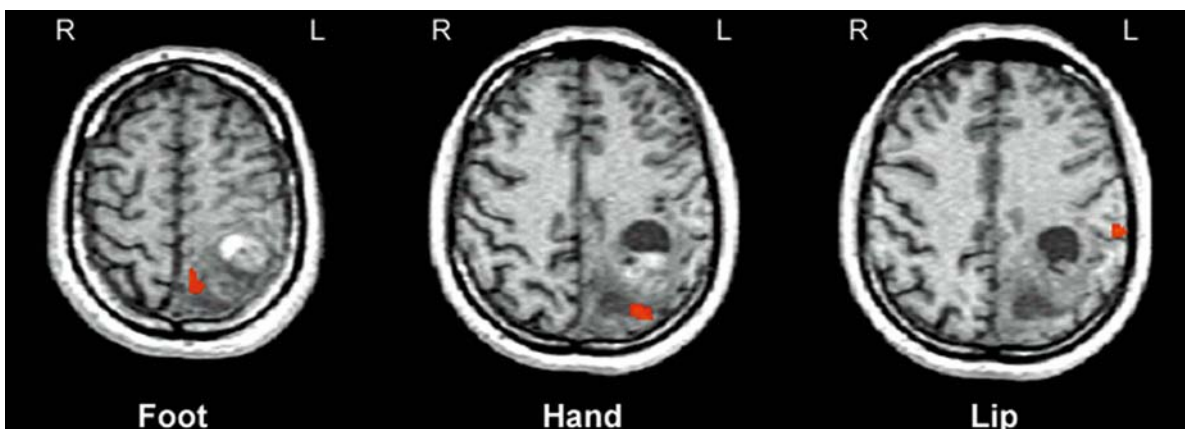


Fig. 4.21. Presurgical fMRI somatotopic mapping of the primary somatosensory cortex (S1) in a left parietal malignant glioma indicated compression of the upper postcentral gyrus at the level of the foot representation and tumor growth into the lower postcentral gyrus with dorsal displacement of the S1 hand representation. Modified from Stippich et al. 1999 with permission

Diagnostic information about the spatial relationship between the central sulcus or precentral gyrus and precentral or frontal brain tumors can be obtained rather indirectly as both anatomical structures are directly adjacent to the postcentral gyrus in the anterior direction.

4.4.6

Localization of the Precentral Gyrus in Patients with Preexisting Paresis

This special protocol was designed in volunteers to help localizing the precentral gyrus in patients with contralateral paresis (STIPPICH, KAPFER et al. 2000). The clinical application is still experimental and requires own validation. In these patients the primary motor cortex is commonly infiltrated by the tumor or severely compressed precluding both, reliable identification of the rolandic anatomy on morphological images and proper performance of contralateral movements for presurgical fMRI. However, as a basic principle, residual contralateral motor function and passive somatosensory stimulation should be used first for the functional localization of the pre- and

postcentral gyrus. As a further adjunct complex finger opposition of the non-paretic hand ipsilateral to the brain tumor can be used to activate the whole cortical motor network in both hemispheres. The premotor activation on the tumors side may serve as an additional functional landmark for the precentral gyrus by localizing the anterior wall of the precentral sulcus with the posterior part of the superior frontal sulcus (Fig. 4.22, 4.23). It is important to note that the risk for surgery related motor deficits cannot be estimated using premotor activation as a functional landmark! However, in healthy volunteers primary motor coactivation can be observed frequently localizing the motor hand area ipsilateral to the moving hand (STIPPICH, BLATOW et al. 2007). Our initial clinical experience indicates, that ipsilateral primary motor coactivation may be supportive to localize the motor hand area on the tumor side in hemiparetic patients. Furthermore the combination of presurgical fMRI with anisotropic diffusion weighted MRI or diffusion tensor imaging (DTI-tractography) to delineate the effects of rolandic brain tumors on the pyramidal tract is recommended (STIPPICH, KRESS et al. 2003) (Fig. 4.24).

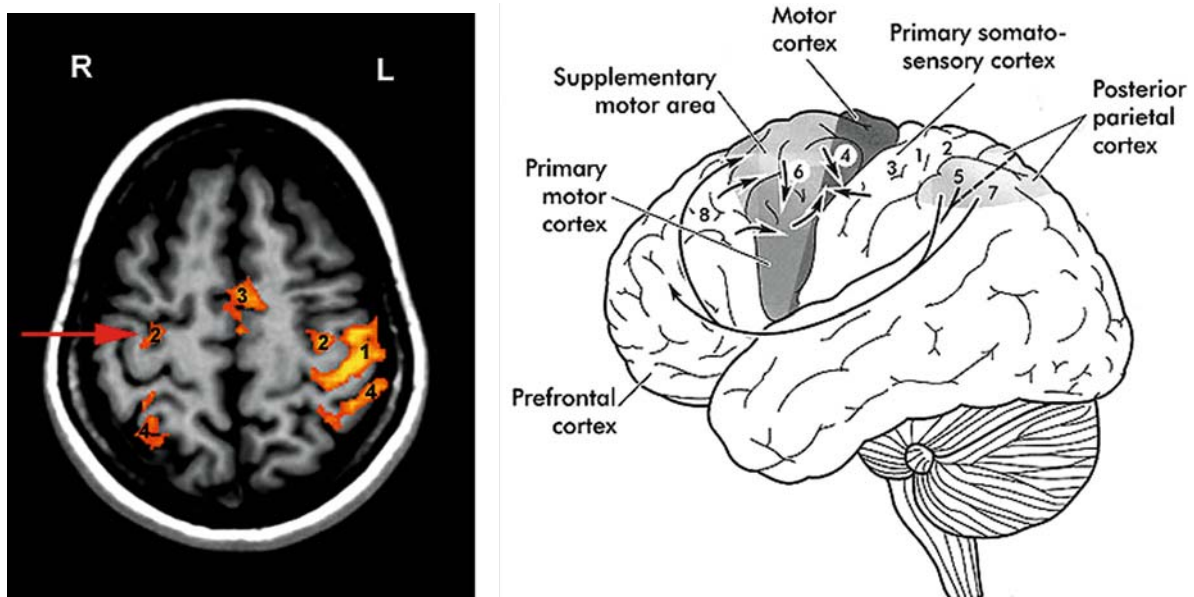


Fig. 4.22. Typical cortical activation pattern of complex finger opposition (right hand). Premotor activation ipsilateral to the moving hand (red arrow) serves as a functional landmark for the precentral gyrus in hemiparetic patients (a clinical case is presented in Figs. 4.23 and 4.24). Premotor activation is typically localized at the anterior wall of the precentral gyrus directly adjacent to the junction of the precentral sulcus with the superior frontal sulcus. It is important to note that this functional landmark does *not* localize the motor hand area! In the drawing of the cortical motor and somatosensory network (right) numbers indicate Brodmann areas (Reprinted from Radiologie up2date 4/2005 317–336 with permission)

Fig. 4.23. Example of fMRI localization of the motor hand area in a hemiparetic patient with a left malignant glioma using contralateral and ipsilateral movements. Residual motor function of the paretic right hand (grade 3/5) is driven by residual activation of the contralateral motor hand area (*black arrow*). Complex finger opposition of the non-paretic left hand is associated with activation of the cortical motor network in both hemispheres. Robust ipsilateral primary motor coactivation (*black arrow*) confirms the localization of the motor hand area. Additional ipsilateral premotor activation (*white arrow*) indicates the ventral wall of the precentral gyrus

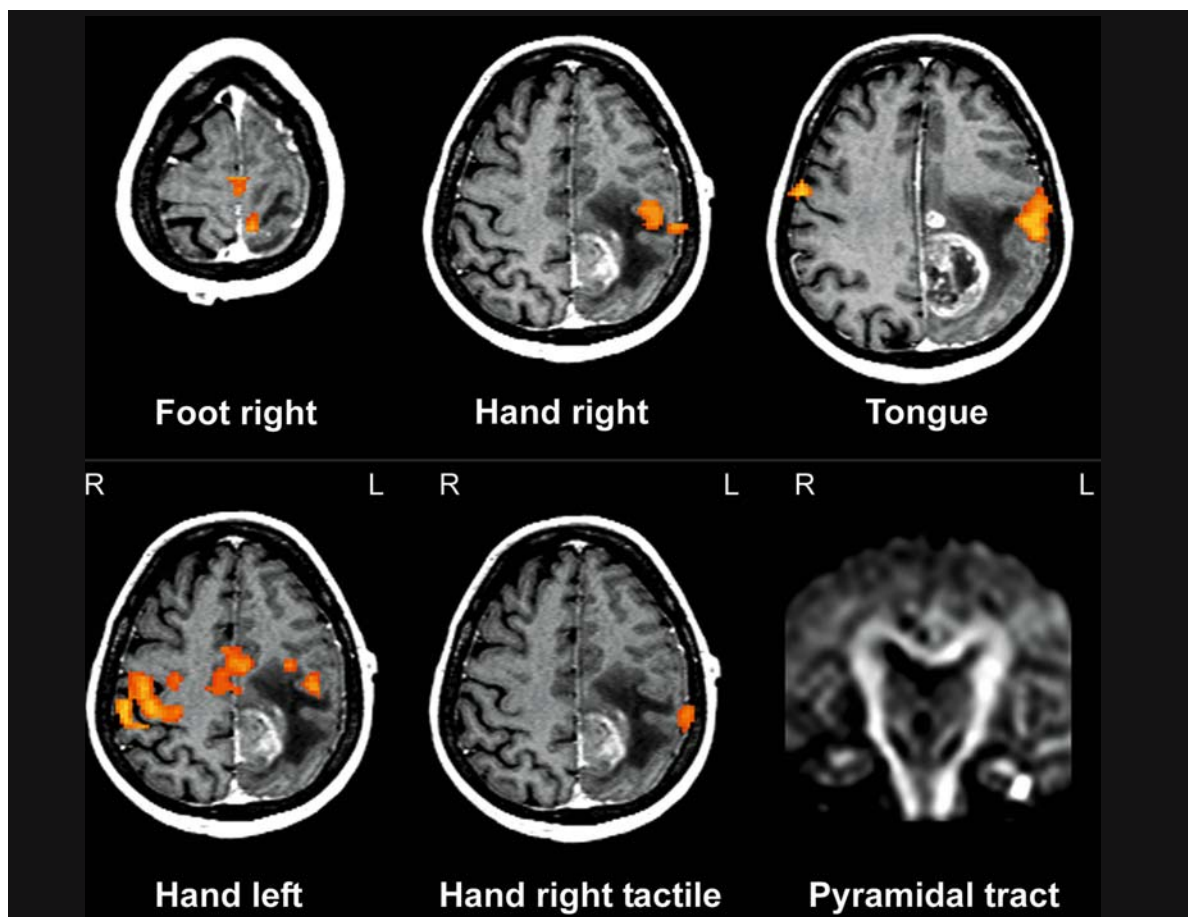
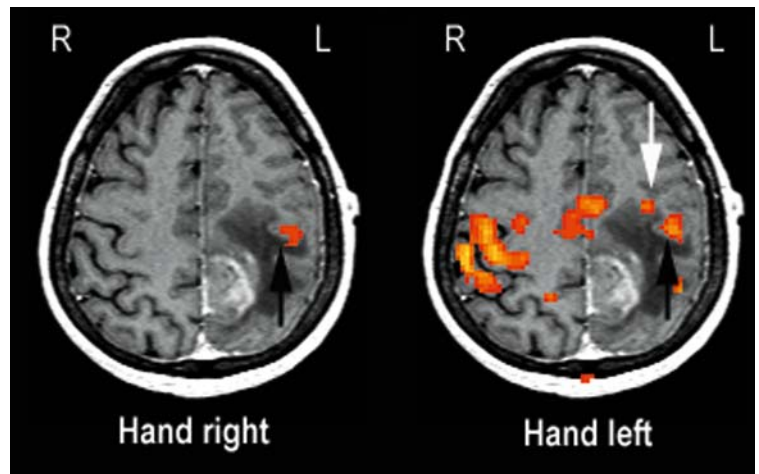


Fig. 4.24. Presurgical fMRI in rolandic brain tumors – standard and special protocols. *Upper row* (standard protocol): somatotopic mapping of the primary motor cortex indicated a parietal localization of the contrast enhancing malignant glioma (same patient as Fig. 23). *Lower row* (special protocols): complex finger opposition of the non-paretic left hand (*left*) and fully automated tactile stimulation of the contralesional right hand (*middle*) localize the pre- and postcentral gyrus in relation to the brain tumor. This diagnostic information is equivalent to that available from contralateral hand movement (please compare *upper row, middle*) and can be obtained also in patients with complete loss of contralateral motor function. Anisotropic diffusion images of the pyramidal tract completed this presurgical MRI protocol. Diffusion tensor tractography could provide more detailed anatomical information. Modified from (Stippich, Kress et al. 2003 with permission)

4.5

Presurgical fMRI of Language Function

The number of working groups localizing language brain function preoperatively is ever growing – the largest collective study to be published to date includes 81 patients (STIPPICH, RAPPS et al. 2007). The diagnostic aims of presurgical language fMRI include localizing Broca's and Wernicke's speech areas in relation to brain tumors or to epileptogenic zones and identifying the language-dominant hemisphere. Unlike motor or somatosensory fMRI, the indication for presurgical fMRI cannot be supported by morphological imaging. Morphological imaging provides only rough information on whether the potentially function-bearing gyri according to the classic language model – namely the left inferior frontal gyrus (Brodmann areas 44 and 45) or the left superior temporal gyrus (Brodmann area 22) – are affected by the tumor (Fig. 4.25). However, it has been demonstrated that the classical language model (LICHTHEIM 1885) (GESCHWIND 1971) is not sufficient to reflect the complexity of cortical language representations (BOOKHEIMER 2002) (GABRIELI, POLDRACK and DESMOND 1998; GRABOWSKI 2000). Hence, clinical and neuropsychological symptoms are ultimately decisive. Presurgical fMRI language protocols should always comprise several different paradigms to increase diagnostic certainty and to account for various linguistic components. There is no such thing as a universal paradigm for fMRI language assessment!

Language fMRI is not used (anywhere near) as frequently in presurgical imaging as motor fMRI. This is partly due to its higher equipment, personnel and logistical requirements, which make implementation of the procedure in clinical routine more problematic. Moreover, almost all laboratories have developed their own methodology, making research results difficult to compare. This variability affects not only the chosen stimulation paradigm, on which examination results depend to a great extent, but also the way in which data are presented – visually or acoustically – as well as measurement and evaluation parameters. Despite this, and on the basis of results from numerous validation studies using established reference procedures (EcoG, Wada test), it can be assumed that fMRI can reliably and non-invasively localize Broca's and Wernicke's language areas prior to brain surgery. Determining language dominance is possible; however, due to partly con-

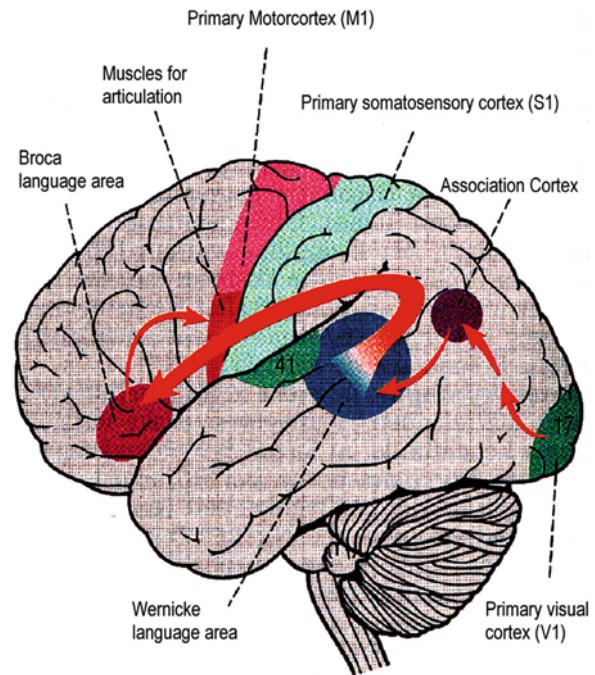


Fig. 4.25. Schematic drawing of language areas in the left hemisphere according to the classical language model (Wernicke-Lichtheim 1871). Red arrows indicate important anatomico-functional connections (e.g. arcuate fascicle). Modified from Roche Lexikon Medizin, 4th edn, 1998, Urban and Fischer, Munich, p 1578

flicting results published in the literature no definitive statement can be made on reliability in this respect (see Chap. 7).

4.5.1**Review of Literature**

In this paragraph we try to lead the reader through the complex and to a certain extent inhomogeneous data published on presurgical language fMRI. Since in many studies patients were included with both brain tumors and with epilepsies it seemed not appropriate to distinguish between those entities. Hence this review covers also information relevant for Chap. 5.

Just 3 years after the first reports on fMRI, a preliminary study showed that the BOLD signal contrast obtained in simple tests of language and motor function was very similar between subjects with epilepsy and normal controls, demonstrating the feasibility of the technique in studies of patients with epilepsy (MORRIS et al. 1994). Since then, fMRI of language

processing has become one of the most clinically relevant applications in the field of epilepsy and also in patients with brain tumors prior to surgery. The main aim of localizing language function is to predict and minimize postoperative language deficits. In patients considered for epilepsy surgery – who are mainly patients with temporal lobe epilepsy (HERMANN et al. 1999) – fMRI is predominantly used for language lateralization (i.e. determination of hemispheric dominance) and only to a lesser extent for intrahemispheric distribution of eloquent cortex.

Numerous studies demonstrate fMRI to identify language hemispheric dominance reliably (BINDER et al. 1995; BENSON et al. 1996; BINDER, SWANSON et al. 1996; BAHN, LIN et al. 1997; BINDER et al. 1997; BINDER et al. 2000) (FITZGERALD, COSGROVE et al. 1997) (STAPLETON, KIRIAKOPOULOS et al. 1997) (SHAYWITZ, SHAYWITZ et al. 1995) (CUENOD et al. 1995) (HERTZ-PANNIER, GAILLARD et al. 1997) (VAN DER KALLEN, MORRIS et al. 1998) (WORTHINGTON, VINCENT et al. 1997) (FROST, BINDER et al. 1999) (SZAFLARSKI, BINDER et al. 2002). However, the areas identified in different studies of language processing have varied markedly, likely relating to use of different linguistic activation or control tasks, imaging and post-processing techniques, among other factors. Again, there is no single fMRI paradigm that identifies „language cortex“. Language is a complex process which involves specialized sensory systems for speech, text, and object recognition, access to whole-word information, access to word meaning, processing of syntax and multiple mechanisms for written and spoken language production (BINDER et al. 2002). Hence, the activation pattern is crucially dependent on the chosen fMRI task design.

Hearing words – whether the task involves passive listening, repeating, or categorizing – activates the superior temporal gyrus bilaterally when compared with a resting state (BINDER, FROST et al. 2000) (PRICE et al. 1996) (WISE et al. 1991). The symmetry of this activation can be explained by the task contrast (complex sounds compared with no sounds). The rest condition contains no control for prelinguistic auditory processing that engage auditory cortex in both superior temporal gyri. Brain areas associated with semantic processing might be also activated during the rest state and hence reduce sensitivity for the activation task (BINDER et al. 1999).

Similar problems occur in designs that contrast reading or naming tasks with a resting or visual-fixation baseline. In a study mostly on patients with lateralized lesions, Benson et al. found that such pro-

cedures do not reliably produce lateralized activation and do not correlate with language dominance measured by Wada testing (BENSON, FITZGERALD et al. 1999).

The most common types of tasks successfully used for lateralization purpose are word generation tasks (also called verbal fluency tasks) and semantic decision-making, the former tending to show relatively consistent activation of anterior language areas and the latter demonstrating a more widely distributed network including anterior and posterior hemispheric regions (BINDER, FROST et al. 1997).

In word generation tasks, subjects are given a beginning letter, a semantic category (e.g. animal, food) and must retrieve a phonologically or semantically associated word. In verb generation tasks, the subject generates a verb in response to seeing or hearing a noun. These tasks reliably activate the dominant inferior and dorsolateral frontal lobe, including prefrontal and premotor areas (WISE, CHOLLET et al. 1991) (WARBURTON et al. 1996) (RAICHLE et al. 1994) (PETERSEN et al. 1988), and lateralization measures obtained from this frontal activation agree well with Wada language lateralization (BAHN, LIN et al. 1997; YETKIN, SWANSON et al. 1998; BENSON, FITZGERALD et al. 1999; LEHERICY, COHEN et al. 2000). There is evidence that semantic language tasks such as verb generation in response to nouns, noun categorization or noun generation within specific categories may be more effective in lateralizing than phonologically based generation tasks such as covert repetition (LEHERICY, COHEN et al. 2000).

Word-generation tasks are usually performed silently in fMRI studies to avoid movement artifacts. The resulting absence of task-performance data is usually not a problem when clear activation is observed, but bars the investigator from assessing the contribution of poor task performance in cases with poor activation.

A semantic decision task was used by Springer and colleagues to address the issue of language dominance in patients with epilepsy (SPRINGER, BINDER et al. 1999). Fifty right-handed patients with epilepsy were compared with 100 right-handed normal controls. Language activation was accomplished by contrasting a semantic decision task with a tone discrimination test. The tone discrimination task was developed to control for non-linguistic components of the task (e.g., attention, sound processing, manual response). Using a categorical dominance classification, 94% of the normal control subjects were considered left hemisphere dominant, 6% had bilateral

language representation, and none of the subjects had rightward dominance. In the epilepsy group there was greater variability of language dominance, with 78% showing left hemisphere dominance, 16% showing a roughly symmetric pattern and 6% showing right hemisphere dominance. Atypical language dominance in the epilepsy patients was associated with an earlier age of brain injury and with weaker right hand dominance. The relatively high prevalence of atypical language representation in epilepsy patients stresses the importance of assessment of hemispheric dominance before interventional procedures are performed in areas potentially relevant for language in either cerebral hemisphere (SPREER, QUISKE et al. 2001).

Further studies with the paradigm described above were performed by Binder and colleagues (BINDER, RAO et al. 1995; BINDER, SWANSON et al. 1996; BINDER, FROST et al. 1997). The activation pattern was in general strongly left lateralized, and involved both prefrontal and posterior association areas. The activation was strongly correlated with Wada language lateralization (BINDER, SWANSON et al. 1996). Another study using a semantic decision task by Desmond and colleagues came to the same result. Seven post-operative patients with temporal lobe epilepsy were examined and the BOLD signal correlates were compared with a pre-operative Wada-test. In all cases, using a region-of-interest based analysis looking only at inferior frontal regions, the lateralization by fMRI was the same as by the Wada test (DESMOND, SUM et al. 1995). An attractive feature of semantic decision tasks is that measured behavioral responses, consisting of simple button presses for stimuli that meet response criteria, permit task performance to be precisely quantified.

As mentioned above, both word generation and semantic decision tasks identify mainly frontal lobe language areas but are less consistent activators of temporal language regions. An fMRI paradigm with consistent temporal lobe activation was reported by (GAILLARD, BALSAMO et al. 2002). The paradigm consisted of silent naming of items in response to silent reading of item description. The authors found language lateralization in 27 of 30 patients with temporal lobe epilepsy. The fMRI dominance was in agreement with the Wada test in 15 of 20 patients.

Word generation tasks are also most frequently used in language fMRI studies on brain tumor patients (LATCHAW, UGURBIL and HU 1995; HERHOLZ, REULEN et al. 1997; HIRSCH, RUGE et al. 2000; HABERG, KVISTAD et al. 2004; HALL, LIU et al. 2005;

VAN WESTEN, SKAGERBERG et al. 2005). Many agree that a combination of different tasks increases paradigm effectiveness. Van Westen et al. used a combination of word generation and rhyming in 20 patients with tumors close to sensorimotor or language areas in a 3T study and report a paradigm effectiveness varying from 79% to 95% (VAN WESTEN, SKAGERBERG et al. 2005). In another study with a large group of patients (56 patients with lesions near language-relevant areas) the authors achieved activation of the Wernicke area in 91% and of the Broca area in 77% applying a combination of silent word generation task (picture naming) and listening to spoken words. In the same study language lateralization with fMRI and Wada test was congruent in all 13 patients examined (HIRSCH, RUGE et al. 2000).

There are several fMRI studies reported in children with epilepsy (BENSON, LOGAN et al. 1996; HERTZ-PANNIER, GAILLARD et al. 1997; STAPLETON, KIRIAKOPOULOS et al. 1997; LOGAN 1999). Successful fMRI lateralization paradigms have been reported on children as young as 6 years (HERTZ-PANNIER, CHIRON et al. 2002). The hemodynamic response appears to be similar in children and adults (BENSON, LOGAN et al. 1996; HERTZ-PANNIER, GAILLARD et al. 1997). Word generation tasks are the most commonly used tasks for evaluation of pediatric epilepsy surgery candidates, and, as in adults, show general agreement with Wada testing and electrocortical stimulation (HERTZ-PANNIER, GAILLARD et al. 1997; STAPLETON, KIRIAKOPOULOS et al. 1997; LOGAN 1999). There is some evidence that young children activate more widely than adults, in verbal fluency tasks at least (GAILLARD, HERTZ-PANNIER et al. 2000). Other fMRI studies in children were performed with reading tasks or naming to description (GAILLARD, PUGLIESE et al. 2001). Special considerations in children, like choice of suitable experimental and control conditions, have been recently reviewed (BOOKHEIMER 2000; GAILLARD, GRANDIN et al. 2001).

In addition to information on lateralization, fMRI has the potential to provide detailed maps of the intrahemispheric localization of critical language areas. There are a number of studies suggesting a close spatial relation between fMRI activation and intraoperative electrocortical stimulation (FITZGERALD, COSGROVE et al. 1997; YETKIN, MUELLER et al. 1997; RUGE, VICTOR et al. 1999; RUTTEN, VAN RIJEN et al. 1999; SCHLOSSER et al. 1999; LURITO, LOWE et al. 2000; CARPENTIER et al. 2001). A recent study by Rutten et al. (2002) compared the results of fMRI

quantitatively with intraoperative electrocortical stimulation mapping in thirteen patients (RUTTEN, RAMSEY et al. 2002). In eight patients critical language areas were detected by electrocortical stimulation, and in seven out of eight patients sensitivity of fMRI was 100% (i.e. fMRI correctly detected all critical language with high spatial accuracy). This indicates that such areas could be safely resected without the need for intraoperative electrocortical stimulation. A combination of three different fMRI language tasks (verb generation, picture naming, and sentence processing) was needed to ensure this high sensitivity, as no single task was sufficient for this purpose. On the other hand, on average only 51% of fMRI activations were confirmed by electrocortical stimulation, resulting in a low specificity of fMRI. Both sensitivity and specificity are strongly dependent on the statistical threshold. This study illustrates the current problems of basing clinical decisions (e.g. surgical strategies) on fMRI activation maps. Different language-related paradigms activate a different set of brain regions and a combination of different tasks is necessary to achieve high sensitivity in identifying critical areas (RAMSEY, SOMMER et al. 2001).

However, a generally accepted standard protocol has not been established yet. Further, the extent of the activation is also critically dependent on the applied statistical threshold (for details see Sect. 4.3). Finally, the presence of fMRI activation at noncritical language sites limits the predictive value of fMRI for the presence of critical language areas. Some regions activated during language tasks play obviously a minor, supportive role for language function, and resection of these areas may not necessarily produce clinically relevant deficits. Still, because of these problems, the clinical role of fMRI in identifying eloquent cortical areas of cognitive function is limited. Currently, it can be useful to facilitate intraoperative electrocortical stimulation rather than replace this method (DEBLAERE, BACKES et al. 2002).

Another possible goal of fMRI is to replace Wada testing as the reference procedure for determining language and memory dominance in candidates for brain surgery. If established as a valid and reliable technique, fMRI will either render the Wada test obsolete, or at least reduce its role to a secondary procedure to be used only when fMRI is not practical because of either technical considerations or patient variables. In the Wada test (intracarotid amobarbital test) the portions of one hemisphere

supplied by the anterior circulation are transiently anesthetized using a bolus of short-acting amobarbital, allowing the contralateral hemisphere to be assessed independently (WADA and RASMUSSEN 1960). The Wada test is invasive, carries significant risks and the validity of individual Wada test results can be compromised by acute drug effects, which may produce behavioral confounds of sedation and agitation. Although the Wada test is commonly designated the reference procedure in language lateralization tests (RAUSCH, SILFVENIUS et al. 1993), it is not a single standardized procedure. Differences in almost every aspect of methodology and design can be found in the Wada test protocols described in the literature and make between-center comparisons of the results difficult.

In a review by Baxendale (BAXENDALE 2002), 70 patients were found in the literature that have undergone both fMRI language studies and Wada testing (DESMOND, SUM et al. 1995; BINDER, SWANSON et al. 1996; BAHN, LIN et al. 1997; HERTZ-PANNIER, GAILLARD et al. 1997; WORTHINGTON, VINCENT et al. 1997; BENBADIS et al. 1998; YETKIN, SWANSON et al. 1998; BENSON, FITZGERALD et al. 1999; BAZIN, COHEN et al. 2000; LEHERICY, COHEN et al. 2000; CARPENTIER, PUGH et al. 2001). With the exception of one study (WORTHINGTON, VINCENT et al. 1997), which showed a comparatively low concordance of only 75% with a verbal fluency task used as fMRI paradigm, all other report impressive concordance rates between the two techniques despite the use of different language tasks and Wada test protocols. A study by Binder and colleagues correlated the Wada test and fMRI assessment of language laterality, using a laterality index for the Wada test (a continuous variable) and a laterality index from fMRI calculated as an asymmetry in the voxels activated in each hemisphere by a semantic decision task (BINDER, SWANSON et al. 1996). The correlation was extremely strong ($r=0.96$, $p<0.0001$) and all 22 subjects were classified to the same laterality by the two tests. Concordance at or near 100% was also found in the other studies that have employed categorical analyses to classify language representation (BENBADIS, BINDER et al. 1998; YETKIN, SWANSON et al. 1998). While these findings are promising, there are reasons to be cautious about replacing the Wada test with fMRI procedures at this time. In all of the Wada-fMRI comparison studies reviewed above, there were less than 30 cases collectively with crossed or atypical cerebral dominance patterns as defined by Wada, an extremely limited sample

on which to base clinical decisions. As mentioned above, there is evidence for a greater variability of language dominance in epilepsy subjects compared to normal controls (SPRINGER, BINDER et al. 1999; CARPENTIER, PUGH et al. 2001). Atypical language representation is the very condition that is perhaps the most important to detect, and the small numbers currently available do not allow any firm conclusions to be drawn about sensitivity or specificity of the various fMRI tests. Moreover, the incidence of significant discrepancy between fMRI and Wada lateralization measures is not known, nor have the reasons for the occasional discrepancies been investigated. For example, Hammeke and colleagues reported a significant discrepancy between fMRI and Wada lateralization indices in approximately one in ten patients (HAMMEKE, BELLGOWAN et al. 2000). In particular temporal tumors of the dominant hemisphere have been reported to lead to false-negative activation of the dominant hemisphere (WESTERVELD, STODDARD and MCCARTHY 1999; GAILLARD, BOOKHEIMER and COHEN 2000).

Finally, it has to be emphasized that the Wada test is not only undertaken to determine language dominance, but, perhaps more important, to reveal the ability of each hemisphere to sustain verbal memory. Before fMRI can fully displace the Wada test, further large scale studies are necessary to establish its equivalence to the Wada test, which has been repeatedly validated with respect to memory function, language representation, and prediction of both cognitive and seizure outcome (BINDER, ACHTEN et al. 2002). Moreover, acceptance of fMRI will largely depend on the perceived clinical need for the "lesion test" aspect of the Wada test, which provides more direct information about how well language and memory functions can be supported after functional removal of the contralateral hemisphere. Presently, the diagnostic value of fMRI and the Wada test seems to be rather complementary. KILLGORE et al. found that, when combined, fMRI and Wada test provided complementary data that resulted in improved prediction of postoperative seizure control compared with either procedure alone (KILLGORE, GLOSSER et al. 1999).

4.5.2

Special Practical Issues in Presurgical fMRI of Language Function

In contrast to the easy-to-perform movement tasks in motor fMRI, assessing cognitive brain function – and thereby language function – requires even closer cooperation from the patient. Therefore, all patients must be well prepared for fMRI. The individual patient training required prior to any language fMRI alone can – depending on the degree of tumor-associated language deficit – take up several hours of the investigator's time. Such training should guarantee the best possible match between the paradigms used in the fMRI protocol and linguistic ability, in order to ensure robust functional localizations and BOLD signals; for good reason it is combined with neuropsychological testing, including detailed documentation of language deficit. The problem of objective assessment of task performance in cognitive paradigms is difficult to solve in a clinical setting. Particularly in non-vocalized paradigms, it is difficult to test the patient's performance during block designed fMRI. Response devices used in non-clinical fMRI research can only be used on cooperative patients and are thus often unsuited to routine presurgical fMRI. The best guarantee of sufficient patient cooperation during clinical fMRI scanning remains the intensive training mentioned above. In addition, patients are asked to give their subjective appraisal of examination success after each measurement. Online evaluation of fMRI data ("real time fMRI") is an important aid offered in current product ranges by most manufacturers of clinical MR imagers, enabling immediate control of the examination success (FERNANDEZ, DE GREIFF et al. 2001). Hence, erroneous measurements can be detected immediately and repeated.

For the examination itself, the visual or acoustic stimulation unit must be assembled and later disassembled within a short period of time to avoid unnecessary disruption to routine clinical neuroimaging. If one assumes a time-frame of 1 h for the entire examination, including assembly, disassembly and adjustment of all stimulation devices, acquisition of a morphological contrast enhanced T1-weighted 3D data set for neuronavigation and possibly another two or three diagnostic imaging sequences, approximately 20 min remain for the actual fMRI examination. Within this time, several different language paradigms (HIRSCH, RUGE

et al. 2000; RAMSEY, SOMMER et al. 2001; RUTTEN, RAMSEY et al. 2002; VAN WESTEN, SKAGERBERG et al. 2005), preferably of varying degrees of difficulty and each with a repeat measurement (RUTTEN et al. 2002) to confirm functional localization should be applied, that is to say that each clinical language fMRI measurement cannot take much longer than 5 min.

4.5.3

Selection of Candidates for Presurgical Language fMRI

In contrast to patients with rolandic brain tumors, the selection of suitable candidates for presurgical language fMRI among patients with frontal and temporoparietal tumors is made largely irrespective of morphological changes in potentially function-bearing anatomical structures due to the absence of unequivocal morphological landmarks and due to significant anatomic variations in important language areas. Clinical and neuropsychological symptoms are of key importance. In our opinion, presurgical fMRI of language-associated brain activation makes sense in the following scenarios:

- Patients with tumor associated language deficit – also with tumor in the right hemisphere, since in this instance atypical organization of the language-relevant cortical representations must be assumed (see Fig. 4.31).
- Patients without language deficit but with left-sided brain tumor of classic localization, i.e., in close proximity to the inferior frontal gyrus (Broca area) or to the superior temporal gyrus, supramarginal gyrus or angular gyrus (Wernicke area) according to MR-morphological criteria (see Figs. 4.27 and 4.28).
- Left-handed patients, including patients with right-sided brain tumor.
- Multilingual patients.

In these patients, fMRI makes it easier to verify the indication to operate, as well as to plan sparing surgery and function-preserving procedures, while taking atypical language representations or tumor-induced neuroplastic changes into consideration.

Note: the selection criteria mentioned here are meant as suggestions arising from typical MR-morphological and clinical findings in patients with

frontal or temporoparietal brain tumors. It is currently not possible to make a medical indication in a strict sense for fMRI. This is due to the lack of controlled prospective studies demonstrating the clinical benefit of presurgical fMRI in terms of reduced postoperative morbidity or mortality.

4.5.4

Language Paradigms for Presurgical fMRI

Human language is conveyed over an extensive network of multiple functional areas to the frontal, temporal and parietal lobes in both cerebral hemispheres (see Chap. 3). As demonstrated above, language fMRI can be performed using various paradigms. For this reason no recommendations can be made. The choice of clinically appropriate fMRI protocols should be made on the basis of the above-mentioned diagnostic aims and clinical requirements: to obtain reliable BOLD activations paradigms need to be standardized and adjustable to the individual abilities of each patient. The language areas essential for intact speech (Broca and Wernicke) must be localized, where as the importance to localize other areas in order to preserve them during surgery is not that clear. An array of word-generation tasks are suitable to this end, whereby increased language-associated memory, as well as other linguistic and cognitive processes can also be scanned using task categories for free generation of several words per trigger (BOOKHEIMER 2002). Sentence-generation tasks pose an even greater challenge (JUST et al. 1996; SAKAI, HASHIMOTO and HOMAE 2001). These are easily standardized when a defined sentence is generated per trigger.

Clinical feasibility tests showed that the individual triggers must be as simply structured, unambiguous and easy to detect as possible. The stimulus frequency must be adjustable within a wide range to the linguistic abilities of different patients, without changing the basic structure of the block design. Task-synchronous motion artifacts can be reduced by using non-vocalized language tasks (overt speech) (HINKE et al. 1993; RUECKERT et al. 1994; PALMER et al. 2001), although the brain activation is not identical to that in the corresponding vocalized paradigm.

The examination protocol suggested here has been specially designed to fulfill these clinical requirements (STIPPICH, MOHAMMED et al. 2003).

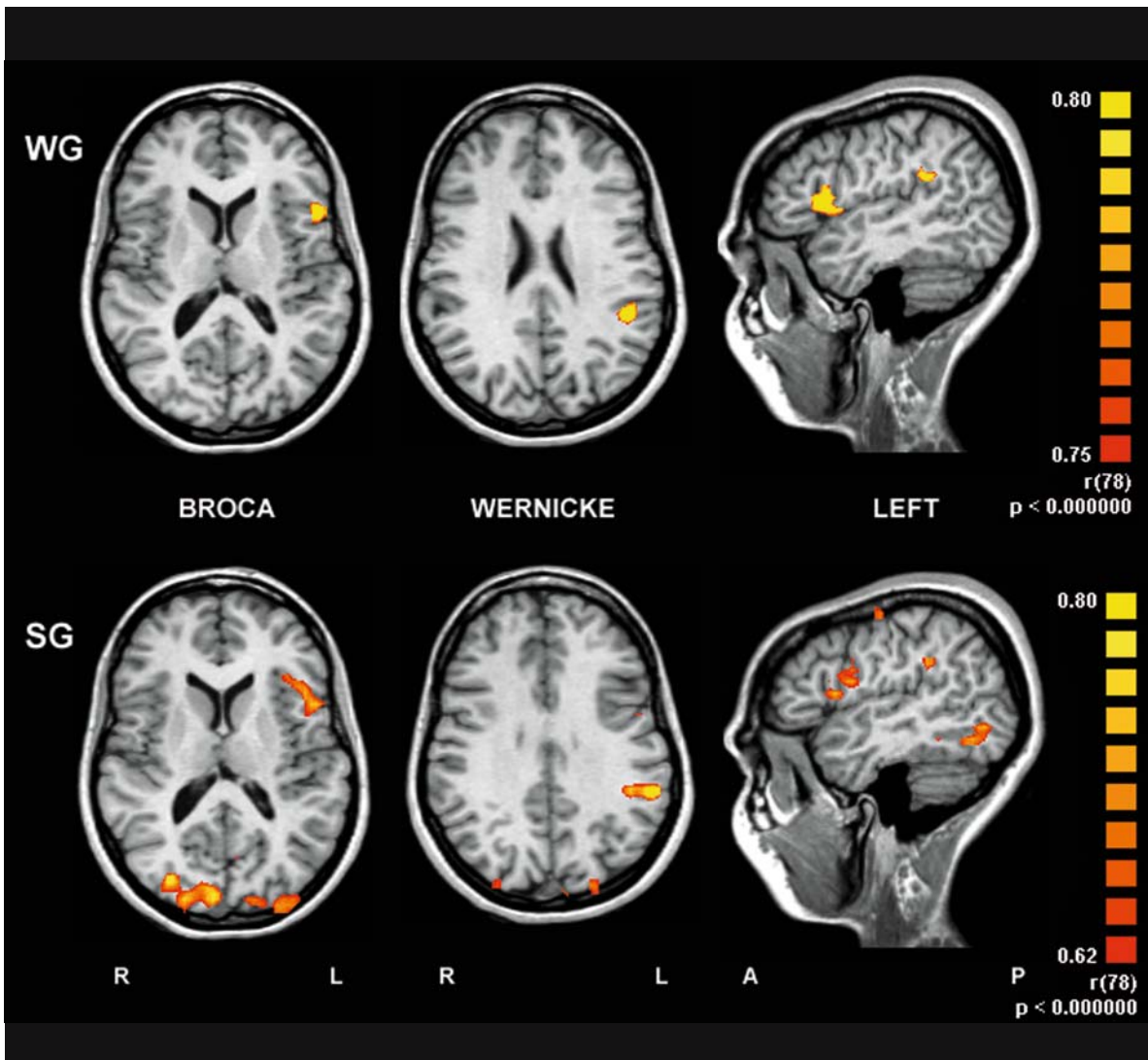


Fig. 4.26. Functional localization of Broca's and Wernicke's areas using the word generation (WG) and sentence generation (SG) paradigms. Note that the functional localizations are congruent, but not perfectly identical. Modified from Stippich, Mohammed et al. 2003 with permission

At a measurement time of approximately 4 min (234 s) per paradigm reliable functional localization of Broca's and Wernicke's areas can be achieved, as well as of the anatomically homologous areas in the right hemisphere as a basis on which to calculate regional lateralization indices. At 1.5 Tesla the physiological BOLD signals are robust in the different mentioned functional language areas, with mean correlations between signals measured and hemodynamic reference function range from $r=0.55$ to $r=0.80$; BOLD signal intensities range from 1.5% to 2.5% (Fig. 4.26). Both paradigms (sentence and

word generation) are visually triggered and can be adjusted to the linguistic ability of the patient by varying the trigger frequency. By using non-magnetic, optically correctable reflective glasses with a slot for commercial optical lenses it is possible to correct ametropia (STIPPICH, RAPS et al. 2007). At the same time, visual stimulation prevents possible undesired superposition of language-associated activations in the Wernicke speech area (BA21) onto activation in the directly adjacent auditory cortex (BA41, 42), which can occur with acoustic stimulation (BINDER, RAO et al. 1995).

4.5.5

Presurgical fMRI of Language Function

In patients with brain tumors, presurgical language fMRI localizes Broca's and Wernicke's area in relation to the pathology and provides a measure of hemispheric dominance (Figs. 4.27 and 4.28). Besides providing functional landmarks for surgical decision making, planning and operation different patterns of language activation can be identified, that may be roughly characterized by

left dominance, right dominance, mixed or crossed dominance and equidominance. This information is available noninvasively and exceeds that from Wada-Test (Fig. 4.29). However, diagnostic results from the different paradigms may differ (Fig. 4.30). Until now there is no clear cut rationale how to handle this problem. In addition, the current state of data on the reliability of fMRI

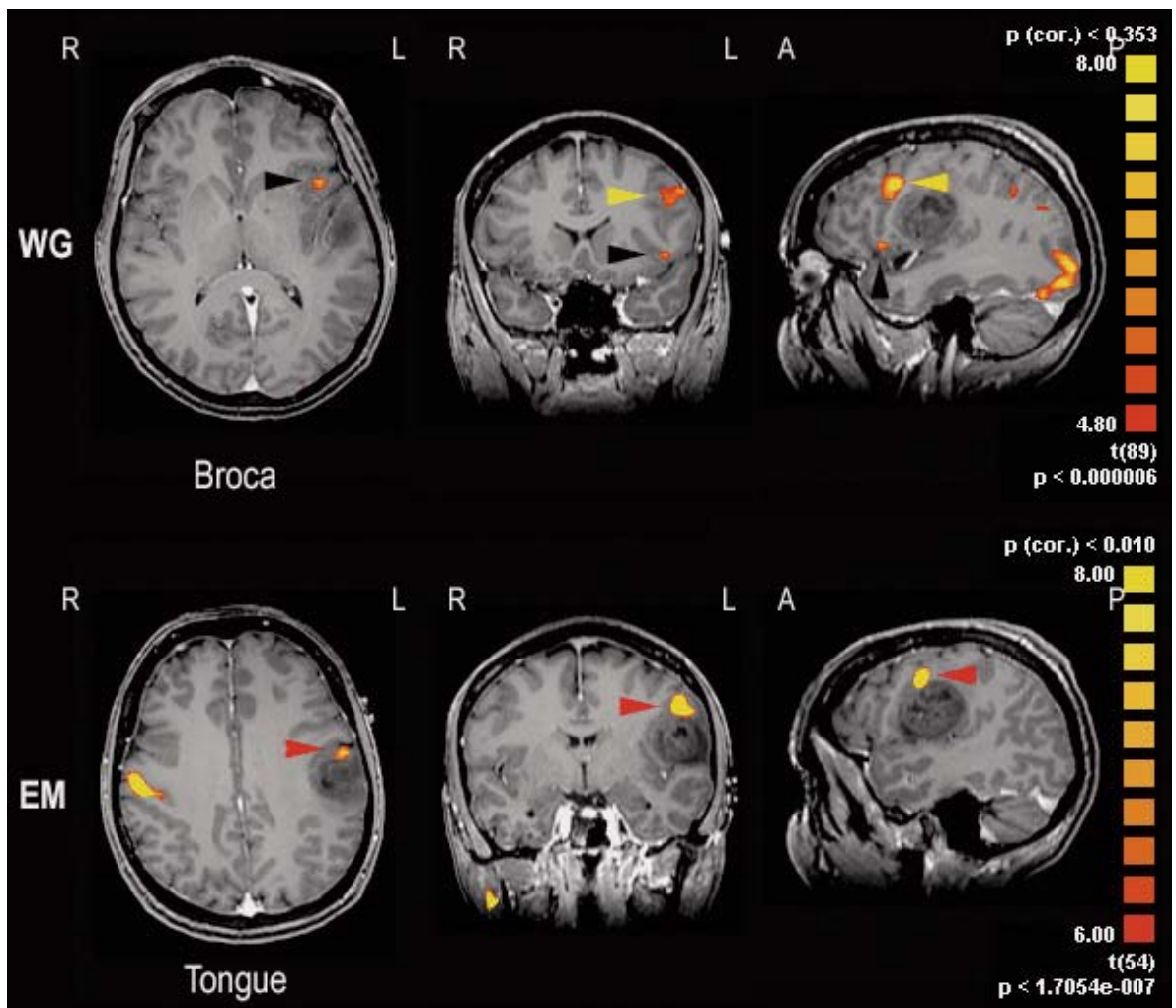


Fig. 4.27. Presurgical fMRI localization of Broca's area using the word generation paradigm (WG) in a patient with a left inferior frontal astrocytoma as reflected by the typical activation of the inferior frontal gyrus, pars opercularis (black arrowhead). Note the additional strong language associated activation (yellow arrowhead) at the upper edge of the inferior frontal gyrus (pars opercularis). This activation can be distinguished clearly from primary motor tongue activation (EM = executed movement) of the inferior precentral gyrus (red arrowhead)

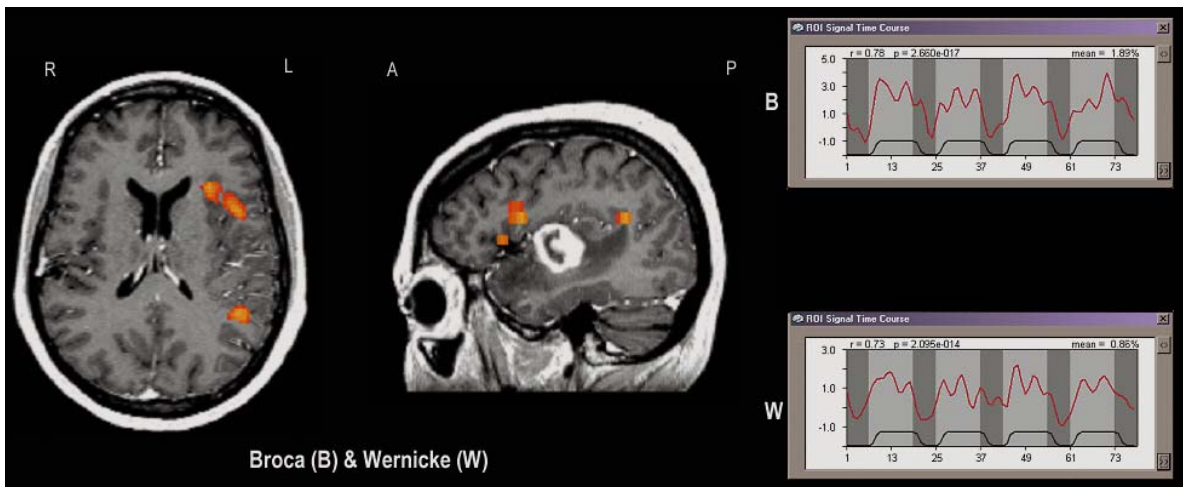


Fig. 4.28. Presurgical fMRI language localization and lateralization in a right handed patient with a malignant glioma of the left superior temporal gyrus – critical to Wernicke's area by anatomical consideration. Sentence generation (SG) revealed clear left language dominance and localized Wernicke's area at the dorsal end of the superior temporal gyrus. BOLD-signal time courses for Broca's area (B, $r=0.78$, $\Delta S=1.89\%$) and Wernicke's area (W, $R=0.73$, $\Delta S=0.86\%$). Note again the two BOLD-activations in Broca's area (small cluster at the pars triangularis, larger cluster at the upper pars opercularis)

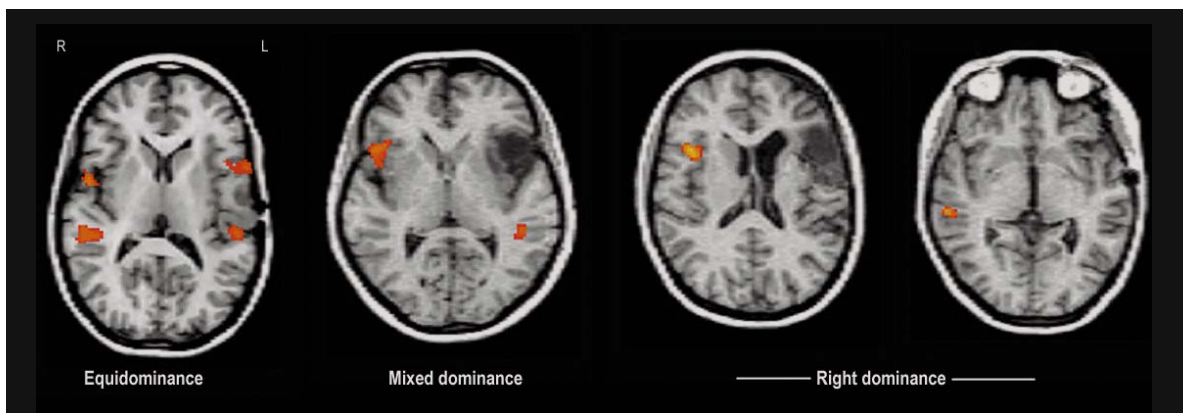


Fig. 4.29. Patterns of atypical language dominance as revealed by presurgical fMRI: equidominance between both hemispheres, mixed dominance (here with a right dominance for Broca's area and a normal left dominance for Wernicke's area), and pure right dominance for Broca's and Wernicke's areas

for determining language hemisphere dominance is not clear. To resolve this issue, further validation studies are needed on a larger number of patients in whom fMRI, referencing and clinico-neuropsychological testing are all carried out in a standardized way. With regard to language lateralization, it appears acceptable to dispense with

extensive invasive diagnostics in cases where, by using several paradigms, a typical left-dominance is proven on fMRI. Consequently, to eliminate any doubt, an additional, invasive validation should be performed in the case of conflicting results from various paradigms and atypical language dominance (Fig. 4.31).

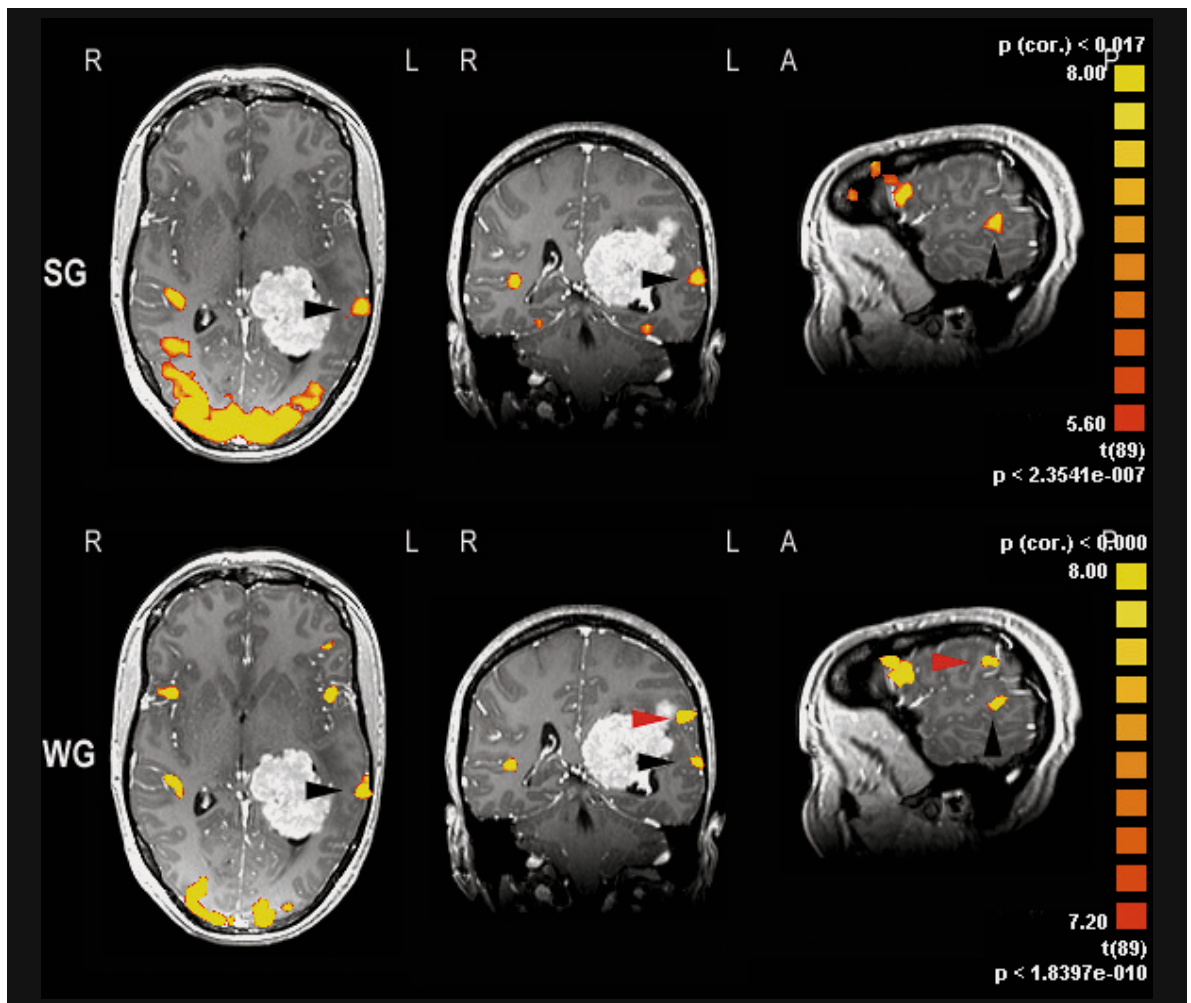


Fig. 4.30. Presurgical fMRI language localization and lateralization in a patient with a giant intraventricular meningioma using different paradigms. The diagnostic results are not identical, but congruent and support each other. Sentence generation (SG) localized Wernicke's area in its typical localization of the left superior temporal gyrus adjacent to the superior temporal sulcus (*black arrowhead*) and revealed an equidominance. Word generation (WG) confirmed this finding, but localized a second language center in Wernicke's area in the left supramarginal gyrus (*red arrowhead*) that was also taken into consideration for operation planning and execution. Note the bilateral Broca activation (also equidominant)

4.6 Diagnostic Capabilities and Limitations of Presurgical fMRI

Traditionally, functional areas are electrophysiologically mapped intraoperatively to reliably assess the spatial relationship between brain tumor and functional cortex (OJEMANN, OJEMANN et al. 1989; OJEMANN 1991; DUFFAU, CAPELLE et al. 1999; DUFFAU, SICHEL et al. 2000; DUFFAU 2001; DUFFAU, BAUCHET et al. 2001; DUFFAU, CAPELLE et al. 2002; DUFFAU, DENVIL et al. 2002; DUFFAU et al. 2003;

DUFFAU 2005; DUFFAU 2006). Intraoperative EcoG is considered very reliable, but comprises several disadvantages. Surgery time can be substantially prolonged and patients often need to be subjected to awake craniotomy. Furthermore, it is possible to derive activations only from the brain surface, while the by far larger portion of the cortex deep in the cerebral convolutions remains inaccessible (COSGROVE, BUCHBINDER et al. 1996). Another significant disadvantage of EcoG is that the information is not available preoperatively and can not be implemented in the assessment of the indication to operate and the

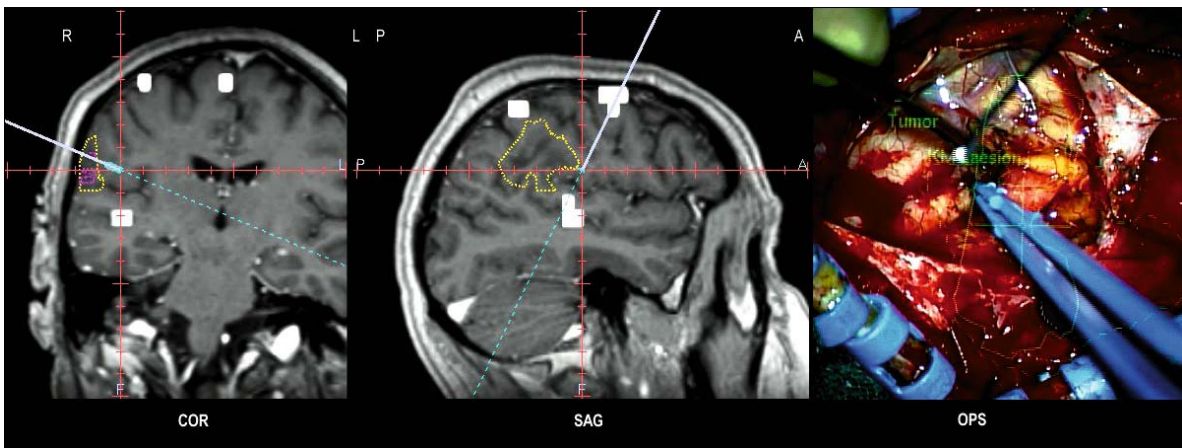


Fig. 4.31. Intraoperative validation of preoperative fMRI language localization in a right-handed male patient with a right parietal oligoastrocytoma (WHO II) and aphasic symptoms. Atypical right language dominance was diagnosed preoperatively using fMRI and Wada-test. Stimulation of the area that showed BOLD-activation in the STG (WR) interrupted language production during awake craniotomy, confirming preoperative fMRI localization. *Yellow lines* indicate planned resection borders in neuronavigation. *Left:* Coronal (COR) and sagittal (SAG) views; functional activations (*white clusters*). *Right:* operative site (OPS)

planning of function-preserving surgery. Likewise, the Wada test as a reference procedure for lateralization of speech and memory puts the patient under strain, involves all the risks of arterial catheter angiography and is not standardized – test results can therefore vary (WADA and RASMUSSEN 1960; RAUSCH, SILFVENIUS et al. 1993). After all, morphological imaging provides very detailed information on intracranial pathologies (OSBORN 2004), but not on brain function. FMRI is capable to overcome these disadvantages of the “traditional diagnostic procedures” by visualizing anatomy, pathology and function non-invasively in a single examination already prior to surgery.

When carried out in a standard way, fMRI is basically capable of providing a clinical “functional diagnosis” for individual patients (THULBORN 2006); however, currently only within the framework of scientific studies. Functional landmarks help to estimate possible therapy-related deficits and are thus particularly useful in providing patient information, verifying the indication and selecting a sparing therapeutic procedure. Once the operation has been decided upon, careful planning and appropriate selection of incision, trepanation, surgical access and resection margins are essential to function-preserving surgery. Intraoperatively, functional localizations facilitate surgical orientation, although inaccuracies resulting from displaced brain tissue need to be taken into consideration (STIPPICH, HEILAND

et al. 2002; STIPPICH, KRESS et al. 2003). All these factors increase patient safety and reduce the risk of postoperative deficits which additionally reduce quality of life.

According to current knowledge, one can assume that presurgical fMRI is able to contribute to a reduction of invasive diagnostic procedures both before and during neurosurgical interventions in patients with brain tumors. Whether fMRI can have a positive effect on surgery-related morbidity and disease-related mortality remains to be determined in prospective studies. Prerequisites for this include a consensus on performance, analysis and medical appraisal of presurgical fMRI, as well as the delineation of recommendations and guidelines by the assigned medical societies.

Preoperative fMRI has limitations imposed by patient-specific and methodological factors. Despite intensive patient training, optimized examination protocols and appropriate head fixation, some patients cannot be examined due to poor cooperation or marked restlessness. When motor paradigms are used, undesirable continuation of movement during resting periods or undesirable and mostly uncontrolled and interspersed accompanying movements in other parts of the body can significantly compromise the quality of the examination, even if individually adjusted evaluation is used to register the error precisely. In the end, after this time-consuming process, examination results often need to

be discarded. The same holds true for strong motion artifacts which cannot be corrected at later data processing stages. Stimulus-related motion artifacts can simulate activations, leading to false high BOLD signals or even to incorrect localization (HAJNAL, MYERS et al. 1994; KRINGS, REINGES et al. 2001; HOELLER, KRINGS et al. 2002; STEGER and JACKSON 2004). With regard to the appearance of motion artifacts, tongue and toe movements, as well as finger opposition tasks are less critical than hand, foot and lip movements; when language paradigms are used, non-vocalized are less critical than vocalized tasks.

The problems associated with investigating motor function in patients with tumor-related hemipareses have already been addressed (see Sect. 4.4.6). In most cases, functional localization of the pre- and postcentral gyrus can be achieved by using residual motor function in the affected extremities and applying special paradigms (STIPPICH, KRESS et al. 2003). Compared to motor fMRI, BOLD signals are significantly weaker on tactile stimulation. Particularly in the lower extremities, tactile stimulation does not always achieve sufficient activation. This is accounted for by the lower number of receptors in toe tips, the comparatively small cortical toe representation and ill defined compressed air pulses when long pneumatic tubes are used.

The success of language fMRI depends pivotally on patient training and optimal adjustment of the paradigm to suit language ability (STIPPICH, HEILAND et al. 2002). If patients are over-tested, they perform only a portion of the required language tasks, leading to lower activation. The same is true of under-testing where too few triggers are given. Additionally, "free thinking" can then lead to uncontrolled activation, e.g. when patients get bored. Since, using our paradigms, neither source of error can be controlled during fMRI, the paradigm which has proven to be optimal in training is always used for measurement. To increase certainty, the patient is interviewed after each fMRI measurement about whether the task was successfully accomplished. If this was not the case, the task is repeated. Training always takes place immediately prior to fMRI and lasts at least 20 min in order for the patients to master the paradigms and to avoid overlap of learning effect and examination results. The training period can last longer in patients with limited linguistic ability. Special issues regarding medication and drug effects in cognitive clinical fMRI have been addressed in 5.2.1.

The BOLD signals based on fMRI originate mainly in the capillary bed of the activated brain area

and downstream veins (FRAHM, MERBOLDT et al. 1994; MENON, OGAWA et al. 1995). Thus fMRI measures a hemodynamic secondary phenomenon and not neuronal activity directly. Possible localization errors due to BOLD signals from draining veins can be identified by superimposing functional image data onto contrast-enhanced anatomical T1-weighted image sequences (KRINGS et al. 1999). Careful analysis of the signal-time curves of functional raw data helps to distinguish between parenchymatous and venous activation, since these rise at different rates (KRINGS, REINGES et al. 2001). By causing vessel compression and pathological changes in vascular autoregulation, brain tumors can affect the localization and intensity of the BOLD signals measured (HOLODNY, SCHULDER et al. 1999; HOLODNY, SCHULDER et al. 2000; KRINGS, REINGES et al. 2002; ULMER et al. 2003; ULMER et al. 2004; KIM, HOLODNY et al. 2005; LIU, FELDMAN et al. 2005; HOU et al. 2006; LUDEMANN, FORSCHLER et al. 2006). Whether artificial activations can occur due to their neovascularization remains to be clarified. For this reason, activations within contrast-enhanced tumor portions should be assessed as artifacts until reliable study results are available. Such activations should not be used for risk assessment, surgery planning or functional neuronavigation. The same is true for BOLD signals in strongly vascularized cerebral metastases or arteriovenous malformations (LAZAR, MARSHALL et al. 1997; ALKADHI, KOLLIAS et al. 2000; LEHERICY, BIONDI et al. 2002; OZDOBA, NIRKKO et al. 2002).

Investigator-dependent inaccuracies occur in manual superposition of EPI data distorted by the method onto anatomical 3D data sets. As a precaution, a possible localization error of approximately 0.5 cm should always be assumed (STIPPICH, KRESS et al. 2003). Improvements are expected in the future when distortion corrections for EPI data sets are available for clinical application (WEISKOPF, KLOSE et al. 2005; LIU and OGAWA 2006; PRIEST, DE VITA et al. 2006), enabling superposition routines to be automated. We consider defining resection margins in presurgical diagnostics on the basis of fMRI data as unreliable, since the spatial extent of activated areas depends on the evaluation parameters chosen and can therefore vary. In addition, the position of brain structures can change intraoperatively ("brain shift"), with the result that data obtained preoperatively no longer accurately reflect the intraoperative situation (WIRTZ et al. 1997; WITTEK et al. 2005; NIMSKY, GANSLANDT et al. 2006). Effluent cerebrospinal fluid alone can lead to shifts or several millimeters after opening

of the dura. Moreover, there is often a sharp shift in the position of the brain due to tissue resection. For these reasons, preoperative fMRI cannot replace intraoperative mapping of brain function completely. Irrespective of functional imaging, additional technical inaccuracies must be taken into consideration in neuronavigation and referencing.

References

- Achten E, Jackson GD, et al (1999) Presurgical evaluation of the motor hand area with functional MR imaging in patients with tumors and dysplastic lesions. *Radiology* 210(2):529–538
- Akbar M, Stippich C and Aschoff A (2005) Magnetic resonance imaging and cerebrospinal fluid shunt valves. *N Engl J Med* 353(13):1413–1414
- Alkadhi H, Kollias SS, et al (2000) Plasticity of the human motor cortex in patients with arteriovenous malformations: a functional MR imaging study. *AJNR Am J Neuroradiol* 21(8):1423–1433
- Atlas SW, Howard RS 2nd, et al (1996) Functional magnetic resonance imaging of regional brain activity in patients with intracerebral gliomas: findings and implications for clinical management. *Neurosurgery* 38(2):329–338
- Avila C, Barros-Loscertales A, et al (2006) Memory lateralization with 2 functional MR imaging tasks in patients with lesions in the temporal lobe. *AJNR Am J Neuroradiol* 27(3):498–503.
- Baci M, Le Bas JF, et al (2003) Presurgical fMRI evaluation of cerebral reorganization and motor deficit in patients with tumors and vascular malformations. *Eur J Radiol* 46(2):139–146
- Bahn MM, Lin W, et al (1997) Localization of language cortices by functional MR imaging compared with intracarotid amobarbital hemispheric sedation. *AJR Am J Roentgenol* 169(2):575–579
- Bandettini PA, Wong EC, et al (1992) Time course EPI of human brain function during task activation. *Magn Reson Med* 25(2):390–397
- Baudendistel K, Schad LR, et al (1996) Monitoring of task performance during functional magnetic resonance imaging of sensorimotor cortex at 1.5 T. *Magn Reson Imaging* 14(1):51–58
- Baumann SB, Noll DC, et al (1995) Comparison of functional magnetic resonance imaging with positron emission tomography and magnetoencephalography to identify the motor cortex in a patient with an arteriovenous malformation. *J Image Guid Surg* 1(4):191–197
- Baxendale S (2002) The role of functional MRI in the presurgical investigation of temporal lobe epilepsy patients: a clinical perspective and review. *J Clin Exp Neuropsychol* 24(5):664–676
- Bazin B, Cohen L, et al (2000) Study of hemispheric lateralization of language regions by functional MRI. Validation with the Wada test. *Rev Neurol (Paris)* 156(2):145–148
- Belliveau JW, Kennedy Jr. DN, et al (1991) Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* 254 (5032):716–719
- Bello L, Acerbi F, et al (2006) Intraoperative language localization in multilingual patients with gliomas. *Neurosurgery* 59(1):115–125; discussion 115–125
- Benbadis SR, Binder JR, et al (1998) Is speech arrest during wada testing a valid method for determining hemispheric representation of language? *Brain Lang* 65(3):441–446
- Benson RR, Fitzgerald DB, et al (1999) Language dominance determined by whole brain functional MRI in patients with brain lesions. *Neurology* 52(4):798–809
- Benson RR, Logan WJ, et al (1996). Functional MRI localization of language in a 9-year-old child. *Can J Neurol Sci* 23(3):213–219
- Berger H (1929) Über das Elektroenzephalogramm des Menschen. *Arch Psychiatr Nerven* 87:527–570.
- Binder JR, Achten E, et al (2002) Functional MRI in epilepsy. *Epilepsia* 43(Suppl 1):51–63
- Binder JR, Frost JA, et al (1997). Human brain language areas identified by functional magnetic resonance imaging. *J Neurosci* 17(1):353–62.
- Binder JR, Frost JA, et al (1999) Conceptual processing during the conscious resting state. A functional MRI study. *J Cogn Neurosci* 11(1):80–95
- Binder JR, Frost JA, et al (2000). Human temporal lobe activation by speech and nonspeech sounds. *Cereb Cortex* 10(5):512–28.
- Binder JR, Rao SM, et al (1995). Lateralized human brain language systems demonstrated by task subtraction functional magnetic resonance imaging. *Arch Neurol* 52(6):593–601.
- Binder JR, Swanson SJ, et al (1996) Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology* 46(4):978–984
- Bittar RG, Olivier A, et al (1999) Localization of somatosensory function by using positron emission tomography scanning: a comparison with intraoperative cortical stimulation. *J Neurosurg* 90(3):478–483
- Bittar RG, Olivier A, et al (1999) Presurgical motor and somatosensory cortex mapping with functional magnetic resonance imaging and positron emission tomography. *J Neurosurg* 91(6):915–921
- Bittar RG, Olivier A, et al (2000) Cortical motor and somatosensory representation: effect of cerebral lesions. *J Neurosurg* 92(2):242–248
- Bogen JE (1976) Wernicke's region – where is it? *Ann NY Acad Sci* 290: 834–843
- Bookheimer S (2002) Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci* 25:151–188
- Bookheimer SY (2000) Methodological issues in pediatric neuroimaging. *Ment Retard Dev Disabil Res Rev* 6(3): 161–165
- Buckner RL, Bandettini PA, et al (1996) Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proc Natl Acad Sci USA* 93(25):14878–14883
- Carpentier A, Pugh KR, et al (2001) Functional MRI of language processing: dependence on input modality and temporal lobe epilepsy. *Epilepsia* 42(10):1241–1254
- Carpentier AC, Constable RT, et al (2001) Patterns of functional magnetic resonance imaging activation in associa-

- tion with structural lesions in the rolandic region: a classification system. *J Neurosurg* 94(6):946–954
- Cedzich C, Taniguchi M, et al (1996) Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region. *Neurosurgery* 38(5):962–970
- Cosgrove GR, Buchbinder BR and Jiang H (1996) Functional magnetic resonance imaging for intracranial navigation. *Neurosurg Clin N Am* 7(2):313–322
- Cox RW (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29(3):162–173
- Cuenod CA, Bookheimer SY, et al (1995) Functional MRI during word generation, using conventional equipment: a potential tool for language localization in the clinical environment. *Neurology* 45(10):1821–1827
- Davis, FG, Freels S, et al (1998). Survival rates in patients with primary malignant brain tumors stratified by patient age and tumor histological type: an analysis based on Surveillance, Epidemiology, and End Results (SEER) data, 1973–1991. *J Neurosurg* 88(1): 1–10
- Davis FG, McCarthy B and Jukich P (1999) The descriptive epidemiology of brain tumors. *Neuroimaging Clin N Am* 9(4): 581–594
- Davis FG, McCarthy BJ, et al (1999) The conditional probability of survival of patients with primary malignant brain tumors: surveillance, epidemiology, and end results (SEER) data. *Cancer* 85(2):485–491
- Deblaere K, Backes WH, et al (2002) Developing a comprehensive presurgical functional MRI protocol for patients with intractable temporal lobe epilepsy: a pilot study. *Neuroradiology* 44(8):667–673
- Desmond JE, Sum JM, et al (1995) Functional MRI measurement of language lateralization in Wada-tested patients. *Brain* 118 (Pt 6):1411–1419
- Duffau H (2001). Acute functional reorganisation of the human motor cortex during resection of central lesions: a study using intraoperative brain mapping. *J Neurol Neurosurg Psychiatry* 70(4):506–513
- Duffau H (2005) Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol* 4(8):476–486
- Duffau H (2006). New concepts in surgery of WHO grade II gliomas: functional brain mapping, connectionism and plasticity – a review. *J Neurooncol* 79(1):77–115
- Duffau H, Bauchet L, et al (2001) Functional compensation of the left dominant insula for language. *Neuroreport* 12(10):2159–2163
- Duffau H, Capelle L, et al (1999) Intra-operative direct electrical stimulations of the central nervous system: the Salpetriere experience with 60 patients. *Acta Neurochir (Wien)* 141(11):1157–1167
- Duffau H, Capelle L, et al (2002) Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* 125(Pt 1): 199–214
- Duffau H, Capelle L, et al (2003) Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. *J Neurosurg* 98(4):764–778
- Duffau H, Denvil D and Capelle L (2002) Long term reshaping of language, sensory, and motor maps after glioma resection: a new parameter to integrate in the surgical strategy. *J Neurol Neurosurg Psychiatry* 72(4):511–56.
- Duffau H, Sichez JP and Lehericy S (2000) Intraoperative unmasking of brain redundant motor sites during resection of a precentral angioma: evidence using direct cortical stimulation. *Ann Neurol* 47(1):132–135.
- Dymarkowski S, Sunaert S, et al (1998) Functional MRI of the brain: localisation of eloquent cortex in focal brain lesion therapy. *Eur Radiol* 8(9):1573–1580.
- Fandino J, Kollias SS, et al (1999) Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumors involving the primary motor cortex. *J Neurosurg* 91(2):238–250.
- Fernandez G, de Greiff A, et al (2001) Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. *Neuroimage* 14(3):585–594.
- Fesl G, Moriggl, et al (2003) Inferior central sulcus: variations of anatomy and function on the example of the motor tongue area. *Neuroimage* 20(1):601–610.
- FitzGerald DB, Cosgrove GR, et al (1997) Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. *AJNR Am J Neuroradiol* 18(8):1529–1539.
- Fox PT, Mintun MA, et al (1986) Mapping human visual cortex with positron emission tomography. *Nature* 323(6091):806–809.
- Frahm J, Merboldt KD, et al (1994) Brain or vein – oxygenation or flow? On signal physiology in functional MRI of human brain activation. *NMR Biomed* 7(1-2):45–53.
- Friston K (1996) Statistical parametric mapping and other analyses of functional imaging data. *Brain mapping: the methods*. MJ Toga AW. New York, Academic press: 363–386.
- Frost JA, Binder JR, et al (1999) Language processing is strongly left lateralized in both sexes. Evidence from functional MRI. *Brain* 122 (Pt 2):199–208.
- Gabrieli JD, Poldrack RA and Desmond JE (1998) The role of left prefrontal cortex in language and memory. *Proc Natl Acad Sci USA* 95(3):906–913.
- Gaillard WD, Balsamo L, et al (2002) Language dominance in partial epilepsy patients identified with an fMRI reading task. *Neurology* 59(2):256–265.
- Gaillard WD, Bookheimer SY and Cohen M (2000) The use of fMRI in neocortical epilepsy. *Adv Neurol* 84:391–404.
- Gaillard WD, Grandin GB and Xu B (2001) Developmental aspects of pediatric fMRI: considerations for image acquisition, analysis, and interpretation. *Neuroimage* 13(2):239–249.
- Gaillard WD, Hertz-Pannier L, et al (2000) Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology* 54(1):180–185.
- Gaillard WD, Pugliese M, et al (2001) Cortical localization of reading in normal children: an fMRI language study. *Neurology* 57(1):47–54.
- Gasser T, Ganslandt O, et al (2005) Intraoperative functional MRI: implementation and preliminary experience. *Neuroimage* 26(3):685–693.
- Georgi JC, Stippich C, et al (2004) Active deep brain stimulation during MRI: a feasibility study. *Magn Reson Med* 51(2):380–388.
- Geschwind N (1971) Current concepts: aphasia. *N Engl J Med* 284(12):654–656.
- Gevens A (1995) High-resolution electroencephalographic

- studies of cognition. *Adv Neurol* 66:181–195; discussion 195–198.
- Gevins A, Leong H, et al (1995) Mapping cognitive brain function with modern high-resolution electroencephalography. *Trends Neurosci* 18(10):429–436.
- Golaszewski SM, Siedentopf CM, et al (2004) Modulatory effects on human sensorimotor cortex by whole-hand afferent electrical stimulation. *Neurology* 62(12):2262–2269.
- Golaszewski SM, Siedentopf CM, et al (2006) Human brain structures related to plantar vibrotactile stimulation: a functional magnetic resonance imaging study. *Neuroimage* 29(3):923–239.
- Golaszewski SM, Zschiegner F, et al (2002) A new pneumatic vibrator for functional magnetic resonance imaging of the human sensorimotor cortex. *Neurosci Lett* 324(2): 125–128.
- Gold S, Christian B, et al (1998) Functional MRI statistical software packages: a comparative analysis. *Hum Brain Mapp* 6(2):73–84.
- Grabowski TJ (2000) Investigating language with functional neuroimaging. *Brain mapping: the systems*. MJ Toga AW. San Diego, San Francisco, New York, Boston, London, Sydney, Tokio: Academic Press: 425–461.
- Grummich P, Nimsky C, et al (2006) Combining fMRI and MEG increases the reliability of presurgical language localization: A clinical study on the difference between and congruence of both modalities. *Neuroimage* 32(4): 1793–1803.
- Haberg A, Kvistad KA, et al (2004). Preoperative blood oxygen level-dependent functional magnetic resonance imaging in patients with primary brain tumors: clinical application and outcome. *Neurosurgery* 54(4):902–914; discussion 914–915.
- Hajnal JV, Myers R, et al (1994) Artifacts due to stimulus correlated motion in functional imaging of the brain. *Magn Reson Med* 31(3):283–291.
- Hall WA, Liu H and Truwit CL (2005) Functional magnetic resonance imaging-guided resection of low-grade gliomas. *Surg Neurol* 64(1):20–27; discussion 27.
- Hämäläinen M, Ilmoniemi RJ, Knuutila J, Lounasmaa OV (1993) Magnetoencephalography -theory, instrumentation and applications to noninvasive studies of the working human brain. *Review of modern physics* 65: 413–487.
- Hammeke TA, Bellgowan PS and Binder JR (2000) fMRI: methodology – cognitive function mapping. *Adv Neurol* 83:221–233.
- Hammeke TA, Yetkin FZ, et al (1994) Functional magnetic resonance imaging of somatosensory stimulation. *Neurosurgery* 35(4):677–681.
- Hari R and Ilmoniemi RJ (1986) Cerebral magnetic fields. *Crit Rev Biomed Eng* 14(2): 93–126.
- Hasegawa M, Carpenter PA and Just MA (2002). An fMRI study of bilingual sentence comprehension and workload. *Neuroimage* 15(3):647–660.
- Herholz K, Reulen HJ, et al (1997) Preoperative activation and intraoperative stimulation of language-related areas in patients with glioma. *Neurosurgery* 41(6):1253–1260; discussion 1260–1262.
- Hermann BP, Perrine K, et al (1999) Visual confrontation naming following left anterior temporal lobectomy: a comparison of surgical approaches. *Neuropsychology* 13(1):3–9.
- Hernandez AE, Dapretto M, et al (2001) Language switching and language representation in Spanish-English bilinguals: an fMRI study. *Neuroimage* 14(2):510–520.
- Hertz-Pannier L, Chiron C, et al (2002) Late plasticity for language in a child's non-dominant hemisphere: a pre- and post-surgery fMRI study. *Brain* 125(Pt 2):361–372.
- Hertz-Pannier L, Gaillard WD, et al (1997) Noninvasive assessment of language dominance in children and adolescents with functional MRI: a preliminary study. *Neurology* 48(4):1003–1012.
- Hinke RM, Hu X, et al (1993) Functional magnetic resonance imaging of Broca's area during internal speech. *Neuroreport* 4(6): 675–678.
- Hirsch J, Ruge MI, et al (2000) An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. *Neurosurgery* 47(3):711–721; discussion 721–722.
- Hoeller M, Krings T, et al (2002) Movement artefacts and MR BOLD signal increase during different paradigms for mapping the sensorimotor cortex. *Acta Neurochir (Wien)* 144(3):279–284; discussion 284.
- Holman BL and Devous Sr. MD (1992) Functional brain SPECT: the emergence of a powerful clinical method. *J Nucl Med* 33(10):1888–1904.
- Holodny AI, Schulder M, et al (1999) Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol* 20(4):609–612.
- Holodny AI, Schulder M, et al (2000) The effect of brain tumors on BOLD functional MR imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol* 21(8):1415–1422.
- Holodny AI, Schulder M, et al (2002) Translocation of Broca's area to the contralateral hemisphere as the result of the growth of a left inferior frontal glioma. *J Comput Assist Tomogr* 26(6):941–943.
- Holodny AI, Schwartz TH, et al (2001) Tumor involvement of the corticospinal tract: diffusion magnetic resonance tractography with intraoperative correlation. *J Neurosurg* 95(6):1082.
- Hou BL, Bradbury M et al (2006) Effect of brain tumor neovascularity defined by rCBV on BOLD fMRI activation volume in the primary motor cortex. *Neuroimage* 32(2): 489–497.
- Hsu CC, Wu MT and Lee C (2001) Robust image registration for functional magnetic resonance imaging of the brain. *Med Biol Eng Comput* 39(5):517–524.
- Hulvershorn J, Bloy L, et al (2005) Spatial sensitivity and temporal response of spin echo and gradient echo bold contrast at 3 T using peak hemodynamic activation time. *Neuroimage* 24(1):216–223.
- Hulvershorn J, Bloy L, et al (2005) Temporal resolving power of spin echo and gradient echo fMRI at 3T with apparent diffusion coefficient compartmentalization. *Hum Brain Mapp* 25(2):247–258.
- Illes J, Francis WS, et al (1999) Convergent cortical representation of semantic processing in bilinguals. *Brain Lang* 70(3):347–363.
- Jack Jr. CR, Thompson PM, et al (1994) Sensory motor cortex: correlation of presurgical mapping with functional MR imaging and invasive cortical mapping. *Radiology* 190(1): 85–92.

- Jacobs AH, Kracht LW, et al (2005) Imaging in neurooncology. *NeuroRx* 2(2):333–347.
- Just MA, Carpenter PA, et al (1996) Brain activation modulated by sentence comprehension. *Science* 274(5284):114–116.
- Kampe KK, Jones RA and Auer DP (2000) Frequency dependence of the functional MRI response after electrical median nerve stimulation. *Hum Brain Mapp* 9(2):106–114.
- Killgore WD, Glosser, et al (1999) Functional MRI and the Wada test provide complementary information for predicting post-operative seizure control. *Seizure* 8(8):450–455.
- Kim KH, Relkin NR, et al (1997) Distinct cortical areas associated with native and second languages. *Nature* 388(6638):171–174.
- Kim MJ, Holodny AI, et al (2005) The effect of prior surgery on blood oxygen level-dependent functional MR imaging in the preoperative assessment of brain tumors. *AJNR Am J Neuroradiol* 26(8):1980–1985.
- Klein D, Milner B, et al (1995) The neural substrates underlying word generation: a bilingual functional-imaging study. *Proc Natl Acad Sci USA* 92(7):2899–2903.
- Kober H, Nimsky C, et al (2001) Correlation of sensorimotor activation with functional magnetic resonance imaging and magnetoencephalography in presurgical functional imaging: a spatial analysis. *Neuroimage* 14(5):1214–1228.
- Kokkonen SM, Kiviniemi V, et al (2005) Effect of brain surgery on auditory and motor cortex activation: a preliminary functional magnetic resonance imaging study. *Neurosurgery* 57(2):249–256; discussion 249–256.
- Konrad F, Nennig E, et al (2005) Does the individual adaptation of standardized speech paradigms for clinical functional magnetic resonance imaging (fMRI) effect the localization of the language-dominant hemisphere and of Broca's and Wernicke's areas. *Rofo* 177(3):381–385.
- Krainik A, Duffau H, et al (2004) Role of the healthy hemisphere in recovery after resection of the supplementary motor area. *Neurology* 62(8):1323–1332.
- Krainik A, Lehericy S, et al (2001) Role of the supplementary motor area in motor deficit following medial frontal lobe surgery. *Neurology* 57(5):871–878.
- Krainik A, Lehericy S, et al (2003) Postoperative speech disorder after medial frontal surgery: role of the supplementary motor area. *Neurology* 60(4): 587–594.
- Krings T, Buchbinder, et al (1997) Functional magnetic resonance imaging and transcranial magnetic stimulation: complementary approaches in the evaluation of cortical motor function. *Neurology* 48(5):1406–1416.
- Krings T, Erberich SG, et al (1999) MR blood oxygenation level-dependent signal differences in parenchymal and large draining vessels: implications for functional MR imaging. *AJNR Am J Neuroradiol* 20(10):1907–1914.
- Krings T, MH Reinges, et al (2001) Functional MRI for presurgical planning: problems, artefacts, and solution strategies. *J Neurol Neurosurg Psychiatry* 70(6):749–760.
- Krings T, Reinges MH, et al (2002) Factors related to the magnitude of T2* MR signal changes during functional imaging. *Neuroradiology* 44(6):459–466.
- Krings T, Reul J, et al (1998) Functional magnetic resonance mapping of sensory motor cortex for image-guided neurosurgical intervention. *Acta Neurochir (Wien)* 140(3):215–222.
- Krings T, R Topper, et al (2002) Activation in primary and secondary motor areas in patients with CNS neoplasms and weakness. *Neurology* 58(3):381–390.
- Krishnan R, Raabe A, et al (2004) Functional magnetic resonance imaging-integrated neuronavigation: correlation between lesion-to-motor cortex distance and outcome. *Neurosurgery* 55(4):904–914; discussion 914–915.
- Kurth R, Villringer K, et al (1998) fMRI assessment of somatotopy in human Brodmann area 3b by electrical finger stimulation. *Neuroreport* 9(2):207–212.
- Kwong KK, Belliveau JW, et al (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA* 89(12):5675–5679.
- Landis SH, Murray T, et al (1999) Cancer statistics, 1999. *CA Cancer J Clin* 49(1):8–31, 1.
- Latchaw RE, Ugurbil K and Hu X (1995) Functional MR imaging of perceptual and cognitive functions. *Neuroimaging Clin N Am* 5(2):193–205.
- Lazar RM, Marshall RS, et al (1997) Anterior translocation of language in patients with left cerebral arteriovenous malformation. *Neurology* 49(3):802–808.
- Lee CC, Grimm RC, et al (1998) A prospective approach to correct for inter-image head rotation in fMRI. *Magn Reson Med* 39(2):234–243.
- Lee CC, Jack Jr. CR, et al (1996) Real-time adaptive motion correction in functional MRI. *Magn Reson Med* 36(3):436–444.
- Lee CC, Jack Jr. CR and Riederer SJ (1998) Mapping of the central sulcus with functional MR: active versus passive activation tasks. *AJNR Am J Neuroradiol* 19(5):847–852.
- Lee CC, Jack Jr. CR, et al (1998) Real-time reconstruction and high-speed processing in functional MR imaging. *AJNR Am J Neuroradiol* 19(7):1297–1300.
- Lee CC, Ward HA, et al (1999) Assessment of functional MR imaging in neurosurgical planning. *AJNR Am J Neuroradiol* 20(8):1511–1519.
- Lehericy S, Biondi A, et al (2002) Arteriovenous brain malformations: is functional MR imaging reliable for studying language reorganization in patients? Initial observations. *Radiology* 223(3):672–682.
- Lehericy S, Cohen L, et al (2000) Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. *Neurology* 54(8):1625–1633.
- Lehericy S, Duffau H, et al (2000) Correspondence between functional magnetic resonance imaging somatotopy and individual brain anatomy of the central region: comparison with intraoperative stimulation in patients with brain tumors. *J Neurosurg* 92(4):589–598.
- Lichtheim L (1885) On aphasia. *Brain* 7:433–484.
- Liu G and Ogawa S (2006) EPI image reconstruction with correction of distortion and signal losses. *J Magn Reson Imaging* 24(3):683–689.
- Liu H, Hall WA and Truwit CL (2003) The roles of functional MRI in MR-guided neurosurgery in a combined 1.5 Tesla MR-operating room. *Acta Neurochir Suppl* 85:127–135.
- Liu WC, Feldman SC, et al (2005) The effect of tumour type and distance on activation in the motor cortex. *Neuroradiology* 47(11):813–819.
- Logan WJ (1999) Functional magnetic resonance imaging in children. *Semin Pediatr Neurol* 6(2):78–86.
- Logothetis NK (2002) The neural basis of the blood-oxygen-

- level-dependent functional magnetic resonance imaging signal. *Philos Trans R Soc Lond B Biol Sci* 357(1424): 1003–1037.
- Logothetis NK (2003) The underpinnings of the BOLD functional magnetic resonance imaging signal. *J Neurosci* 23(10):3963–3971.
- Logothetis NK, Pauls J, et al (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412(6843): 150–157.
- Logothetis NK and J Pfeuffer (2004) On the nature of the BOLD fMRI contrast mechanism. *Magn Reson Imaging* 22(10):1517–1531.
- Logothetis NK and Wandell BA (2004) Interpreting the BOLD signal. *Annu Rev Physiol* 66:735–769.
- Ludemann L, Forschler A, et al (2006) BOLD signal in the motor cortex shows a correlation with the blood volume of brain tumors. *J Magn Reson Imaging* 23(4):435–443.
- Lurito JT, Lowe MJ, et al (2000) Comparison of fMRI and intra-operative direct cortical stimulation in localization of receptive language areas. *J Comput Assist Tomogr* 24(1):99–105.
- Majos A, Tybor K, et al (2005) Cortical mapping by functional magnetic resonance imaging in patients with brain tumors. *Eur Radiol* 15(6):1148–1158.
- Mazziotta JC, Phelps ME, et al (1982) Tomographic mapping of human cerebral metabolism: auditory stimulation. *Neurology* 32(9):921–937.
- Menon RS, Ogawa S, et al (1995) BOLD based functional MRI at 4 Tesla includes a capillary bed contribution: echoplanar imaging correlates with previous optical imaging using intrinsic signals. *Magn Reson Med* 33(3):453–459.
- Moller M, Freund M, et al (2005) Real time fMRI: a tool for the routine presurgical localisation of the motor cortex. *Eur Radiol* 15(2):292–295.
- Morris GL 3rd, Mueller, et al (1994) Functional magnetic resonance imaging in partial epilepsy. *Epilepsia* 35(6): 1194–1198.
- Mueller WM, Yetkin FZ, et al (1996) Functional magnetic resonance imaging mapping of the motor cortex in patients with cerebral tumors. *Neurosurgery* 39(3):515–520; discussion 520–521.
- Naidich TP, Hof PR, et al (2001) Anatomic substrates of language: emphasizing speech. *Neuroimaging Clin N Am* 11(2):305–341, ix.
- Nimsky C, Ganslandt O, et al (2006) Intraoperative visualization for resection of gliomas: the role of functional neuronavigation and intraoperative 1.5 T MRI. *Neurol Res* 28(5): 482–487.
- Nitschke MF, Melchert, et al (1998) Preoperative functional magnetic resonance imaging (fMRI) of the motor system in patients with tumours in the parietal lobe. *Acta Neurochir (Wien)* 140(12):1223–1229.
- Ogawa S, Lee TM, et al (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA* 87(24):9868–9872.
- Ogawa S, Lee TM, et al (1990) Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med* 14(1):68–78.
- Ogawa S, Menon RS, et al (1993) Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophys J* 64(3):803–812.
- Ogawa S, Tank DW, et al (1992) Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci USA* 89(13):5951–5955.
- Ojemann GA (1991) Cortical organization of language. *J Neurosci* 11(8):2281–2287.
- Ojemann G, Ojemann J, et al (1989) Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg* 71(3):316–326.
- Osborn A (2004) *Diagnostic Imaging – Brain*. Salt Lake City, USA, Amirsys.
- Ozdoba C, Nirkko AC, et al (2002) Whole-brain functional magnetic resonance imaging of cerebral arteriovenous malformations involving the motor pathways. *Neuroradiology* 44(1):1–10.
- Palmer ED, Rosen HJ, et al (2001) An event-related fMRI study of overt and covert word stem completion. *Neuroimage* 14(1 Pt 1):182–193.
- Parkin DM and Muir CS (1992). Cancer Incidence in Five Continents. Comparability and quality of data. *IARC Sci Publ* (120):45–173.
- Parmar H, Sitoh YY and Yeo TT (2004) Combined magnetic resonance tractography and functional magnetic resonance imaging in evaluation of brain tumors involving the motor system. *J Comput Assist Tomogr* 28(4):551–556.
- Penfield W (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60:389–443.
- Penfield W (1950). *The cerebral cortex of man*. New York, MacMillan:57 ff.
- Petersen SE, Fox PT, et al (1988) Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 331(6157):585–589.
- Petrovich NM, Holodny AI, et al (2004) Isolated translocation of Wernicke's area to the right hemisphere in a 62-year-man with a temporo-parietal glioma. *AJNR Am J Neuroradiol* 25(1):130–133.
- Pouratian N, Bookheimer SY, et al (2002) Utility of preoperative functional magnetic resonance imaging for identifying language cortices in patients with vascular malformations. *J Neurosurg* 97(1):21–32.
- Price, CJ (2000) The anatomy of language: contributions from functional neuroimaging. *J Anat* 197 Pt 3:335–359.
- Price CJ, Wise, et al (1996) Hearing and saying. The functional neuro-anatomy of auditory word processing. *Brain* 119 (Pt 3):919–931.
- Priest AN, De Vita E, et al (2006) EPI distortion correction from a simultaneously acquired distortion map using TRAIL. *J Magn Reson Imaging* 23(4):597–603.
- Puce A, Constable RT, et al (1995) Functional magnetic resonance imaging of sensory and motor cortex: comparison with electrophysiological localization. *J Neurosurg* 83(2):262–270.
- Pujol J, Conesa G, et al (1996) Presurgical identification of the primary sensorimotor cortex by functional magnetic resonance imaging. *J Neurosurg* 84(1):7–13.
- Pujol J, Conesa G, et al (1998). Clinical application of functional magnetic resonance imaging in presurgical identification of the central sulcus. *J Neurosurg* 88(5):863–9.
- Raichle ME (1983) Positron emission tomography. *Annu Rev Neurosci* 6:249–267.
- Raichle ME, Fiez JA, et al (1994) Practice-related changes

- in human brain functional anatomy during nonmotor learning. *Cereb Cortex* 4(1):8–26.
- Ramsey NF, Sommer IE, et al (2001). Combined analysis of language tasks in fMRI improves assessment of hemispheric dominance for language functions in individual subjects. *Neuroimage* 13(4):719–733.
- Rausch R, Silfvenius H, et al (1993) Intra-arterial amobarbital procedures. Surgical treatment of the epilepsies. JJ Engel. New York, Raven Press: 341–357.
- Reinges MH, Krings T, et al (2004) Preoperative mapping of cortical motor function: prospective comparison of functional magnetic resonance imaging and [^{15}O]- H_2O -positron emission tomography in the same co-ordinate system. *Nucl Med Commun* 25(10):987–997.
- Reinges MH, T Krings, et al (2005) Prospective demonstration of short-term motor plasticity following acquired central pareses. *Neuroimage* 24(4):1248–1255.
- Roberts TP, (2003). Functional magnetic resonance imaging (fMRI) processing and analysis. ASNR Electronic Learning Center Syllabus: 1–23.
- Roessler K, Donat M, et al (2005) Evaluation of preoperative high magnetic field motor functional MRI (3 Tesla) in glioma patients by navigated electrocortical stimulation and postoperative outcome. *J Neurol Neurosurg Psychiatry* 76(8):1152–1157
- Roux FE, Boulanouar K, et al (1999) Cortical intraoperative stimulation in brain tumors as a tool to evaluate spatial data from motor functional MRI. *Invest Radiol* 34(3):225–229.
- Roux FE, Boulanouar K, et al (1999) Usefulness of motor functional MRI correlated to cortical mapping in Rolandic low-grade astrocytomas. *Acta Neurochir (Wien)* 141(1):71–79.
- Roux FE, Boulanouar K, et al (2000) Functional MRI and intraoperative brain mapping to evaluate brain plasticity in patients with brain tumours and hemiparesis. *J Neurol Neurosurg Psychiatry* 69(4):453–463.
- Roux FE, Boulanouar K, et al (2003) Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery* 52(6): 1335–1345; discussion 1345–1347.
- Roux FE, Ibarrola D, et al (2001) Methodological and technical issues for integrating functional magnetic resonance imaging data in a neuronavigational system. *Neurosurgery* 49(5):1145–1156; discussion 1156–1157.
- Roux FE, Ranjeva JP, et al (1997) Motor functional MRI for presurgical evaluation of cerebral tumors. *Stereotact Funct Neurosurg* 68(1–4 Pt 1):106–111.
- Roux FE and Tremoulet M (2002) Organization of language areas in bilingual patients: a cortical stimulation study. *J Neurosurg* 97(4):857–864.
- Rueckert L, Appollonio I, et al (1994) Magnetic resonance imaging functional activation of left frontal cortex during covert word production. *J Neuroimaging* 4(2):67–70.
- Ruge MI, Victor J, et al (1999) Concordance between functional magnetic resonance imaging and intraoperative language mapping. *Stereotact Funct Neurosurg* 72(2–4):95–102.
- Rutten GJ, Ramsey NF, et al (2002) FMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. *Neuroimage* 17(1):447–460.
- Rutten GJ, Ramsey NF, et al (2002) Interhemispheric reorganization of motor hand function to the primary motor cortex predicted with functional magnetic resonance imaging and transcranial magnetic stimulation. *J Child Neurol* 17(4):292–297.
- Rutten GJ, Ramsey NF, et al (2002) Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. *Ann Neurol* 51(3):350–360.
- Rutten GJ, Ramsey NF, et al (2002) Reproducibility of fMRI-determined language lateralization in individual subjects. *Brain Lang* 80(3):421–437.
- Rutten GJ, van Rijen PC, et al (1999) Language area localization with three-dimensional functional magnetic resonance imaging matches intrasulcal electrostimulation in Broca's area. *Ann Neurol* 46(3):405–408.
- Sakai KL, Hashimoto R and F Homae (2001) Sentence processing in the cerebral cortex. *Neurosci Res* 39(1):1–10.
- Schiffbauer H, Berger MS, et al (2003) Preoperative magnetic source imaging for brain tumor surgery: a quantitative comparison with intraoperative sensory and motor mapping. *Neurosurg Focus* 15(1):E7.
- Schlaggar BL, Brown TT, et al (2002) Functional neuro-anatomical differences between adults and school-age children in the processing of single words." *Science* 296(5572):1476–1479.
- Schlosser, MJ, M Luby, et al (1999). "Comparative localization of auditory comprehension by using functional magnetic resonance imaging and cortical stimulation. *J Neurosurg* 91(4): 626–35.
- Schlosser MJ, McCarthy G, et al (1997) Cerebral vascular malformations adjacent to sensorimotor and visual cortex. Functional magnetic resonance imaging studies before and after therapeutic intervention. *Stroke* 28(6):1130–1137.
- Schreiber A, Hubbe U, et al (2000) The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement. *AJNR Am J Neuroradiol* 21(6):1055–1063.
- Schulder M, Maldjian JA, et al (1998) Functional image-guided surgery of intracranial tumors located in or near the sensorimotor cortex. *J Neurosurg* 89(3):412–418.
- Schwinda C, Siminotto E, et al (2005) Real-time functional magnetic resonance imaging (rt-fMRI) in patients with brain tumours: preliminary findings using motor and language paradigms. *Br J Neurosurg* 19(1):25–32.
- Shaywitz BA, Shaywitz SE, et al (1995) Sex differences in the functional organization of the brain for language. *Nature* 373(6515):607–609.
- Shinoura N, Yamada R, et al (2005) Preoperative fMRI, tractography and continuous task during awake surgery for maintenance of motor function following surgical resection of metastatic tumor spread to the primary motor area. *Minim Invasive Neurosurg* 48(2):85–90.
- Spreer J, Quiske A, et al (2001) Unsuspected atypical hemispheric dominance for language as determined by fMRI. *Epilepsia* 42(7):957–959.
- Springer JA, Binder JR, et al (1999) Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. *Brain* 122 (Pt 11):2033–2046.
- Stapleton SR, Kiriakopoulos E, et al (1997) Combined utility of functional MRI, cortical mapping, and frameless

- stereotaxy in the resection of lesions in eloquent areas of brain in children. *Pediatr Neurosurg* 26(2):68–82.
- Steger, TR and Jackson EF (2004) Real-time motion detection of functional MRI data. *J Appl Clin Med Phys* 5(2):64–70.
- Stippich, C (2005) Clinical functional magnetic resonance imaging: basic principles and clinical applications. *Radiologie up2date* 5:317–336
- Stippich C, Blatow M, et al (2007) Global activation of primary motor cortex during voluntary movements in man. *Neuroimage* 34:1227–1237.
- Stippich C, Heiland S, et al (2002) Functional magnetic resonance imaging: Physiological background, technical aspects and prerequisites for clinical use. *Rofo* 174(1):43–49.
- Stippich C, Hofmann R, et al (1999) Somatotopic mapping of the human primary somatosensory cortex by fully automated tactile stimulation using functional magnetic resonance imaging. *Neurosci Lett* 277(1):25–28.
- Stippich C, Kapfer D, et al (2000) Robust localization of the contralateral precentral gyrus in hemiparetic patients using the unimpaired ipsilateral hand: a clinical functional magnetic resonance imaging protocol. *Neurosci Lett* 285(2):155–159.
- Stippich C, Kress B, et al (2003) Preoperative functional magnetic resonance tomography (fMRI) in patients with rolandic brain tumors: indication, investigation strategy, possibilities and limitations of clinical application. *Rofo* 175(8):1042–1050.
- Stippich C, Mohammed J, et al (2003) Robust localization and lateralization of human language function: an optimized clinical functional magnetic resonance imaging protocol. *Neurosci Lett* 346(1–2):109–113.
- Stippich C, Ochmann H and Sartor K (2002) Somatotopic mapping of the human primary sensorimotor cortex during motor imagery and motor execution by functional magnetic resonance imaging. *Neurosci Lett* 331(1):50–54.
- Stippich C, Rapps, et al (2007). Feasibility of routine preoperative functional magnetic resonance imaging for localizing and lateralizing language in 81 consecutive patients with brain tumors. *Radiology* in press.
- Stippich C, Romanowski A, et al (2004) Fully automated localization of the human primary somatosensory cortex in one minute by functional magnetic resonance imaging. *Neurosci Lett* 364(2): 90–93.
- Stippich C, Romanowski A, et al (2005) Time-efficient localization of the human secondary somatosensory cortex by functional magnetic resonance imaging. *Neurosci Lett* 381(3):264–268.
- Szaflarski JP, Binder JR, et al (2002) Language lateralization in left-handed and ambidextrous people: fMRI data. *Neurology* 59(2):238–244.
- Ternovoi SK, Sinitsyn VE, et al (2004) Localization of the motor and speech zones of the cerebral cortex by functional magnetic resonance tomography. *Neurosci Behav Physiol* 34(5):431–437.
- Thulborn K (2006) Clinical functional Magnetic Resonance Imaging. *Current Protocols in Magnetic Resonance Imaging*. EM Haacke, John Wiley & Sons, Inc.
- Thulborn KR and Shen GX (1999) An integrated head immobilization system and high-performance RF coil for fMRI of visual paradigms at 1.5 T. *J Magn Reson* 139(1):26–34.
- Towle VL, Khorasani L, et al (2003) Noninvasive identification of human central sulcus: a comparison of gyral morphology, functional MRI, dipole localization, and direct cortical mapping. *Neuroimage* 19(3):684–697.
- Ulmer JL, Krouwer HG, et al (2003) Pseudo-reorganization of language cortical function at fMRI imaging: a consequence of tumor-induced neurovascular uncoupling. *AJNR Am J Neuroradiol* 24(2):213–217.
- Ulmer JL, Salvan CV, et al (2004) The role of diffusion tensor imaging in establishing the proximity of tumor borders to functional brain systems: implications for preoperative risk assessments and postoperative outcomes. *Technol Cancer Res Treat* 3(6):567–576.
- van der Kallen BF, Morris GL, et al (1998) Hemispheric language dominance studied with functional MR: preliminary study in healthy volunteers and patients with epilepsy. *AJNR Am J Neuroradiol* 19(1):73–77.
- Van Westen D, Skagerberg G, et al (2005) Functional magnetic resonance imaging at 3T as a clinical tool in patients with intracranial tumors. *Acta Radiol* 46(6):599–609.
- Wada J and Rasmussen T (1960) Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. Experimental and clinical observations. *J Neurosurg* 17:266–282.
- Warburton E, Wise RJ, et al (1996) Noun and verb retrieval by normal subjects. *Studies with PET*. *Brain* 119 (Pt 1):159–179.
- Weiskopf N, Klose U, et al (2005) Single-shot compensation of image distortions and BOLD contrast optimization using multi-echo EPI for real-time fMRI. *Neuroimage* 24(4):1068–1079.
- Weiskopf N, Scharnowski F, et al (2004) Self-regulation of local brain activity using real-time functional magnetic resonance imaging (fMRI). *J Physiol Paris* 98(4–6):357–373.
- Weiskopf N, Veit 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(3):577–586.
- Westerveld K, Stoddard K and McCarthy K (1999) Case report of false lateralization using fMRI: comparison of language localization, Wada testing, and cortical stimulation. *Arch Clin Neuropsychol* 14:162–163.
- Wienbruch C, Candia V, et al (2006) A portable and low-cost fMRI compatible pneumatic system for the investigation of the somatosensory system in clinical and research environments. *Neurosci Lett* 398(3):183–188.
- Wirtz CR, Tronnier VM, et al (1997) Image-guided neurosurgery with intraoperative MRI: update of frameless stereotaxy and radicality control. *Stereotact Funct Neurosurg* 68(1–4 Pt 1):39–43.
- Wise R, Chollet F, et al (1991) Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* 114 (Pt 4):1803–1817.
- Wittek A, Kikinis R, et al (2005) Brain shift computation using a fully nonlinear biomechanical model. *Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv* 8(Pt 2):583–590.
- Woolsey CN, Erickson TC and Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. *J Neurosurg* 51(4):476–506.

- Worthington C, Vincent DJ, et al (1997) Comparison of functional magnetic resonance imaging for language localization and intracarotid speech amygdala testing in presurgical evaluation for intractable epilepsy. Preliminary results. *Stereotact Funct Neurosurg* 69(1-4 Pt 2):197-201.
- Wunderlich G, Knorr U, et al (1998) Precentral glioma location determines the displacement of cortical hand representation. *Neurosurgery* 42(1):18-26; discussion 26-27.
- Yetkin FZ, Mueller WM, et al (1997) Functional MR activation correlated with intraoperative cortical mapping. *AJNR Am J Neuroradiol* 18(7):1311-1315.
- Yetkin FZ, Swanson S, et al (1998) Functional MR of frontal lobe activation: comparison with Wada language results. *AJNR Am J Neuroradiol* 19(6):1095-1098.
- Yousry I, Naidich TP and Yousry TA (2001) Functional magnetic resonance imaging: factors modulating the cortical activation pattern of the motor system. *Neuroimaging Clin N Am* 11(2):195-202, viii.
- Yousry TA, Schmid UD, et al (1995) Topography of the cortical motor hand area: prospective study with functional MR imaging and direct motor mapping at surgery. *Radiology* 195(1):23-29.
- Yousry TA, Schmid UD, et al (1996) The central sulcal vein: a landmark for identification of the central sulcus using functional magnetic resonance imaging. *J Neurosurg* 85(4):608-617.
- Yousry TA, Schmid UD, et al (1997) Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain* 120 (Pt 1): 141-57.
- Zentner J, Hufnagel A, et al (1996) Functional results after resective procedures involving the supplementary motor area. *J Neurosurg* 85(4):542-549.
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Presurgical Functional MRI in Epilepsy

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KEY POINTS

Epilepsy surgery is performed in patients with medically intractable epilepsies to completely resect or disconnect the “epileptogenic zone” - the cortical area which is indispensable to the generation of the seizures. To achieve therapeutic success the epileptogenic zone must be accurately lateralized and localized. Eloquent brain areas in the vicinity of the surgical target need to be preserved as intraoperative damage may result in postoperative neurological deficits. Therefore electrophysiological measures are applied by means of electroencephalography (EEG) and intraoperative electrocorticography (EcoG). However, functional magnetic resonance imaging (fMRI) has potential to noninvasively lateralize and to localize both, epileptic activity and important brain functions such as sensorimotor function, language and memory. For the latter tasks fMRI has proven clinical feasibility. The application of EEG-correlated ictal and interictal fMRI is still experimental. This chapter reviews the current state of knowledge and provides insight into methodology, possibilities and limitations of presurgical fMRI in patients with epilepsies.

5.1

Epilepsy and Epilepsy Surgery

Epilepsy is one of the most common serious neurological conditions, with an incidence approximately of 80 cases per 100,000 persons per year and a point prevalence of about 4–10 cases per 1000 persons (0.4%–1% of the population). Epilepsy is an unspecific symptom of neurological dysfunction. Almost every brain disorder can cause epileptic seizures and

aetiology differs greatly in different populations, geographic locations, and different age groups. Syndromatic classification divides the epilepsies into two broad categories: focal and generalized. Each category is further subdivided into idiopathic and symptomatic. Idiopathic generalized epilepsies are age-related, have well-defined EEG-characteristics and a favourable prognosis. Symptomatic generalized epilepsies are age-dependent encephalopathies characterized by onset in infancy and poor prognosis for both seizure control and development. Idiopathic focal epilepsies commence in childhood and have a good prognosis. Symptomatic focal epilepsies

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are the most common category and occur at any age with the most likely cause determined by the age of onset. Approximately 60% of all patients with epilepsy suffer from symptomatic focal epilepsy syndromes. In ~20% of these patients, the seizures are not adequately controlled with antiepileptic drugs. The characteristics of this group of patients are ill defined, but possible unfavourable prognostic factors include an early onset of epilepsy and the presence of structural abnormalities, multiple types of seizures, large numbers of seizures before treatment, and interictal epileptiform activity on electroencephalography.

Under the conservative assumption that 50% of such patients are potential candidates for surgical epilepsy treatment, 4.5% of all patients with epilepsy (0.03% of the population) could potentially profit from epilepsy surgery (ENGEL 1993). Depending on the epilepsy syndrome and the ability to define clearly and resect completely the epileptogenic zone, 30%–85% of epilepsy patients operated on remain seizure-free. The larger epilepsy centres report average seizure-free rates of ~60% (ENGEL 1993). Therefore, considering the severity of the epilepsy in the population operated on, epilepsy surgery can be considered a successful therapy (ROSENOW and LÜDERS 2001). The objective of resective epilepsy surgery is the complete resection or complete disconnection of the epileptogenic zone (the cortical area indispensable to the generation of seizures) with preservation of eloquent cortex. In the presurgical evaluation, information about the epileptogenic zone can be derived only indirectly from convergence of diverse investigations, such as analysis of seizure semiology, electrophysiological recordings, functional testing and structural and functional neuroimaging techniques (ROSENOW and LÜDERS 2001). This chapter addresses the current contribution of fMRI to the presurgical of patients with epilepsy.

5.2 Presurgical fMRI in Patients with Epilepsies

Since the demonstration a decade ago that fMRI is able to provide high spatial resolution maps of brain function, considerable effort has been directed at applying this technique to study patients with epilepsy, in particular patients with intractable focal

epilepsy considered for epilepsy surgery. Functional MRI can be used in different ways in the presurgical evaluation of patients with epilepsy. First, through identification of eloquent cortical areas, fMRI may predict deficits in cognitive (e.g., language and memory) or sensorimotor functions that might arise from surgical intervention. Second, fMRI can provide evidence for the localization of the epileptic focus through identification of BOLD signal changes associated with ictal or interictal epileptic activity. Third, asymmetries in physiological activation can facilitate the lateralization and localization of an epileptogenic focus.

5.2.1 Special Issue for Presurgical fMRI in Patients with Epilepsy

Only in the last decade has fMRI been increasingly applied to larger numbers of neurological patients. Working with clinical populations in general and patients with epilepsy in particular requires special considerations.

The issue of task difficulty and compliance has to be carefully addressed in neurological patients. Patients may be less motivated than normal volunteers to perform well on tasks. If the epilepsy is associated with intellectual impairment, patients may be less able to perform cognitive tasks that were developed for neurologically normal subjects. For details see also 4.5.2, 4.6.

Emotional distress from MRI scanning is reported to interfere with completion of the procedure in as many as 20% of patients (MELENDEZ and MCCRANK 1993; THORP et al. 1990). Although these situations are often managed with tranquilizing agents in standard MRI studies, use of such drugs in fMRI complicates interpretation of cognitive activation pattern. The effects of medication on the BOLD signal response have not been systematically studied yet. In a study by JOKEIT et al. (2001a), the extent of fMRI activation of the mesial temporal lobes induced by a task based on the retrieval of individually visuo-spatial knowledge was correlated with the carbamazepine serum level in 21 patients with refractory temporal lobe epilepsy. Compared to normal controls, the activation over the supposedly normal temporal lobe (i.e., contralateral to the seizure onset) was smaller in patients. More interestingly, in the patient group the extent of the BOLD activation over the mesial temporal lobes was inversely corre-

lated to the carbamazepine drug level. The reduction of fMRI cluster size was most marked when the drug levels were close to toxic levels. There was no behavioral data concerning memory function described for the patient group and a possible bias of the study was the possibility that a high carbamazepine level is associated with more severe epilepsy. However, these preliminary data provide some evidence that antiepileptic drug treatment may significantly influence fMRI activation of cognitive tasks.

Another consideration with epilepsy patients relates to the effects of ictal and interictal epileptic activity to fMRI activation. There is evidence that epileptic activity can influence the lateralization of mesiotemporal memory functions studied by memory-activated fMRI (JANSZKY et al. 2004). In a case report, a patient was described in whom fMRI falsely lateralized language cortex to the right hemisphere when performed after a cluster of left temporal lobe seizures (JAYAKAR et al. 2002). In a recent study it was shown that significant BOLD signal changes can occur several minutes before the onset of a seizure (pre-ictal BOLD signal changes) (FEDERICO et al. 2005). These signal changes can comprise both signal increases and decreases and can be localized to the site of the presumed seizure focus, as well as to distant brain regions. The complex interaction between ictal and interictal activity with the BOLD signal is unclear and requires further investigation. In patients with frequent seizures or epileptiform discharges, results of fMRI activation studies should be interpreted carefully and in some patients EEG monitoring before or during the fMRI study might be necessary.

5.3

FMRI Applications in the Definition of Eloquent Cortical Areas in Epilepsy

No technique used in the identification of eloquent cortical areas is without a limiting sensitivity and specificity, including the gold standard direct cortical stimulation. Whereas cortical stimulation is essentially a “lesion” study, fMRI measures endogenous function (see Chap. 7). Thus, these modalities may be expected to differ somewhat in functional localization.

fMRI has the advantage of being able to acquire functional and anatomic maps concurrently and

preoperatively, it is equally sensitive to superficial and deep regions, non-invasive, cost effective and easy to employ, even using routine clinical scanners (FERNANDEZ et al. 2001).

5.3.1

Lateralization and Localization of Language

Just three years after the first reports on fMRI, a preliminary study showed that the BOLD signal contrast obtained in simple tests of language and motor function was very similar between subjects with epilepsy and normal controls, demonstrating the feasibility of the technique in studies of patients with epilepsy (MORRIS et al. 1994). Since then, fMRI of language processing has become one of the most clinically relevant applications in the field of epilepsy. The main aim of localizing language functions is to predict and minimize postoperative language deficits in patients considered for epilepsy surgery, who are mainly patients with temporal lobe epilepsy (HERMANN et al. 1999). In these patients, fMRI is predominantly used for language lateralization (i.e., determination of hemispheric dominance) and only to a lesser extent for intrahemispheric distribution of eloquent cortex. An overview of the application of fMRI to identify language hemispheric dominance is given in Chapter 4.5.

5.3.2

Memory

The use of fMRI in the prediction of postoperative memory deficits is more challenging than for language. This is partly due to the different components involved in memory processing, such as encoding and retrieval, and the fact that the nature of the material being encoded or retrieved influences which brain areas are activated. A further difficulty is how to separate brain activity related specifically to memory from that related to other cognitive processes (JOKEIT et al. 2001b). There is long-standing evidence from animal and clinical lesional studies that memory function depends on the functional integrity of the hippocampus and parahippocampal regions in the mesial temporal lobe (MCGAUGH 2000; SASS et al. 1990; SCOVILLE and MILNER 2000).

Functional imaging studies of these structures are potentially useful in two ways. First, identification of functionally hypoactive temporal lobe structures

may have predictive value for lateralization of seizure foci in temporal lobe epilepsy. Second, maps of fMRI activation associated with memory tasks may help in predicting the risk of postoperative memory deficits from temporal lobe surgery, and could assist in planning surgical strategies that spare functional tissue.

Tasks, which reliably activate the mesial temporal structures in normal subjects using fMRI, have been developed only relatively recently (FERNANDEZ et al. 1998; GABRIELI et al. 1997; STERN et al. 1996), and have rarely been used in patients with epilepsy (BELLGOWAN et al. 1998; DETRE et al. 1998; DUPONT et al. 2000, 2001; GOLBY et al. 2002; JANSZKY et al. 2005; JOKEIT et al. 2001b; RABIN et al. 2004; RICHARDSON et al. 2004). These studies suggest that (1) complex visual and especially spatial memory tasks are generally superior to verbal memory tasks in activating mesial temporal lobe structures, (2) nonverbal materials activate bilateral mesial temporal lobe structures, (3) encoding as well as retrieval recruit overlapping mesial temporal lobe structures, and (4) retrieval rather than encoding tends to activate bilateral mesial temporal lobe structures (JOKEIT et al. 2001b).

Two studies have compared the fMRI activation of memory tasks with the memory assessment procedures in the Wada test. DETRE et al. (1998) were the first to demonstrate that fMRI could be used to detect clinically relevant asymmetries in memory activation in patients with temporal lobe epilepsy. They used an environmental scene-encoding task in which subjects were asked to memorize each stimulus. In the baseline condition, subjects passively viewed a repeating nonsense stimulus (a spatially scrambled picture). Region-of-interest analysis of the resulting bilateral activation of posterior mesial temporal lobe structures was then used to calculate a memory lateralization score. fMRI lateralization scores were compared with lateralization indices derived from Wada memory scores. While temporal lobe activation was symmetrical in a normal control group, significant asymmetries were observed in the epilepsy group. In all nine patients the asymmetry of the activation concurred with the assessment of memory skills from the Wada test, including two patients in which memory was paradoxically located ipsilateral to the seizure focus.

In a study by GOLBY et al. (2002), fMRI was used to study the lateralization of memory encoding processes (patterns, faces, scenes, and words) within the mesial temporal lobe in nine patients with temporal

lobe epilepsy. In eight of nine subjects, lateralization of memory encoding was concordant with that obtained from the Wada test. Group level analysis demonstrated greater activation in the mesial temporal lobe contralateral to the presumed seizure focus. Furthermore, results suggested that there is reorganization of memory encoding to the contralateral mesial temporal lobe.

JOKEIT et al. (2001b) used a task employing mental navigation and recall of landmarks based on the retrieval of individually familiar visuospatial knowledge (Roland's Hometown Walking; ROLAND et al. 1987), which is known to be associated with symmetrical mesial temporal lobe activation. In 14 of 16 patients with left sided temporal lobe epilepsy and 13 of 14 patients with right-sided temporal lobe epilepsy, interhemispheric differences in mesial temporal lobe activation lateralized the side of seizure onset correctly, resulting in a correct classification rate of 90%.

The tasks in the studies mentioned above were partly chosen because they produced bilateral and broadly symmetrical temporal lobe activations in normal controls. Other investigators have utilized memory tasks that produce rather unilateral activations. BELLGOWAN et al. (1998) reported that mesial temporal lobe activation during a verbal encoding task could differentiate between patients with left and right temporal lobe epilepsy. The group with right temporal lobe epilepsy showed much stronger activation of the left mesial temporal lobe than did the left temporal lobe epilepsy group. Neither group showed activation in the corresponding regions of the right hemisphere. However, these findings were on the group level only and do not allow inferences to be made on an individual-subject basis.

Only recently it could be shown that fMRI of memory function can be used to predict postsurgical memory outcome in patients undergoing temporal epilepsy surgery in a clinical setting (RABIN et al. 2004; JANSZKY et al. 2005; RICHARDSON et al. 2004). RABIN et al. (2004) used a complex visual scene-encoding task that causes symmetrical mesial-temporal-lobe activation in controls, to determine a relation between mesial temporal lobe activation asymmetry ratios and postsurgical memory outcome. It was shown that increased activation ipsilateral to the seizure focus is associated with greater memory decline. In an event-related linguistic encoding fMRI study in patients with temporal lobe epilepsy and left hippocampal sclerosis, greater verbal memory encoding activity in the left hip-

pocampus compared with the right hippocampus predicted the extent of verbal memory decline after the left anterior temporal lobectomy (RICHARDSON et al. 2004). fMRI was shown to be a stronger independent predictor of memory decline than both preoperative hippocampal volume and preoperative verbal memory function. These studies are the first examples of fMRI showing predictive value for post-surgical memory outcome at the individual subject level in a clinical setting.

5.3.3

Sensorimotor Systems

Among the earliest clinical applications of fMRI was the localization of motor cortices, in particular in patients with mass lesions around the central sulcus. Lesions in the vicinity of the central sulcus are often associated with epilepsy. However, the treatment strategies in these cases are mainly dependent on the nature of the underlying lesion rather than the epilepsy. A detailed description of presurgical fMRI of motor and somatosensory function is given in Chapter 4.4.

5.4

Malformations of Cortical Development

Malformations of cortical development are an important cause for refractory epilepsy in adults and children (SISODIYA 2000). Results of surgical treatment are less favorable compared with mesial temporal lobe epilepsy, with about 40% of patients rendered seizure-free over a minimum 2-year follow-up period. Space-occupying lesions of the brain primarily displace functional cortex. For this reason, resection within the boundaries of a lesion should not directly damage eloquent cortex and result in a significant deficit. In contrast, cortical stimulation studies showed functional reorganization within dysplastic cortex as well as functional overlap between dysplastic cortex and normal brain tissue. Over the last years, fMRI has shown its ability to demonstrate coactivation of malformations of cortical development during physiological activation tasks (SALEK-HADDADI et al. 2002a). Two studies on patients with subcortical laminar heterotopia (PINARD et al. 2000; SPREER et al. 2001) showed

fMRI activation both in the outer cortex and the subcortical band heterotopia during performance of a motor task. In another patient with epilepsy and a microgyric visual cortex, the dysplastic cortex was activated by visual stimulation (INNOCENTI et al. 2001).

In contrast, another case report found a common cortical representation of both hands on the unaffected hemisphere and no activation in the hemisphere with a complex malformation (STAUDT et al. 2001). Cortical reorganization and participation of ectopic neuronal tissue in physiologic cerebral functions are of clinical importance in patients who are considered for epilepsy surgery with resection of cortical dysplasia. In addition to localize physiological activation, fMRI has the potential to identify epileptogenicity of dysplastic cortex by imaging ictal or interictal events (KOBAYASHI et al. 2005a; KRAKOW et al. 1999, 2001b; SCHWARTZ et al. 1998).

5.5

Localization of the Epileptic Focus

Beside the identification of eloquent cortices and the prediction of functional deficits caused by epilepsy surgery, fMRI is also capable of providing evidence for the localization of the epileptic focus by identifying ictal or interictal epileptic activity.

5.5.1

Ictal fMRI

Ictal fMRI activation has the advantage that it can be expected to reflect changes within the epileptogenic region itself (and propagation sites). Currently, only a few anecdotal reports on ictal fMRI are published. The section provides a brief review of the literature.

The first attempt to use fMRI for localisation of epileptic activity was reported by JACKSON et al. (1994). This case report dealt with a 4-year old patient with the diagnosis of Rasmussen's encephalitis. A standard MRI of the patient's brain showed widespread right hemispheric atrophy primarily over the more dorsal lateral frontal region and inferior Rolandic area. The patient was prone to frequent and prolonged focal motor seizures that involved the left arm, hand, and face. These bouts of epilepsia

partialis continua were then targeted for investigation using a FLASH sequence to obtain susceptibility-weighted images every 8 s from a single slice only. This study demonstrated seizure-related perfusion changes over the right inferior motor cortex, corresponding to the area of maximum atrophy seen on the conventional MRI and to the region of maximum abnormality as identified with an ictal single photon emission tomography (SPECT) study. Another case was reported by WARACH et al. (1994). This patient had prolonged focal status epilepticus and demonstrated a perfusion MRI abnormality over the left parieto-frontal region using a susceptibility-weighted sequence and dynamic enhancement with gadolinium. This abnormal region was in keeping with the localization of the spike focus of scalp EEG and the hyperperfusion defect detected with ictal SPECT. The EEG, perfusion-based MRI abnormality, and SPECT findings normalized after more aggressive medical management. Further case reports with equal findings were subsequently published (DETRE et al. 1995; KRINGS et al. 2000; SCHWARZT et al. 1998). In none of these reports, EEG recording was available during MR image acquisition, seizure detection was only possible by clinical observation of the patient in the MR scanner. The first ictal fMRI with simultaneous EEG recording was reported by SALEK-HADDADI et al. (2002b). A patient with partial and generalized tonic-clonic seizures showed ictal EEG changes (rhythmic delta and theta activity maximum over F7/T3 lasting for about 40 s) in the EEG recorded inside the MR scanner. A continuous BOLD-fMRI series was simultaneously acquired and revealed a 2.5% signal increase mainly over the left temporal lobe peaking at around 6 seconds into the seizure followed later by a prolonged undershoot.

In summary, ictal fMRI studies have demonstrated that fMRI, analogous to ictal SPECT, is capable of imaging reversible perfusion or BOLD abnormalities associated with epileptic seizures, with the abnormality localized closely to the site of maximum electric abnormality. However, in contrast to ictal SPECT (which is costly but feasible in specialized epilepsy units) ictal fMRI is not routinely practicable for a number of reasons: Most ictal events are associated with head and body movement and impairment of consciousness usually to a degree that the required level of cooperation for an MRI scan cannot be achieved. Furthermore, BOLD-fMRI is not sensitive to detecting low frequency state-related changes due to large intersessional effects and scanner noise characteristics. Together with the slow HRF, this

limits detection power to a narrow frequency band and will tend to necessitate capturing both seizure onset and termination. Seizures, however, are usually short lasting and unpredictable. It is impracticable for a patient, even with frequent seizures, to lie for hours in a MR scanner awaiting the onset of one or several seizures. fMRI-studies with concurrent EEG recording are complicated further by the extra time involved in attaching electrodes and equipment set up. For these practical reasons, the investigation of ictal activity will be limited to selected patients who have very frequent seizures without gross head movement, in particular seizure series, status epilepticus, or epilepsy partialis continua, or have epilepsy syndromes with seizures occurring predictably, e.g., reflex epilepsy (ARCHER et al. 2003b).

5.5.2 Interictal fMRI

Like physiological brain activity (and epileptic seizures), interictal epileptiform discharges (IED) are associated with alterations of cerebral blood flow and deoxyglobin concentration in the venous bed. Hence, fMRI should be capable to identify the sources of IED in the same way that it can identify sources of functional activation from movement or cognitive processing. This is in contrast to methods such as dipole modelling, which can find only possible intracerebral sources of surface potentials and rely on assumptions that are not always easy to justify.

Compared with ictal fMRI, mapping of interictal activity has several advantages: (1) IED are a common phenomenon in patients with epilepsy; (2) IED are not associated with stimulus-correlated motion; and (3) fMRI activation associated with single discharges are less likely to be confounded with propagation effects compared with ongoing ictal activity.

On the other hand, fMRI correlated with IED localises brain areas involved in generating these particular EEG events. The area of cortex that generates IED is labelled as the "irritative zone", which is not necessarily indicative for the epileptogenic zone, the area of cortex that is indispensable for the generation of epileptic seizures (ROSENOW and LUDERS 2001).

As IED are by definition a sub-clinical phenomenon, a second modality is necessary to identify these events. Hence, this approach was only made possible by recording EEG inside the MR scanner (EEG-correlated fMRI).

5.5.2.1

Methodological Aspects of EEG-correlated fMRI

The MRI scanner is a hostile environment for EEG-recordings. MR-compatible EEG recording equipment must ensure patient safety, sufficient quality of the EEG signals and avoid compromising MR image quality. Since the first report on EEG recording during MR imaging more than 10 years ago (IVES et al. 1993), these issues have been addressed by several studies and technical solutions have been proposed (KRAKOW et al. 2000a, b; LEMIEUX et al. 1997). Several commercial systems for intra-MR EEG recordings are now available. The main additional features implemented in these systems are a battery-powered nonmagnetic amplifier with a fiberoptic link, a high dynamic range of the amplifier and careful choice of materials for the electrode assembly.

The most crucial practical difficulty that must be overcome before useful functional data can be acquired is EEG quality. The two most relevant artefacts obscuring the EEG recorded inside the MR scanner are (1) pulse artefact (or cardioballistogram) and (2) image-acquisition artefact (ALLEN et al. 1998).

Cardioballistic and other movement-related artefacts are caused by movements of the body and EEG leads relative to the magnetic field of the MR scanner. It can be reduced by minimizing the area of the EEG wire loops, lead fixation and bipolar montage of the EEG with small inter-electrode distances. Remaining pulse artefact can be removed by averaging and subtraction of the artifacts synchronized to the ECG (ALLEN et al. 1998; BONMASSAR et al. 2002; HOFFMANN et al. 2000). These methods provide a degree of EEG quality sufficient for the accurate identification on interictal epileptiform discharges (KRAKOW et al. 1999), sleep stages (PORTAS et al. 2000), or physiological EEG rhythms (GOLDMANN et al. 2002).

During MR image acquisition, the EEG is obscured completely by large artefacts mainly due to induced voltages in the EEG leads subjected to the rapidly changing gradient fields.

Several solutions to the problem of EEG-imaging artifact removal have been proposed (ALLEN et al. 2000; HOFFMANN et al. 2000). These methods rely on amplification with sufficient dynamic range to avoid saturation of the EEG amplifier due to the artefact and a high sampling rate. The method developed by Allen et al. uses a scanner generated slice-timing pulse. For each channel, online subtraction of

a running time-averaged waveform is performed, followed by adaptive noise cancellation to reduce any residual artefact. Hoffmann et al. proposed a post-processing filtering method based on the Fast Fourier transform (FFT): segments of EEG without MR activity are compared with the FFT of the EEG recorded during imaging. Frequencies with amplitudes over a threshold determined based on the FFT of the normal EEG are then discarded. The inverted FFT gives the corrected EEG.

The ability to remove image artefacts determines the data acquisition of EEG-correlated fMRI experiments. Without image artefact removal, the EEG is obscured during imaging and interleaved data acquisition has to be applied. In epilepsy studies, this approach was introduced as spike-triggered fMRI. This method takes advantage of the delayed BOLD response after a neuronal event. This makes it possible to observe the EEG recording on-line (which requires the presence of an experienced electroencephalographer during data acquisition) and start image acquisitions manually at a fixed interval after the event of interest (usually 3 s, as the BOLD response peaks at 2–7 s after an event) or during control periods. However, spike-triggered fMRI suffers from two main limitations, both linked to the obliteration of the EEG during the image acquisition. First, there are constraints on the scanning rate and the duration of each scan. The minimum time gap between successive image acquisitions must be of the order of 15 s to avoid signal variations due to the T1 signal decay, and the maximum duration of each image acquisition must be less than the expected duration of the BOLD response in order to ensure proper separation of the responses from events which may occur during image acquisition, and therefore be undetected. Second, as mentioned above, the spike-triggered approach relies on assumptions about the BOLD response peak time and duration. However, spike-triggered fMRI is not able to reveal the hemodynamic response function due to a delayed image acquisition and the lack of pre-activity baseline images.

With the possibility of image artefact subtraction, these limitations can be overcome by continuous and simultaneous EEG and fMRI. In contrast to spike-triggered fMRI, continuous EEG/fMRI recording allows for full exploration of the temporal dynamics of activation in addition to spatial localization. For each voxel, an entire time series is available for interrogation in contrast to the limited number of time points available for comparison using spike-

triggered fMRI. Another advantage is that continuous EEG/fMRI allows for post hoc analysis of the EEG-events of interest. These advantages should lead to a greater sensitivity of continuous EEG/fMRI to identify BOLD signal changes associated with IED compared to the spike-triggered approach (AL-ASMI et al. 2003).

5.5.2.2

EEG-correlated fMRI in Patients with Epilepsy

So far, about 25 studies applying EEG-correlated fMRI to patients with epilepsy have been published. The older studies used spike-triggered fMRI (ARCHER et al. 2003a–c; JAGER et al. 2002; KRAKOW et al. 1999; LAZEYRAS et al. 2000; PATEL et al. 1999; SEECK et al. 1998; WARACH et al. 1996), since 2001 an increasing number of studies using continuous EEG/fMRI were reported (BAUDEWIG et al. 2001; BENAR et al. 2002; KOBAYASHI et al. 2005b; LEMIEUX et al. 2001). Most of the studies were performed in patients with focal epilepsy, only a few studies concentrated on generalized epilepsy (ARCHER et al. 2003a; AGHAKHANI et al. 2004; GOTMAN et al. 2005; SALEK-HADDADI et al. 2003). An example of an fMRI activation map derived from a continuous EEG/fMRI experiment in a patient with focal epilepsy is provided in Figure 5.1. In summary, these studies showed that EEG-correlated fMRI is a practicable method to be applied to patients with epilepsy showing frequent IED on scalp EEG. The EEG quality was sufficient to detect spontaneous IED off- or on-line. Discomfort or injuries of the patients due to the EEG-recording was not reported and the MR image quality was not significantly compromised by the EEG recording. In total, less than 200 patients were reported. The majority had intractable focal epilepsy, some of the patients were considered for epilepsy surgery and in a few surgery was carried out after the EEG/fMRI experiment. The largest of the studies correlating invasive EEG recordings with EEG/fMRI activations was reported by LAZEYRAS et al. (2000). A total of 11 patients were investigated with EEG-triggered fMRI, who also underwent pre-surgical evaluation for their epilepsy with video-EEG, PET, and SPECT studies. In 8 of 11 patients, intracranial recordings were carried out, and in 5 of them the epileptogenic zone as determined by fMRI was affirmed, but activation was not always anatomically restricted. Patients for EEG/fMRI experiments were in general highly selected, particularly with regard to the frequency of their IED. Neverthe-

less, in many patients the EEG/fMRI experiments failed, mainly because of absence of IED or due to motion artefacts. In the larger studies, fMRI activation was reported in about 50% of patients (KRAKOW et al. 2001a; PATEL et al. 1999; LAZEYRAS et al. 2000; JAGER et al. 2002). The activations were in general anatomically related to the proposed epileptic focus (as defined by interictal EEG, EEG source analysis, structural MRI, ictal video-EEG, or, in less than 10 patients, intracranial EEG).

The possible clinical application of EEG-correlated fMRI would be to contributing to the accurate localization of the epileptogenic zone, which is the basis for successful epilepsy surgery in patients with medically refractory focal seizures. Information on the epileptogenic zone is derived from the convergence of diverse investigations. In some patients, particularly with neocortical cryptogenic epilepsy, additional intracranial EEG recordings often have to be applied to reliably identify the epileptic focus. It still remains unclear whether EEG-correlated fMRI has the potential to replace invasive techniques or, at least, provide additional information to guide the placement of invasive intracranial electrodes where necessary. The clinical implementation of EEG-correlated fMRI and the interpretation of the fMRI activation maps is difficult for various reasons:

- The limitations of surface EEG affect the clinical application of EEG-correlated fMRI. It is well known by electroencephalographers that the majority of EEG recorded in patients with epilepsy are entirely normal or show only unspecific slowing. Cortical spiking in epileptic patients as recorded directly from cortex is often not accessible by surface EEG. Therefore, EEG-correlated fMRI remains limited to the minority of patients with frequent IED on surface EEG.
- The size of the fMRI activation cluster is greatly variable between studies and also between subjects in individual studies. Some patients have a widespread, multifocal activation, others show a circumscribed activation. The extent of the activation is critically dependent on the applied statistical threshold, which partly explains differences between studies. However, the reason for the variability between patients who were studied with identical methodology and thresholds remains unclear. No significant correlations between clinical characteristics (e.g. epilepsy syndrome, spike amplitude) and the size of the fMRI activation were found. The same applies for the number of IED which have been analysed: In

some patients even individual IED are associated with large activations (KRAKOW et al. 2001a), in other patients as many as 50 IED are not associated with significant activations. Hence, EEG-correlated fMRI may contribute to localize the source of IED, but currently it cannot provide information about its extent.

- In patients with widespread fMRI activation, another problem is to distinguish the primary sources from activation, which may represent areas of propagation. In such cases with equivocal information on localization, a combination of fMRI data with EEG source analysis may provide complementary information (SEECK et al. 1998).
- Until now, the results of EEG-correlated fMRI have not been systematically validated with a gold standard, which are intracranial recordings and outcome after epilepsy surgery. Before EEG-triggered fMRI can be used as a decisive method in the presurgical assessment of epilepsy patients, the relation between fMRI results, invasive EEG recordings and surgical outcome in relation to resection of the activated area has to be established.
- The high percentage of negative results (up to 50% in studies using spike-triggered fMRI) currently hinders the wider clinical application of EEG-correlated fMRI. In spike-triggered fMRI, the physiological explanation of a negative fMRI result is most likely that a non-significant difference in the blood oxygenation exists between activation and control states. This might be due to there being only a modest cerebral hyperperfusion following an IED, or due to an absence of a true control state, e.g. such as ongoing epileptic activity not detected on scalp EEG. In both cases the relative signal change within the spike generator may not achieve significance.

As mentioned above, it is conceivable that continuous and simultaneous EEG/fMRI will increase the sensitivity of the method. However, this has to be proven by larger scale studies using this technique and comparative studies between spike-triggered and simultaneous EEG/fMRI. Further, the use of higher strength magnets will increase the signal to noise ratio and hence fMRI sensitivity. Multi-channel EEG has already been recorded in a 4-Tesla MR scanner on humans and in a 7-Tesla MR scanner in animals (SIJBERS et al. 1999).

An improved signal to noise ratio may not only increase the proportion of fMRI-positive experi-

ments, but may also reduce the number of analysed IED necessary for a significant fMRI activation, thus rendering this method applicable to patients with less frequent IED.

5.6 Conclusion

Functional MRI of sensorimotor, language and memory function can be considered as clinical tools to identify eloquent cortex and to predict postoperative deficits of specific functions. It already offers a valid alternative to invasive methods like the Wada test for establishing language dominance, and it is likely that fMRI will also replace the Wada test for assessing presurgical memory function in the nearer future.

EEG-correlated fMRI has proved useful to provide insights into the generation of epileptiform activity in patients with focal epilepsy. In selected patients with frequent IED, EEG-correlated fMRI has the potential to reproducibly identify cortical areas involved in generating IED, i.e., the irritative zone. So far, the sensitivity of the method is in the range of 50%. To determine the specificity of the method, further studies are necessary to compare the EEG/fMRI results with the diagnostic gold standards, which are intracranial EEG recordings and postoperative outcome after epilepsy surgery. Until these results are available, the utility of EEG-correlated fMRI in clinical epileptology cannot be definitely determined.

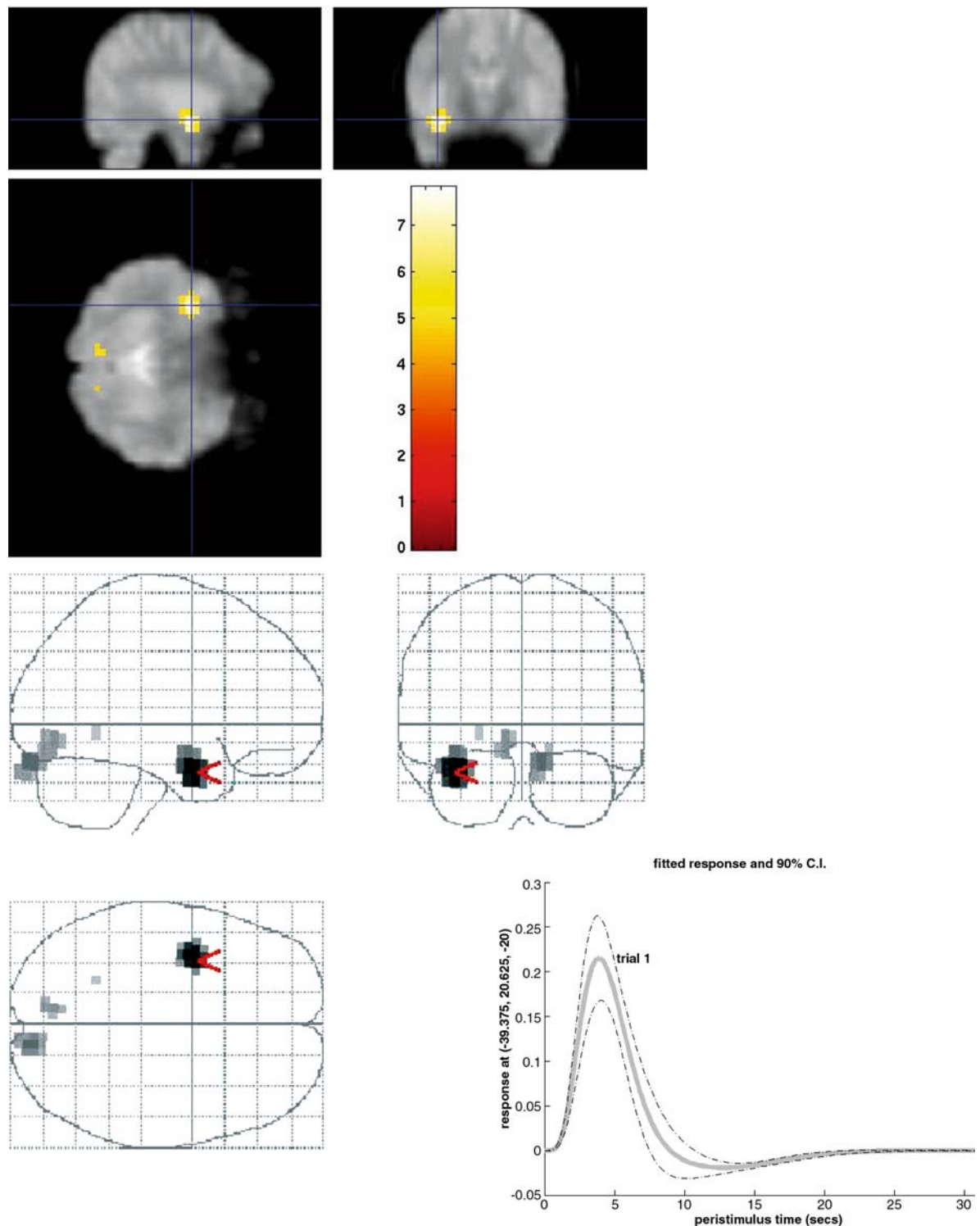


Fig. 5.1. Result of a continuous IED-correlated fMRI study in a patient with complex focal seizures, a left hippocampal sclerosis and frequent left temporal IED. fMRI revealed a left temporal activation associated with IED (maximum indicated by cross hair in the EPI overlay and red arrow in the glass brain), which is concordant with the presumed irritative zone. There were significant negative BOLD signal changes associated with IED in retrosplenial areas (not displayed). The hemodynamic response is displayed below. (Courtesy of Afraim Salek-Haddadi, Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, United Kingdom)

Protocol of Continuous EEG/fMRI Experiments

EEG and Artefact Reduction

EEG during fMRI acquisition was recorded using the BrainAmp MR EEG amplifier (5 kHz), Brain Vision Recorder software (BrainProducts, Munich, Germany) and the BrainCap electrode cap (Falk Minow Services, Herrsching-Breitbrunn, Germany) with 29 electrodes (10–20 system, reference between Fz and Cz). Off-line EEG artefact subtraction was performed as implemented in the Brain Vision Analyzer (BrainProducts).

fMRI Data Acquisition

For fMRI the following imaging parameters were used: 312 T2*-weighted echo-planar images per session covering the entire cerebrum, 3 T Siemens Trio (3T Siemens Allegra for Patient 6; Siemens Erlangen, Germany) standard head coil, voxel size $3 \times 3 \times 4$ mm, 20 slices with 1 mm gap in 1.3 s, volumes recorded every 2.67 s, echo time 20 ms, bilateral temporal

pressure pads. A structural three dimensional T1 sequence (MPRAGE, voxel size $1 \times 1 \times 1$ mm) was performed after removing the EEG cap.

Data Analysis

Statistical parametric mapping (SPM2, <http://www.fil.ion.ucl.ac.uk/spm>) was used for image realignment, normalization, spatial (12 mm FWHM Gaussian kernel) and temporal (128 s high pass filter) smoothing and statistical analysis. Epochs with IED were visually identified and marked. These markers were treated as events, convolved with the canonical hemodynamic response function (HRF) and used as a regressor for event-related fMRI analysis. Motion parameters obtained from realignment were always included as confounds.

Scans at the beginning or end of sessions with intensive movement were not included in the statistical analysis. Statistical significance was set at a threshold of $p < 0.001$, uncorrected for multiple comparisons. Finally, the statistical map was overlaid on the patients normalised T1-weighted MRI and on a T1-weighted template brain.

References

- Aghakhani Y, Bagshaw AP, Benar CG, Hawco C, Andermann F, Dubeau F, Gotman J (2004) fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. *Brain* 127:1127–44
- Al-Asmi A, Benar CG, Gross DW, Khani YA, Andermann F, Pike B, Dubeau F, Gotman J (2003) fMRI activation in continuous and spike-triggered EEG-fMRI studies of epileptic spikes. *Epilepsia* 44:1328–39
- Allen PJ, Polizzi G, Krakow K, Fish DR, Lemieux L (1998) Identification of EEG events in the MR scanner: the problem of pulse artifact and a method for its subtraction. *Neuroimage* 8:229–39
- Allen PJ, Josephs O, Turner R (2000) A method for removing imaging artifact from continuous EEG recorded during functional MRI. *Neuroimage* 12:230–9
- Archer JS, Abbott DF, Waites AB, Jackson GD (2003a) fMRI “deactivation” of the posterior cingulate during generalized spike and wave. *Neuroimage* 20:1915–22
- Archer JS, Briellmann RS, Syngeniotis A, Abbott DF, Jackson GD (2003b) Spike-triggered fMRI in reading epilepsy: Involvement of left frontal cortex working memory area. *Neurology* 60:415–21
- Archer JS, Briellman RS, Abbott DF, Syngeniotis A, Wellard RM, Jackson GD (2003c) Benign Epilepsy with Centrotemporal Spikes: Spike Triggered fMRI Shows Somatosensory Cortex Activity. *Epilepsia* 44:200–4
- Bahn MM, Lin W, Silbergeld DL et al. (1997) Localization of language cortices by functional MR imaging compared with intracarotid amobarbital hemispheric sedation. *AJR Am J Roentgenol* 169:575–9
- Baudewig J, Bittermann HJ, Paulus W, Frahm J (2001) Simultaneous EEG and functional MRI of epileptic activity: a case report. *Clin Neurophysiol* 112:1196–200
- Baxendale S (2002) The role of functional MRI in the presurgical investigation of temporal lobe epilepsy patients: a clinical perspective and review. *J Clin Exp Neuropsychol* 24:664–76
- Bazin B, Cohen L, Lehericy S et al. (2000) [Study of hemispheric lateralization of language regions by functional MRI. Validation with the Wada test]. *Rev Neurol (Paris)* 156:145–8
- Bellgowan PS, Binder JR, Swanson SJ et al. (1998) Side of seizure focus predicts left medial temporal lobe activation during verbal encoding. *Neurology* 51:479–84
- Benar CG, Gross DW, Wang Y et al. (2002) The BOLD response to interictal epileptiform discharges. *Neuroimage* 17:1182–92
- Benbadis SR, Binder JR, Swanson SJ et al. (1998) Is speech arrest during wada testing a valid method for determining hemispheric representation of language? *Brain Lang* 65:441–6
- Benson RR, FitzGerald DB, LeSueur LL et al. (1999) Language

- dominance determined by whole brain functional MRI in patients with brain lesions. *Neurology* 52:798–809
- Binder JR, Swanson SJ, Hammeke TA et al. (1996) Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology* 46:978–84
- Bonmassar G, Purdon P, Jaaskelainen I et al. (2002) Motion and Ballistocardiogram Artifact Removal for Interleaved Recording of EEG and EPs during MRI. *Neuroimage* 16:1127
- Carpentier A, Pugh KR, Westerveld M et al. (2001) Functional MRI of language processing: dependence on input modality and temporal lobe epilepsy. *Epilepsia* 42:1241–54
- Desmond JE, Sum JM, Wagner AD et al. (1995) Functional MRI measurement of language lateralization in Wada-tested patients. *Brain* 118:1411–9
- Detre JA, Sirven JI, Alsop DC, O'Connor MJ, French JA (1995) Localization of subclinical ictal activity by functional magnetic resonance imaging: correlation with invasive monitoring. *Ann Neurol* 38:618–24
- Detre JA, Maccotta L, King D et al. (1998) Functional MRI lateralization of memory in temporal lobe epilepsy. *Neurology* 50:926–32
- Dupont S, Van de Moortele PF, Samson S et al. (2000) Episodic memory in left temporal lobe epilepsy: a functional MRI study. *Brain* 123:1722–32
- Dupont S, Samson Y, Van de Moortele PF et al. (2001) Delayed verbal memory retrieval: a functional MRI study in epileptic patients with structural lesions of the left medial temporal lobe. *Neuroimage* 14:995–1003
- Engel J Jr (1993) Update on surgical treatment of the epilepsies. Summary of the Second International Palm Desert Conference on the Surgical Treatment of the Epilepsies. *Neurology* 43:1612–1617
- Federico P, Abbott DF, Briellmann RS, Harvey AS, Jackson GD (2005) Functional MRI of the pre-ictal state. *Brain* 128:1811–7
- Fernandez G, Weyerts H, Schrader-Bolsche M et al. (1998) Successful verbal encoding into episodic memory engages the posterior hippocampus: a parametrically analyzed functional magnetic resonance imaging study. *J Neurosci* 18:1841–7
- Fernandez G, de Greiff A, von Oertzen J et al. (2001) Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. *Neuroimage* 14:585–94
- Gabrieli JD, Brewer JB, Desmond JE, Glover GH (1997) Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science* 276:264–6
- Gaillard WD, Bookheimer SY, Cohen M (2000) The use of fMRI in neocortical epilepsy. *Adv Neurol* 84:391–404
- Golby AJ, Poldrack RA, Illes J, Chen D, Desmond JE, Gabrieli JD (2002) Memory lateralization in medial temporal lobe epilepsy assessed by functional MRI. *Epilepsia* 43:855–63
- Goldman RI, Stern JM, Engel J Jr, Cohen MS (2002) Simultaneous EEG and fMRI of the alpha rhythm. *Neuroreport* 13:2487–92
- Gotman J, Grova C, Bagshaw A, Kobayashi E, Aghakhani Y, Dubeau F (2005) Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. *Proc Natl Acad Sci USA* 102:15236–40
- Hammeke TA, Bellgowan PS, Binder JR (2000) fMRI: methodology--cognitive function mapping. *Adv Neurol* 83:221–33
- Hermann BP, Perrine K, Chelune GJ et al. (1999) Visual confrontation naming following left anterior temporal lobectomy: a comparison of surgical approaches. *Neuropsychology* 13:3–9
- Hertz-Pannier L, Gaillard WD, Mott SH et al. (1997) Noninvasive assessment of language dominance in children and adolescents with functional MRI: a preliminary study. *Neurology* 48:1003–12
- Hoffmann A, Jager L, Werhahn KJ, Jaschke M, Noachtar S, Reiser M (2000) Electroencephalography during functional echo-planar imaging: detection of epileptic spikes using post-processing methods. *Magn Reson Med* 44:791–8
- Innocenti GM, Maeder P, Knyazeva MG, Fornari E, Deonna T (2001) Functional activation of microgyric visual cortex in a human. *Ann Neurol* 50:672–6
- Ives JR, Warach S, Schmitt F, Edelman RR, Schomer DL (1993) Monitoring the patient's EEG during echo planar MRI. *Electroencephalogr Clin Neurophysiol* 87:417–20
- Jackson GD, Connelly A, Cross JH, Gordon I, Gadian DG (1994) Functional magnetic resonance imaging of focal seizures. *Neurology* 44:850–6
- Jager L, Werhahn KJ, Hoffmann A et al. (2002) Focal epileptiform activity in the brain: detection with spike-related functional MR imaging – preliminary results. *Radiology* 223:860–9
- Janszky J, Ollech I, Jokeit H, Kontopoulou K, Mertens M, Pohlmann-Eden B, Ebner A, Woermann FG (2004) Epileptic activity influences the lateralization of mesiotemporal fMRI activity. *Neurology* 63:1813–7
- Janszky J, Jokeit H, Kontopoulou K, Mertens M, Ebner A, Pohlmann-Eden B, Woermann FG (2005) Functional MRI predicts memory performance after right mesiotemporal epilepsy surgery. *Epilepsia* 46:244–50
- Jayakar P, Bernal B, Santiago Medina L, Altman N (2002) False lateralization of language cortex on functional MRI after a cluster of focal seizures. *Neurology* 58:490–2
- Jokeit H, Okujava M, Woermann FG (2001a) Carbamazepine reduces memory induced activation of mesial temporal lobe structures: a pharmacological fMRI-study. *BMC Neurol* 1:6
- Jokeit H, Okujava M, Woermann FG (2001b) Memory fMRI lateralizes temporal lobe epilepsy. *Neurology* 57:1786–93
- Killgore WD, Glosser G, Casasanto DJ, French JA, Alsop DC, Detre JA (1999) Functional MRI and the Wada test provide complementary information for predicting post-operative seizure control. *Seizure* 8:450–5
- Kobayashi E, Bagshaw AP, Grova C, Dubeau F, Gotman J (2005a) Negative BOLD responses to epileptic spikes. *Hum Brain Mapp* 27:488–497
- Kobayashi E, Bagshaw AP, Jansen A, Andermann F, Andermann E, Gotman J, Dubeau F (2005b) Intrinsic epileptogenicity in polymicrogyric cortex suggested by EEG-fMRI BOLD responses. *Neurology* 64:1263–6
- Krakow K, Woermann FG, Symms MR, et al. (1995) EEG-triggered functional MRI of interictal epileptiform activity in patients with partial seizures. *Brain* 122:1679–88
- Krakow K, Wieshmann UC, Woermann FG et al. (1999) Multimodal MR imaging: functional, diffusion tensor, and chemical shift imaging in a patient with localization-related epilepsy. *Epilepsia* 40:1459–62

- Krakow K, Allen PJ, Symms MR, Lemieux L, Josephs O, Fish DR (2000a) EEG recording during fMRI experiments: image quality. *Hum Brain Mapp* 10:10–5
- Krakow K, Allen PJ, Lemieux L, Symms MR, Fish DR (2000a) Methodology: EEG-correlated fMRI. *Adv Neurol* 83:187–201
- Krakow K, Messina D, Lemieux L, Duncan JS, Fish DR (2001a) Functional MRI activation of individual interictal epileptiform spikes. *Neuroimage* 13:502–5
- Krakow K, Lemieux L, Messina D et al. (2001b) Spatio-temporal imaging of focal interictal epileptiform activity using EEG-triggered functional MRI. *Epileptic Disord* 3:67–74
- Krings T, Topper R, Reinges MH et al. (2000) Hemodynamic changes in simple partial epilepsy: a functional MRI study. *Neurology* 54:524–7
- Lazeyras F, Blanke O, Perrig S et al. (2000) EEG-triggered functional MRI in patients with pharmacoresistant epilepsy. *J Magn Reson Imaging* 12:177–85
- Lehericy S, Cohen L, Bazin B et al. (2000) Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. *Neurology* 54:1625–33
- Lemieux L, Allen PJ, Franconi F, Symms MR, Fish DR (1997) Recording of EEG during fMRI experiments: patient safety. *Magn Reson Med* 38:943–52
- Lemieux L, Salek-Haddadi A, Josephs O et al. (2001) Event-related fMRI with simultaneous and continuous EEG: description of the method and initial case report. *Neuroimage* 14:780–7
- McGaugh JL (2000) Memory – a century of consolidation. *Science* 287:248–51
- Melendez JC, McCrank E (1993) Anxiety-related reactions associated with magnetic resonance imaging examinations. *Jama* 270:745–7
- Morris GL, 3rd, Mueller WM, Yetkin FZ et al. (1994) Functional magnetic resonance imaging in partial epilepsy. *Epilepsia* 35:1194–8
- Patel MR, Blum A, Pearlman JD et al. (1999) Echo-planar functional MR imaging of epilepsy with concurrent EEG monitoring. *AJNR Am J Neuroradiol* 20:1916–9
- Pinard J, Feydy A, Carlier R, Perez N, Pierot L, Burnod Y (2000) Functional MRI in double cortex: functionality of heterotopia. *Neurology* 54:1531–3
- Portas CM, Krakow K, Allen P, Josephs O, Armony JL, Frith CD (2000) Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans. *Neuron* 28:991–9
- Rabin ML, Narayan VM, Kimberg DY, Casasanto DJ, Glosser G, Tracy JL, French JA, Sperling MR, Detre JA (2004) Functional MRI predicts post-surgical memory following temporal lobectomy. *Brain* 127:2286–98
- Richardson MP, Strange BA, Thompson PJ, Baxendale SA, Duncan JS, Dolan RJ (2004) Pre-operative verbal memory fMRI predicts post-operative memory decline after left temporal lobe resection. *Brain* 127:2419–26
- Roland PE, Eriksson L, Stone-Elander S, Widen L (1987) Does mental activity change the oxidative metabolism of the brain? *J Neurosci* 7:2373–89
- Rosenow F, Luders H (2001) Presurgical evaluation of epilepsy. *Brain* 124:1683–700
- Salek-Haddadi A, Lemieux L, Fish DR (2002a) Role of functional magnetic resonance imaging in the evaluation of patients with malformations caused by cortical development. *Neurosurg Clin N Am* 13:63–9, VIII
- Salek-Haddadi A, Merschhemke M, Lemieux L, Fish DR (2002b) Simultaneous EEG-Correlated Ictal fMRI. *Neuroimage* 16:32–40
- Salek-Haddadi A, Lemieux L, Merschhemke M, Friston K, Duncan JS, Fish DR (2003) Functional MRI of human absence seizures. *Ann Neurol* 53:663–7
- Sass KJ, Spencer DD, Kim JH, Westerveld M, Novelly RA, Lencz T (1990) Verbal memory impairment correlates with hippocampal pyramidal cell density. *Neurology* 40:1694–7
- Schwartz TH, Resor SR Jr, De La Paz R, Goodman RR (1998) Functional magnetic resonance imaging localization of ictal onset to a dysplastic cleft with simultaneous sensorimotor mapping: intraoperative electrophysiological confirmation and postoperative follow-up: technical note. *Neurosurgery* 43:639–44; discussion 644–5
- Scoville WB, Milner B (2000) Loss of recent memory after bilateral hippocampal lesions. *J Neuropsychiatry Clin Neurosci* 12:103–13
- Seeck M, Lazeyras F, Michel CM et al. (1998) Non-invasive epileptic focus localization using EEG-triggered functional MRI and electromagnetic tomography. *Electroencephalogr Clin Neurophysiol* 106:508–12
- Sijbers J, Michiels I, Verhoye M, Van Audekerke J, Van der Linden A, Van Dyck D (1999) Restoration of MR-induced artifacts in simultaneously recorded MR/EEG data. *Magn Reson Imaging* 17:1383–91
- Sisodiya SM (2000) Surgery for malformations of cortical development causing epilepsy. *Brain* 123:1075–91
- Spreer J, Martin P, Greenlee MW et al. (2001) Functional MRI in patients with band heterotopia. *Neuroimage* 14:357–65
- Springer JA, Binder JR, Hammeke TA et al. (1999) Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. *Brain* 122:2033–46
- Staudt M, Pieper T, Grodd W, Winkler P, Holthausen H, Krageloh-Mann I (2001) Functional MRI in a 6-year-old boy with unilateral cortical malformation: concordant representation of both hands in the unaffected hemisphere. *Neuropediatrics* 32:159–61
- Stern CE, Corkin S, Gonzalez RG et al. (1996) The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proc Natl Acad Sci USA* 93:8660–5
- Thorp D, Owens RG, Whitehouse G, Dewey ME (1990) Subjective experiences of magnetic resonance imaging. *Clin Radiol* 41:276–8
- Wada J, Rasmussen T (1960) Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. Experimental and clinical observations. *J Neurosurg* 17:266–282
- Warach S, Levin JM, Schomer DL, Holman BL, Edelman RR (1994) Hyperperfusion of ictal seizure focus demonstrated by MR perfusion imaging. *AJNR Am J Neuroradiol* 15:965–8
- Warach S, Ives JR, Schlaug G et al. (1996) EEG-triggered echo-planar functional MRI in epilepsy. *Neurology* 47:89–93
- Westerveld K, Stoddard K, McCarthy K (1999) Case report of false lateralization using fMRI: comparison of language localization, Wada testing, and cortical stimulation. *Arch Clin Neuropsychol* 14:162–163
- Woermann FG, Jokeit H, Luerding R, Freitag H, Schulz R, Guertler S, Okujava M, Wolf P, Tuxhorn I, Ebner A (2003)

- Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology* 9;61(5):699–701
- Worthington C, Vincent DJ, Bryant AE et al. (1997) Comparison of functional magnetic resonance imaging for language localization and intracarotid speech amygdala testing in presurgical evaluation for intractable epilepsy. Preliminary results. *Stereotact Funct Neurosurg* 69:197–201
- Yetkin FZ, Swanson S, Fischer M et al. (1998) Functional MR of frontal lobe activation: comparison with Wada language results. *AJNR Am J Neuroradiol* 19:1095–8
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Functional Neuronavigation

VOLKER M. TRONNIER

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KEY POINTS

Functional neuronavigation is based on the visualization of functional images within a surgical tracking system. This and other developing techniques help the neurosurgeon to tailor surgical procedures in order to increase diagnostic yield and to preserve brain function while maximizing the necessary extent of resection. The final goal is an improvement of postoperative survival and quality of life. A major advantage of functional imaging in comparison with other functional brain mapping techniques, such as direct cortical stimulation (Electrical Cortical Stimulation, ECS) is its non-invasiveness. Furthermore, availability of functional information to surgeon and patient prior to surgery not only allows to define a better indication for the procedure itself but also to plan a function preserving treatment and the appropriate surgical access to the respective brain areas. In order to implement functional neuronavigation into daily clinical routine, optimized imaging protocols are indispensable.

6.1 Introduction

While anatomical MR imaging is widely accepted and has revolutionized surgical decision making and planning, the emergence of functional neuroimaging localizing brain activity has significantly expanded the presurgical role of the different imaging modalities. Non-invasive functional MRI (fMRI) provides the neurosurgeon with images of activated brain regions by detecting indirect effects of neural activity on local blood volume, flow and oxygen saturation. Electroencephalography (EEG) and

magnetencephalography (MEG) allow direct real-time assessment of the brains electrophysiology also displaying the spatial pattern of the neuronal populations generating the underlying neuroelectric and neuromagnetic fields. Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT) imaging do not only offer hemodynamic but also metabolic information, which also holds true for Magnetic Resonance Spectroscopy (MRS).

The following chapter will focus on functional neuronavigation for surgery in eloquent brain areas. In addition, the importance of functional imaging in stereotaxy and procedures for pain and movement disorders will be outlined. Since a separate chapter (Chap. 5) is dedicated to epilepsy surgery, this topic is not addressed here.

6.2

Principles and Technical Aspects of Neuronavigation and Stereotaxy

6.2.1

Neuronavigation

The development of neuronavigation systems was a major technical advance in neurosurgery, especially for small lesions localized in deep or sub-cortical regions, where anatomical landmarks are not available. Such systems facilitate the navigation towards lesions through a narrow corridor avoiding the destruction of eloquent brain areas, in particular when the anatomy is distorted by brain tumors etc.. All navigational systems consist of similar components: the key instrument is a three-dimensional digitizing device (pointer, forceps, ultrasound probe or other localization device) which enables the surgeon to localize targets within the physical space (surgical site). This device is linked to a computer where the same targets are displayed on pre-operative three-dimensional images. The interface is a reference system with defined fiducial markers aligning the physical space to the imaging coordinate system. Although morphological information is usually assessed by 3D- T1-weighted MR images with gadolinium for contrast-enhancing lesions or T2-weighted and Flair images respectively for low grade gliomas, CT can be used for lesions at the skull base or in case of maxillofacial, ENT as well as spinal procedures. Different navigational systems are on

the market: arm-based systems with grading scales in usually six joints, providing six degrees of freedom. Based on the known position of the joints by electrogoniometers and the length of the phalanges, the position of a particular instrument connected to the arm can be calculated. The main problem of these arm-based devices is that it is not suitable for fixing the arm in a specific position which therefore needs to be done by the surgeon manually.

Optical or acoustic devices based on the principle of satellite navigation are more suitable. These devices work with two or three detecting instruments (IR-cameras, video- or ultrasound systems) with a fixed relationship in space. The distance to active markers (e.g. LEDs) or passive reflectors is calculated via a triangulation method. Obstacles within the line of view, as the operating microscope can interfere with navigation. One solution is tracking of the microscope itself, where the focus within the ocular is the image-guided "pointer". Computer systems allow rapid transformation and correction of new coordinates.

The accuracy of navigational devices depends on the accuracy of registration, e. g. the localization of the patients' anatomical landmarks and the preoperatively acquired images. Determination of registered points in a volume around the suspected lesion is important in order to achieve high accuracy in all three planes. Movement of the galea and the skin by head fixation or different patient positioning compared to the supine position inside the scanner will create inaccuracies. Therefore laser scanning methods detecting the surface of the face with several hundred points will increase registration accuracy.

After completion of the registration, each anatomical point can be displayed on the navigational computer. Due to the high amount of data and the need for rapid image transformation powerful workstations are necessary for high-end navigational devices.

The use of fMRI or other functional imaging modalities provides additional information helpful in planning tailored tumor resection while preserving neurological function. Therefore an integration of these functional data with the anatomical information was strongly desired by neurosurgeons. The introduction of frameless intraoperative neuronavigation systems allows the precise coregistration and transfer of fMRI data into the surgical field. Nowadays techniques for displaying sensorimotor, visual, language and cognitive functions are available as outlined further below.

Sequence of events of functional neuronavigation is as follows.

fMRI should be carried out according to a standardised paradigm protocol (see chapter 4) at least one a day prior to neuronavigation-assisted surgery. That ensures sufficient time for the neuroradiologist to analyze the fMRI data, which is still a very labour-intensive task. It also enables the neurosurgeon to critically evaluate the navigational data and plan the surgical approach accordingly. In the same MRI session, a three-dimensional morphological MRI scan is acquired, to critically evaluate the navigational data and plan the surgical approach accordingly.

The combined functional-anatomical data set is sent via net either to the neuronavigation station in the OR, or to a separate planning station outside the OR for further processing. The boundaries of elements of interest (tumor, vessels, ventricles, etc.) can be outlined and colored in different slices displayed by MRI or CT. The following three-dimensional reconstruction allows a 3-D display of these structures, which facilitates surgical planning.

At the time of surgery, the head is usually fixed in a head holder (Mayfield, Sugita etc.), to which the registration system (a three point star in most optical devices) is securely connected. The camera system is adjusted to the surgical field or the surgical microscope. All defined fiducial markers taped to the patients head have to be identified in the imaging data set for a patient-to-image registration using a rigid body transformation. At least four markers are required, but accuracy correlates within the numbers of fiducials used usually six to seven markers are required. Several systems offer nowadays an automated surface matching method, where numerous recognizable points are marked with a laser pointer and detected by three cameras. The computer calculates the best correspondence between the anatomical and imaging data, expressed in RMS (root mean square error) accuracy. Detecting certain well defined anatomical landmarks (nosetip, e.g. medial or lateral orbita) enables the surgeon to check the real accuracy. The internal root mean square (RMS) of different neuronavigational systems is between 2 mm and 3.2 mm. The difference between pointer tip and anatomical landmarks is 1.7 to 2.2 mm. This difference has to be added to the well known difference of 5–10 mm between functional maps and the site of neural activity as determined by direct electrical stimulation (see chapter 7). Once the accuracy of the patient to image registration has been confirmed by the landmark tests, the preplanned contours

including the functional voxels are displayed in the surgeons' viewing field within the microscope.

The additional time necessary for using navigation in the OP is between 15 and 30 min (WIRTZ et al. 1998; KRISHNAN et al. 2004).

The description of the basic principles of neuronavigation and computer-assisted (CAS) or image-guided surgery (IGS) is beyond the scope of this chapter and the reader is kindly referred to other textbooks regarding this topic (MACIUNAS 1993; TAYLOR et al. 1995).

6.2.2

Stereotaxy

Frame-based stereotaxy was the precursor of neuronavigational systems and is based on the concept of overlaying the imaged coordinate system with a coordinate system of the physical space referenced to the stereotactic frame. In order to enhance the diagnostic yield, functional or metabolic imaging is often combined with stereotactic targeting. The main indications are the differentiation between low- and high-grade gliomas and between radionecrosis and recurrent tumor growth. Metabolic imaging procedures with Thallium-SPECT (HEMM et al. 2004), MRS (SON et al. 2001), FDG-PET (PIROTTE et al. 2004) or perfusion-weighted MRI (MAIA et al. 2004) or CT are able to indicate target areas of higher metabolic activity resembling more aggressive tumor or higher grading. The recent development of 11-C-methionine, a specific marker for amino-acid transport, as a sensitive indicator of tumor recurrence enables the 11-C-Met-PET to differentiate between radionecrosis and recurrent tumor and renders it useful for stereotactic confirmation (KRACHT et al. 2004; PIROTTE et al. 2004; TSUYUGUCHI et al. 2004).

6.2.3

Intraoperative Imaging

Although the development of neuronavigation systems was a major breakthrough in neurosurgical technique, one serious problem is the so-called brain shift that is tissue movement during tumor resection by loss of CSF, or insertion of brain spatula (NABAVI et al. 2001) etc. Despite critical presurgical planning (KIKINIS et al. 1996) and modeling of brain shift effects (MIGA et al. 2001), there is still a considerable

degree of uncertainty concerning the precise match of surgical site and the images provided by the neuronavigation system. Intraoperative imaging modalities as intraoperative CT (OKUDERA et al. 1993), ultrasound (KOIVUKANGAS et al. 1993; UNSGAARD et al. 2002) or MRI (BLACK et al. 1997; NIMSKY et al. 2000, 2001; ROBERTS DW et al. 1999; TRONNIER et al. 1997) are one important measure to overcome the problems of brain shift. Most recently also functional data were implemented into intraoperative imaging (MOCHÉ et al. 2001; NIMSKY et al. 2004; STADLBAUR et al. 2004).

6.3

Aims and Indications for Functional Neuronavigation

Combining neuronavigation with functional data, usually acquired by fMRI or MEG, helps to minimize postoperative neurological deficits and allows in the same time maximal removal of pathological tissue. Consequently, application of functional neuronavigation results in a better selection of surgical candidates, a safer resection with reduced morbidity and finally shortens hospital stays and therefore a reduction in costs. The advantage of fMRI

over other functional imaging techniques is that MRI is already used for navigation itself in most cases, due to its high quality tissue contrast between normal brain and pathological tissue. Therefore morphological three-dimensional MRI can be easily matched with fMRI data, yielding an overlay of functional areas onto anatomical images (Fig. 6.1). There is no need for additional instrumentation or for matching different image formats. In addition, being a non-invasive procedure, it allows repetitive examinations providing information on postoperative reorganization or neuroplasticity (CARPENTIER et al. 2001; FANDINO et al. 1999).

Historically, neurosurgeons have mapped cortical functions invasively by direct cortical stimulation either intraoperatively or preoperatively using implanted subdural grids. However, these methods have severe limitations in terms of presurgical planning and direct intraoperative evaluation of function and are nowadays only used for confirmation or validation of functional imaging data or intraoperatively when the anatomy has changed due to the procedure.

fMRI imaging studies of motor, somatosensory and language function as part of the presurgical evaluation are considered very helpful and used to define the patient's individual risk for a decline in neurological function. This enables most patients to decide between a more aggressive (gross total) and

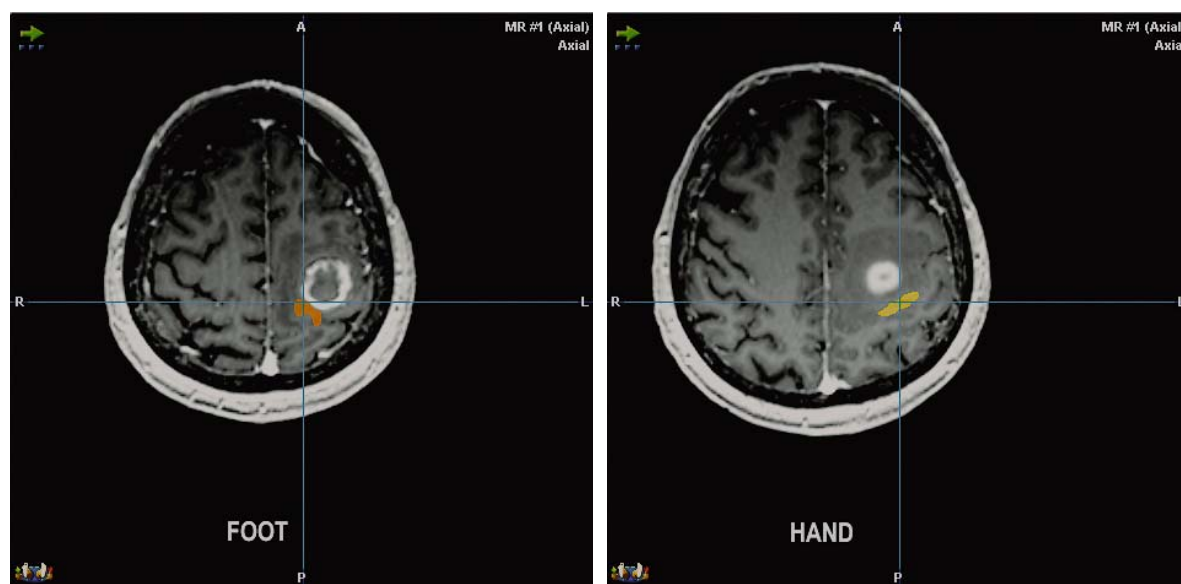


Fig. 6.1. Overlay of functional activation maps on morphological images (contrast enhanced T1 weighted 3D-data set) visualizing the critical spatial relationship between the left precentral high grade glioma and the primary motor foot (orange cluster) and hand (yellow cluster) representations. Transverse sections. Images: courtesy of C. Stippich, MD

conservative (subtotal or extended biopsy) resection. Finally this information is used to choose the “cortical entry” of lowest risk and to plan the surgical approach avoiding functional “no entry” areas in all cases. fMRI is confirmed intraoperatively with surgical inspection, intraoperative neuronavigation and in selected cases with cortical stimulation or evoked potentials. Optimized preoperative protocols were developed by STIPPICH et al. (1999, 2000, 2003) and performed together with a 3D T1-weighted MR sequence used for neuronavigation. Limitations are reduced patient’s compliance, motion artifacts, uncontrolled movements during the resting phase or co-movements of other body parts or paresis due to tumor growth. Minor inaccuracies can be eliminated by correction algorithms; in rare cases, however, the data acquisition has to be repeated.

Implementation of fMRI information in navigational systems is straight-forward to the surgeon, when the functional information is already integrated and displayed in the data volume normally read into these systems. When the anatomical and functional information is acquired in the same session no additional registration of fMRI data is necessary, hence reducing registration errors.

A major drawback is the fact, that fMRI is still very labour-intensive, requiring a group of MRI specialists for training the patient, acquiring the MRI and fMRI data and the post-processing of the data which requires approx. 4–6 hours. New real-time fMRI packages of the manufactures (see later) will help to solve these problems (MOELLER et al. 2004).

The importance and usefulness of navigation in neurosurgical cases was evaluated in 200 neurosurgical cases (WIRTZ et al. 1998, 2000) with regard to approach planning, determination of functional areas, detection of lesion and of tumor boundaries in low and high grade gliomas and finally radicality of glioma resection.

For planning the operative approach, in 90% the use of neuronavigation was considered beneficial by six neurosurgeons, the definition of anatomy and functional areas in 80%, lesion detection in 90%, tumor boundaries 75% and resection radicality in 65%.

In a recent study (WINKLER et al. 2005) the additional use of functional MRI was considered especially helpful in glioma surgery with extended amount of resection and reduction of postoperative morbidity as compared to landmark oriented resection. Less impressive were the results in metastases or meningiomas.

Actual work involving higher field magnets (3–7 T) has conclusively shown an increase in spatial resolution and signal to noise ratio (CHEN and UGURBIL 1999; THULBORN 1999). The use of modern contrast media will demonstrate larger lesions, which can be identified and encircled with the navigation tool. Both developments will have further implications for functional presurgical evaluation with regard to lesion delineation and preservable neurological function.

6.4

Applications of Functional Neuronavigation

6.4.1

Motor and Sensory Systems

Integration of functional data on sensorimotor function into the neuronavigational system yields a substantial benefit for patients with peritumoral tumors, in terms of preoperative risk assessment, surgical access and trajectory planning (Fig. 6.2). A patient admitted with a hemiparesis due to a focal central lesion with surrounding edema, is first administered a corticosteroid (e.g. 16 mg dexamethasone) in order to evaluate, whether the neurological symptoms will resolve with edema suppression. Persisting paresis strongly indicates tumor involvement in the precentral gyrus or subcortical fiber tracts, which can be confirmed by morphological MRI and diffusion tensor imaging (DTI, see below). In this case, a functional task (e.g. finger tapping) cannot usually be performed contralaterally to the lesion due to the impaired neurological function. However, some information can be obtained from an ipsilateral task eliciting bilateral brain responses (STIPPICH et al. 2003). Thus, voluntary movements of the unimpaired hand can display the ipsilateral precentral gyrus and premotor area, which together with postcentral activation due to contralateral passive somatosensory stimulation can serve as functional landmarks of the affected motor cortex (see chapter 4.4.6). In patients with distinct motor deficiencies a more robust approach is required with tasks like opening and closing a fist, need to be performed to establish signal changes in fMRI (Fig. 6.3).

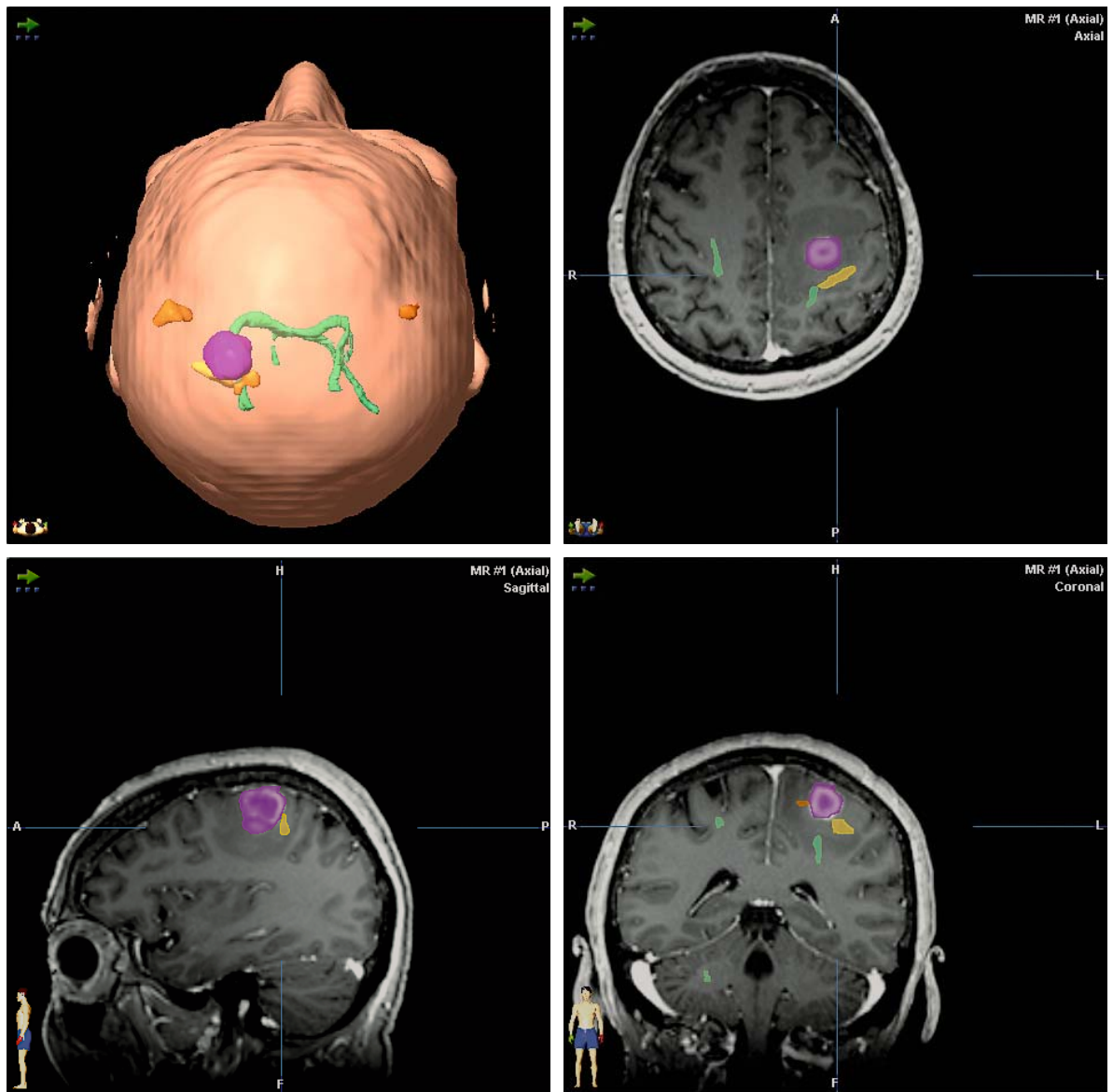


Fig. 6.2. Integration of BOLD-fMRI somatotopic mapping of the primary motor cortex and of Diffusion Tensor Imaging (DTI) tractography of the pyramidal tract for functional neuronavigation in a patient with a left precentral glioblastoma (same patient in Fig. 6.1). Segmented tumor (*pink*), foot and tongue representations (*orange clusters*), hand representation (*yellow cluster*), pyramidal tract (*green lines*). The neurosurgeon is provided with detailed information about the spatial relationship between envisaged site of surgery, functional cortex and fibertracts, facilitating the planning and the performance of function preserving resection. Conventional surgical view (top left: *left – left, right – right*). Transverse, sagittal and coronal views, radiological imaging convention (*right – left, left – right*). Images: courtesy of C. Stippich, MD



Fig. 6.3. Hemiparetic patient with a left rolandic metastasis from adenocarcinoma. BOLD-fMRI was performed using hand opening and closure (fist) as motor task. Primary sensorimotor fMRI activation indicated tumor growth into the central region via the postcentral gyrus. A parietal approach was chosen to resect the lesion from a posterior direction. Transverse sections with an overlay of functional activation maps on a T1-weighted contrast enhanced 3D-data set readily prepared for dicom export to neuronavigation.

Thus, functional imaging allows to display sensorimotor activation in relation to rolandic brain tumors (BITTAR et al. 2000; FANDINO et al. 1999; GALLEN et al. 1994; JANNIN et al. 2002) and its validity can be confirmed by direct electrocortical stimulation during surgery (LEHERICI et al. 2000; YOUSRY et al. 1995). However, effects of plastic changes and reorganization also have to be considered (CARPENTIER et al. 2001; FANDINO et al. 1999) and certain limitations with regard to variability in venous drainage and regional hemodynamic responses due to the pathology have to be taken into account.

Finally, promising new imaging techniques such as DTI can track subcortical fibers through the corona radiata, the internal capsule and the crura cerebri (COENEN et al. 2003; KRINGS et al. 2001; LE BIHAN 2003) (see Chap. 8). Although this technique is limited when these tracts pass through the tumor or surrounding edema and correlations between DTI data and electrophysiological information from subcortical stimulation identifying fiber tracts (DUFFAU et al. 2002, 2003; KELES and BERGER 2004) have to be performed, the integration of DTI and fMRI into one neuronavigation system will be a major step towards safe surgical planning and performing cortical and subcortical tumor resection (KAMADA et al. 2003).

6.4.2 Language

Classical functional neuroanatomy locates the motor output of language to the left inferior frontal gyrus (Broca's area, BA 44, 45) and the perception of language to the posterior temporal lobe (Wernicke's area, BA 22). Until now, language-related functional mapping for neurosurgical planning relied on two invasive procedures, the Wada-Test (intracarotid amytal injection) and intraoperative direct cortical stimulation. Language mapping is especially important in patients with lesions in and around the language-dominant hemisphere as well as in epilepsy surgery where it determines the amount of resection. The distance of resection from language sites, as determined by cortical stimulation, is the most important variable predicting recovery from postoperative speech disturbances. Thus an accurate localization of all essential language areas is critical for the speed of recovery as well as the avoidance of postoperative neurological deficits.

For neurosurgical purposes it was firstly important to demonstrate whether fMRI could replace the Wada test or not (see Chap. 7). In general, there is excellent correlation between the findings of the Wada test and fMRI for language lateralization

(BINDER et al. 1996; RUTTEN et al. 2002), especially in epilepsy patients (BENSON et al. 1999; WOERMANN et al. 2003). fMRI studies were also correlated with direct electrical cortical stimulation and a good correlation was found, depending on the language task (BENSON et al. 1999; FITZGERALD et al. 1997; SIGNORELLI et al. 2003). Based on the preoperative findings in functional imaging, the decision will be made, whether a biopsy, a subtotal resection or a maximal resection using awake craniotomy will be carried out in brain tumor patients (Fig. 6.4).

6.4.3 Visual Cortex

The cerebral cortex involved in vision constitutes up to one-third of the cerebral cortex. This reflects the importance of vision in everyday life. Visual information is transferred from the retina to the lateral geniculate nucleus and finally to the visual cortex following a well known retinotopic organization. Orig-

nally this information was yielded with PET imaging studies (FOX et al. 1986, 1987) and later confirmed by fMRI (BELLIVEAU et al. 1991, 1992). Since it is important to select an optimal stimulation frequency for visual paradigms (FOX and RAICHLE, 1984; KWONG et al. 1992), stimulation was originally performed with LED goggles. Nowadays computer simulated patterns are commercially available. Tumors affecting the visual cortex around the calcarine fissure or the optic radiation can produce changes in functional imaging tasks. Particularly in high grade gliomas involving the occipital lobe or tumors situated in the posterior temporal horn as intraventricular meningeomas or plexus papillomas, critical planning regarding the extent of resection or the surgical access is necessary to avoid interruption of the optic radiation (Fig. 6.5). Despite the widespread use of functional mapping in surgery, the identification of visual structures is rarely reported with fMRI (HIRSCH et al. 2000; ROUX et al. 2001a; SCHULDER et al. 1999), MEG (NAKASATO and YOSHIMOTO 2000) or PET (FRIED et al. 1995). A combination of fMRI and DTI displaying visual

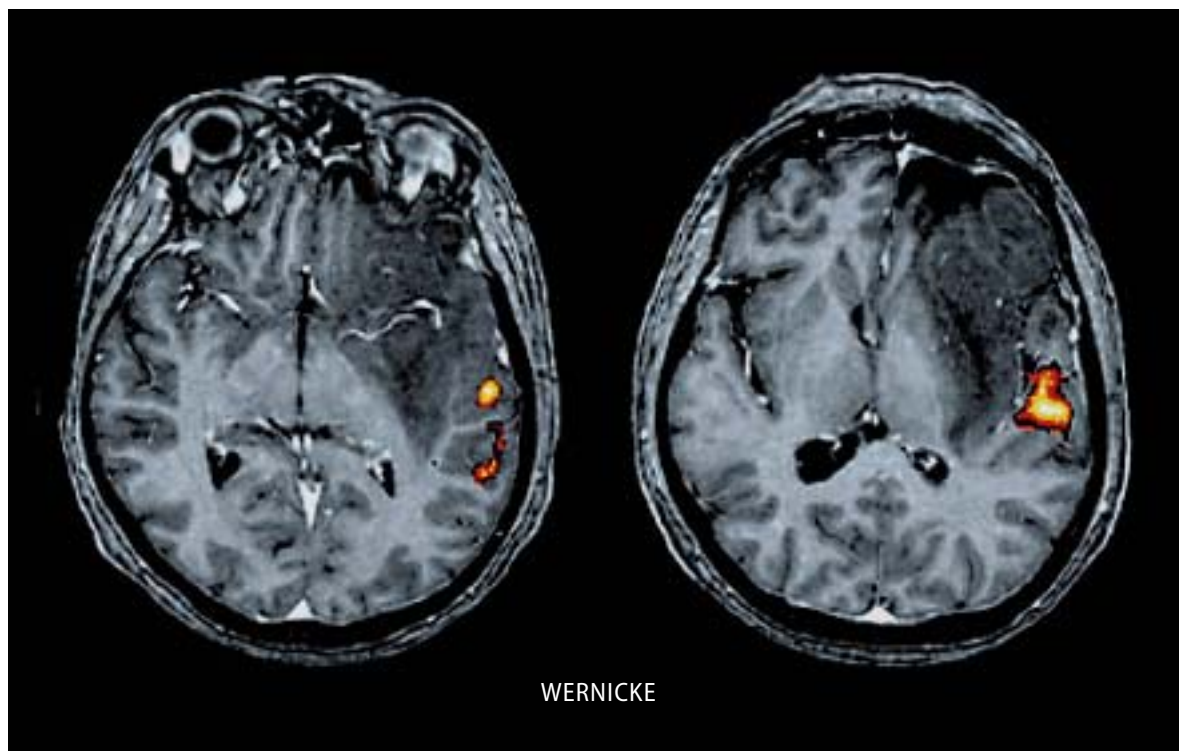


Fig. 6.4. Functional localization of the Wernicke language area in relation to a left fronto-temporal low grade glioma involving the basal ganglia and insula. Word listening (auditory stimulation) was used to elicit BOLD-activation. Transverse sections with an overlay of functional activation maps on a T1-weighted contrast enhanced 3D-data set.

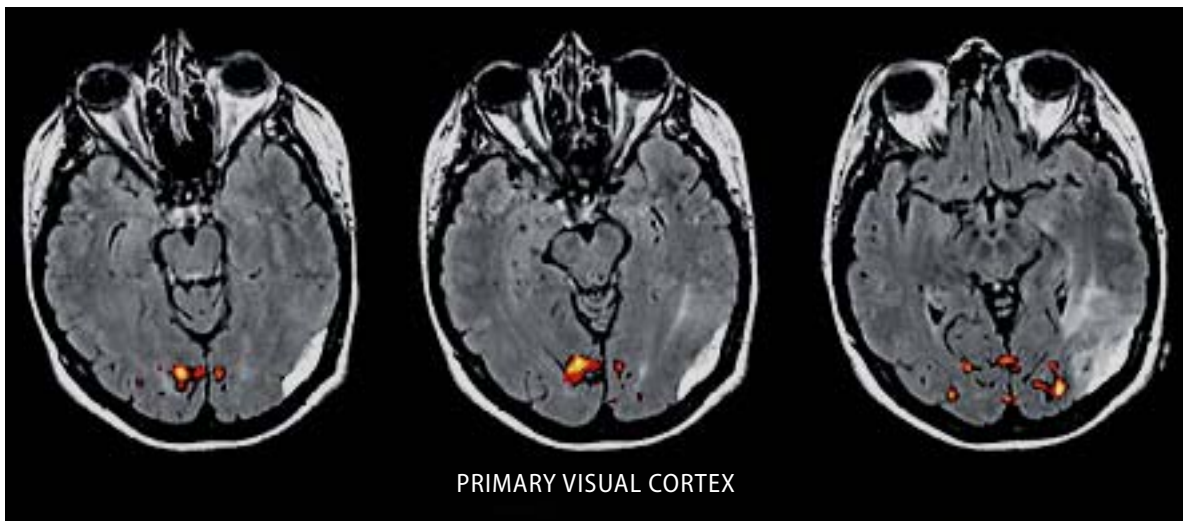


Fig. 6.5. Functional localization of the primary visual cortex in relation to a left parieto-occipital meningioma with signal alterations (perifocal edema) in the left optic radiation. Transverse sections with an overlay of functional activation maps on a T2-weighted fluid attenuated inversion recovery MR-sequence (FLAIR).

cortical areas as well as the optic radiation would be desirable to minimize the postoperative risk of visual field defects, which can tremendously affect the quality of life.

6.4.4 Auditory Cortex

Functional activation of the auditory cortex has not been used for neurosurgical procedures or neuronavigation yet. It is well known, that a tonotopic organization of blood flow responds to different tonal frequencies exists. Sound stimulation activates the primary auditory cortex in the contralateral hemisphere, whereas speech creates bilateral activation (BINDER et al. 1994; LAUTER et al. 1985). Based on new hypotheses about the origins or consequences of tinnitus, causing neuroplastic changes in the auditory cortex (LANGGUTH et al. 2003; MAHLKE and WALLHÄUSER-FRANKE 2004; MÜHLNICKEL et al. 1998), a recent case report describes the effects of chronic auditory cortex stimulation implanted with the help of auditory-fMRI neuronavigation (DERIDDER et al. 2004). Auditory fMRI was superimposed on morphological 3D-MRI and displayed together in a neuronavigation system, which was used to place an epidural paddle electrode. After successful test stimulation, an impulse

generator was implanted with an excellent result after 10 months.

6.4.5 Pain

There are numerous studies dealing with the activation of different cortical and subcortical brain areas evoked by mechanical or thermal noxious stimuli. Also therapeutic effects of surgical and non-surgical measures were studied. FMRI is used for neuronavigation in cases with central or peripheral neuropathic pain and therapeutic motor cortex stimulation (PIROTTE et al. 2005; ROUX et al. 2001b; SOL et al. 2001). Depending on the localization of the painful area and the patients' ability to perform the required tasks a mapping of the motor cortex is performed. The fMRI data are integrated into a neuronavigation system and displayed in the operating room together with the morphological MRI. In cases of missing limbs or in plegic patients virtual movements can be trained or the opposite healthy motor cortex is projected to the affected site, although in these latter cases neuroplastic distortions have to be taken into consideration. Via a burrhole approach an epidural lead electrode then can be placed over the somatotopic representation corresponding to the painful body area (Figs. 6.6 and 6.6). Challeng-

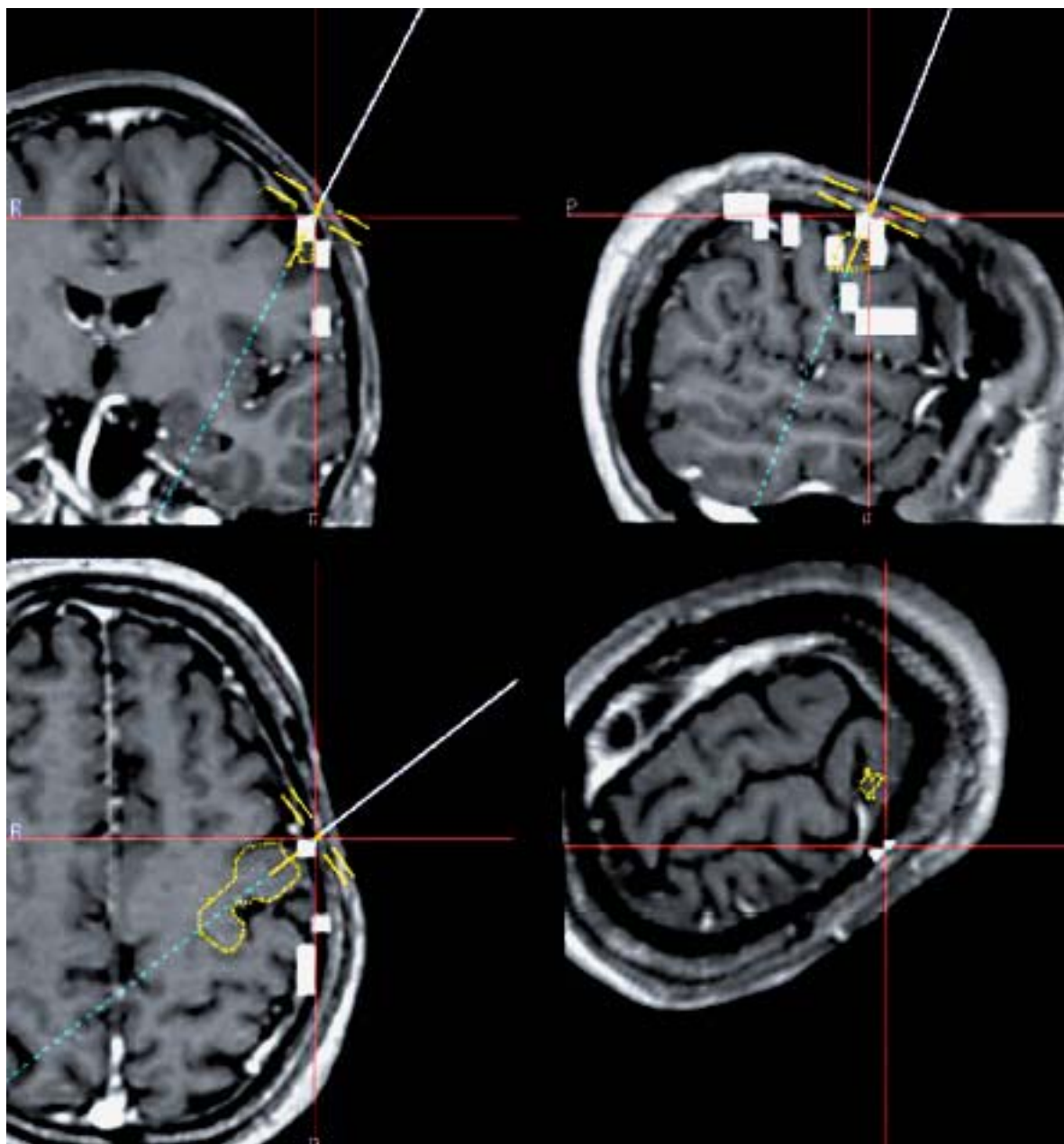


Fig. 6.6. Functional neuronavigation used for computer assisted placement of an epidural motor cortex stimulation lead in treatment of chronic pain. The fused images display anatomical and functional information as well as the site planned for electrode placement (yellow circular lines) along with the navigation device (pointer instrument, blue line). Coronal (top left), sagittal (top right) and transverse views (bottom left), “navigation view” (bottom right). White clusters indicate primary sensorimotor BOLD-activation after dicom export.



Fig. 6.7. Lateral x-ray plain film showing the localization of a paddle electrode implanted via a burrhole.

ing is the fact, that due to neuroplastic changes the functional areas might differ from the morphological data, which is known from several studies on the neuroplasticity of pain (FLOR 2003; KARL et al. 2004). However, a valid correlation between direct cortical stimulation and fMRI with a mean distance of 3.8 mm was found in the majority of cases in a recent study (PIROTTE et al. 2005).

6.4.6

Psychological Function, Memory

Obsessive-compulsive disorder (OCD) patients responding to “disgusting” stimuli revealed changes of activity in the orbital and dorsolateral prefrontal cortex (BREITER ET AL. 1996). These and other studies demonstrate the functional circuitry of these disorders, but have no direct surgical implication. More interesting is the possibility to predict

memory changes or deficits after surgical procedures (HENKE et al. 2003). This is most important in patients undergoing epilepsy surgery, especially temporal lobectomy (POWELL et al. 2004; RABIN et al. 2004). Implementation of activation patterns in the medial temporal lobe (for episodic-like or “event”-memory) or temporal cortex (for semantic-like or “fact” memory) into a neuronavigation system will increase the possibility of reduced postoperative memory deficits. This also holds true for frontal lesions, whereby patients, different from temporal amnesia, exhibit impairments in memory of temporal events (order, source or context). The (pre-) frontal cortex is responsible for active retrieval of memory and encoding, while the temporal cortex is mainly responsible for storage and automatic retrieval (MIYASHITA 2004). Therefore in the future specifically designed event-related fMRI paradigms will help to predict the risk of certain types of postoperative memory deficits.

6.4.7 Implementation of Functional Imaging Data into Intraoperative Imaging

The benefits of integrating functional imaging data into a neuronavigation system have been described so far. However neither MEG nor fMRI are used on a clinical routine basis. MEG is not available at many centers and fMRI requires an intense and time consuming processing phase before integrating and merging the data into a neuronavigational system. New real-time fMRI packages provided by MR scanner manufacturers enable now the radiologist to get immediate post-imaging results. In a recent study (MOELLER et al. 2004) two different routine clinical 1.5-T scanners were used (Magnetom Vision, Siemens and Intera, Philipps) for a motor paradigm (finger-tapping). The integrated software performed an automatic motion correction and cluster filtering displaying the activated brain area during each scan. An overlay with 3D T1-weighted imaging can be performed semiautomatically. Integrating these software packages into high field MR scanners situated in the operating theatre would for the first time allow direct intraoperative functional imaging (NIMSKY et al. 2004). Then the extent of resection of brain tumors or lesions in epilepsy surgery could be further tailored with regard to the functional information yielded by intraoperative fMRI.

Most recently DTI was also performed intraoperatively and displayed the intraoperative shift of white matter tracts during brain surgery (NIMSKY et al. 2005).

6.4.8 Implementation of Functional Imaging Data into Intraoperative Mapping

Delineation of cortical structures can be performed intraoperatively either by direct visualization, anatomical correlation to a navigational device or neurophysiological methods. In case of a large craniotomy the surgeon is able to identify anatomical landmarks on the exposed cortex and to determine various gyri. The localization of eloquent areas by direct inspection of the brains surface is very limited as there are no reliable landmarks except for the motor hand area of the precentral gyrus. Especially in cognitive functions localization of the recruited brain areas is highly

variable precluding any reliable prediction in individual patients. In patients with distorted anatomy or limited surgical exposure, neuronavigational devices or neurophysiological techniques help the surgeon to securely determine the boundaries of eloquent brain regions. Especially in perirolandic tumors, neurophysiological methods facilitate the delineation of the motor or sensory cortex. Direct electrical stimulation elicits movements in muscle groups corresponding to the homunculus. However intraoperatively, electrical cortical stimulation can be hampered by agents as relaxants causing a neuromuscular blockade or by the depth of anesthesia. On the other hand motor responses are also elicited by stimulation of premotor and even sensory areas. Sensory responses by electrical stimulation of the median or the tibial nerve are able to delineate the sensory cortex. The combination of somatosensory evoked potentials (SEPs) and cortical stimulation were already described in the late 1970s (WOOLSEY et al. 1979) and later refined by the use of the phase reversal to differentiate between motor and sensory cortex (CEDZICH et al. 1996; ROMSTÖCK et al. 2002) in brain tumor surgery. Nowadays these techniques are used for validation of functional imaging data displaying the distance between cortical activation and neurophysiological response and finally correlating the data with the clinical outcome or neurological function (COSGROVE et al. 1996; KOBER et al. 2001; KRISHNAN et al. 2004; PUCE et al. 1995; SCHIFFBAUER et al. 2003) (Fig. 6.9). Functional imaging has the advantage of being able to display activation deep in a sulcus, which is not easily accessible for direct stimulation. For further data regarding the validity of functional imaging data see Chap. 7. A combination of both techniques is also used in functional surgery as motor cortex stimulation for chronic pain states or tinnitus (SOL et al. 2001; TRONNIER et al. 1996).

6.4.9 Cost-Effectiveness

There are no direct cost analyses of functional imaging in presurgical evaluation. However it is well demonstrated that neuronavigation is able to lower the inpatient days in a hospital (PALEOLOGOS et al. 2000) therefore significantly reducing the expenses. Another study found the costs of the Wada test 3.7 times higher as compared to fMRI (MEDINA et al. 2004).



Fig. 6.8. Operative site showing the correlation of intraoperative cortical stimulation and fMRI localization.

6.5

Perspectives

6.5.1

Single-Rack Solution

The creation of a single rack information system for the surgeon consisting of data for functional imaging data (MEG, fMRI, DTI and Perfusion-MRI), navigation and electrophysiological monitoring with online information to support the surgeon's intraoperative decisions would be an additional goal. A special focus should be put on the imaging and electrophysiological localization of subcortical pathways. This integrated "functional" neuronavigational approach should be beneficial in surgical planning and pre- and intraoperative decision making, providing online information to improve surgical resection and decrease postoperative morbidity by protecting eloquent cortical and subcortical areas. Up to now the surgeon has to work with different information systems and to integrate all this information during surgery intellectually. An integrated multimodal navigation system taking over these tasks would reduce the time of surgery, allow safer resection of brain tumors and ultimately improve the patients' outcome.

Several topics have to be addressed to create such a system:

- Fusion of 3D navigational (morphological data) with fMRI, MEG, Perfusion-MRI and DTI.
- Correction of fusion inaccuracies due to the fact that up to now only a few anatomic landmarks are used for data merging.
- Correction of distortions of the different techniques (reduction of distortion by new imaging techniques; correction of remaining distortion by data processing) and their fusion.
- Automated export of electrophysiological data into a navigation system.
- Automatic recognition of electrode or grid configurations by the navigational system and display on the monitor or microscope (see below) for the operating surgeon.

6.5.2

Overlay of Functional Imaging Data in the Operation Microscope

It would be desirable to overlay the surgical site in the operation microscope with the different imaging data, e.g. not only delineating a tumor volume but also important functional cortical and subcortical sites. Interruptions or distractions caused by switching the focus between monitor and the microscope repeatedly is disturbing and time consuming. Using the methods of augmented reality can realize a more

efficient use of the different planning data. This could be realized by using or superimposing heads-up-displays with integration of the microscopic view or the respective planning data in the microscopic view (TRONNIER et al. 2000). Dedicated micro-optical overlay modules are already designed to provide the insertion and overlay of three dimensional data within the operating microscope (ASCHKE et al. 2003; MAKELA et al. 2001). Further refinements to enhance the surgeon's three-dimensional perception and fast integration of these data have to be performed in order to implement intraoperative imaging data.

Special tracking methods to compensate intraoperative brain shift have to be developed. Tracking points could be vessel branches, other anatomical landmarks or implanted markers (e.g. LEDs). Additional information provided by intraoperative imaging such as ultrasound should be integrated into the surgical workflow by automated actualization and integration of these imaging data into the microscopic view. This will make different import filters and a matching of different data formats necessary.

6.5.3 Imaging the Basal Ganglia

First trials were performed examining the basal ganglia with functional somatotopic mapping (MAILLARD et al. 2000). If it was possible to demonstrate the somatotopy of hand, foot or face areas in distinct basal ganglia nuclei as the internal pallidum or the subthalamic nucleus, these data could be used for surgical planning of the target and trajectories in stereotactic functional procedures such as pallidotomies or deep brain stimulation.

6.5.4 Neuroplasticity

Although it is known that over- or under use of specific function will create cortical neuroplasticity, either by enhanced afferent normal or pathological activity (musicians, writer's cramp), decreased afferent activity (blind individuals, patients with amputation) or disproportion of agonist/antagonist function (focal dystonia), pathological changes of the cortex (stroke, brain tumor, brain surgery) also demonstrate the brain's capacity for plastic changes (FUJII and NAKADA 2003). This

has serious implications for the different forms of therapy (LOTZE et al. 1999; WU and KAAS 1999; YOU et al. 2005). To the best of our knowledge, no longitudinal study has been performed looking for immediate postoperative changes in fMRI and long-term changes after surgical resection and neurological recovery.

6.5.5 Imaging the Spinal Cord

Functional imaging of the spinal cord is still in development. Movement artifacts of the cord itself and CSF flow make the interpretation of the images quite difficult. Up to now only healthy persons with experimental stimuli were examined (MOFFIT et al. 2005; STROMAN et al. 2005). The detection of changes of function by pathological lesions is far from being technically solved (GIOVE et al. 2004).

6.5.6 Molecular Imaging

A variety of imaging technologies are being investigated as tools for studying gene expression in living subjects, especially after gene therapy. The applications of such tools for presurgical planning in humans is desired though it still seems like a far way to implement them and overcome technical difficulties. SPECT and PET are the most mature of the current imaging technologies with high sensitivity and good access to scanners. MRI is also currently used for molecular imaging of different pathologies including brain tumors in rodents in order to supervise gene therapy protocols (MOFFAT et al. 2003; REHEMTULLA et al. 2002). However, if applicable to humans in the future, these images could also be used for surgical targeting and neuronavigation.

6.6 Summary

Functional imaging can provide information on the localization of essential functional cortex pre-operatively. It enables the surgeon to evaluate a risk assessment, to take therapeutic decisions and to advise the patient carefully about the estimated

risks and benefits of the procedure. He is able to make his resection plan estimating the position and relationship of the abnormal and the important functional tissue that should be preserved. Preoperative functional imaging can guide the resection according to function and not only morphology as with neuronavigation alone. Limiting factors are the interference with tumor mass and/or surrounding edema compromising local blood flow and the possible presence of preoperative neurological deficits preventing the performance of functional tasks during imaging. Resection borders can not be determined reliably based on fMRI data. However first reports in a very limited number of patients have suggested that resection of tumor in a distance of at least 10 mm may be safe and may cause no decline in neurological function. On the other hand resection in an area less than 5 mm apart from functional cortex will most likely result in – at least temporarily – neurological deficits. To overcome the problem of intraoperative brain shift, a correlation with direct electrical stimulation for motor cortex, SEPs for visual, auditory and sensory cortex can be applied. Finally the use of intraoperative high-field MR-scanners will enable us to evaluate some functions intraoperatively. Intraoperative mapping of speech and other higher cognitive functions still requires awake craniotomy.

References

- Aschke M, Wirtz CR, Raczekowsky J et al. (2003) Augmented reality in operating microscopes for neurosurgical interventions. *Proc IEEE* 652–655
- Belliveau JW, Kennedy DN, McKinstry RC et al. (1991) Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* 254:716–719
- Belliveau JW, Kwong KK, Kennedy DN et al. (1992) Magnetic resonance imaging mapping for brain function. *Human visual cortex. Invest Radiol* 27: S59–65
- Benson RR, FitzGerald DB, LeSueur LL et al. (1999) Language dominance determined by whole brain functional MRI in patients with brain lesions. *Neurology* 52:798–809
- Binder JR, Rao SM, Hammeke TA et al. (1994) Functional magnetic resonance imaging of human auditory cortex. *Ann Neurol* 35:662–672
- Binder JR, Swanson SJ, Hammeke TA et al. (1996) Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology* 46:978–984
- Bittar RG, Olivier A, Sadikot AF et al. (2000) Cortical and somatosensory representation: effect of cerebral lesions. *J Neurosurg* 92:242–248
- Black PM, Moriarty TM, Alexander EA III et al. (1997) The development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications. *Neurosurgery* 41:831–845
- Breiter HC, Rauch SL, Kwong KK et al. (1996) Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. *Arch Gen Psychiatry* 53:595–606
- Carpentier A, Constable RT, Schlosser MJ et al. (2001) Patterns of functional magnetic resonance imaging activation in association with structural lesions in the rolandic region: a classification system. *J Neurosurg* 94:946–954
- Cedzich C, Taniguchi M, Schaefer S et al. (1996) Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region. *Neurosurgery* 38:962–970
- Chen W, Ugurbil K (1999) High spatial resolution functional magnetic resonance imaging at very high magnetic field. *Top Magn Reson Imaging* 10:63–78
- Coenen VA, Krings T, Axer H et al. (2003) Intraoperative three-dimensional visualization of the pyramidal tract in a neuronavigation system (PTV) reliably predicts true position of principal pathways. *Surg Neurol* 60:381–390
- Cosgrove GR, Buchbinder BR, Jiang H (1996) Functional magnetic resonance imaging for intracranial neuronavigation. *Neurosurg Clin North Am* 7:313–322
- DeRidder D, De Mulder G, Walsh V et al. (2004) Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus. Case report. *J Neurosurg* 100:560–564
- Duffau H, Capelle L, Sichez N et al. (2002) Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* 125:199–214
- Duffau H, Capelle L, Denvil D et al. (2003) Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a series of 103 patients. *J Neurosurg* 98:764–768
- Fandino J, Kollias S, Wieser HG et al. (1999) Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumors involving the motor cortex. *J Neurosurg* 91:238–250
- FitzGerald DB, Cosgrove GR, Ronner S et al. (1997) Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. *AJNR* 18:1529–1539
- Flor H (2003) Remapping somatosensory cortex after injury. *Adv Neurol* 93:195–204
- Fox PT, Raichle ME (1984) Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. *J Neurophysiol* 51:1109–1120
- Fox PT, Mintum MA, Raichle ME et al. (1986) Mapping human visual cortex with positron emission tomography. *Nature* 323:806–809
- Fox PT, Miezin FM, Allman JM et al. (1987) Retinotopic organization of human visual cortex mapped with positron-emission tomography. *J Neurosci* 7:913–922
- Fried I, Nenov V, Ojemann SG et al. (1995) Functional MR and PET imaging of rolandic and visual cortices for neurosurgical planning. *J Neurosurg* 83:854–861

- Fujii Y, Nakada T (2003) Cortical reorganization in patient with subcortical hemiparesis: neural mechanisms of functional recovery and prognostic implication. *J Neurosurg* 98:64–73
- Gallen CC, Bucholz RD, Sobel DF (1994) Intracranial neurosurgery guided by functional imaging. *Surg Neurol* 42:523–530
- Giove F, Gareffa G, Giuletti G et al. (2004) Issues about the fMRI of the human spinal cord. *Magn Reson Imaging* 22:1505–1516
- Hemm S, Vaissiere N, Zanca M et al. (2004) Thallium SPECT-based stereotactic targeting brain tumor biopsies. A technical note. *Stereotact Funct Neurosurg* 82:70–76
- Henke K, Treyer V, Weber B et al. (2003) Functional neuroimaging studies predicts individual memory outcome after amygdalohippocampectomy. *Neuroreport* 14:1197–1202
- Hirsch J, Ruge MI, Kim KHS et al. (2000) An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language and visual functions. *Neurosurgery* 47:711–722
- Jannin P, Morandi X, Fleig OJ et al. (2002) Integration of sulcal and functional information for multimodal neuronavigation. *J Neurosurg* 96:713–723
- Kamada K, Houkin K, Takeuchi F et al. (2003) Visualization of the eloquent motor system by integration of MEG. Functional, and anisotropic diffusion-weighted MRI in functional neuronavigation. *Surg Neurol* 59:353–362
- Karl A, Mühlhnickel W, Kurth R et al. (2004) Neuroelectric source imaging of steady-state movement-related cortical potentials in human upper extremity amputees with and without phantom limb pain. *Pain* 110:90–102
- Keles GE, Berger MS (2004) Advances in neurosurgical technique in the current management of brain tumors. *Semin Oncol* 31:659–665
- Kikinis R, Gleason PL, Moriarty TM et al. (1996) Computer-assisted interactive three-dimensional planning for neurosurgical procedures. *Neurosurgery* 38:640–651
- Kober H, Nimsky C, Moeller M et al. (2001) Correlation of sensorimotor activation with functional magnetic resonance imaging and magnetoencephalography in presurgical functional imaging: a spatial analysis. *Neuroimage* 14:1214–1228
- Koivukangas J, Louhisalmi Y, Alakuijala J et al. (1993) Ultrasound-controlled neuronavigator-guided brain surgery. *J Neurosurg* 79:36–42
- Kracht LW, Miletic H, Busch S et al. (2004) Delineation of brain tumor extent with (11C)L methionine positron emission tomography: local comparison with stereotactic histopathology. *Clin Cancer Res* 10:7163–7170
- Krings T, Reinges MH, Thies R et al. (2001) Function and diffusion-weighted magnetic resonance images of space-occupying lesions affecting the motor system: imaging the motor cortex and pyramidal tracts. *J Neurosurg* 95:816–824
- Krishnan R, Raabe A, Hattungen E et al. (2004) Functional magnetic resonance imaging-integrated neuronavigation: correlation between lesion-to-motor cortex distance and outcome. *Neurosurgery* 55:904–915
- Kwong KK, Belliveau JW, Chesler DA et al. (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA* 89:5675–5679
- Langguth B, Eichhammer P, Wiegand R et al. (2003) Neuro-navigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment. *Neuroreport* 23:977–980
- Lauter JL, Herscovitch P, Formby C et al. (1985) Tonotopic organization in human auditory cortex revealed by positron emission tomography. *Hear Res* 20:199–205
- Le Bihan D (2003) Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci* 4:469–480
- Leherici S, Duffeau H, Cornu P et al. (2000) Correspondence between functional magnetic resonance imaging somatotopy and individual brain anatomy of the central region: comparison with intraoperative stimulation in patients with brain tumors. *J Neurosurg* 92:589–598
- Lotze M, Grodd W, Birbaumer N et al. (1999) Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain. *Nature Neurosci* 2:501–502
- Maciunas RJ (1993) Interactive image-guided surgery. In: Barrow D (ed) *Neurosurgical topics*. American Association of Neurological Surgeons
- Mahlke C, Wallhauser-Franke E (2004) Evidence for tinnitus-related plasticity in the auditory and limbic system, demonstrated by arg3.1 and c-fos immunocytochemistry. *Hear Res* 195:17–34
- Maia AC, Malheiros SM, da Rocha AJ et al. (2004) Stereotactic biopsy guidance in adults with supratentorial non-enhancing gliomas: role of perfusion-weighted magnetic resonance imaging. *J Neurosurg* 101:970–976
- Maillard L, Ishii K, Bushara K et al. (2000) Mapping the basal ganglia. FMRI evidence for somatotopic representation of face, hand and foot. *Neurology* 55:377–383
- Makela JP, Kirveskari E, Seppä M et al. (2001) Three-dimensional integration of brain anatomy and functions to facilitate intraoperative navigation around the sensorimotor strip. *Hum Brain Mapp* 12:180–192
- Medina LS, Aguirre E, Bernal B, et al. (2004) Functional MR imaging versus Wada test for evaluation of language lateralization: cost analysis. *Radiology* 230:49–54
- Miga MI, Roberts DW, Kennedy FE et al. (2001) Modeling of retraction and resection for intraoperative updating of images. *Neurosurgery* 49:75–85
- Miyashita Y (2004) Cognitive memory: cellular and network machineries and their top-down control. *Science* 306:435–440
- Moche M, Busse H, Dannenberg C et al. (2001) Fusion von MRT-, fMRT- und intraoperativen MRT-Daten. *Radiologe* 41:993–1000
- Moeller M, Freund M, Greiner C et al. (2004) Real-time fMRI. a tool for the routine presurgical localisation of the motor cortex. *Eur Radiol* 15:292–295
- Moffat BA, Reddy GR, McKonville P et al. (2003) A novel polyacrylamide magnetic nanoparticle contrast agent for molecular imaging using MRI. *Mol Imaging* 2:324–332
- Moffit MA, Dale BM, Duerk JL et al. (2005) Functional magnetic resonance imaging of the human lumbar spinal cord. *J Magn Reson Imaging* 21:527–535
- Mühlhnickel W, Elbert T, Taub E et al. (1998) Reorganization of auditory cortex in tinnitus. *Proc Natl Acad Sci USA* 95:10340–10343
- Nabavi A, Black PM, Gering DT et al. (2001) Serial intraoperative magnetic resonance imaging of brain shift. *Neurosurgery* 48:787–798
- Nakasato N, Yoshimoto T (2000) Somatosensory, auditory

- and visual evoked magnetic fields in patients with brain diseases. *J Clin Neurophysiol* 17:20–22
- Nimsky C, Ganslandt O, Cerny S et al. (2000) Quantification of, visualization of, and compensation for brain shift using intraoperative magnetic resonance imaging. *Neurosurgery* 47:1070–1079
- Nimsky C, Ganslandt O, Kober H et al. (2001) Intraoperative magnetic resonance imaging combined with neuronavigation: a new concept. *Neurosurgery* 48:1082–1091
- Nimsky C, Ganslandt O, Fahlbusch R (2004) Functional neuronavigation and intraoperative MRI. *Adv Tech Stand Neurosurg* 29:229–263
- Nimsky C, Ganslandt O, Hastreiter P et al. (2005) Intraoperative diffusion tensor MR imaging: shifting of white matter tracts during neurosurgical procedures - initial experience. *Radiology* 234:218–225
- Okudera H, Takemae T, Kobayashi K (1993) Intraoperative computer tomographic scanning during transsphenoidal surgery. *Neurosurgery* 32:1041–1043
- Paleologos TS, Wadley JP, Kitchen ND et al. (2000) Clinical utility and cost-effectiveness of interactive image-guided craniotomy: clinical comparison between conventional and imag-guided meningioma surgery. *Neurosurgery* 47:40–47
- Pirotte B, Goldman S, Massager N et al. (2004) Combined use of 18F-fluorodeoxyglucose and 11C-methionine in 45 positron emission tomography guided stereotactic brain biopsies. *J Neurosurg* 101:476–483
- Pirotte B, Voordecker P, Neugroschl C et al. (2005) Combination of functional magnetic resonance imaging-guided neuronavigation and intraoperative cortical brain mapping improves targeting of motor cortex stimulation in neuropathic pain. *Neurosurgery* 56 (ONS Suppl):344–359
- Powell HWR, Koepp MJ, Richardson MP et al. (2004) The application of functional MRI of memory in temporal lobe epilepsy. a clinical review. *Epilepsia* 45:855–863
- Puce A, Constable RT, Luby ML et al. (1995) Functional magnetic resonance imaging of sensory and motor cortex: comparison with electrophysiological localization. *J Neurosurg* 83:262–270
- Rabin ML, Narayan VM, Kimberg DY et al. (2004) Functional MRI predicts post surgical memory following temporal lobectomy. *Brain* 127:2286–2298
- Rehmtulla A, Hall DE, Stegman LD et al. (2002) Molecular imaging of gene expression and efficacy following adenoviral-mediated brain tumour gene therapy. *Mol Imaging* 1:43–55
- Roberts DW, Miga MI, Hartov A et al. (1999) Intraoperatively updated neuroimaging using brain modeling sparse data. *Neurosurgery* 45:1199–1206
- Romstöck J, Fahlbusch R, Ganslandt O et al. (2002) Localisation of the sensorimotor cortex during surgery for brain tumours: feasibility and waveform patterns of somatosensory evoked potentials. *J Neurol Neurosurg Psychiatr* 72:221–229
- Roux FE, Ibarrola D, Lotterie JA et al. (2001a) Perimetric visual field and functional MRI correlation: implications for image-guided surgery in occipital brain tumors. *J Neurol Neurosurg Psychiatr* 71:505–514
- Roux FE, Ibarrola D, Tremoulet M et al. (2001b) Methodological and technical issues for integrating functional magnetic resonance imaging data in a neuronavigational system. *Neurosurgery* 49:1145–1157
- Rutten GJ, Ramsey NF, van Rijen PC et al. (2002) FMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. *Neuroimage* 17:447–460
- Schiffbauer H, Berger MS, Ferrari P et al. (2003) Preoperative magnetic source imaging for brain tumor surgery: a quantitative comparison with intraoperative sensory and motor mapping. *Neurosurg Focus* 7
- Schulder M, Holodny A, Liu WC et al. (1999) Functional magnetic resonance image-guided surgery of tumors in or near the primary visual cortex. *Stereotact Funct Neurosurg* 73:31–36
- Signorelli F, Guyotat J, Schneider F et al. (2003) Technical refinements for validating functional MRI-based neuronavigation data by electrical stimulation during cortical language mapping. *Min Invas Neurosurg* 46:265–268
- Sol JC, Casaux J, Roux FE et al. (2001) Chronic motor cortex stimulation for phantom limb pain: correlations between pain relief and functional imaging. *Stereotact Funct Neurosurg* 77:172–176
- Son BC, Kim MC, Choi BG et al. (2001) Proton magnetic resonance chemical shift imaging (1H CSI)-directed stereotactic biopsy. *Acta Neurochir* 143:45–49
- Stadlbauer A, Moser E, Gruber S et al. (2004) Integration of biochemical images of a tumor into frameless stereotaxy achieved using a magnetic resonance imaging/magnetic resonance spectroscopy hybrid data set. *J Neurosurg* 101:287–294
- Stippich C, Hofmann R, Kapfer D et al. (1999) Somatotopic mapping of the human primary somatosensory cortex by fully automated tactile stimulation using functional MRI. *Neurosci Lett* 277:25–28
- Stippich C, Kapfer D, Hempel E et al. (2000) Robust localization of the contralateral precentral gyrus in hemiparetic patients using the unimpaired ipsilateral hand. *Neurosci Lett* 285:155–159
- Stippich C, Kress B, Ochmann H et al. (2003) Preoperative functional magnetic resonance imaging (fMRI) in patients with rolandic brain tumors: indication, investigation strategy, possibilities and limitations of clinical application. *Fortschr. Roentgenstr* 175:1042–1050
- Stroman PW, Kornelsen J, Lawrence J (2005) An improved method for spinal functional MRI with large volume coverage of the spinal cord. *J Magn Reson Imaging* 21:520–526
- Taylor RH, Lavallée S, Burdea GC et al. (eds) (1995) Computer integrated surgery. Technology and clinical application. MIT Press, Boston
- Thulborn KR (1999) Clinical rationale for very-high-field (3.0 Tesla). *Functional magnetic resonance imaging*. *Top Magn Reson Imaging* 10:37–50
- Tronnier VM, Wirtz CR, Knauth M et al. (1996) Intraoperative computer-assisted neuronavigation in functional neurosurgery. *Stereotact Funct Neurosurg* 66:65–68
- Tronnier VM, Wirtz CR, Knauth M et al. (1997) Intraoperative diagnostic and interventional magnetic resonance imaging in neurosurgery. *Neurosurgery* 40:891–902
- Tronnier V, Staubert A, Bonsanto MM et al. (2000) Virtuelle Realität in der Neurochirurgie. *Radiologe* 40:211–217
- Tsuyuguchi N, Takami T, Sunada I et al. (2004) Methionine positron emission tomography for differentiation of recurrent brain tumor and radiation necrosis after

- stereotactic radiosurgery in malignant glioma. *Ann Nucl Med* 18
- Unsgaard G, Gronningsaeter A, Ommedahl S et al. (2002) Brain operations guided by real-time two-dimensional ultrasound: new possibilities as a result of improved image quality. *Neurosurgery* 51:402–412
- Winkler D, Strauss G, Lindner D et al. (2005) The importance of functional magnetic resonance imaging in neurosurgical treatment of tumors in the central region. *Clin Neuroradiol* 15:182–189
- Wirtz CR, Knauth M, Hassfeld et al. (1998) Neuronavigation – first experience with three commercially available systems. *Zentralbl Neurochir* 59:14–22
- Wirtz CR, Albert FK, Schwaderer M, et al. (2000) The benefit of neuronavigation for neurosurgery analyzed by its input on glioblastoma surgery. *Neurol Res* 22:354–360
- Woermann FG, Jokeit H, Luerding R et al. (2003) Language lateralization by Wada test and fMR in 100 patients with epilepsy. *I. Neurology* 61:699–701
- Woolsey CN, Erickson TC, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked responses and electrical stimulation. *J Neurosurg* 51:476–506
- Wu CWH, Kaass JH (1999) Reorganization in primary motor cortex of primates with long-standing therapeutic amputations. *J Neurosci* 19:7679–7697
- You SH, Jang SH, Kim YH et al. (2005) Virtual-reality-induced cortical reorganization and associated locomotor recovery in chronic stroke: an experimenter-blinded study. *Stroke* 36:1166–1171
- Yousry TA, Schmid U, Jassoy AG et al. (1995) Topography of the cortical motor hand area: prospective study with functional MR imaging and direct motor mapping at surgery. *Radiology* 195:23–29
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Validity of

Presurgical Functional Localization

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and CHRISTINE DELMAIRE

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KEY POINTS

Over the last decade, presurgical mapping using functional neuroimaging techniques – and in particular fMRI – has made considerable progress. FMRI is now approaching clinical practice and is no longer just used for research applications. One of the best established clinical applications is presurgical functional neuroimaging with its contributions to surgical planning and performance and possibly to the prediction of postoperative outcome.

Validation studies of functional imaging techniques have suggested a great potential to localize motor areas, to lateralize and localize language and more recently memory functions. However, particularly for cognitive brain functions the imaging results strongly depend on the methodology used – established clinical standard procedures are not available yet. Currently functional neuroimaging should be considered as complementary to direct electrical stimulations (DES) and intracarotid amobarbital procedure (IAP) providing additional information, such as information on the entire functional network and on the contralateral hemisphere, which is not accessible to DES. Until now a full replacement of these established reference procedures is not justified. This issue requires further study.

Diffusion tensor imaging (DTI) fiber tracking is a more recent technique and much work remains to be done to validate its value in presurgical mapping. Correlation between DTI fiber tracking and DES of subcortical white matter in larger series of patients still need to be performed.

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7.1

Possibilities and Limits of Functional Brain Mapping

In presurgical functional mapping, determining the accuracy of functional maps is a critical issue if functional images are to contribute to the presurgical localization of functional areas at risk of postoperative deficit. Among functional imaging methods, functional MRI (fMRI) is the most widely used. fMRI can be easily performed on clinical magnets. It provides at the same time the anatomical characterization of the brain lesion, high resolution 3D images of the brain and functional images without any contrast injection. The following paragraphs will focus on the possibilities and limits of blood-oxygen-level-dependent (BOLD) contrast fMRI.

7.1.1

Spatial Localization of BOLD Signal

Validation studies of functional imaging techniques have suggested a great potential to localize motor areas, to lateralize and localize language and more recently memory functions. However, particularly for cognitive brain functions the imaging results strongly depend on the methodology used, including the imaging parameters. The following paragraphs review some properties of BOLD contrast that allows better understand the spatial specificity of BOLD signal.

7.1.1.1

Spatial Specificity of Deoxyhemoglobin-Based (BOLD fMRI) Methods

Multiple-site single-unit recordings and fMRI studies on the same animal have suggested that the limit of spatial specificity of T_2^* BOLD contrast might be in the range of 4–5 mm for single condition maps, i.e. the task compared with rest (UGURBIL et al. 2003). This may be adequate for presurgical brain mapping currently performed in the human brain with an image resolution of 3–5 mm but a much better resolution can be achieved under certain circumstances (HAREL et al. 2006).

The explanation for this is that deoxyhemoglobin changes that are initiated at the point of increased neuronal activity do not remain stationary and

propagate into large ‘draining’ vessels. Thus, deoxyhemoglobin changes incorrectly appear as ‘activation’ away from the actual site of neuronal activity. Therefore, increased contribution of small vessels (capillaries) vs large ‘draining’ vessels is a critical issue for improving the spatial resolution of BOLD contrast images. The respective contribution of small versus large vessels will depend on several factors, including the field strength and the type of sequence.

7.1.1.2

The Type of Sequence: Spin Echo (T_2) vs Gradient Echo (T_2^*) BOLD fMRI Methods

7.1.1.2.1

The Intra- and Extravascular Components of BOLD Signal

The most commonly used fMRI approach was introduced in 1992 and is based on T_2^* (i.e. gradient echo) BOLD contrast. BOLD contrast images the regional alterations in deoxyhemoglobin that accompany changes in neuronal activity (HEEGER et al. 2002; LOGOTHETIS and WANDELL 2004).

BOLD contrast originates from the intravoxel magnetic field inhomogeneity induced by paramagnetic deoxyhemoglobin inside red blood cells, which in turn are compartmentalized within the blood vessels. Magnetic susceptibility differences between the deoxyhemoglobin-containing compartments vs the surrounding space generate magnetic field gradients across and near the boundaries of these compartments. BOLD contrast has thus an intravascular and extravascular contribution (Fig. 7.1).

The intravascular T_2 BOLD effect is associated with the magnetic field gradient generated outside the red blood cells and inside the vessels. The field gradients extent around the red blood cells is very small compared to diffusion distances around and across membranes of these cells (Fig. 7.1). Therefore, the effect is dynamically averaged and is detectable as a T_2 effect, and in the presence of regional deoxyhemoglobin content increase, the T_2 of blood decreases (Thulborn et al. 1982). This intravascular effect is present in large as well as in small vessels.

The extravascular BOLD effect is associated with the magnetic field gradient generated outside the boundaries of the blood vessels. This gradient is due to the difference in magnetic susceptibility induced by deoxyhemoglobin between the vessel and the sur-

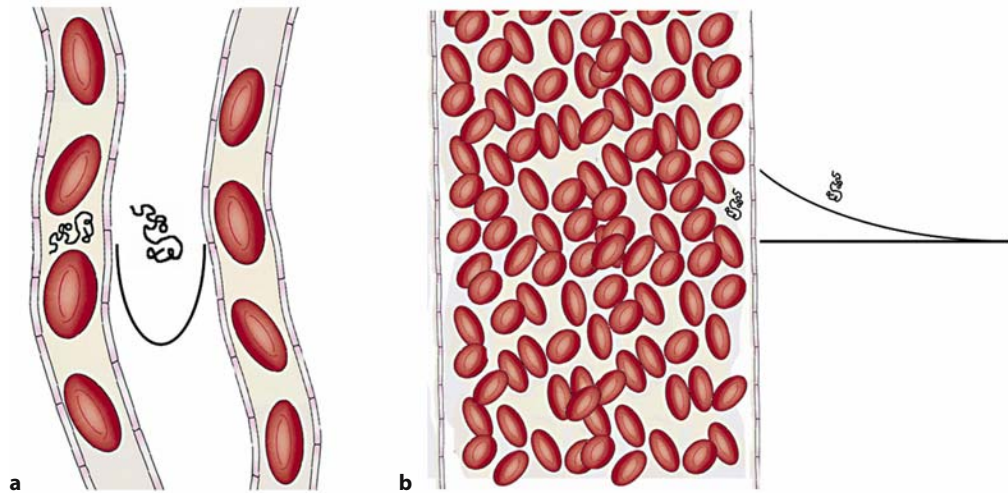


Fig. 7.1a,b. The extravascular BOLD effect is associated with the magnetic field gradient generated outside the boundaries of the blood vessels, which is due to the difference in magnetic susceptibility induced by deoxyhemoglobin between the vessel and the surrounding diamagnetic tissue (after HOPPEL et al. 1993). The *black curves* outside the vessels represent the field gradient produced by the blood, which is inside the vessels. **a** For small vessels such as capillaries, the field gradients around the vessels are large compared with diffusion distances, therefore the extravascular BOLD is a T2 effect because water diffusion dynamically averages in the magnetic field gradient. **b** For large vessels, the field gradients around the vessels are small compared to diffusion distances. The signal loss in the voxel is the result of static averaging, therefore the extravascular BOLD is a T2* effect. In **a** and **b** the intravascular BOLD effect is associated with the magnetic field gradient generated outside the red blood cells inside the vessels. Similarly to the extravascular BOLD effect around capillaries, the intravascular BOLD is detectable as a T2 effect.

rounding diamagnetic tissue. For small vessels such as capillaries, water diffusion during image acquisition (typically 50–100 ms for echo planar images (EPI)) dynamically averages the experienced magnetic field gradients and results in a T2 effect, similarly to the intravascular BOLD effect. For large vessels, dynamic averaging does not occur any more. Instead, static averaging will result in signal loss in the voxel. A water molecule located in the vicinity of the blood vessel will see an approximately static magnetic field (B_0) which will vary with the proximity to the vessel (Fig. 7.1). As this magnetic field varies across the voxel, the signal of the entire voxel will be dephased, resulting in a T2* effect.

7.1.1.2.2

Specificity of Spin Echo (T_2) vs Gradient Echo (T_2^*) BOLD

As detailed above, BOLD signal comes from intra and extravascular effects originating from small and large vessels. The T_2 -based BOLD signal comes from the intravascular (T_2 changes in large as well as small vessels), and the extravascular effect associated with small vessels only. Thus, spin echo (SE)

BOLD fMRI response is due to apparent changes in T_2 originating from the diffusion of water in the presence of magnetic-field gradients generated in the extravascular space around microvasculature (OGAWA et al. 1993; BOXERMAN et al. 1995), as well as from the exchange of water into and out of red blood cells in the blood itself (PAWLIK et al. 1981; VAN ZIJL et al. 1998; UGURBIL et al. 1999). At high magnetic field such as 7 Tesla, blood has a short T_2 , shorter than the echo times that are used in fMRI experiments. Therefore, the blood is not expected to contribute significantly to signal changes. Therefore, at high field strength, SE BOLD originates mainly from the extravascular space around microvasculature and therefore provides greater specificity to changes in neuronal activity (LEE et al. 1999; DUONG et al. 2003; UGURBIL et al. 2003; YACOB et al. 2003).

7.1.1.2.3

Field Dependence of BOLD Signal

High magnetic fields will increase the spatial localization value of BOLD fMRI (UGURBIL et al. 2003). Higher fields will increase the signal to noise ratio

of functional images. They will also attenuate the relative macrovascular contribution.

BOLD response is expected to behave differently with increasing magnetic fields in small vs large blood vessels (OGAWA et al. 1993). The dependence on the external magnetic field strength varies quadratically for capillaries. In contrast, the dependence on the static magnetic field is linear for large blood vessels contribution (OGAWA et al. 1993). Therefore, in addition to increasing the fMRI signal, higher magnetic fields will specifically enhance the signal components originating from parenchymal capillary tissue. In contrast, BOLD signal originating from large vessels will be over-represented at lower magnetic fields.

7.1.2 fMRI Artifacts and Limitations

Different types of artifacts and methodological limitations need to be considered in clinical fMRI. They may also interfere with the results of validation studies using established reference procedures – the most important are discussed below. For details see Chap. 10.

7.1.2.1 Movement Artifacts

Head motion is a critical issue in BOLD fMRI. Head motion is mostly represented by rigid body global deformations and translations. When voxels have side lengths smaller than 1 mm, motion control becomes a crucial issue. Head motion does not depend on which part of the brain is imaged. Using single shot EPI, each image is virtually devoid of motion artifacts, given the very short acquisition time (<100 ms). However, head motion may occur between successive images of the fMRI series. Most fMRI studies are currently performed using a spatial resolution of 3–4 mm in plane voxel size and 4–5 mm slice thickness (e.g. matrix: 64×64, FOV=24 cm). Head motion artifacts predominate in regions of tissue interface where changes in signal intensity are high (Fig. 7.2). When temporally correlated with task performance, a movement of one-tenth of a voxel (300–400 μm) may result in signal changes similar or even larger than the actual signal increase due to task performance and are virtually impossible to distinguish from it by motion correction software (Fig. 7.2). A careful setup of the subject in the magnet (padding foams) allows reducing these

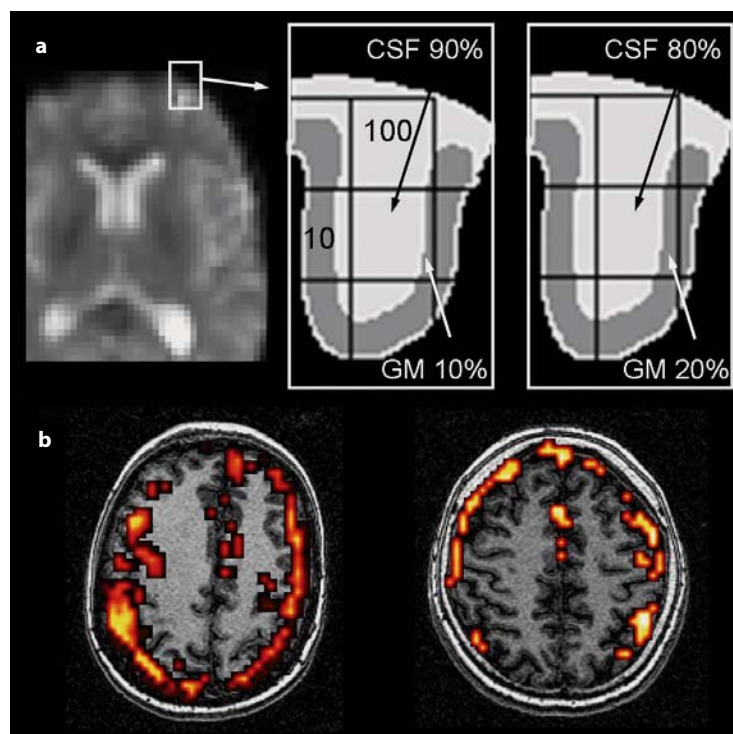


Fig. 7.2a,b. Head motion artifact. When temporally correlated with task performance, a movement of 1/10th of a voxel (300–400 μm) may result in signal changes similar or even larger than the actual signal increase due to task performance and are virtually impossible to distinguish from it by motion correction software. Artifacts predominate in regions of tissue interface where changes in signal intensity are high. **a** The diagrams represent an enlargement of a frontal sulcus from the left image. In condition 1, the 4-mm voxel of interest in the middle of the image contains 90% cerebrospinal fluid (CSF, signal=100 arbitrary units) and 10% gray matter (GM, signal=10) resulting in an average signal of 91 (*left diagram*). In condition 2, a 0.4 mm motion (1/10th of the voxel size) will result in an average signal intensity of 82 (80% CSF and 20% GM, *right diagram*). **b** Typical head motion artifacts in two different subjects

artifacts. External devices, such as a bite bar setup, can be used to minimize further head motion but are rarely used in clinical practice. A careful explanation of the task to the subject may also help reducing head motion. Head motion should be corrected using currently available methods. Real time motion correction software are also available.

Cardiac and respiratory motion results in physiological fluctuations of BOLD signal. Brain motion due to cardiac pulsation is negligible in the motor cortex but becomes significant in the upper brain stem and diencephalon (ENZMANN and PELC 1992). Brain motion due to cardiac pulsation is of small amplitude (0.16 mm) but can represent as much as 30% of voxel size at ultra high spatial resolution (0.5 mm in plane). EPI images are particularly sensitive to changes in resonance frequency which can arise from respiration and are more significant at high magnetic fields (VAN DE MOORTELE et al. 2002). Noise generated from respiration-induced phase and frequency fluctuations and from cardiac-induced fluctuations can be corrected using different algorithms (PFEUFFER et al. 2002), some of them based on physiological recordings (HU et al. 1995).

7.1.2.2

Magnetic Susceptibility Artifacts

These artifacts are due to the differences in magnetic susceptibility between bone, air and brain structures. Susceptibility differences generate field gradients, which result in inhomogeneous static magnetic field. The consequence is image signal loss, as well as distortion in EPI images and blurring in spiral images. These artifacts are particularly predominant in regions containing air and bone, such as

sinuses and inner ear structures. They are observed in calcified structures and after brain hemorrhage because of metallic particle deposition, such as in vascular malformations (Fig. 7.3). They are also frequently observed following brain surgery because of the presence of metallic particles deposited during the surgical procedure.

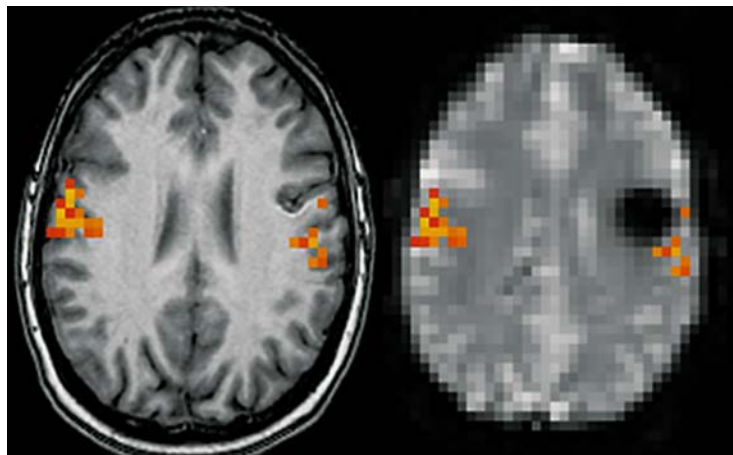
Magnetic susceptibility artifacts increase with field strength. Their impact can be reduced using higher bandwidth, shorter TE, thinner slices, better shimming procedures, and parallel imaging.

7.1.2.3

BOLD Response Alterations Induced by the Lesion

Neurovascular coupling that underlies BOLD contrast can be altered in normal ageing as well as vascular diseases (PINEIRO et al. 2002; D'ESPOSITO et al. 2003; HAMZEI et al. 2003). Pathologies that affect neurovascular coupling, can affect the characteristics of BOLD signal. This is particularly important in BOLD fMRI studies in patients with brain tumor because abnormal vasculature is an essential feature of tumor growth (FOLKMAN et al. 1989). Decreased activation has been reported on the side of the tumor and predominated in high grade glioma (HOLODNY et al. 1999, 2000). It has been suggested that negative BOLD correlates with decreased neuronal activity (SHMUEL et al. 2006) or neuronal inhibition in epilepsy patients (KOBAYASHI et al. 2005), but the different factors contributing to decreased BOLD activation in patients with brain tumors are not fully understood. They may also include a loss of autoregulation in the tumor vasculature, venous or pressure effects (HOLODNY et al. 1999, 2000). In a model of rat brain glioma, the intratumoral region

Fig. 7.3. Magnetic susceptibility artifact. Patient presenting a cavernous angioma of the left central area. *Left:* activation map during lip movements superimposed on transverse T1-weighted images suggesting that the lesion is located at distance from activation in the primary motor area. *Right:* same activation map superimposed on transverse EPI T2* image showing that the lesion is surrounded by a large area of signal drop due to T2* shortening susceptibility artifact. Although no activation is visible inside the area of signal drop, it is not possible to conclude that the functional area does not extend inside this area



had a significant increase in regional blood volume (JULIEN et al. 2004). Using perfusion MRI, several studies have suggested that regional cerebral blood volume (rCBV) was altered in gliomas (LUDEMANN et al. 2001; CHA et al. 2003; LAW et al. 2004).

In patients with brain arteriovenous malformation (AVM), flow abnormalities may interfere with fMRI detection of language related areas (LEHERICY et al. 2002). In patients with severe flow abnormalities, results of Wada examination and/or postembolization fMRI showed that abnormal language lateralization was at least partly due to severe flow abnormalities that impaired detection of BOLD signal (LEHERICY et al. 2002). Neurovascular coupling can be altered in several ways in patients with brain AVM. Hypotension or the presence of a so-called “steal phenomenon” may alter the normal functions in areas adjacent to an AVM (BARNETT et al. 1987; FOGARTY-MACK et al. 1996). Changes in cerebral blood flow (BARNETT et al. 1987; YOUNG et al. 1990), perfusion pressure (HASSLER and STEINMETZ 1987; FOGARTY-MACK et al. 1996), oxygen metabolism (FINK 1992), autoregulation processes, and vasoreactivity (BARNETT et al. 1987; HASSLER and STEINMETZ 1987; YOUNG et al. 1994; FOGARTY-MACK et al. 1996), all of which have been reported in areas adjacent to AVMs, may alter BOLD signal intensity and detection.

7.2

Validation of Presurgical Mapping Using Established Reference Procedures

7.2.1

Direct Electrical Stimulations

Currently, invasive electrophysiological investigations remain the reference procedure (“gold-standard”) for brain surgery, in particular for tumors located near or within eloquent cortical and/or subcortical structures (KELES and BERGER 2004; DUFFAU et al. 2005). Direct electrical stimulations (DES) allow mapping of a large number of motor, somatosensory, and cognitive functions. DES also permits the study of the anatomo-functional connectivity by directly stimulating the white matter tracts (DUFFAU et al. 2002, 2003; KELES et al. 2004). Therefore, DES represent an accurate and reliable technique to localize cortical and subcorti-

cal regions at risk for brain function. Consequently, a reproducible functional disturbance induced by DES will indicate where to interrupt the resection, both for cortical as well as subcortical structures. The tumor removal is then performed according to functional boundaries, in order to optimize the quality of tumor removal while minimizing the risk of postoperative permanent deficit.

DES have some limitations, however. They only allow loco-regional and not whole brain mapping. They are time-consuming and the number of tasks that can be performed during surgery is limited. Therefore, the combination of DES with other metabolic and functional methods seems currently mandatory.

7.2.1.1

Basic Principles

Electrical stimulations increase membrane excitability, via an initial phase of passive modification of the local membrane potential (MP) at the level of the cathode (the negative electrode). The inner side of the membrane becomes progressively less negative than the outer side (the membrane becomes inversely hyperpolarized with regard to the anode). The intensity of this phenomenon depends on the parameters of electrical stimulation and the characteristics of the membrane (JAYAKAR 1993). Stimulation of the membrane is easier at the level of the initial segment of the axon (GUSTAFSSON and JANKOWSKA 1976), in myelinated fibers and in fibers of greater diameter (RANCK 1975). If the MP reaches the depolarization threshold, voltage-dependent ion channels will open and allow entry of Na^+ ions inside the neuron. This Na^+ entry will invert the MP between +20 mV and +30 mV. A secondary output of K^+ ions, associated with an inhibition of the inward flux of Na^+ ions, brings the MP back to its resting state. Once generated, this rapid sequence of MP fluctuations – the action potential – is always the same, regardless of the stimulation parameters (law of “all or nothing”).

7.2.1.2

Risks Associated with DES

Stimulations can damage the brain. Tissue damage can result from numerous causes. Accumulation of negative charge at the level of the cathode or through production of metal ions at the level of the anode can damage the brain (AGNEW 1987;

YEOMANS 1990). Biphasic impulses prevent this risk, because the second stimulus inverses the effects of the first (GIRVIN 1978). Excessive heat produced by hydrolysis induces vacuolization and chromatolysis (DOTY and BARNETT 1981). “Leaking” of the intracellular current, which goes from the anode to the cathode through the cytoplasm, can lesion the mitochondria and the endoplasmic reticulum (PUDENZ et al. 1977). Repetitive and synchronous stimulation of the neurons can alter neuronal homeostasis (AGNEW 1987; FERTZIGER and RANCK 1970). These risks are directly linked to the density of the charge. Animal studies showed that when the charge did not exceed 55 microcoulombs/cm²/phase, no lesions were observed (GORDON et al. 1990).

Stimulations can also generate seizures. The frequency of seizures is estimated at 5–20% (SARTORIUS and BERGER 1998). Monitoring of the stimulation using intra-stimulation electrocorticographic recording allows avoiding the occurrence of “after-discharge” (LESSER et al. 1984), except in children who have non-myelinated fibers (JAYAKAR et al. 1992). Recording electrodes should ideally be located in the immediate proximity of each stimulation and therefore should “follow” the stimulation electrode. They should also have a small diameter to allow stimulation of the cortex.

Finally, the accumulation of any conductive substance such as cerebro-spinal fluid or blood can favor the distribution of current beyond the target tissue, thus increasing the risk of false negatives: any stimulated structure must therefore be kept dry.

7.2.1.3

Practical Stimulation Methods

The optimal stimulation parameters (best benefit / risk ratio) have been extensively studied (DUFFAU 2004; NATHAN et al. 1993). They can be significantly modified by the degree of cerebral maturation and fiber myelination (JAYAKAR et al. 1992), and by anesthetic drugs and pathological processes (tumor, epilepsy, post-ictal status) (JAYAKAR et al. 1993).

Bipolar stimulation is usually performed using a probe with two tips separated by 5 mm (Fig. 7.4) and the following parameters: rectangular impulses, biphasic current at 50 Hz (LESSER et al. 1987) or 60 Hz (BERGER 1995; OJEMANN et al. 1989), and intensities of 1–18 mA. Under local anesthesia, current intensity of less than 6–8 mA with an impulse duration of 0.3 ms (LESSER et al. 1987) to 1 ms (BERGER 1995; OJEMANN et al. 1989) are stand-

ard parameters. Typically, stimulation intensity is progressively increased from 4 mA (under general anesthesia) or 1 mA (under local anesthesia), by increments of 1 mA, in order to find the optimal threshold generating responses without causing seizure.

In children, rates of response are lower than in adults (less than 20% < 5 years or even no response < 1 year) because of the immaturity of the fibers (higher chronaxie in non-myelinated fibers). Therefore, a sequential increase of impulse intensity and duration has been proposed, by progressively and alternatively increasing the intensity as well as the duration of the impulse (JAYAKAR 1992).

7.2.1.4

Neuropsychological Evaluation

Defining the “eloquent” nature of cortical areas using DES requires appropriate tasks and accurate recording of clinical responses to determine whether there is any interference with function during stimulation of the site. Speech therapists or neuropsychologists are present in the operative room, in order to interpret the disorders induced by DES (DUFFAU et al. 2002, 2005).

Mapping of motor functions can be performed in awake patients or under general anesthesia, by inducing involuntary motor response. Awake patients are generally passive during stimulation. Rarely, when looking for “negative motor areas” in the premotor cortex (LÜDERS et al. 1995), the

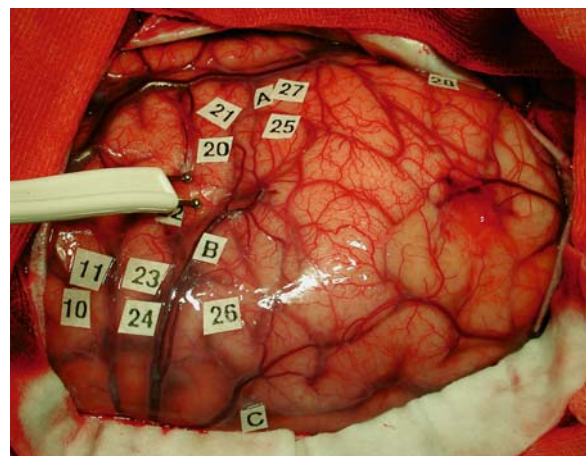


Fig. 7.4. Intraoperative view of a patient showing bipolar stimulation using a probe with two tips separated by 5 mm. During surgery, the probe is placed on the cortical surface of the patient. Stimulation sites are labeled using small tags

patient is asked to make regular movements during the stimulation. Changes in movement parameters are recorded (slowdown, decrease in precision or amplitude, interruption). Under general anesthesia, small movements can be overlooked. This is a frequent problem for neck movements because the intubation cannula often prevents muscular contractions from being perceived. Concomitant intraoperative electromyographic recording and motor evoked potentials improve the detection of positive responses (YINGLING et al. 1999). These methods are constraining, however. They require additional equipment, the presence of an electrophysiologist in the operating room, and the positioning of electrodes on the entire hemibody contralateral to stimulation if the lesion is in the vicinity of the corona radiata or the internal capsule (DUFFAU et al. 2003). Sensory functions are mapped by eliciting dysesthesia described by the patient himself intraoperatively (responses are therefore subjective).

For cognitive functions, study of language (spontaneous speech, naming, comprehension...), calculation, memory, reading or writing is performed in awake patients by generating transient disturbances (DUFFAU et al. 2003; OJEMANN et al. 1989). The choice of the tests is a critical issue. Eloquent sites can be detected only if the “proper” function has been tested. This is why sensitive tasks are used rather than specific ones.

Language mapping usually includes a counting task followed by an object naming task. The counting task is likely to alter articulatory production while these automatic series are being carried out (slowing down, dysarthria, anarthria, complete speech arrest, more or less associated with facial movements and/or hoarseness and or automatic swallowing). The object naming task induces various symptoms such as articulatory disorders, pure anomia, phonemic or semantic paraphrasias, or even perseverations. These tasks are short (less than 4 s duration) and therefore compatible with surgical requirements under local anesthesia). Depending on the localization of the lesion, a third more specific task is also carried out. This task is chosen in each patient based on the individual cortical language organization, as evaluated pre-operatively using a neuropsychological assessment and functional neuroimaging. Tasks include verb-generation, tasks in foreign languages in bilingual individuals, memory, calculation, repetition, reading, or even comprehension tasks for posterior temporo-parietal lesions (GATIGNOL et al. 2004).

7.2.1.5

Coregistration with Functional Imaging Data

Comparison between DES and functional imaging data has been performed using several methods. Initially, simple visual comparisons were obtained between peroperative views and fMRI data (JACK et al. 1994; YOUSRY et al. 1995). Coregistration was also performed by comparing pictures of DES positive sites to the preoperative 3D render of the brain (PUJOL et al. 1996; LEHERICY et al. 2000b) (Fig. 7.5). These methods have limitations, however, as they are not quantitative. A 3D render displays brain activation as viewed in transparency from the surface of the brain, and therefore the display includes activation that is located in the depth of the sulci and gyri. More recently, coregistration was obtained using stereotactic neuronavigation procedures (LEHERICY et al. 2000b; KRINGS et al. 2001b; KRISHNAN et al. 2004). This technique allows a 3D multiplanar comparison of the DES positive sites and the functional data, as well as measurements of distances and overlap.

7.2.1.6

Limits of Functional and DES Comparison

DES and functional imaging methods provide fundamentally different types of data. DES interfere directly by blocking the ability of the patient to perform the task. Therefore, it is assumed that DES map critical language areas only. In contrast, functional imaging methods provide activation maps obtained during performance of motor, language or cognitive tasks. Consequently, these techniques not only include critical areas but also activity in nonessential areas that are only associated with task performance but could be resected. Functional maps are displayed using a statistical threshold. Therefore, a low threshold may increase both the number of non essential areas as well as the size of the critical areas, whereas a stringent threshold may result in critical areas not reaching statistical significance. Craniotomy and debulking may induce deformation, which reduces image registration (HILL et al. 2000; KRINGS et al. 2001b). Finally, tasks performed during neurofunctional imaging and intraoperative procedures are not identical because of the different setups (LURITO et al. 2000). These issues are to keep in mind when comparisons between these different techniques are performed.

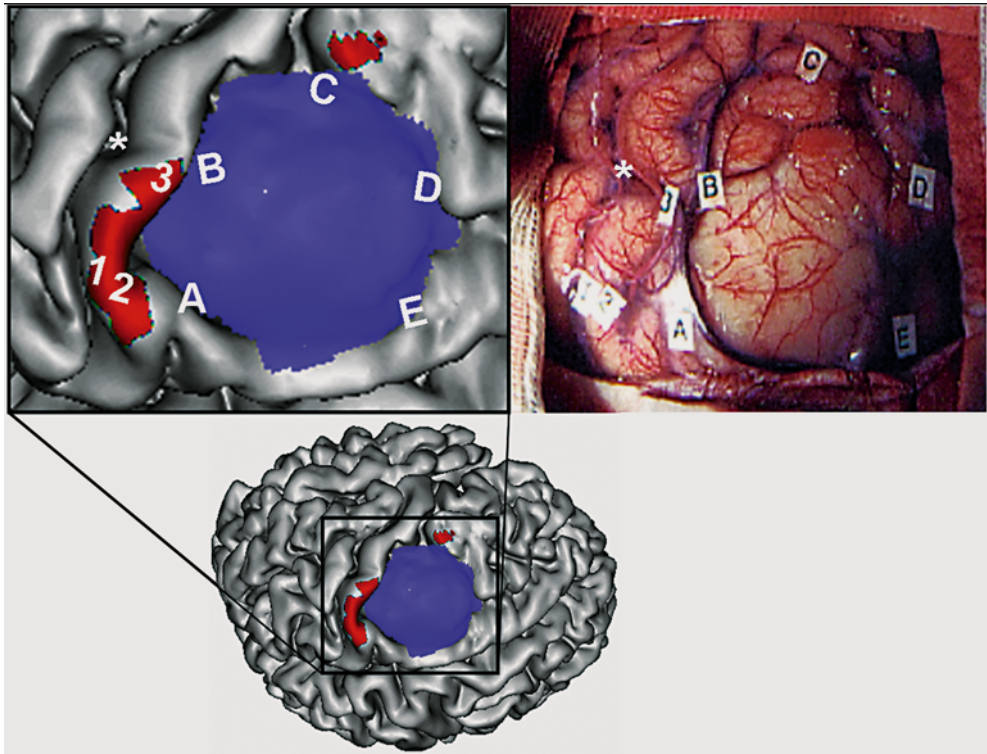


Fig. 7.5. Correspondence between fMRI and peroperative cortical stimulation. *Upper left:* surface render of the cortex in a patient with a left premotor low grade glioma (enlarged view of the figure in the lower row). The tumor is represented in *blue*. Activation obtained during performance of right hand movement is represented in red. The asterisk indicates the central sulcus. *Upper right:* intraoperative view of the same patient (same orientation). The *letters* outline the tumor margins. The *numbers* indicate the stimulation sites that elicited hand movements. Note the good correspondence between the fMRI activation map and direct electrical stimulations

7.2.2

Intracarotid Amobarbital Procedure (IAP) or Wada Test

The intracarotid amobarbital procedure (IAP), or Wada test, was first reported as a means to identify the hemisphere of language dominance in patients with epilepsy (WADA and RASMUSSEN 1960). IAP was then modified to measure memory function in patients undergoing surgery for epilepsy (MILNER et al. 1962). The role of IAP is to screen for language and amnesic risks by ensuring that the hemisphere contralateral to the operated one is able to subserve language and memory functions. Thus, IAP helps predict and prevent postoperative language and memory deficits and therefore improves the neuropsychological outcome (SPERLING et al. 1994; LORING et al. 1995).

7.2.2.1

Methods

IAP is performed in the angiography suite in the presence of a neurological and neuroscience team (RAUSCH et al. 1993; AKANUMA et al. 2003). The patient is positioned on the angiography table. EEG monitoring is performed. After local skin anesthesia, the femoral artery is accessed and selective catheter placement is performed in one internal carotid artery (ICA) under fluoroscopic guidance. Amobarbital is injected in each carotid artery. Therefore, the IAP induces a temporary inactivation of the cortex supplied by the anterior and middle cerebral arteries in the hemisphere ipsilateral to the injection. The two hemispheres can be tested on two consecutive days. During the 10–15 min of the procedure, patients receive a battery of language and memory tasks following amobarbital injection (JONES-GOTMAN 1987). Language tasks usually include productive speech (serial speech, naming), recep-

tive speech (simple motor commands, token test) and other speech tasks, such as reading aloud and spelling. Tasks are scored so that a lateralization index (LI) can be calculated for each task. LI can be expressed as the difference between scores during left injection minus scores during right injection, divided by the maximum possible score.

7.2.2.2

Risks and Limitations of the Wada Test

The IAP has several disadvantages, however (SIMKINS-BULLOCK 2000). Risks include those of the intracarotid catheterization. Following cerebral angiography, the ischemic event rate was estimated between 0.3% and 1.8% (0.07–0.3% permanent) (DION et al. 1987; CLOFT et al. 1999). Test–retest reliability and validity evaluation cannot be performed. IAP evaluation is performed within a short period of time (approximately 3–10 min). Anesthesia can induce behavioral effects (e.g. aphasia, attention deficits, neglect and somnolence). Amobarbital injected via the ICA will inactivate the amygdala and the anterior hippocampus but not or rarely the posterior two thirds of the hippocampus (JACK et al. 1989; HONG et al. 2000). This represents a critical concern for the validity of memory assessment. Moreover, mesial temporal perfusion can be unaffected during IAP in some patients (DE SILVA et al. 1999). It also inactivates the rest of the hemisphere ipsilateral to the injection and in some patients the contralateral hemisphere (HONG et al. 2000). To overcome these limitations, selective IAP via an injection in the posterior cerebral artery has therefore been proposed to test for memory function (JACK et al. 1989). The risk of morbidity of this procedure is much greater than in the ICA and thus it is not widely used (JACK et al. 1989). For language functions, the IAP provides information on hemispheric language dominance but not on the anatomical location of language areas and their relation with the lesion. Lastly, the total direct costs of the Wada test was estimated to be 3.7 times higher than that of fMRI (MEDINA et al. 2004).

7.2.2.3

Validation of the Wada Test

Validation of IAP was performed in several ways. Recording of intrahippocampal activity using depth electrodes has shown that EEG background activity was significantly suppressed in the posterior hippo-

campal regions even in the absence of amobarbital perfusion in these areas (URBACH et al. 1999). Using HMPAO-SPECT, hypoperfusion in the territories of the anterior and middle cerebral arteries was evidenced during the IAP (DE SILVA et al. 1999). Hypoperfusion in medial temporal structures occurred in the great majority of these patients (DE SILVA et al. 1999). In the epileptogenic hemisphere, the degree of hippocampal damage correlated with the impairment in Wada memory performance (Davies epilepsy 96, O'Rourke neurosurgery 93, Rausch Arch 89, Sass Arch 91).

In a few patients with unilateral temporal lobe epilepsy, IAP may also paradoxically lateralize memory function. In these patients, the IAP showed poorer memory performance in the non-epileptogenic hemisphere (DAVIES et al. 1996; ROULEAU et al. 1997; DETRE et al. 1998; SPENCER et al. 2000). Paradoxical IAP memory lateralization (i.e. ipsilateral to the seizure focus) was still concordant with fMRI

lateralization scores in two patients with temporal lobe epilepsy (DETRE et al. 1998). SPENCER et al. (2000) suggested that in patients with medial temporal lobe epilepsy not well lateralized by the noninvasive evaluation, and in neocortical or mesial frontal epilepsy, the IAP may provide incorrect localization that ultimately alters surgical management (SPENCER et al. 2000). These paradoxical lateralization have rarely been reported using FDG-PET (SPERLING et al. 1995; NAGARAJAN et al. 1996). In such cases, combined FDG-PET with IAP studies did not report memory impairment contralateral to the hypometabolic zone (SALANOVA et al. 1992).

7.3

Important Results of Validation Studies in Brain Tumors and Epilepsies, Overview and Current State

7.3.1

Motor Function

7.3.1.1

Functional Mapping

Validation of more recent functional noninvasive methods, such as fMRI, magnetoencephalography (MEG) and transcranial magnetic stimulation

(TMS), can be performed by comparison with PET. However, ultimately, DES remains the current reference procedure and comparison of functional non-invasive methods with DES is the best validation method.

Functional mapping of motor areas can be performed either to localize the central area or to locate motor areas at risk of functional deficit. Therefore, there are two different levels of validation. The first level is to determine whether functional imaging methods can accurately localize the sensorimotor cortex. In normal brains, the hand area and therefore the central sulcus can be accurately localized using anatomical landmarks only (YOUSRY et al. 1997) (Fig. 7.6). In patients with brain tumors, mass effect frequently distorts normal cortical anatomy and makes the localization of the central area difficult using anatomical landmarks alone (LEHERICY et al. 2000b). In such a case, preoperative functional localization is of special interest. See also Chap. 4.

Compared with PET, 96% of the fMRI activation peaks were located on either the same or adjacent sulci and gyri (BITTAR et al. 1999a). Compared with

TMS, fMRI peaks produced no motor evoked potential (MEP) when located more than 2 cm from TMS sites (KRINGS et al. 1997a).

Compared with DES, fMRI was very reliable in localizing the motor cortex, with complete or almost complete agreement using visual comparison with 3D MRI (JACK et al. 1994; YOUSRY et al. 1995; PUJOL et al. 1996, 1998; ROUX et al. 1999) (Fig. 7.5) or preoperative ultrasonography (FANDINO et al. 1999), coregistration of preoperative pictures with 3D render of the brain (PUCE et al. 1995; LEHERICY et al. 2000b) or neuronavigation procedures (HIRSCH et al. 2000; LEHERICY et al. 2000b). Discordant results were mostly observed when no correlation was possible (no activation or movement artifacts on fMRI, no response using DES). $^{15}\text{H}_2\text{O}$ PET was also reliable in showing the central area compared to DES (REINGES et al. 2004).

The second level is to determine whether functional imaging data can accurately localize motor areas and how reliable is this information to the neurosurgeon when he has to determine where to end the surgical resection.

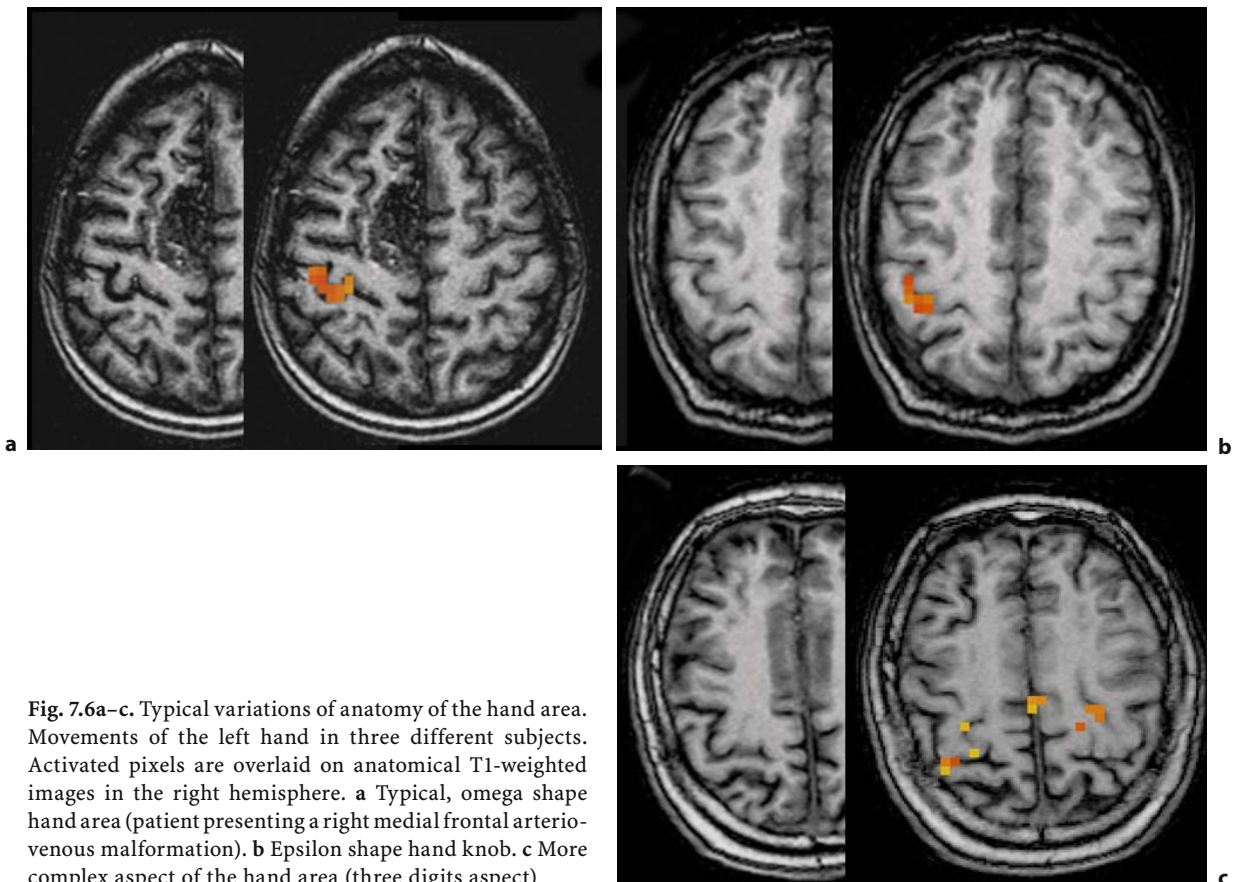


Fig. 7.6a–c. Typical variations of anatomy of the hand area. Movements of the left hand in three different subjects. Activated pixels are overlaid on anatomical T1-weighted images in the right hemisphere. **a** Typical, omega shape hand area (patient presenting a right medial frontal arterio-venous malformation). **b** Epsilon shape hand knob. **c** More complex aspect of the hand area (three digits aspect)

Several studies have compared the localization accuracy of fMRI to DES. Early studies in 28 patients with surgical brain lesions reported that 100% of positive MR activation sites were within 20 mm of DES positive sites and 87% of correlations within 10 mm (YETKIN et al. 1997). Moreover, 67% or more of the intraoperative stimulation maps correlated within 10 mm of the MR activation site. Another study in eight patients with brain tumors reported a good correlation between fMRI activation and DES sites, with each fMRI activation related to a positive DES response (ROUX et al. 1999). In 26 patients with brain tumors, fMRI data overlapped with peroperative electrical stimulation in 92% of positive sites (LEHERICY et al. 2000b). In patients with intra-axial lesions, overlapping results were obtained in 25–63% (<1 cm), neighboring in 29–75% (<2 cm), and no contradictory results were observed (KRINGS et al. 2001b; REINGES et al. 2004). Results are less good with extra-axial lesions overlapping results obtained in 33%, neighboring in 25%, and contradictory results in 42% (activation in a different gyrus or >2 cm from DES site) (REINGES et al. 2004). In another study, quantitative comparison of noninvasive methods with direct intraoperative stimulation and recording studies did not reveal a significant difference in accuracy (TOWLE et al. 2003).

PET results are similar to fMRI for intra-axial lesions with 95.6% of PET activation foci, spatially concordant sites on DES (BITTAR et al. 1999b). PET results were overlapping with DES in 60–92% (<1 cm), neighboring in 29–75% (<2 cm) (KRINGS et al. 2001b; REINGES et al. 2004). The mean localization difference between fMRI and PET was 8.1 ± 4.6 mm (range 2–18 mm) (REINGES et al. 2004). Another study reported that evaluation of the PET findings by cortical stimulation yielded a 94% sensitivity and a 95% specificity for identification of motor-associated brain areas (SCHRECKENBERGER et al. 2001). PET results for extra-axial lesions were even superior to those obtained using fMRI with 75% overlapping, 25% neighboring and no contradictory results (REINGES et al. 2004).

TMS has also been evaluated by comparison to fMRI and DES. TMS sites further than 2 cm from fMRI peaks produced no motor evoked potentials (MEP) with a mean distance between the two peaks of 0.6 ± 0.4 mm (KRINGS et al. 1997a, 2001b). The distances between the fMRI activation peaks and the cortical area where TMS elicited the maximum MEPs ranged between 0 and 1.2 cm (mean 0.6 ± 0.4 cm)

(KRINGS et al. 2001a). In patients with mass lesions, compared to DES, all TMS responses eliciting more than 75% of the maximum motor evoked potential fell within 1 cm of the electrical cortical stimulation sites (KRINGS et al. 1997b).

Magnetic source imaging (MSI) using somatosensory stimulation was also evaluated in patients with brain tumors (SCHIFFBAUER et al. 2002). In this study, the distance between two corresponding points determined using MSI and DES was 12.5 ± 1.3 mm for somatosensory–somatosensory and 19 ± 1.3 mm for somatosensory–motor comparisons. Intraoperative sites at which DES evoked the same patient response exhibited a spatial variation of 10.7 ± 0.7 mm (SCHIFFBAUER et al. 2002).

Overall, these studies suggest that the localization accuracy of all functional methods is similar. Earlier studies have suggested that, in patients with >2 cm between the margin of the tumor and the activation, no decline in motor function occurred from surgical resection (MUELLER et al. 1996; YETKIN et al. 1997). More recent studies suggest that shorter distance can be achieved (KRISHNAN et al. 2004). Thus, these methods are still suboptimal as compared to DES.

The value of functional imaging techniques in accurately localizing areas at risk of functional deficit can also be assessed empirically by comparison to the postoperative outcome of the patients. To this regard, fMRI has proven very accurate in predicting the occurrence of motor and language deficits following surgery of the medial frontal lobe (KRAINIK et al. 2001, 2003).

It should be kept in mind that fMRI results should be interpreted cautiously as they are highly dependent on several factors, such as the quality of the examination (movement artifacts), data processing (smoothing), statistical thresholds and ultimately the experience of the reader. Lastly, functional brain mapping techniques alone can not assess subcortical white matter tracts. It is well known that intraoperative stimulation of subcortical pathways, shows positive responses on areas not identified by functional imaging methods (VINAS et al. 1997). Combined fMRI and DTI fiber tracking methods have the potential to provide a more complete presurgical mapping than any other functional techniques.

7.3.1.2

DTI Fiber Tracking

DTI fiber tracking is a more recent technique and fewer validation studies have been published. Using DTI and fiber tracking algorithms, previous studies have shown reconstruction of well-known fiber tracts, including the corticospinal, long association (ROUX et al. 1999; MORI et al. 2002) and brain stem fiber tracts (STIELTJES et al. 2001). Parcellation of the thalamus (BEHRENS et al. 2003) and the striatum (LEHERICY et al. 2004) into nuclei or territories described in histological studies was obtained based on cortical DTI connectivity patterns, providing demonstration of reliable inference of anatomical connectivity in humans. Results of fiber tracking has also been correlated with post-mortem animal studies (HOLMES et al. 2000; DAMON et al. 2002). These studies have shown that DTI fiber tracking accurately mapped the fibrous architecture of formalin-fixed hearts in rabbits (HOLMES et al. 2000) and the fiber orientation in skeletal muscle in vivo in rats (DAMON et al. 2002). More recently, in vivo DTI was compared to ex vivo DTI and the uptake transport of Wheat Germ Agglutinin-Horse Radish Peroxidase (WGA-HRP) stained histological sections in the macaque monkey (PELED et al. 2005). A good correspondence was reported between DTI fiber tracts originating in the left somatosensory cortex and the histological reference.

There are few validation studies of DTI fiber tracking using subcortical DES in patients with brain lesions. Two studies from the same group have used cortical positive DES as seeding points for fiber tracking (BERMAN et al. 2004; HENRY et al. 2004). Tracks originating from the mouth motor positive DES were directed to the SMA and inferiorly joined the cortico-spinal tract (via the posterior limb of the internal capsule), therefore matching the known connections of the primary motor area. In another study, DTI fiber tracking prediction of the principal motor pathways' position was correct in 11 out of 13 patients (92%) (COENEN et al. 2003). In the two remaining patients, the tumor was falsely localized postcentrally in one patient with a meningioma and no motor responses were elicited in the other patient. In six patients with brain lesions adjacent to the corticospinal tract, stimulation of the DTI reconstructed corticospinal tract elicited motor evoked potentials in three patients, whereas in the other three, stimulation at the resection borders more than 1 cm away from

the supposed corticospinal tract showed no motor response (KAMADA et al. 2005).

Therefore, preliminary data are encouraging but comparisons between DTI and DES in larger series of patients are needed.

7.3.2

Language Function

For language function, functional imaging can determine language dominance and localize language areas. To validate functional imaging for hemispheric language dominance, the reference procedure is the IAP. To validate functional brain mapping as a tool for localization of language areas (corticography), the reference procedure is DES.

7.3.2.1

Hemispheric Dominance for Language

fMRI has shown a high concordance (>90%) between the degree of asymmetry of activation during appropriately selected language tasks, and hemispheric dominance as determined with the IAP (DESMOND et al. 1995; BINDER et al. 1996; BAHN et al. 1997; HERTZ-PANNIER et al. 1997; BENSON et al. 1999; LEHERICY et al. 2000a; CARPENTIER et al. 2001; GAILLARD et al. 2002; RUTTEN et al. 2002a; SABBABH et al. 2003; WOERMANN et al. 2003). A good correlation was observed using productive tasks, such as word or verb generation, and semantic decision tasks, whereas no correlation was observed for receptive tasks (LEHERICY et al. 2000a) (Fig. 7.7).

Overall, language fMRI studies largely agreed on a 10% failure rate to lateralize language as compared to the IAP (DESMOND et al. 1995; BINDER et al. 1996; BAHN et al. 1997; HERTZ-PANNIER et al. 1997; BENSON et al. 1999; LEHERICY et al. 2000a; CARPENTIER et al. 2001; GAILLARD et al. 2002; RUTTEN et al. 2002a; SABBABH et al. 2003; WOERMANN et al. 2003). False categorization using fMRI were more frequent in patients with left temporal lobe epilepsy (Woermann et al. 2003).

The use of well controlled paradigms with recording of patient's performance (such as semantic decisions or picture naming) apparently do not provide better results than more simple paradigms without control of patients performance (such as silent generation task with a low-level reference condition). The same may also apply to quantitative post-processing (counting the number of

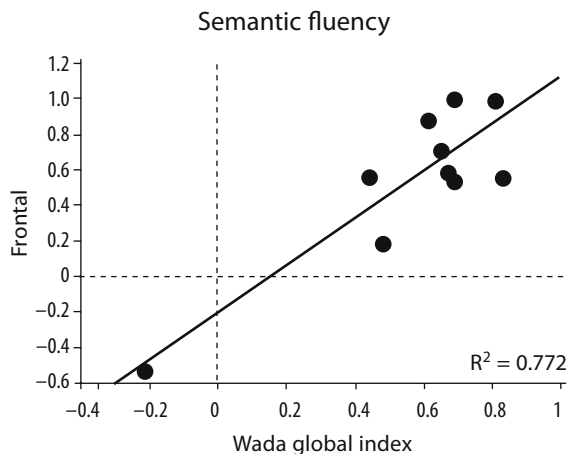


Fig. 7.7. Correspondence between fMRI and Wada results. Pearson linear regression between the Wada laterality index and fMRI laterality index in the frontal lobes in a semantic fluency task obtained in ten patients with temporal lobe epilepsy (from LEHERICY et al. 2000a with permission)

activated voxels to calculate laterality indices) vs visual examination of fMRI maps (WOERMANN et al. 2003).

7.3.2.2

Localization of Language Areas

To date, only a few studies have made a quantitative comparison between functional imaging data and DES. DES were consistent with the MEG-based localization in 13 patients during a visual and auditory word-recognition task (SIMOS et al. 1999). Using a verb generation task in eight patients with glioma, PET activated areas had 73% sensitivity and 81% specificity to predict aphasic disturbance during intraoperative stimulation (HERHOLZ et al. 1997). In seven patients with intractable epilepsy, cortical regions that showed increased rCBF during both visual and auditory naming tasks were located in the same regions as subdural electrodes which disrupted language during electrical stimulation (BOOKHEIMER et al. 1997). Cortical regions underlying electrodes that did not disrupt language also showed no consistent rCBF changes during PET activation (BOOKHEIMER et al. 1997).

In three patients with primary tumors, regions involved in receptive language function identified by fMRI and DES were similar but non-identical (LURITO et al. 2000). In 11 patients with surgical

brain lesions, the sensitivity/specificity of a battery of five language tasks ranged from 81%/53% for areas that touched DES positive sites to 92%/0% for areas separated by 2 cm (FITZGERALD et al. 1997). Using a combination of three fMRI tasks, the sensitivity of fMRI was 100% in seven out of eight patients with temporal lobe epilepsy (<6.4 mm of the DES site). In the remaining patient, the sensitivity was only 38% (RUTTEN et al. 2002b). Overall, these data yielded a specificity of 61% (RUTTEN et al. 2002b). Compared to DES, the sensitivity and specificity of language tasks were 22% and 97% for a naming task and 36% and 98% for a verb generation task, respectively (ROUX et al. 2003). Better correlation (sensitivity, 59%; specificity, 97%) was achieved by combining the two fMRI tasks (ROUX et al. 2003). As pointed out by these studies, correspondence between fMRI and DES mapping depended heavily on statistical threshold and varied between patients and tasks (FITZGERALD et al. 1997; RUTTEN et al. 2002b; ROUX et al. 2003). Individual language tasks were not as sensitive as a battery of language tasks combined (Fig. 7.8).

7.3.2.3

DTI Fiber Tracking

Very few comparisons between DTI fiber tracking and DES were performed in patients with brain lesions (Fig. 7.9). DTI fiber tracking has been used to delineate the pathways between functional regions (HENRY et al. 2004). Tracks from stimulated sites in the inferior frontal cortex resulting in mouth motor, speech arrest, and anomia were generated from the DTI data. Connections were found between speech arrest, mouth motor, and anomia sites and the SMA proper and cerebral peduncle (HENRY et al. 2004). More recently, fiber tracking was performed in brain tumor patients and normal controls to study the connection between the frontal and parietotemporal lobes through the arcuate fasciculus. Three tracks connecting the inferior frontal gyrus to the supramarginal gyrus, the posterior superior temporal gyrus and the middle temporal gyrus were delineated (CHUNG et al. 2005). The tracks were closely located to the intraoperative cortical stimulation speech arrest sites. These studies suggest that DTI fiber tracking allows investigating the neural connectivity of language functions (CHUNG et al. 2005). Direct comparison of DES and language fiber bundles is still awaited, however.

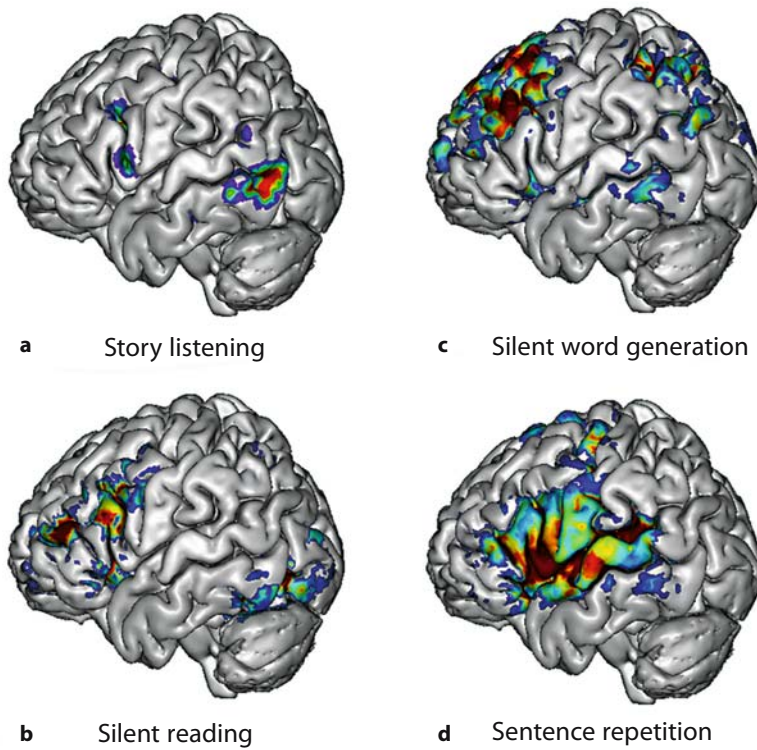


Fig. 7.8a–d. Activation pattern during four language tasks. *Left*: receptive tasks. **a** Story listening task compared to listening to the same story played backwards. Activation is mainly located in posterior temporal areas. **b** Silent reading compared to fixation. Activation is located in the infero-temporal cortical areas and Broca's area. *Right*: productive tasks. **c** Silent word generation task compared to rest. Activation predominates in dorsolateral frontal areas and inferior parietal areas, including the angular gyrus. **d** Sentence repetition aloud compared to rest. Activation includes frontal (Broca's area and the lower part of the primary sensorimotor area in the face region) and temporal areas (including the primary auditory cortex)

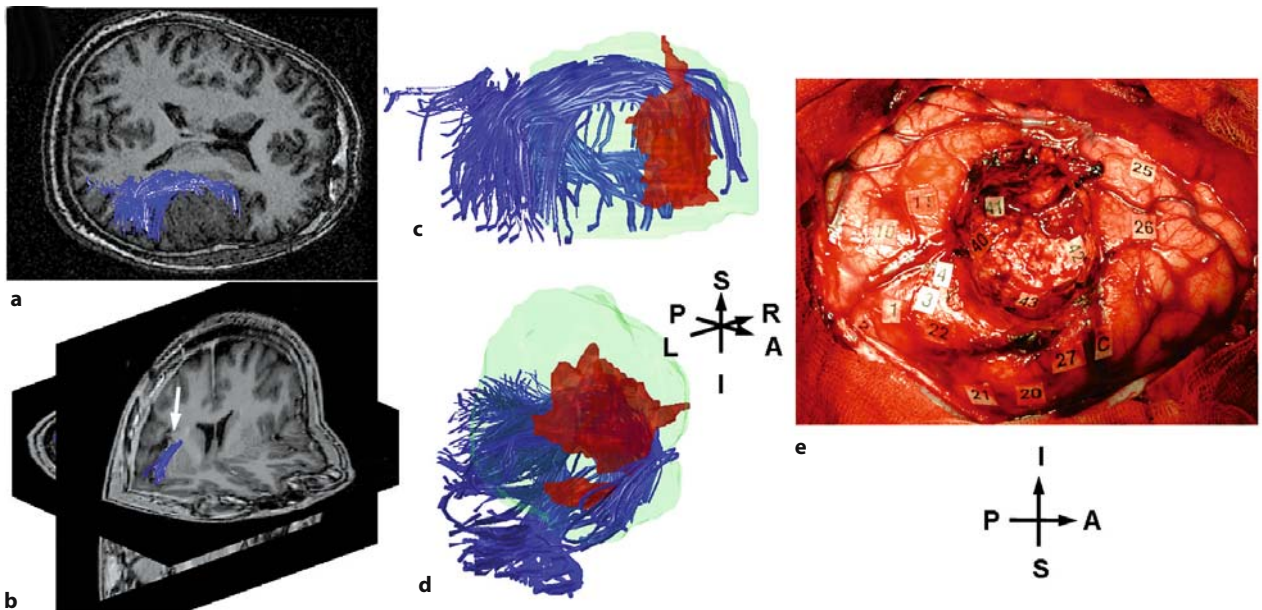


Fig. 7.9a–e. Correspondence between DTI fiber tracking and peroperative electrical stimulations in a patient presenting a low grade glioma of the left insula. Electrical stimulations performed during surgery in the depth of the resection cavity resulted in speech arrest. **a** DTI fiber tract reconstruction of the arcuate fasciculus (transverse section, the fiber tract is represented in blue as if viewed from above). **b** Oblique 3D reconstruction of the arcuate fasciculus in blue showing the close proximity between the deep part of the resection cavity and the fiber tract (arrow). **c, d** A 3D reconstructions of the fiber tract (blue), the tumor (light green) and the surgical resection (red) showing the close proximity between the deep part of the surgical resection and the fiber tract (**c** superior view as in **a**; and **d**: oblique 3D reconstruction, same view as in **b**). Note that the resection cavity touches the fiber tract in agreement with DES findings. **e** Surgical view showing positive DES sites for motor responses (1–4 and 40), somatosensory responses (10–11), speech responses (paraphrasias: 25–26, and 41–43). Sites positive for language were obtained in the depth of the resection cavity (41–43). Abbreviations: A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior

7.3.3

Memory Function

There is a good correlation between PET and IAP results. Patients with mesial temporal lobe epilepsy show ^{18}F -fluorodeoxyglucose (FDG) PET hypometabolism in the hemisphere ipsilateral to the lesion, functional deficits on the IAP, or both, as well as verbal memory and word fluency impairments (RAUSCH et al. 1994; ARNOLD et al. 1996; SALANOVA et al. 2001). IAP hemispheric memory performance and hippocampal glucose metabolism were correlated with the frequency of seizures and negatively with the duration of epilepsy (JOKEIT et al. 1999). The results of the FDG-PET were predictive of impaired IAP memory performance (SALANOVA et al. 2001). Memory impairment contralateral to the temporal PET hypometabolism was never seen (SALANOVA et al. 2001). In patients with temporal lobe epilepsy, FDG-PET asymmetry index in the mesial temporal lobe correlated with the IAP asymmetry index for memory performance (HONG et al. 2000).

Recently, fMRI studies have demonstrated consistent activation of medial temporal structures during memory tasks in normal subjects (SMALL et al. 1999; DUPONT et al. 2000; ZEINEH et al. 2003). In patients with epilepsy, several studies have evaluated the lateralization value of fMRI activation (DETRE et al. 1998; DUPONT et al. 2001; JOKEIT et al. 2001; GOLBY et al. 2002; RABIN et al. 2004; JANSZKY et al. 2005). Preoperative fMRI asymmetry index of memory functions correlated with the change between pre- and postsurgical measures of memory retention (RABIN et al. 2004; JANSZKY et al. 2005). Asymmetry ratios in the medial temporal lobe also correlated significantly with memory lateralization by IAP testing (DETRE et al. 1998; GOLBY et al. 2002; RABIN et al. 2004). In ten right handed patients with hippocampal sclerosis, fMRI provided the strongest independent predictor of memory outcome after surgery (RICHARDSON et al. 2004). At the individual subject level, the fMRI data had high positive predictive value for memory decline (RICHARDSON et al. 2004). Overall, these studies suggest that fMRI has great potential to lateralize memory functions and predict postoperative memory outcome.

References

- Agnew WF, McCreery DB (1987) Considerations for safety in the use of extracranial stimulation for motor evoked potentials. *Neurosurgery* 20:143–147.
- Akanuma N, Koutroumanidis M, Adachi N, Alarcon G, Binnie CD (2003) Presurgical assessment of memory-related brain structures: the Wada test and functional neuroimaging. *Seizure* 12:346–358
- Arnold S, Schlaug G, Niemann H, Ebner A, Luders H, Witte OW, Seitz RJ (1996) Topography of interictal glucose hypometabolism in unilateral mesiotemporal epilepsy. *Neurology* 46:1422–1430
- Bahn MM, Lin W, Silbergeld DL, Miller JW, Kuppusamy K, Cook RJ, Hammer G, Wetzel R, Cross D III (1997) Localization of language cortices by functional MR imaging compared with intracarotid amobarbital hemispheric sedation. *AJR Am J Roentgenol* 169:575–579
- Barnett GH, Little JR, Ebrahim ZY, Jones SC, Friel HT (1987) Cerebral circulation during arteriovenous malformation operation. *Neurosurgery* 20:836–842
- Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, Barker GJ, Sillery EL, Sheehan K, Ciccarelli O, Thompson AJ, Brady JM, Matthews PM (2003) Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci* 6:750–757
- Benson RR, FitzGerald DB, LeSueur LL, Kennedy DN, Kwong KK, Buchbinder BR, Davis TL, Weisskoff RM, Talavage TM, Logan WJ, Cosgrove GR, Belliveau JW, Rosen BR (1999) Language dominance determined by whole brain functional MRI in patients with brain lesions. *Neurology* 52:798–809
- Berger MS (1995) Functional mapping-guided resection of low-grade gliomas. *Clin Neurosurg* 1995; 42: 437–452.
- Berman JI, Berger MS, Mukherjee P, Henry RG (2004) Diffusion-tensor imaging-guided tracking of fibers of the pyramidal tract combined with intraoperative cortical stimulation mapping in patients with gliomas. *J Neurosurg* 101:66–72
- Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, Benbadis S, Frost JA, Rao SM, Haughton VM (1996) Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology* 46:978–984
- Bittar RG, Olivier A, Sadikot AF, Andermann F, Pike GB, Reutens DC (1999a) Presurgical motor and somatosensory cortex mapping with functional magnetic resonance imaging and positron emission tomography. *J Neurosurg* 91:915–921
- Bittar RG, Olivier A, Sadikot AF, Andermann F, Comeau RM, Cyr M, Peters TM, Reutens DC (1999b) Localization of somatosensory function by using positron emission tomography scanning: a comparison with intraoperative cortical stimulation. *J Neurosurg* 90:478–483
- Bookheimer SY, Zeffiro TA, Blaxton T, Malow BA, Gaillard WD, Sato S, Kufta C, Fedio P, Theodore WH (1997) A direct comparison of PET activation and electrocortical stimulation mapping for language localization. *Neurology* 48:1056–1065
- Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM (1995) MR contrast due to intravascular magnetic susceptibility perturbations. *Magn Reson Med* 34:555–566

- Carpentier A, Pugh KR, Westerveld M, Studholme C, Skrinjar O, Thompson JL, Spencer DD, Constable RT (2001) Functional MRI of language processing: dependence on input modality and temporal lobe epilepsy. *Epilepsia* 42:1241–1254
- Cha S, Johnson G, Wadghiri YZ, Jin O, Babb J, Zagzag D, Turnbull DH (2003) Dynamic, contrast-enhanced perfusion MRI in mouse gliomas: correlation with histopathology. *Magn Reson Med* 49:848–855
- Chung SW, Berger MS, Berman JI, Gorno-Tempini ML, Henry RG (2005) Delineation of subcortical language pathways by DTI fiber tracking and cortical stimulation mapping. *International Society of Magnetic Resonance in Medicine, Miami Beach*
- Cloft HJ, Joseph GJ, Dion JE (1999) Risk of cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation: a meta-analysis. *Stroke* 30:317–320
- Coenen VA, Krings T, Axer H, Weidemann J, Kranzlein H, Hans FJ, Thron A, Gilsbach JM, Rohde V (2003) Intraoperative three-dimensional visualization of the pyramidal tract in a neuronavigation system (PTV) reliably predicts true position of principal motor pathways. *Surg Neurol* 60:381–390; discussion 390
- D'Esposito M, Deouell LY, Gazzaley A (2003) Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nat Rev Neurosci* 4:863–872
- Damon BM, Ding Z, Anderson AW, Freyer AS, Gore JC (2002) Validation of diffusion tensor MRI-based muscle fiber tracking. *Magn Reson Med* 48:97–104
- Davies KG, Hermann BP, Foley KT (1996) Relation between intracarotid amobarbital memory asymmetry scores and hippocampal sclerosis in patients undergoing anterior temporal lobe resections. *Epilepsia* 37:522–525
- de Silva R, Duncan R, Patterson J, Gillham R, Hadley D (1999) Regional cerebral perfusion and amygdal distribution during the Wada test. *J Nucl Med* 40:747–752
- Desmond JE, Sum JM, Wagner AD, Demb JB, Shear PK, Glover GH, Gabrieli JD, Morrell MJ (1995) Functional MRI measurement of language lateralization in Wada-tested patients. *Brain* 118(6):1411–1419
- Detre JA, Maccotta L, King D, Alsop DC, Glosser G, D'Esposito M, Zarahn E, Aguirre GK, French JA (1998) Functional MRI lateralization of memory in temporal lobe epilepsy. *Neurology* 50:926–932
- Dion JE, Gates PC, Fox AJ, Barnett HJ, Blom RJ (1987) Clinical events following neuroangiography: a prospective study. *Stroke* 18:997–1004
- Doty RW, Barnett JR (1981) Stimulation of the brain via metallic electrodes. In: Patterson MM, Kesner RP, eds. *Electrical stimulation research methods*. New York : Academic Press pp 71–103.
- Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, Bitar A, Fohanno D (2002) Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* 125:199–214
- Duffau H. (2004) Peroperative functional mapping using direct electrical stimulations. *Methodological considerations*. *Neurochirurgie* 50:474–483.
- Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Taillandier L, Lopes M, Mitchell MC, Roche S, Muller JC, Bitar A, Sichez JP, van Effenterre R (2003) Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. *J Neurosurg* 98:764–778
- Duffau H, Lopes M, Arthuis F, Bitar A, Sichez JP, Van Effenterre R, Capelle L (2005) Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985–96) and with (1996–2003) functional mapping in the same institution. *J Neurol Neurosurg Psychiatry* 76:845–851
- Duong TQ, Yacoub E, Adriany G, Hu X, Ugurbil K, Kim SG (2003) Microvascular BOLD contribution at 4 and 7 T in the human brain: gradient-echo and spin-echo fMRI with suppression of blood effects. *Magn Reson Med* 49:1019–1027
- Dupont S, Van de Moortele PF, Samson S, Hasboun D, Poline JB, Adam C, Lehericy S, Le Bihan D, Samson Y, Baulac M (2000) Episodic memory in left temporal lobe epilepsy: a functional MRI study. *Brain* 123(8):1722–1732
- Dupont S, Samson Y, Van de Moortele PF, Samson S, Poline JB, Adam C, Lehericy S, Le Bihan D, Baulac M (2001) Delayed verbal memory retrieval: a functional MRI study in epileptic patients with structural lesions of the left medial temporal lobe. *Neuroimage* 14:995–1003
- Enzmann DR, Pelc NJ (1992) Brain motion: measurement with phase-contrast MR imaging. *Radiology* 185:653–660
- Fandino J, Kollias SS, Wieser HG, Valavanis A, Yonekawa Y (1999) Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumors involving the primary motor cortex. *J Neurosurg* 91:238–250
- Fertziger AL, Ranck JB (1970) Potassium accumulation in interstitial space in epileptiform seizures. *Exp Neurol* 26:571–585.
- Fink GR (1992) Effects of cerebral angiomas on perifocal and remote tissue: a multivariate positron emission tomography study. *Stroke* 23:1099–1105
- FitzGerald DB, Cosgrove GR, Ronner S, Jiang H, Buchbinder BR, Belliveau JW, Rosen BR, Benson RR (1997) Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. *AJNR Am J Neuroradiol* 18:1529–1539
- Fogarty-Mack P, Pile-Spellman J, Hacein-Bey L, Ostapkovich N, Joshi S, Vulliemoz Y, Young WL (1996) Superselective intraarterial papaverine administration: effect on regional cerebral blood flow in patients with arteriovenous malformations. *J Neurosurg* 85:395–402
- Folkman J, Watson K, Ingber D, Hanahan D (1989) Induction of angiogenesis during the transition from hyperplasia to neoplasia. *Nature* 339:58–61
- Gaillard WD, Balsamo L, Xu B, Grandin CB, Braniecki SH, Papero PH, Weinstein S, Conry J, Pearl PL, Sachs B, Sato S, Jabbari B, Vezina LG, Frattali C, Theodore WH (2002) Language dominance in partial epilepsy patients identified with an fMRI reading task. *Neurology* 59:256–265
- Gatignol P, Capelle L, Le Bihan R, Duffau H (2004) Double dissociation between picture naming and comprehension: an electrostimulation study. *Neuroreport* 15:191–195

- Girvin JP (1978) A review of the basic aspects concerning chronic cerebral stimulation. In : Cooper IS, ed. Cerebellar stimulation in man. New York: Raven pp 1–12.
- Golby AJ, Poldrack RA, Illes J, Chen D, Desmond JE, Gabrieli JD (2002) Memory lateralization in medial temporal lobe epilepsy assessed by functional MRI. *Epilepsia* 43:855–863
- Gordon B, Lesser RP, Rance NE, Hart J Jr, Webber R, Uematsu S, Fisher RS (1990) Parameters for direct cortical electrical stimulation in the human : histopathologic confirmation. *Electroencephalogr Clin Neurophysiol* 75:371–377.
- Gustafsson B, Jankowska E (1976) Direct and indirect activation of nerve cells by electrical pulses applied extracellularly. *J Physiol (Lond)* 258:33–61.
- Hamzei F, Knab R, Weiller C, Rother J (2003) The influence of extra- and intracranial artery disease on the BOLD signal in fMRI. *Neuroimage* 20:1393–1399
- Harel N, Lin J, Moeller S, Ugurbil K, Yacoub E (2006) Combined imaging-histological study of cortical laminar specificity of fMRI signals. *Neuroimage* 29:879–887
- Hassler W, Steinmetz H (1987) Cerebral hemodynamics in angioma patients: an intraoperative study. *J Neurosurg* 67:822–831
- Heeger DJ, Huk AC, Geisler WS, Albrecht DG (2002) What does fMRI tell us about neuronal activity? *Nat Rev Neurosci* 3:142–151
- Henry RG, Berman JI, Nagarajan SS, Mukherjee P, Berger MS (2004) Subcortical pathways serving cortical language sites: initial experience with diffusion tensor imaging fiber tracking combined with intraoperative language mapping. *Neuroimage* 21:616–622
- Herholz K, Reulen HJ, von Stockhausen HM, Thiel A, Ilmberger J, Kessler J, Eisner W, Yousry TA, Heiss WD (1997) Preoperative activation and intraoperative stimulation of language-related areas in patients with glioma. *Neurosurgery* 41:1253–1260; discussion 1260–1252
- Hertz-Pannier L, Gaillard WD, Mott SH, Cuenod CA, Bookheimer SY, Weinstein S, Conry J, Papero PH, Schiff SJ, Le Bihan D, Theodore WH (1997) Noninvasive assessment of language dominance in children and adolescents with functional MRI: a preliminary study. *Neurology* 48:1003–1012
- Hill DL, Smith AD, Simmons A, Maurer CR Jr., Cox TC, Elwes R, Brammer M, Hawkes DJ, Polkey CE (2000) Sources of error in comparing functional magnetic resonance imaging and invasive electrophysiological recordings. *J Neurosurg* 93:214–223
- Hirsch J, Ruge MI, Kim KH, Correa DD, Victor JD, Relkin NR, Labar DR, Krol G, Bilsky MH, Souweidane MM, DeAngelis LM, Gutin PH (2000) An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. *Neurosurgery* 47:711–721; discussion 721–712
- Holmes AA, Scollan DF, Winslow RL (2000) Direct histological validation of diffusion tensor MRI in formaldehyde-fixed myocardium. *Magn Reson Med* 44:157–161
- Holodny AI, Schulder M, Liu WC, Maldjian JA, Kalnin AJ (1999) Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol* 20:609–612
- Holodny AI, Schulder M, Liu WC, Wolko J, Maldjian JA, Kalnin AJ (2000) The effect of brain tumors on BOLD functional MR imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol* 21:1415–1422
- Hong SB, Kim KW, Seo DW, Kim SE, Na DG, Byun HS (2000) Contralateral EEG slowing and amobarbital distribution in Wada test: an intracarotid SPECT study. *Epilepsia* 41:207–212
- Hu X, Le TH, Parrish T, Erhard P (1995) Retrospective estimation and correction of physiological fluctuation in functional MRI. *Magn Reson Med* 34:201–212
- Jack CR Jr, Nichols DA, Sharbrough FW, Marsh WR, Petersen RC, Hinkeldey NS, Ivnik RJ, Cascino GD, Ilstrup DM (1989) Selective posterior cerebral artery injection of amytal: new method of preoperative memory testing. *Mayo Clin Proc* 64:965–975
- Jack CR Jr, Thompson RM, Butts RK, Sharbrough FW, Kelly PJ, Hanson DP, Riederer SJ, Ehman RL, Hangiandreou NJ, Cascino GD (1994) Sensory motor cortex: correlation of presurgical mapping with functional MR imaging and invasive cortical mapping. *Radiology* 190:85–92
- Janszky J, Jokeit H, Kontopoulou K, Mertens M, Ebner A, Pohlmann-Eden B, Woermann FG (2005) Functional MRI predicts memory performance after right mesiotemporal epilepsy surgery. *Epilepsia* 46:244–250
- Jayakar P (1993) Physiological principles of electrical stimulation. *Adv Neurol* 63:17–27
- Jayakar P (1993) Physiological principles of electrical stimulation. In : Devinsky O, Beric A and Dogali M, eds. *Electrical and Magnetic Stimulation of the Brain and Spinal Cord*. Raven Press, Ltd., New York
- Jayakar P, Alvarez LA, Duchowny MS, Resnick TJ (1992) A safe and effective paradigm to functionally map the cortex in childhood. *J Clin Neurophysiol* 9:288–293.
- Jokeit H, Ebner A, Arnold S, Schuller M, Antke C, Huang Y, Steinmetz H, Seitz RJ, Witte OW (1999) Bilateral reductions of hippocampal volume, glucose metabolism, and wada hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy. *J Neurol* 246:926–933
- Jokeit H, Okujava M, Woermann FG (2001) Memory fMRI lateralizes temporal lobe epilepsy. *Neurology* 57:1786–1793
- Jones-Gotman M (1987) Psychological evaluation-testing of hippocampal function. In: Engel J (ed) *Surgical treatment of the epilepsies*. Raven Press, New York, pp 203–211
- Julien C, Payen JF, Tropres I, Farion R, Grillon E, Montigon O, Remy C (2004) Assessment of vascular reactivity in rat brain glioma by measuring regional blood volume during graded hypoxic hypoxia. *Br J Cancer* 91:374–380
- Kamada K, Todo T, Masutani Y, Aoki S, Ino K, Takano T, Kirino T, Kawahara N, Morita A (2005) Combined use of tractography-integrated functional neuronavigation and direct fiber stimulation. *J Neurosurg* 102:664–672
- Keles GE, Berger MS (2004) Advances in neurosurgical technique in the current management of brain tumors. *Semin Oncol* 31:659–665
- Keles GE, Lundin DA, Lamborn KR, Chang EF, Ojemann G, Berger MS (2004) Intraoperative subcortical stimu-

- lation mapping for hemispherical perirolandic gliomas located within or adjacent to the descending motor pathways: evaluation of morbidity and assessment of functional outcome in 294 patients. *J Neurosurg* 100:369–375
- Kobayashi E, Bagshaw AP, Grova C, Dubeau F, Gotman J (2005) Negative BOLD responses to epileptic spikes. *Hum Brain Mapp* 22 (electronic ahead of print)
- Krainik A, Lehericy S, Duffau H, Vlaicu M, Poupon F, Capelle L, Cornu P, Clemenceau S, Sahel M, Valery CA, Boch AL, Mangin JF, Bihan DL, Marsault C (2001) Role of the supplementary motor area in motor deficit following medial frontal lobe surgery. *Neurology* 57:871–878
- Krainik A, Lehericy S, Duffau H, Capelle L, Chainay H, Cornu P, Cohen L, Boch AL, Mangin JF, Le Bihan D, Marsault C (2003) Postoperative speech disorder after medial frontal surgery: role of the supplementary motor area. *Neurology* 60:587–594
- Krings T, Buchbinder BR, Butler WE, Chiappa KH, Jiang HJ, Cosgrove GR, Rosen BR (1997a) Functional magnetic resonance imaging and transcranial magnetic stimulation: complementary approaches in the evaluation of cortical motor function. *Neurology* 48:1406–1416
- Krings T, Buchbinder BR, Butler WE, Chiappa KH, Jiang HJ, Rosen BR, Cosgrove GR (1997b) Stereotactic transcranial magnetic stimulation: correlation with direct electrical cortical stimulation. *Neurosurgery* 41:1319–1325; discussion 1325–1316
- Krings T, Foltys H, Reinges MH, Kemeny S, Rohde V, Spetzger U, Gilsbach JM, Thron A (2001a) Navigated transcranial magnetic stimulation for presurgical planning—correlation with functional MRI. *Minim Invasive Neurosurg* 44:234–239
- Krings T, Schreckenberger M, Rohde V, Foltys H, Spetzger U, Sabri O, Reinges MH, Kemeny S, Meyer PT, Moller-Hartmann W, Korinth M, Gilsbach JM, Buell U, Thron A (2001b) Metabolic and electrophysiological validation of functional MRI. *J Neurol Neurosurg Psychiatry* 71:762–771
- Krishnan R, Raabe A, Hattingen E, Szelenyi A, Yahya H, Hermann E, Zimmermann M, Seifert V (2004) Functional magnetic resonance imaging-integrated neuro-navigation: correlation between lesion-to-motor cortex distance and outcome. *Neurosurgery* 55:904–914; discussion 914–905
- Law M, Kazmi K, Wetzel S, Wang E, Iacob C, Zagzag D, Golfinos JG, Johnson G (2004) Dynamic susceptibility contrast-enhanced perfusion and conventional MR imaging findings for adult patients with cerebral primitive neuroectodermal tumors. *AJNR Am J Neuroradiol* 25:997–1005
- Lee SP, Silva AC, Ugurbil K, Kim SG (1999) Diffusion-weighted spin-echo fMRI at 9.4 T: microvascular/tissue contribution to BOLD signal changes. *Magn Reson Med* 42:919–928
- Lehericy S, Cohen L, Bazin B, Samson S, Giacomini E, Rougetet R, Hertz-Pannier L, Le Bihan D, Marsault C, Baulac M (2000a) Functional MR evaluation of temporal and frontal language dominance compared with the Wada test. *Neurology* 54:1625–1633
- Lehericy S, Duffau H, Cornu P, Capelle L, Pidoux B, Carpentier A, Auliac S, Clemenceau S, Sichez JP, Bitar A, Valery CA, Van Effenterre R, Faillot T, Srou A, Fohanno D, Philippon J, Le Bihan D, Marsault C (2000b) Correspondence between functional magnetic resonance imaging somatotopy and individual brain anatomy of the central region: comparison with intraoperative stimulation in patients with brain tumors. *J Neurosurg* 92:589–598
- Lehericy S, Biondi A, Sourour N, Vlaicu M, du Montcel ST, Cohen L, Vivas E, Capelle L, Faillot T, Casasco A, Le Bihan D, Marsault C (2002) Arteriovenous brain malformations: is functional MR imaging reliable for studying language reorganization in patients? Initial observations. *Radiology* 223:672–682
- Lehericy S, Ducros M, Van de Moortele PF, Francois C, Thivard L, Poupon C, Swindale N, Ugurbil K, Kim DS (2004) Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Ann Neurol* 55:522–529
- Lesser RP, Luders H, Klem G, Dinner DS, Morris HH, Hahn J (1984) Cortical afterdischarge and functional response thresholds: results of extraoperative testing. *Epilepsia* 25: 615–621.
- Lesser RP, Luders H, Klem G, Dinner DS, Morris HH, Hahn JF, Wyllie E (1987) Extraoperative cortical functional localization in patients with epilepsy. *J Clin Neurophysiol* 4:27–53.
- Logothetis NK, Wandell BA (2004) Interpreting the BOLD signal. *Ann Rev Physiol* 66:735–769
- Loring DW, Meador KJ, Lee GP, King DW, Nichols ME, Park YD, Murro AM, Gallagher BB, Smith JR (1995) Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy. *Neurology* 45:1329–1333
- Ludemann L, Grieger W, Wurm R, Budzisch M, Hamm B, Zimmer C (2001) Comparison of dynamic contrast-enhanced MRI with WHO tumor grading for gliomas. *Eur Radiol* 11:1231–1241
- Luders HO, Dinner DS, Morris HH, Wyllie E, Comair, YG (1995) Cortical electrical stimulation in humans. The negative motor areas. *Adv Neurol* 67:115–129.
- Lurito JT, Lowe MJ, Sartorius C, Mathews VP (2000) Comparison of fMRI and intraoperative direct cortical stimulation in localization of receptive language areas. *J Comput Assist Tomogr* 24:99–105
- Medina LS, Aguirre E, Bernal B, Altman NR (2004) Functional MR imaging versus Wada test for evaluation of language lateralization: cost analysis. *Radiology* 230:49–54
- Milner B, Branch C, Rasmussen T (1962) Study of short-term memory after intracarotid injection of sodium amytal. *Trans Am Neurol Assoc* 87:224–226
- Mori S, Kaufmann WE, Davatzikos C, Stieltjes B, Amodei L, Fredericksen K, Pearlson GD, Melhem ER, Solaiyappan M, Raymond GV, Moser HW, van Zijl PC (2002) Imaging cortical association tracts in the human brain using diffusion-tensor-based axonal tracking. *Magn Reson Med* 47:215–223
- Mueller WM, Yetkin FZ, Hammeke TA, Morris GL III, Swanson SJ, Reichert K, Cox R, Haughton VM (1996) Functional magnetic resonance imaging mapping of the motor cortex in patients with cerebral tumors. *Neurosurgery* 39:515–520; discussion 520–511
- Nagarajan L, Schaul N, Eidelberg D, Dhawan V, Fraser R, Labar DR (1996) Contralateral temporal hypometabo-

- lism on positron emission tomography in temporal lobe epilepsy. *Acta Neurol Scand* 93:81–84
- Nathan SS, Sinha SR, Gordon B, Lesser RP, Thakor NV (1993b) Determination of current density distributions generated by electrical stimulation of the human cerebral cortex. *Electroencephalogr Clin Neurophysiol* 86:183–192.
- Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Ugurbil K (1993) Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophys J* 64:803–812
- Ojemann G.A., Ojemann, J.G., Lettich, E., Berger, M.S (1989) Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. *J Neurosurg* 71:316–326.
- Pawlik G, Rackl A, Bing RJ (1981) Quantitative capillary topography and blood flow in the cerebral cortex of cats: an in vivo microscopic study. *Brain Res* 208:35–58
- Peled S, Berezovskii V, Hendrickson P, Born R, Westin C-F (2005) Histological Validation of DTI using WGA-HRP in a Macaque. In: 13th International Society for Magnetic Resonance in Medicine, Miami Beach, p 1323
- Pfeuffer J, Van de Moortele PF, Ugurbil K, Hu X, Glover GH (2002) Correction of physiologically induced global off-resonance effects in dynamic echo-planar and spiral functional imaging. *Magn Reson Med* 47:344–353
- Pineiro R, Pendlebury S, Johansen-Berg H, Matthews PM (2002) Altered hemodynamic responses in patients after subcortical stroke measured by functional MRI. *Stroke* 33:103–109
- Puce A, Constable RT, Luby ML, McCarthy G, Nobre AC, Spencer DD, Gore JC, Allison T (1995) Functional magnetic resonance imaging of sensory and motor cortex: comparison with electrophysiological localization. *J Neurosurg* 83:262–270
- Pudenz RH, Agnew WF, Bullara LA (1977) Effects of electrical stimulation of brain. Light and electron-microscopic studies. *Brain Behav Evol* 14:103–125.
- Pujol J, Conesa G, Deus J, Vendrell P, Isamat F, Zannoli G, Marti-Vilalta JL, Capdevila A (1996) Presurgical identification of the primary sensorimotor cortex by functional magnetic resonance imaging. *J Neurosurg* 84:7–13
- Pujol J, Conesa G, Deus J, Lopez-Obarrio L, Isamat F, Capdevila A (1998) Clinical application of functional magnetic resonance imaging in presurgical identification of the central sulcus. *J Neurosurg* 88:863–869
- Rabin ML, Narayan VM, Kimberg DY, Casasanto DJ, Glosser G, Tracy JJ, French JA, Sperling MR, Detre JA (2004) Functional MRI predicts post-surgical memory following temporal lobectomy. *Brain* 127:2286–2298
- Ranck JB Jr (1975) Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Res* 98:417–440.
- Rausch R, Silfvenius H, Wieser HG, Dodrill CB, Meader KJ, Jones-Gotman M (1993) Interarterial amobarbital procedures. In: Engel JJ (ed) *Surgical treatment of the epilepsies*. Raven Press, New York, pp 341–357
- Rausch R, Henry TR, Ary CM, Engel J Jr, Mazziotto J (1994) Asymmetric interictal glucose hypometabolism and cognitive performance in epileptic patients. *Arch Neurol* 51:139–144
- Reinges MH, Krings T, Meyer PT, Schreckenberger M, Rohde V, Weidemann J, Sabri O, Mulders EJ, Buell U, Thron A, Gilsbach JM (2004) Preoperative mapping of cortical motor function: prospective comparison of functional magnetic resonance imaging and [15O]-H₂O-positron emission tomography in the same coordinate system. *Nucl Med Commun* 25:987–997
- Richardson MP, Strange BA, Thompson PJ, Baxendale SA, Duncan JS, Dolan RJ (2004) Pre-operative verbal memory fMRI predicts post-operative memory decline after left temporal lobe resection. *Brain* 127:2419–2426
- Rouleau I, Robidoux J, Labrecque R, Denault C (1997) Effect of focus lateralization on memory assessment during the intracarotid amobarbital procedure. *Brain Cogn* 33:224–241
- Roux FE, Boulanouar K, Ranjeva JP, Tremoulet M, Henry P, Manelfe C, Sabatier J, Berry I (1999) Usefulness of motor functional MRI correlated to cortical mapping in Rolandic low-grade astrocytomas. *Acta Neurochir (Wien)* 141:71–79
- Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I (2003) Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. *Neurosurgery* 52:1335–1345; discussion 1345–1337
- Rutten GJ, Ramsey NF, van Rijen PC, Alpherts WC, van Veelen CW (2002a) FMRI-determined language lateralization in patients with unilateral or mixed language dominance according to the Wada test. *Neuroimage* 17:447–460
- Rutten GJ, Ramsey NF, van Rijen PC, Noordmans HJ, van Veelen CW (2002b) Development of a functional magnetic resonance imaging protocol for intraoperative localization of critical temporoparietal language areas. *Ann Neurol* 51:350–360
- Sabbah P, Chassoux F, Leveque C, Landre E, Baudoin-Chial S, Devaux B, Mann M, Godon-Hardy S, Nioche C, Ait-Ameur A, Sarrazin JL, Chodkiewicz JP, Cordoliani YS (2003) Functional MR imaging in assessment of language dominance in epileptic patients. *Neuroimage* 18:460–467
- Salanova V, Morris HH III, Rehm P, Wyllie E, Dinner DS, Luders H, Gilmore-Pollak W (1992) Comparison of the intracarotid amobarbital procedure and interictal cerebral 18-fluorodeoxyglucose positron emission tomography scans in refractory temporal lobe epilepsy. *Epilepsia* 33:635–638
- Salanova V, Markand O, Worth R (2001) Focal functional deficits in temporal lobe epilepsy on PET scans and the intracarotid amobarbital procedure: comparison of patients with unitemporal epilepsy with those requiring intracranial recordings. *Epilepsia* 42:198–203
- Sartorius CJ, Berger MS (1998) Rapid termination of intraoperative stimulation-evoked seizures with application of cold Ringer's lactate to the cortex. Technical note. *J Neurosurg* 88:349–351.
- Schiffbauer H, Berger MS, Ferrari P, Freudenstein D, Rowley HA, Roberts TP (2002) Preoperative magnetic source imaging for brain tumor surgery: a quantitative comparison with intraoperative sensory and motor mapping. *J Neurosurg* 97:1333–1342
- Schreckenberger M, Spetzger U, Sabri O, Meyer PT, Zeggel T, Zimny M, Gilsbach J, Buell U (2001) Localisation of

- motor areas in brain tumour patients: a comparison of preoperative [18F]FDG-PET and intraoperative cortical electrostimulation. *Eur J Nucl Med* 28:1394–1403
- Shmuel A, Augath M, Oeltermann A, Logothetis NK (2006) Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nat Neurosci* 9:569–577
- Simkins-Bullock J (2000) Beyond speech lateralization: a review of the variability, reliability, and validity of the intracarotid amobarbital procedure and its nonlanguage uses in epilepsy surgery candidates. *Neuropsychol Rev* 10:41–74
- Simos PG, Papanicolaou AC, Breier JI, Wheless JW, Constantinou JE, Gormley WB, Maggio WW (1999) Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. *J Neurosurg* 91:787–796
- Small SA, Perera GM, DeLaPaz R, Mayeux R, Stern Y (1999) Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. *Ann Neurol* 45:466–472
- Spencer DC, Morrell MJ, Risinger MW (2000) The role of the intracarotid amobarbital procedure in evaluation of patients for epilepsy surgery. *Epilepsia* 41:320–325
- Sperling MR, Saykin AJ, Glosser G, Moran M, French JA, Brooks M, O'Connor MJ (1994) Predictors of outcome after anterior temporal lobectomy: the intracarotid amobarbital test. *Neurology* 44:2325–2330
- Sperling MR, Alavi A, Reivich M, French JA, O'Connor MJ (1995) False lateralization of temporal lobe epilepsy with FDG positron emission tomography. *Epilepsia* 36:722–727
- Stieltjes B, Kaufmann WE, van Zijl PC, Fredericksen K, Pearlson GD, Solaiyappan M, Mori S (2001) Diffusion tensor imaging and axonal tracking in the human brainstem. *Neuroimage* 14:723–735
- Thulborn KR, Waterton JC, Matthews PM, Radda GK (1982) Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochim Biophys Acta* 714:265–270
- Towle VL, Khorasani L, Uftring S, Pelizzari C, Erickson RK, Spire JP, Hoffman K, Chu D, Scherg M (2003) Non-invasive identification of human central sulcus: a comparison of gyral morphology, functional MRI, dipole localization, and direct cortical mapping. *NeuroImage* 19:684–697
- Ugurbil K, Hu X, Chen W, Zhu XH, Kim SG, Georgopoulos A (1999) Functional mapping in the human brain using high magnetic fields. *Philos Trans R Soc Lond B Biol Sci* 354:1195–1213
- Ugurbil K, Toth L, Kim DS (2003) How accurate is magnetic resonance imaging of brain function? *Trends Neurosci* 26:108–114
- Urbach H, Kurthen M, Klemm E, Grunwald T, Van Roost D, Linke DB, Biersack HJ, Schramm J, Elger CE (1999) Amobarbital effects on the posterior hippocampus during the intracarotid amobarbital test. *Neurology* 52:1596–1602
- Van de Moortele PF, Pfeuffer J, Glover GH, Ugurbil K, Hu X (2002) Respiration-induced B0 fluctuations and their spatial distribution in the human brain at 7 Tesla. *Magn Reson Med* 47:888–895
- van Zijl PC, Eleff SM, Ulatowski JA, Oja JM, Ulug AM, Traystman RJ, Kauppinen RA (1998) Quantitative assessment of blood flow, blood volume and blood oxygenation effects in functional magnetic resonance imaging. *Nat Med* 4:159–167
- Vinas FC, Zamorano L, Mueller RA, Jiang Z, Chugani H, Fuerst D, Muzik O, Mangner TJ, Diaz FG (1997) [15O]-water PET and intraoperative brain mapping: a comparison in the localization of eloquent cortex. *Neurol Res* 19:601–608
- Wada J, Rasmussen T (1960) Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: experimental and clinical observations. *J Neurosurg* 17:266–282
- Woermann FG, Jokeit H, Luerding R, Freitag H, Schulz R, Guertler S, Okujava M, Wolf P, Tuxhorn I, Ebner A (2003) Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology* 61:699–701
- Yacoub E, Duong TQ, Van De Moortele PF, Lindquist M, Adriany G, Kim SG, Ugurbil K, Hu X (2003) Spin-echo fMRI in humans using high spatial resolutions and high magnetic fields. *Magn Reson Med* 49:655–664
- Yeomans JS (1990) Principles of brain stimulation. New York: Oxford University Press
- Yetkin FZ, Mueller WM, Morris GL, McAuliffe TL, Ulmer JL, Cox RW, Daniels DL, Haughton VM (1997) Functional MR activation correlated with intraoperative cortical mapping. *AJNR Am J Neuroradiol* 18:1311–1315
- Yingling CD, Ojemann S, Dodson B, Harrington MJ, Berger MS (1999) Identification of motor pathways during tumor surgery facilitated by multichannel electromyographic recording. *J Neurosurg* 91:922–927
- Young WL, Prohovnik I, Ornstein E, Ostapkovich N, Sisti MB, Solomon RA, Stein BM (1990) The effect of arteriovenous malformation resection on cerebrovascular reactivity to carbon dioxide. *Neurosurgery* 27:257–266; discussion 266–257
- Young WL, Pile-Spellman J, Prohovnik I, Kader A, Stein BM (1994) Evidence for adaptive autoregulatory displacement in hypotensive cortical territories adjacent to arteriovenous malformations. Columbia University AVM Study Project. *Neurosurgery* 34:601–610; discussion 610–611
- Yousry TA, Schmid UD, Jassoy AG, Schmidt D, Eisner WE, Reulen HJ, Reiser MF, Lissner J (1995) Topography of the cortical motor hand area: prospective study with functional MR imaging and direct motor mapping at surgery. *Radiology* 195:23–29
- Yousry TA, Schmid UD, Alkadhi H, Schmidt D, Peraud A, Buettner A, Winkler P (1997) Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. *Brain* 120(1):141–157
- Zeineh MM, Engel SA, Thompson PM, Bookheimer SY (2003) Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science* 299:577–580

Multimodality in Functional Neuroimaging

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KEY POINTS

The multimodal approach which is conceptually based on the combination of different non-invasive functional neuroimaging tools and their *registration* and co-integration into *neuronavigational systems* is increasingly used in presurgical diagnostics. In particular, the combination of imaging techniques that map different functional systems is a useful procedure, such as *functional MRI* as a technique for the localization of eloquent cortex and *diffusion-tensor imaging* as a technique for mapping of white matter fiber bundles/tracts. *Magnetic source imaging* as an additional imaging technique of cortical function is of particular advantage in epilepsy surgery. Advanced pathoanatomy-based techniques such as *nuclear medicine imaging* (multi-ligand imaging) or *MR spectroscopy* additionally guide in the delineation of cerebral lesions and their borders (e.g., neoplasms). Although multimodal imaging may be complex in data acquisition and postprocessing, it is a valuable instrument to improve surgical planning and performance.

8.1

The Concept of Multimodal Presurgical Imaging

The integration of function localization into neurosurgery is most important since follow-up nowadays concentrates more on performance than on survival, and the preservation of function during and after operation is crucial. For the first, modern imaging techniques are increasingly used for characterization of lesions and peri-lesional tissue. Second, in order to identify and to map the areas near a lesion that contain critical function such as language, vision, contralateral motor control etc., different neuroimaging

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techniques are used. The functional imaging methods *sensu stricto* which are mainly used for pre-operative functional mapping are functional MRI (fMRI), positron emission tomography (PET) or single photon emission computerized tomography (SPECT), and evoked response mapping by magnetoencephalography (MEG) or multi-channel electroencephalography (EEG) (MAZZIOTTA 2000; LEIJTEN *et al.* 2004). As the basic principle, all these techniques compare an activated state during which a specific task is performed with a resting state, and the difference between the two states implies involvement of the corresponding area in that specific function, within the connectivity and complexity in the nervous system (SPORNS *et al.* 2000). However, the spatial resolution of the results depends on the kind of signal that is measured and the technical properties, and this differs markedly between the named imaging tools. Furthermore, the relationship between the results of the computer-based analysis and the underlying neurophysiology is often complex, for example in fMRI. Independent of these considerations, the functional maps of all techniques have to be co-registered to an anatomical individual image of the patient's brain, i.e. a volume-rendering high-resolution MRI, as the structural brain framework requiring computerized post-processing. For that purpose, the data have to be integrated into the same stereotactic coordinate system as the 3-D MRI to be correctly superimposed. The functional maps which were gained preoperatively are registered to the predefined coordinate system in the same way as the (pre-operative) 3-D anatomy.

Spatial normalization processing aims at providing the spatial relationship between functional location and structure (BRETT *et al.* 2002) at a multiple-subject level, classically using proportional scaling systems to reference an individual brain to an atlas brain, such as the human atlas by TALAIRACH and TOURNOUX (1988). Nowadays the template of the Montreal Neurological Institute (MNI template) which has been created from the brain MRI data of 152 healthy subjects (BRETT *et al.* 2002) is mostly used for that purpose. It has to be held that the spatial normalization, i.e. the registration of data within standardized stereotactic space, is only a prerequisite for co-registration of imaging results from different individuals to each other, whereas individual features of data (which are of course important in surgical planning as a *per se* individual-based action) may get lost within this process.

The secondary image postprocessing has the advantage of enabling the image fusion of additional

functional information (WINKLER *et al.* 2004). It is possible to combine all these different imaging data into one composite image to be visualized during the course of the surgical procedure (TURKINGTON *et al.* 1995; NIMSKY *et al.* 2005a; TOGA *et al.* 2000). However, the multitude of technical approaches to achieve the information of the localization of the data collected before surgery relative to the anatomy during surgery and to its changes during surgery (which are caused by many factors such as the so-called brain shift phenomenon) is beyond the scope of this chapter. The coregistration procedure generally enables multiple-modality comparisons in the same subject. This aspect is all the more important with respect to additional applications of presurgical multimodality imaging: the characterization of the lesion itself being under consideration for resection can as well be performed by non-invasive techniques in a wide range of disorders, particularly in cerebral neoplasms and in epilepsy surgery. Composite presurgical brain mapping techniques with respect to the pharmacological characterization are primarily found in the domain of PET and SPECT which give important information on the metabolic state and molecular events within the tumor (JACOBS *et al.* 2005) and can be combined with various MRI techniques beyond the structural 3-D data set. Moreover, patients with medial temporal lobe epilepsy and complex partial seizures have been investigated by ligand imaging such as ^{11}C -flumazenil PET (KOEPP *et al.* 1997) and can be further characterized by perfusion and metabolic imaging using PET, spike localization using fMRI and electrophysiological techniques; in particular, comparisons of ligand data with automated and objective analysis of high-resolution structural MRI, based on statistical parametric mapping (SPM), are helpful to identify structural epileptogenic lesions (KOEPP and WOERMANN 2005; RICHARDSON *et al.* 1997). By this composite use of preoperative brain mapping for actual lesion identification and for delineation of functionally relevant cortical areas adjacent to the operation area, multimodal presurgical imaging is an important element of modern neurosurgical planning. The concept of individual visualization of functional landmarks and even networks has recently evolved to a broader spectrum of MRI applications beyond fMRI activation maps (which describe cortical areas) to preoperative assessment of infiltration zones around (neoplastic) brain lesions and of eloquent fiber systems within the white matter which will be described in the following.

8.2

Combination of Neuroimaging Modalities and their Applications

8.2.1

Combination of MRI Techniques: Intramodal Multimodality

Conventional MRI with and without contrast media is the method of choice to image brain structure and for the primary diagnosis of structural lesions at good soft-tissue contrast and high (<1 mm) spatial resolution, and for all brain mapping in which postprocessing results in activation clusters, an individual coregistered 3-D MRI data set (including any lesions) serves as the reference. However, additional MRI applications offer various tools to visualize both the extent of brain lesions and damage associated with them and the function of cortical and subcortical areas localized in vicinity to lesions. As an example for lesion characterization in particular of neoplastic origin, diffusion-weighted MRI (DWI) detects therapy-induced water diffusion changes and has been suggested to provide an early surrogate marker for quantification of treatment response, i.e. changes indicating high tissue viability imply better response and comparison of values from tumor regions with control regions were useful in the differentiation of radiation effects in the longitudinal assessment (CHENEVERT et al. 2000, 2002). As another technique, dynamic contrast enhanced MRI is a surrogate marker for angiogenesis and might be useful for monitoring antiangiogenic therapies in brain tumors (GOSSMANN et al. 2002).

Besides these more structure-oriented MRI applications in the course of primary diagnostics and prognosis assessment, MRI-based techniques with computerized post hoc processing can be combined in the presurgical setting as a composite instrument for tissue characterization and function localization. Due to this complex information gained from one basic imaging approach, it is reasonable to speak of “intramodal multimodality” with respect to MRI.

As outlined above, the classical functional presurgical MRI approach comprises preoperative activation paradigms by use of fMRI. However, there are advanced techniques such as computer-based analysis of 3-D MRI, diffusion tensor imaging, and MR spectroscopy which are increasingly integrated into presurgical brain mapping protocols and broaden the spectrum of the non-invasively assessable functional neuroanatomy in patients with brain lesions.

8.2.1.1

Functional MRI (fMRI)

fMRI enables to the indirect measurement of neuronal activity via differential local oxygen extraction and therefore regional blood flow changes and is nowadays an established procedure in the course of presurgical cortical mapping in cases of lesions adjacent to eloquent brain areas. Patients with such lesions undergo fMRI with paradigms that activate the appropriate topographic region, and the relative distance between the lesion and the activation sites provides a measure of surgery risk. These paradigms are chosen to identify the regions associated with motor or somatosensory functions in patients with lesions near sensorimotor cortices and such responsible for language or memory function in patients with lesions near medial temporal lobes. The complex setup of fMRI investigation conception, data acquisition and postprocessing together with its underlying neurophysiological basics is detailed in Chapters 2 and 4. In the context of these chapters, the aspect of fMRI use within the multimodal approach is to be depicted.

The activation maps resulting from fMRI data postprocessing are usually overlaid onto the individual 3-D MRI. These voxel clusters are considered to delineate critical areas for the particular function, but might be only the tip of the iceberg within a neural network (an argument which is of course as well feasible for other functional imaging techniques using thresholds of significance for determination of activation). It is thus useful to combine fMRI cortical mapping with techniques such as DTI (see below) to visualize in addition the subcortical (white matter) structures, i.e. fiber tracts, that might also be crucial for maintaining the particular function. Furthermore, the extent of a lesion might only be incompletely assessable by T1-weighted 3-D MRI, and thus a combination with techniques imaging the peri-lesional tissue infiltration such as MR spectroscopy, metabolic imaging such as fluorodesoxyglucose PET (FDG-PET) or other ligand imaging might be useful to improve the estimation of the distance between lesion and critical cortex. It could be demonstrated that ^{11}C methionine (MET)-PET seems to be more sensitive than MRI for differentiating between tumor and edema or gliosis and that simultaneous integration of MRI and MET-PET data into neuronavigation can facilitate total tumor removal in glioma surgery (BRAUN et al. 2002), and an additional combination with functional land-

marks gained from fMRI might further improve the surgical results. Consecutively, the co-integration of fMRI data using different paradigms and MET-PET data into neuronavigation in cases of brain tumor surgery was performed with good postoperative outcome (BRAUN et al. 2000).

With respect to methodological considerations, the maximum of fMRI activation will in general be found close to vessels (draining veins) and not be localized directly to neurons. Thus, a comparison or combination with alternative functional mapping techniques might be useful, but is of course restricted to few specialized centers. Here, MEG/magnetic source imaging is a useful composite technique to map eloquent cortical areas (see below). In particular with respect to presurgical localization of epileptic activity, MEG might add to the results of fMRI with simultaneously-recorded epileptiform discharges on EEG (spike-triggered fMRI and continuous EEG/fMRI recordings) (cf. Chap. 5) – which then again might be combined with DTI and MRS for improvement of presurgically gained information (KRAKOW et al. 1999). A combination of fMRI with functional PET (fPET) using ^{15}O - H_2O as another perfusion-based technique is less promising although fPET was shown to be a similarly sensitive and reliable tool to map the central region in a comparative study using the same frame of reference (REINGES et al. 2004). The mean localization difference in this study ranged between 2 and 18 mm, and the authors comment that fMRI is more prone to artifacts, whereas fPET depicts capillary perfusion changes and therefore shows activation closer to the parenchyma. However, the application of fPET and the tracer ^{15}O - H_2O with its half time of about 2 min is restricted to dedicated PET centers including a cyclotron unit and needs the repetitive injection of radiopharmaceuticals in opposite to fMRI which is easy to perform on each 1.5 T scanner and has no known side effects.

8.2.1.2

Computer-Based Analysis of Structural MRI

The so-called computational neuroanatomy is a novel methodology to characterize neuroanatomical configuration of different brains, encompassing mainly the following techniques, voxel-based morphometry (VBM) which compares neuroanatomical differences on a voxel by voxel basis, deformation-based morphometry (DBM) which provides information about global differences in brain shape, and

tensor-based morphometry (TBM) which provides information about local shape differences (GOOD et al. 2001a, b). Especially VBM has proven to be a powerful tool for analyzing changes in grey or white matter volumes of the brain (ASHBURNER and FRISTON 2000) since its introduction in 1995 by use of an automated segmentation procedure and standardized parametric statistics in comparison to a normal data base within the SPM software (Wellcome Department of Imaging Neuroscience Group, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). Both this whole brain-based approach and the multiple different 3-D MRI analysis techniques which make use of local registration algorithms, however, mostly aim at finding morphological signatures of mainly neurodegenerative brain diseases (cf. ASHBURNER et al. 2003 for review) and are only validated for analyses at group level: it could be demonstrated that VBM could not satisfactorily delineate the spatial extent of focal lesions in individuals, even in simulations that avoided preprocessing artifacts (MEHTA et al. 2003). To be applicable to clinical practice in general and in a presurgical setting in particular, the techniques need to be sensitive to quantitative or qualitative alterations of normal brain structure in an individual. In that respect, it is not useful to perform this computerized approach in lesions which are clearly assessable by conventional high-resolution MRI such as neoplasms. There are nevertheless applications of computerized analysis of structural 3-D MRI to presurgical diagnostics, in particular in the field of epilepsy surgery of malformations of cortical development (MCD). First, there have been voxel-based 3-D MRI analysis tools developed towards the goal of automated observer-independent MCD lesion detection (ANTEL et al. 2002a; KASSUBEK et al. 2002, HUPPERTZ et al. 2005). These algorithms serve mainly as image screening tools in comparison to a healthy control sample in order to facilitate MCD detection and localization. Second, as a consequent continuation of the multimodality approach in the sense of combined voxel-based mapping (KASSUBEK et al. 2000), a combination of ligand imaging using PET (which is able to provide relevant information on MCD; CROSS 2003) and SPM-based MRI analysis was proposed for the investigation of MCD (RICHARDSON et al. 1997). Although at the expense of the measurement of absolute quantitative values, the voxel-based comparison of MRI and PET enables for automated objective whole brain analysis, issues concerning partial volume effects and mixed tissue sampling in ligand images to be resolved, and

disproportionate changes in function and structure to be identified. It could be demonstrated as well in a study using the approach of voxel-based MRI analysis and subtraction ictal SPECT coregistered to MRI (SISCOM) that multimodal assessment of MCD may contribute to advanced observer-independent preoperative assessment of seizure origin and might thus improve presurgical diagnostics in symptomatic epilepsy (WIEST et al. 2005).

8.2.1.3

Diffusion Tensor Imaging (DTI)

Diffusion is a physical process involving the translational movement of molecules via thermally driven random motions, so-called Brownian motion. The underlying cellular tissue microstructure influences the overall mobility of the diffusing molecules by providing numerous barriers and by creating various individual compartments within the tissue (e.g. intra-/extracellular, neurons, glial cells, axons). Signal intensity of diffusion measured via DWI shows a greater signal enhancement along the direction parallel to the axis of fiber bundles relative to the perpendicular direction. In the presence of this phenomenon called anisotropy, diffusion is characterized by hindrances of equal molecular movement caused by oriented barriers and requires a tensor which fully describes the mobility of molecules along each direction and the correlation between these directions. A common way to summarize diffusion measurements in DTI is the calculation of a parameter that reflects anisotropy, such as the fractional anisotropy (FA) as a measure of the portion of the magnitude of the diffusion tensor due to anisotropy. The FA can be presented as a grey scale image, or the principal diffusion direction of the brain structure to be examined can be encoded with color, resulting in color-coded parameter maps (BASSER and JONES 2002; LE BIHAN and VAN ZIJL 2002). For this DTI postprocessing, many different software packages besides SPM are in use, often locally developed in-house solutions.

Concretely, DTI measures the mean longitudinal direction of axons in white matter tracts, and application of fiber tracking algorithms allows a delineation of major white matter pathways (MORI and VAN ZIJL 2002). With respect to presurgical mapping, the DTI technique provides information about the deformation, displacement or even the interruption of white matter tracts around a lesion. SINHA et al. (2002), for instance, used DTI to differentiate nor-

mal white matter, edematous brain, and enhancing tumor margins in patients with high-grade gliomas, and WITWER et al. (2002) reported that visualization of white matter tracts by DTI was beneficial in the surgical planning for patients with intrinsic brain tumors showing that anatomically intact fibers may be present in abnormal-appearing areas of the brain. The knowledge of the course of clinically eloquent major white matter tracts in relationship to the exact location of the lesion is of great value to the neurosurgeon in planning the appropriate surgical strategy and may help to prevent new postoperative neurological deficits (CLARK et al. 2003).

Consecutively, DTI measurements are increasingly used in so-called advanced neuronavigation protocols (ROHDE et al. 2005). That way, the course of pyramidal tracts can be displayed by DTI for an intraoperative visualization in functional neuronavigation (NIMSKY et al. 2005b). Moreover, DTI is helpful in optic radiation (OR) visualization to maintain patients' visual fields in surgery of lesions adjacent to its course, as COENEN et al. (2005) showed by using DTI of OR within neuronavigation and preoperative and postoperative neuroophthalmological testing including perimetry. Also in epilepsy surgery, visual field defects are a well recognized complication of anterior temporal lobe resection and occur because of disruption of the Meyer loop. By use of DTI tractography to visualize the OR before and after surgery, POWELL et al. (2005) demonstrated the disruption of the Meyer loop in a patient who developed a quadrantanopia, and they concluded that preoperative OR imaging will be useful in predicting and perhaps preventing from visual field defects following temporal lobe resection.

The integration of DTI into presurgical mapping protocols is also useful with respect to MRI multimodality, since the combination of DTI and fMRI provides valuable information that cannot be gained by use of either technique alone. The validity and sensitivity of non-invasive functional mapping for surgical guidance can be improved by considering results obtained with both methods, and the use of 3-D visualization seems crucial and unique for viewing and understanding the complicated spatial relationship among the lesion, gray matter activation, and white matter fiber bundles (HENDLER et al. 2003). In neoplastic brain lesions, the combined use of fMRI and DTI can provide a better estimation of the proximity of tumor borders to eloquent brain systems sub-serving language, speech, vision, motor and premotor functions (ULMER et al. 2004).

DTI and fMRI can thus be used as complimentary techniques for delineation of eloquent subcortical and cortical areas (Fig. 8.1). As an elegant approach, fMRI results might be used as seed regions for the DTI tracking algorithms, e.g. for mapping of the primary motor cortex and the pyramidal tracts.

However, there are also limitations to DTI since the technique is limited in the correct identification of fiber crossings due to its inability to resolve more than a single axon direction within each voxel. Novel approaches, such as the technique called q-ball imaging, can resolve intra-voxel white matter fiber crossing as well as white matter insertions into the cortex and might be able to resolve complex intra-voxel fiber architecture and thus eliminate a key obstacle to noninvasively mapping neural connectivity in the human brain (TUCH et al. 2003). One additional technical problem especially in presurgical mapping, i.e. the intraoperative displacement of major white matter tracts during mass resection due to the brain shift, was addressed by a comparison of preoperative and intraoperative DTI-based fiber tracking (NIMSKY et al. 2005c). The authors described a marked shifting and deformation of major white matter tracts because of tumor removal, and they conclude that this shifting emphasizes the need for an intraoperative update of navigation systems during resection of deep-seated tumor portions near eloquent brain areas and that fiber tracking is a method not only for preoperative neurosurgical visualization but also for further intraoperative planning.

8.2.1.4

MR Spectroscopy

In vivo proton (^1H)-MR spectroscopy (MRS) visualizes signals from carbon-bound, non-exchangeable protons, showing the highest information density in the spectral region from 1 to 5 ppm (TRABESINGER et al. 2003). Principal metabolites detected by MRS include the neuronal marker *N*-acetylaspartate as an indirect expression of the integrity of neurons, choline-containing compounds (such as metabolites involved in phospholipid membrane synthesis) as markers for glial activity, creatine (including phosphocreatine) as a marker for energy metabolism and lactate as an indicator for anaerobic glycolysis detected under pathologic conditions. For data acquisition, there are single voxel- and multiple voxel-techniques, depending on the information required; if performed in the investigation of a location of a regional pathological alteration, the latter would be preferable as a screening for abnormalities in different locations (BARKER 2005).

In the presurgical diagnostics of epilepsy surgery, MRS was shown to have potential to be used in imaging protocols to aid in the presurgical evaluation of non-lesional frontal lobe epilepsy (GUYE et al. 2005) and in the assessment of the surgical outcome in temporal lobe epilepsy patients (ANTEL et al. 2002b). In that context, the combination of different approaches such as MRS and 3-D MRI-based measurements of regions-of-interest (ROI) such as

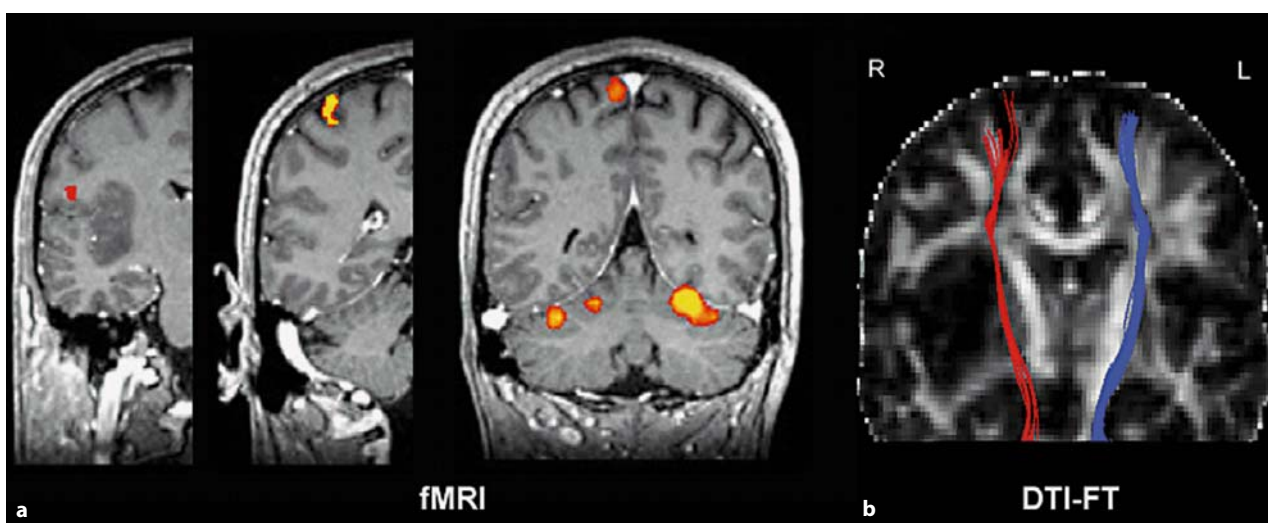


Fig. 8.1a,b. DTI-based fiber tracking of pyramidal tracts for presurgical delineation of eloquent white matter areas. **a** Somatotopic mapping of primary motor cortex shows normal activation patterns. From left to right: tongue, hand and foot movements. **b** DTI fiber tracking shows spatial relationship of the pyramidal tract to an astrocytoma of the right insula. Images courtesy of C. Stippich, MD

amygdala-hippocampal volumes has been found to produce concordant results in presurgical neuroimaging protocols (CENDES et al. 1997). MRS has been established as part of presurgical multimodality neuroimaging studies using various MRI-based techniques and PET in patients with nonlesional unilateral temporal lobe epilepsy (KNOWLTON et al. 1997) and in the in-vivo analysis of metabolic disturbances associated with partial epilepsy in general (KNOWLTON 2004).

MRS is increasingly used in diagnostics of brain tumors to identify regions of viable tumor, to investigate the tumor extent and to monitor the effectiveness of therapy (VIGNERON et al. 2001). Consecutively, MRS has now been integrated into presurgical mapping protocols in glioma surgery to indicate the degree of tumor invasion by co-registration of the metabolic maps derived from MRS postprocessing onto anatomical 3-D MRI for interactive use with neuronavigation/frameless stereotaxy (GANSLANDT et al. 2005). Here, the stereotactic biopsies were acquired by use of the spectral data, and the tumor areas defined by the metabolic maps and histopathologically confirmed by biopsy exceeded the T2-weighted signal change in all seven cases investigated. The authors concluded that MRS may be useful to define more exactly the tumor infiltration zone in glioma surgery than conventional anatomical MRI alone. Furthermore, to continue the principles of multimodality, a combination of this kind of MRS results with functional landmarks gained from fMRI is possible to increase the sensitivity in the assessment of tumor tissue borders and localization of eloquent function. Furthermore, intraoperative high-field MRI with integrated microscope-based neuronavigation enables for acquisition of MRS also during the surgical procedure for immediate intraoperative control (Nimsky et al. 2005a).

8.2.2

Combination of MRI and Nuclear Medicine

8.2.2.1

Principles of PET and SPECT

The integration of PET and SPECT into presurgical multimodal functional neuroimaging allows adding quantitative information of regionally disturbed brain function or regional tumor metabolism into the common framework of image analysis and display, depending on the radiopharmaceutical used for

the imaging study. In general, PET as well as SPECT generates images of the regional and temporal distribution of a radio-labeled pharmaceutical after i.v. injection. For SPECT, pharmaceuticals are usually labeled with the photon emitters ^{99m}Tc or ^{123}I , which due to their radiochemical properties and their half-life of 6 and 13 h, respectively, allow either a daily on-site preparation of the radiopharmaceuticals or a delivery from a regional provider. The positron emitters needed for PET, however, have half-lives ranging from 2 h (^{18}F) to 2 min (^{15}O) which implies that for all preparations of radiopharmaceuticals apart from ^{18}F labeled compounds, a local cyclotron facility is mandatory. Image resolution is depending on technique and instrumentation, ranging from a physical resolution of 10–15 mm full width at half maximum (FWHM) for SPECT to 4 mm FWHM for PET/CT in high-resolution technique. In SPECT, image resolution is directly correlated to the distance between detector and the patient's head, and the number of detectors used (single headed cameras versus triple headed cameras) markedly improves image quality as well. From a technical point of view, there is no doubt that, whenever possible, PET should be preferred to SPECT and, when not available, SPECT using triple headed cameras should be preferred to SPECT using a double headed camera.

8.2.2.2

Radiopharmaceuticals, their Applications and Clinical Indications for Combined MRI and Nuclear Medicine Imaging

^{99m}Tc -D,L-Hexamethylene-propylenamin-oxime (^{99m}Tc -HMPAO) and ^{99m}Tc -ethyl-cysteinat-dimer (^{99m}Tc -ECD) are lipophilic molecules with a high first-pass extraction and near total intracranial fixation, used for depiction of regional blood flow. As these tracers are trapped within the perfused cortex within seconds, the time of injection and not the time of brain scanning determines the measured perfusion state which makes these two tracers ideal for ictal studies where the imaging itself can be postponed to a time after seizure cessation. Sensitivity and specificity of detection of the ictally hyperperfused epileptogenic zone is increased when using the SISCOM procedure, where an interictal SPECT perfusion scan using HMPAO-SPECT or ECD-SPECT is subtracted from a strictly ictally injected perfusion scan and then coregistered to 3-D MRI (O'BRIEN et al. 2004). Recent work has shown that the combination of SISCOM with voxel-based analysis of MRI

may further improve the detection of temporal as well as extratemporal epileptogenic lesions (Wiest et al. 2005) (Fig. 8.2).

In addition, ^{123}I -iomazenil is used as a selective antagonist for the central GABA-A-Benzodiazepine-receptor complex, used for presurgical epilepsy diagnostics, and ^{123}I -tyrosine is an amino acid tracer used for depiction of tumor metabolism of amino acids (cf. JUENGLING and KASSUBEK 2002; KASSUBEK and JUENGLING 2002 for reviews).

^{18}F -Fluorodeoxyglucose (FDG), the most commonly used PET radiopharmaceutical, is a glucose analogon which is actively transported into the cell compartment by the glucose transporter GT-1 and

which is then metabolically trapped within the cell. Tumor cells express more glucose transporters on their cell membrane and are usually characterized by an increased demand in glucose, and brain tumors are contrasted to normal tissue by an increased FDG uptake. As normal cortical FDG uptake is already high, coregistration of a 3-D MRI is mandatory to differentiate tumor uptake and cortical uptake. An increased FDG uptake may also occur due to locally increased cell density or an increased neuronal activity during the uptake period (usually 60–90 min). Decreased FDG-uptake is correlated to regional neuronal dysfunction. FDG-PET may thus delineate as well peritumoral neuronal dys-

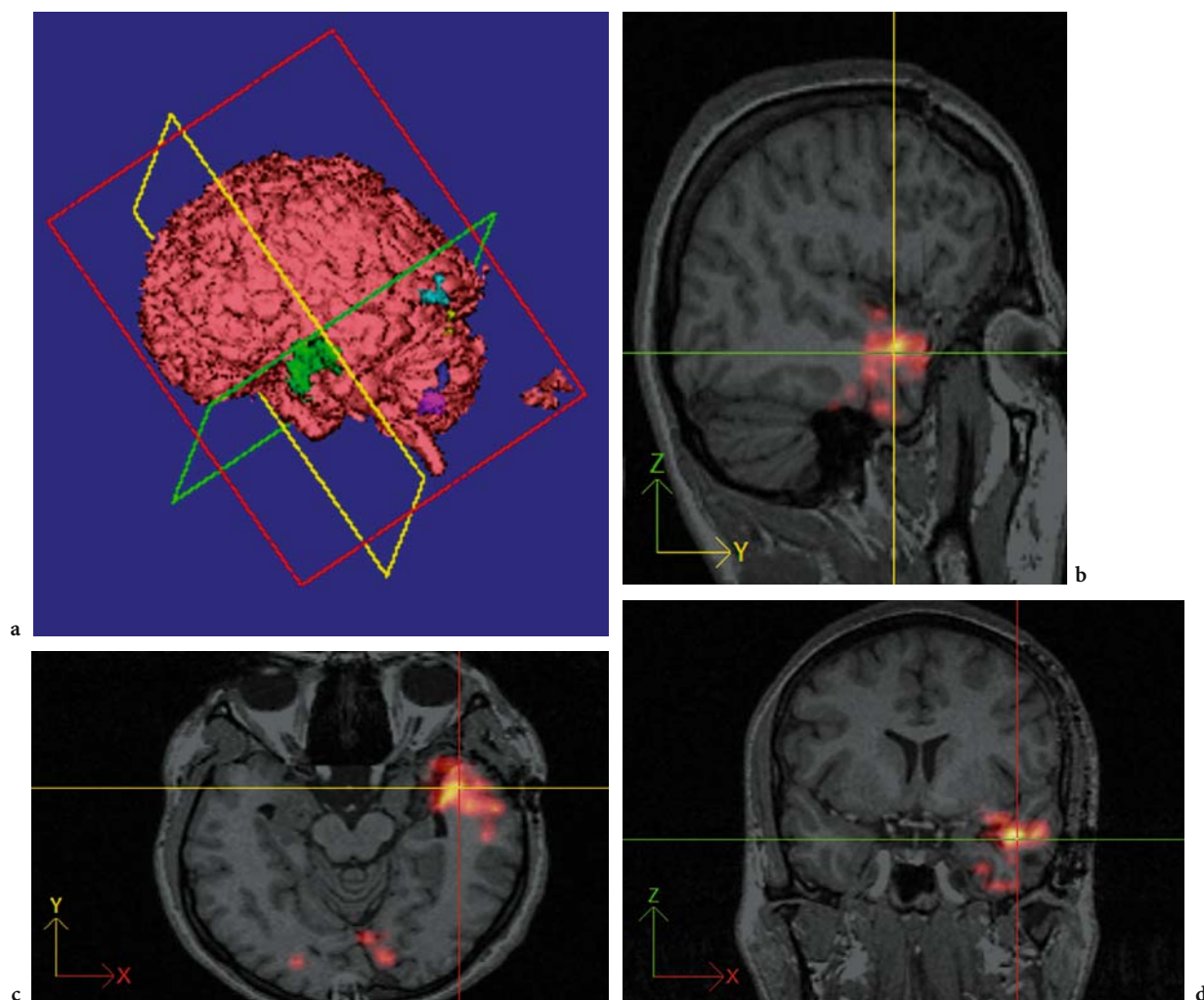


Fig. 8.2a–d. Presurgical activation map of ictally hyperperfused brain areas (using the SISCOM procedure and $^{99\text{m}}\text{Tc}$ ECD for the SPECT scan) in a patient with left temporal seizures scheduled for epilepsy surgery. Activated brain areas (a) (i.e., perfusion differs more than two standard deviations from the mean difference) are projected onto the coregistered individual 3-D MRI in sagittal (c), coronal (d) and transverse (b) planes as well as on a surface reconstruction.

function as the interictal area of the regional functional deficit in epilepsy. FDG-PET has been demonstrated to indicate the metabolically most active tumor part and thus the most informative location for taking a biopsy which otherwise could be misleading if the most malignant part of the tumor was missed (LEVIVIER et al. 1995; GOLDMAN et al. 1997; PIROTTE et al. 2003). In epilepsy surgery, changes of focal uptake in FDG PET (regional decreases) guide in the localization of cortical abnormalities (MUZIK et al. 2005).

^{18}F -Ethyl-tyrosine and ^{18}F -tyrosine (FET/F-TYR) are radio-labeled amino acids with the same physical half-life as FDG, developed as substitutes for ^{11}C -methionine (MET), the most commonly used amino acid tracer with a physical half-life of 20 min. FET, FMT and MET show very low uptake in the normal brain, while they are avidly taken up by gliomas of any grade. Their uptake is mainly mediated by the L-type amino acid transporter system at the blood-brain-barrier (BBB). Therefore, increased uptake is typical even for low-grade gliomas in the absence of BBB disruption, which is a substantial advantage over contrast-enhanced CT or MRI. In contrast-enhancing gliomas, the spatial extent of increased MET uptake is larger than that of contrast enhancement (ERICSON et al. 1985; OGAWA et al. 1993) and may include not only solid tumor but also surrounding tumor infiltration zone. There is a close correlation with tumor vessel density (KRACHT et al. 2003) and prognosis (RIBOM et al. 2001). In a series of 89 low-grade gliomas, MET uptake was a significant survival factor among patients with astrocytomas and with oligodendrogliomas (RIBOM et al. 2001). These results suggest that MET uptake (or FET/F-TYR-Uptake) should be evaluated with respect to guidance of therapy because tumor resection was a favorable prognostic factor in patients with high MET uptake but not in patients with low uptake.

Herholz et al. showed the sensitivity and specificity of MET-PET in differentiating between non-tumoral tissue and low-grade gliomas to be 76% and 87%, respectively (HERHOLZ et al. 1998). Comparative analyses between CT, MRI, MET-PET and stereotactic biopsies have suggested that MET-PET has a greater accuracy in defining the extent of gliomas than CT and MRI alone (BERGSTROM et al. 1983; BRAUN et al. 2002; MOSSKIN et al. 1989; OGAWA et al. 1993). To improve intraoperative tumor delineation, fused images of FET/FMT/MET-PET and contrast enhanced MRI have been integrated into neuronavigation systems such as the Zeiss MKM

system (BRAUN et al. 2002) or the BrainLab Vector Vision system (GROSU et al. 2003; CIZEK et al. 2004; VOLLMAR 2006). Since it has been shown that MET-PET detects solid parts of brain tumors as well as the infiltration area at high sensitivity and specificity at a threshold of 1.3-fold uptake relative to normal brain tissue (KRACHT et al. 2004), a suitable tumor normalization and thresholding method has been implemented in a dedicated visualization tool called "VINCI" (VOLLMAR et al. 2004) (Figs. 8.3 and 8.4).

^{15}O - H_2O (physical half-life 2 min) is the most frequently used CBF tracer for PET, used for functional activation (fPET) and allowing up to 12 quantitative measurements of CBF. Compared to fMRI, fPET provides a more physiologically specific and robust signal (HERHOLZ et al. 1997; KAPLAN et al. 1999; KRINGS et al. 2001a; VINAS et al. 1997). An essential advantage of fPET on fMRI may be the clinical application of language activation studies, where active speaking during language production tasks does not induce technical artifacts (as is common with fMRI), and therefore, direct monitoring of task performance is possible even in functionally impaired subjects (THIEL et al. 1998). However, recent advanced fMRI language mapping protocols might overcome this problem, thus equalizing this fPET advantage.

^{18}F -Flumazenil and ^{11}C -Flumazenil (FMZ) are selective antagonists for the GABA-A-benzodiazepine-receptor complex and are mainly used for detection of epileptogenic areas. It has been demonstrated that FMZ binding is reduced in epileptogenic foci that probably is correlated to a decrease in the affinity of the tracer to the receptor than in reduced receptor density alone. Foci of reduced FMZ binding may be found with a high sensitivity of up to 94% in TLE (RYVLIN et al. 1998). As the area of focally decreased FMZ binding probably indicates the epileptogenic zone to be resected to become seizure free (MUZIK et al. 2000; JUHASZ et al. 2001), the need for integration of FMZ into a multimodal approach for tailoring epilepsy resection becomes obvious. The coregistration of PET and SPECT findings to a volumetric MR image and their incorporation into an image-guided system has allowed surgeons to offer surgery to patients who may not previously have been considered eligible, with outcomes comparable to those in patients with more straightforward lesional epilepsy (MURPHY et al. 2004).

^{11}C -Alpha-methyl-tyrosine (AMT) is a marker of the serotonin synthesis capacity, and its uptake is elevated in tuberous sclerosis (CHUGANI et al. 1998).

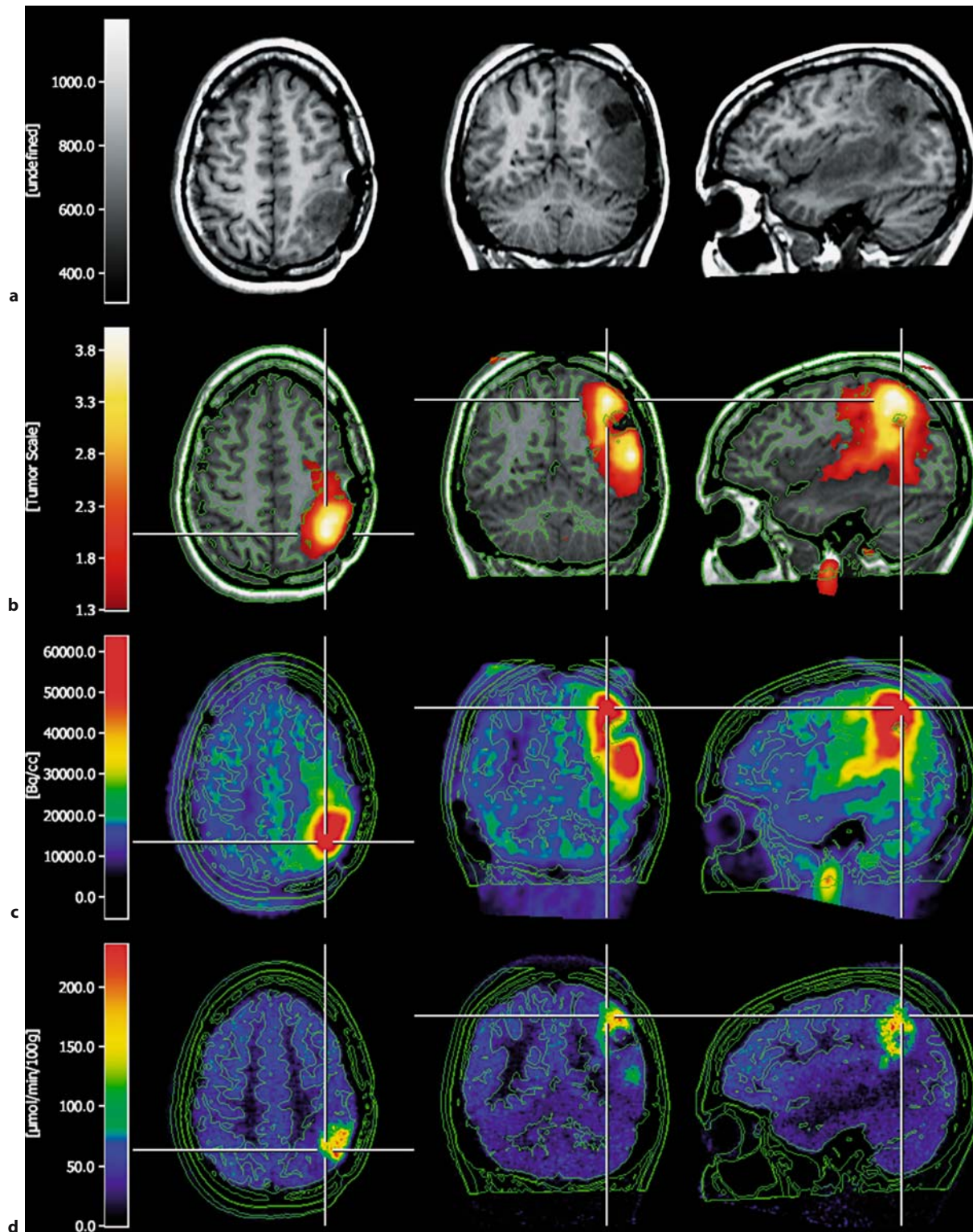


Fig. 8.3a-d. Example of presurgical multimodality imaging in a patient with glioblastoma multiforme. T1-weighted MRI (a), fused with the tumor-normalized MET-PET (b) within VINCI (Vollmar et al. 2004). The full range MET-PET is shown in c, the co-registered FDG-PET study in d. Two contours for quality control of the coregistration have been defined on the T1-weighted MRI. Observe that the FDG-PET also shows areas of increased glucose utilization; the corresponding regions in the MET-PET study are significantly larger. The FDG-PET study was performed on a HRRT brain scanner, the agreement of anatomical detail with the contour of the T1-weighted MRI is very good and due to its high resolution. (Images courtesy of Dr. S. Vollmar and Prof. Dr. K. Herholz, Max-Planck-Institut für Neurologische Forschung, Cologne, Germany, with kind permission)

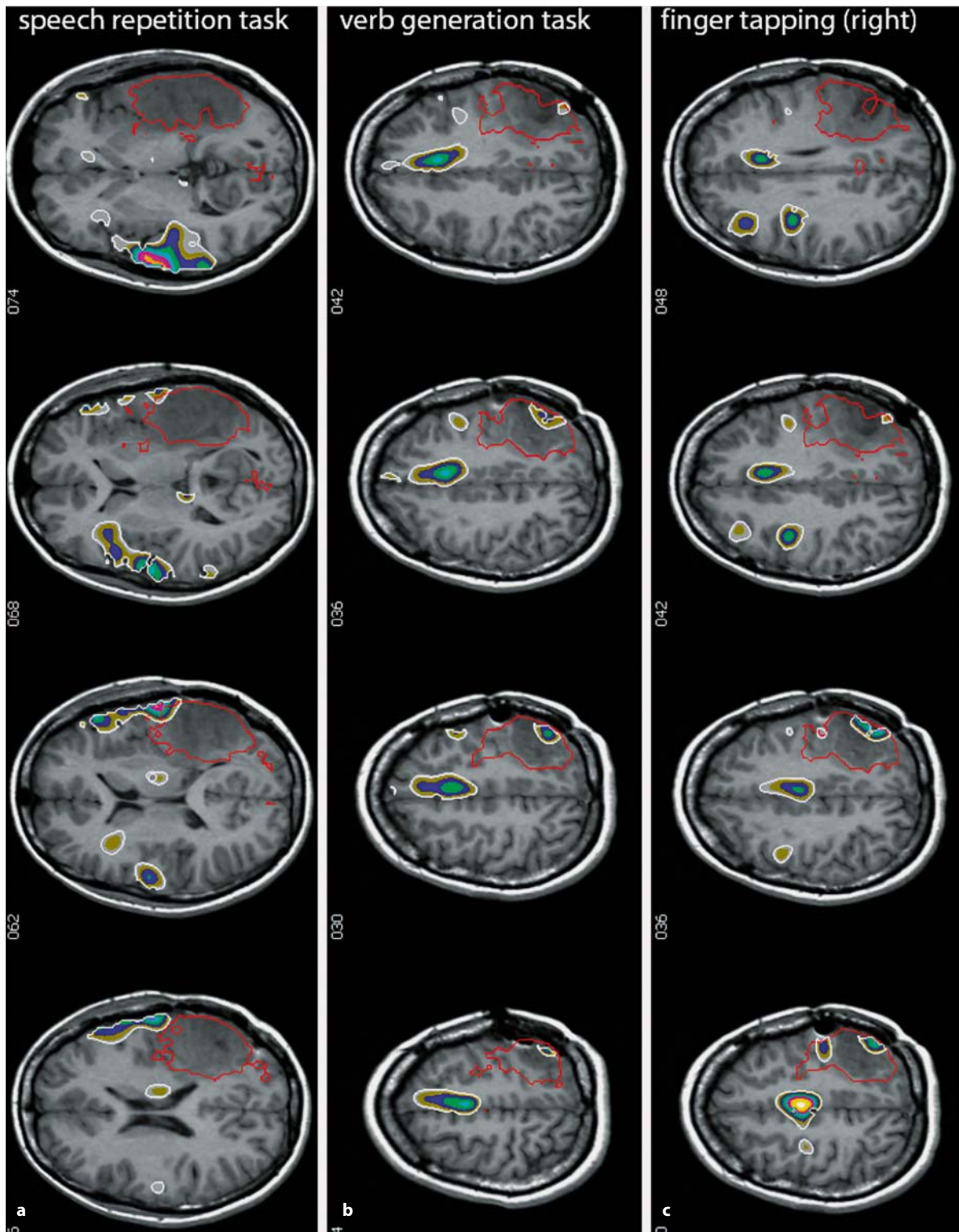


Fig. 8.4a–c. T1-weighted MRI of the same patient as in Fig. 8.1, fused with fPET activation studies. The red contour has been generated from the tumor-normalized MET-PET study and refers to 1.3-fold uptake (reported as being the tumor-specific cut-off). Observe that for some slices (e.g. 030, 042, second column) the area of this increased MET uptake is significantly larger than any visible changes in the MRI study. Both activations for language and motor skills show signals in the area of increased MET uptake and are consistent with a mild aphasia. (Images courtesy of Dr. S. Vollmar and Prof. Dr. K. Herholz,

In tuberous sclerosis, the multiplicity of tubers precludes the resection of all potentially epileptogenic tissue, and no MRI technique has yet proven to be able to differentiate epileptogenic from non-epileptogenic tubers. Recent work has shown that AMT-PET may detect specifically epileptogenic tubers in tuberous sclerosis (ASANO et al. 2000), in particular within a multimodality imaging approach (including video-EEG monitoring, FDG-PET, and different MRI techniques), and may even be helpful in the detection of cortical dysplasia (JUHASZ et al. 2003). AMT-PET may contribute to the presurgical planning of invasive electroencephalography by determining the localization and extent for the implantation of grid electrodes and consecutively for the definition of the resection volume. There are data suggesting that AMT-PET can detect non-resected epileptic foci in patients with previously failed neocortical resection and is improving outcome after reoperation of AMT positive tissue (Juhasz et al. 2004). Based on surgical outcome data, resection of tubers with increased AMT uptake yielded an optimal accuracy of 83% for detecting tubers that needed to be resected to achieve a seizure-free outcome. These findings suggest presurgical multimodal imaging for resection of tubers with increased AMT uptake is highly desirable to achieve seizure-free surgical outcome in children with tuberous sclerosis complex and intractable epilepsy (KAGAWA et al. 2005). One major drawback, however, is that radiosynthesis of AMT is complicated, and thus its use is still restricted to specialized PET centers.

8.2.3 Combination of MRI and MEG/EEG

Magnetoencephalography (MEG) is an analysis technique which uses electromagnetic signals to localize the source of biomagnetic fields derived from the intracellular electric current flows in the brain, thus providing direct information about neural activity (HAMALAINEN et al. 1993). One of the most important advantages of MEG is that its temporal resolution is very high (i.e., on the order of 1 ms) and is mainly restricted only by the sampling frequency of the recording system (LOUNASMAA et al. 1996). Since magnetic fields are not distorted by conduction inhomogeneities in the head, MEG is a potentially powerful localization tool of brain function, providing spatial discrimination below 5 mm. However, MEG has a fundamental source identi-

fication problem (inverse problem), determining the active site in the brain from the magnetic field pattern recorded outside the skull. Thus, some a priori assumptions must be made about the source. Usually, signal generators in the brain are described as current dipoles which are physiologically reasonable models for relatively small active cortical areas. MEG results can be directly co-registered to 3-D MRI; the merge of data obtained from MEG with anatomical MRI images is called magnetic source imaging (MSI), thus integrating the functional information of MEG with the structural information of MR (ORRISON 1999).

MEG is still a rare commodity due to the complex and cost-intensive technology. However, the potential of MSI for presurgical mapping of functionally important cortex has been extensively demonstrated. MSI can be used for decision-making and planning of surgical treatment in brain lesions (in particular tumors) in order to minimize postoperative deficits (GANSRANDT et al. 2002). The most frequently used application is MSI with motor evoked fields and somatosensory evoked fields for mapping of sensorimotor cortex in patients with lesions around the motor cortex (HUND et al. 1997; GANSRANDT et al. 1997, 1999) (Fig. 8.5). Also, the determination of primary visual cortex by the investigation of visual evoked fields was reported (GANSRANDT et al. 2004). For these purposes, mostly the single equivalent dipole model is sufficient in MEG data analysis. In more complex tasks such as those intended for language lateralization and localization, more differentiated models have to be used for source localization to simultaneously separate multiple sources of activity. Nevertheless, MSI has been successfully used for identification of the speech dominant hemisphere and functional mapping of speech-related brain areas (primary language areas) in individuals (KOBER et al. 2001a).

Based on these MSI protocols, the surgeons of the institutions where the investigations were performed in decided if the surgical removal of the lesion was possible anyway or which operative strategy had to be chosen. As strengthened by the authors of an overview of MSI application in 119 own glioma patients, a relatively high number of patients (46.2%) was not eligible for surgical therapy but received conservative treatment (GANSRANDT et al. 2004) – with respect to the lower frequency to postoperative neurological deficits than in other cohorts of glioma patients who did not undergo presurgical functional mapping, perhaps due to the more differentiated patient selec-

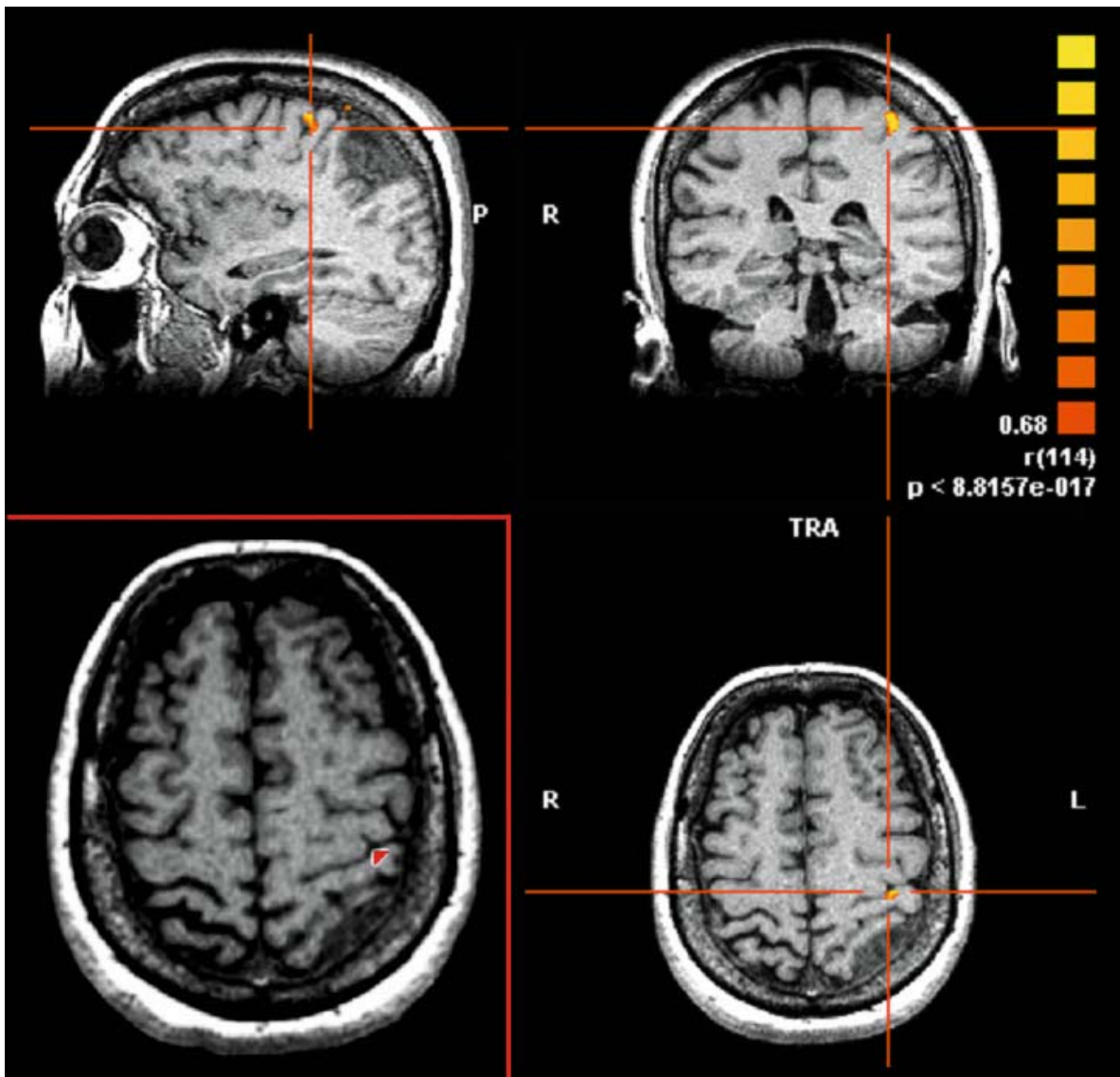


Fig. 8.5. Presurgical fMRI (central sulcus) (upper row and lower row, right: sagittal, coronal, and axial view of center of activation) and MSI (somatosensory evoked fields) in a patient with a glioma. (Images courtesy of PD Dr. Oliver Ganslandt, Dept. of Neurosurgery, University of Erlangen, Germany, with kind permission)

tion criteria. A large-scale direct comparison with different presurgical mapping protocols using, for example, fMRI with respect to the rates of patients not operated on, however, is missing.

MEG has the additional advantage of adding information to epilepsy surgery: beyond the presurgical identification of eloquent cortex (OSSENBLÖK et al. 2003), MEG has a potential to directly detect and localize epilepsy-associated activity (epileptic discharges), like EEG. That way, MSI is used for presurgical evaluation in epilepsy surgery to iden-

tify the brain tissue generating epileptic activity (EBERSOLE 1997; FISCHER et al. 2005); here, it was found to be an appropriate technique for temporal lobe epilepsy and even for extratemporal epilepsies as reported for a large case series by STEFAN et al. (2003). Furthermore, interictal spike localizations on MEG were found to be concordant with ictal and, where relevant, functional somatosensory mapping localizations (TANG et al. 2003). With respect to the multimodality approach, combined MEG and EEG acquisition and postprocessing can identify subcom-

partments of the temporal lobe involved in epileptic activity and may be helpful to differentiate between subtypes of mesial temporal lobe epilepsy noninvasively (PATARAIA et al. 2005). In another study, MEG and video-EEG results were equivalent in one-third of the cases, and additional localization information was obtained using MEG in 40% of the patients. The authors found MEG to be most useful for presurgical planning in patients who have either partially or nonlocalizing video-EEG results (PATARAIA et al. 2004). Although aspects of this study were criticized, it had to be admitted that MSI is another non-invasive tool that, when used in conjunction with further elements of the presurgical evaluation, can allow clinicians increased confidence in establishing an accurate localization in epilepsy surgery and may reduce the need for invasive intracranial monitoring (MARKS 2004).

With respect to the multimodality concept in the presurgical evaluation of functionally important cortex, a combination of techniques with basically different underlying neurophysiological correlates such as MEG/MSI and fMRI (see above) is not redundant but promising. Spatial comparisons between the localizational capability in particular of the sensorimotor cortex of MSI and fMRI have been performed by measurement of the distances between MEG and fMRI activation sites after coregistration and overlay onto the same anatomical 3-D MRI set, both in healthy subjects (STIPPICH et al. 1998) and in patients (KOBEL et al. 2001b). In both studies, the MSI and fMRI localization results were in agreement with respect to the gyrus which was localized; however, they showed different activation sites for the motor and sensory task within a range distance of 10 mm and 15 mm, probably as a reflection of the correlation between electrophysiological and hemodynamic responses. In a validation study of the same group, the MSI results were controlled for by the intraoperative cortical recording of somatosensory evoked potentials (so-called “phase reversal”), and the localizations in the pre- and postcentral gyrus were verified in each case (GANSLANDT et al. 1997). In a study with a similar technical approach using MEG and phase reversal technique in 30 patients with space-occupying lesions in or around the central region, MEG-based functional neuronavigation was also found to be practicable and useful in finding a safe approach to tumors in or adjacent to the central region (FIRSCHING et al. 2002).

Thus, although both modalities MSI and fMRI are useful for the estimation of the sensorimotor cortex,

a single modality may error in the exact topographical labeling and, if possible, a combination of both methods should be used in order to avoid neurological deficits in certain unclear cases (KOBEL et al. 2001b). Consecutively, the value of this integration of these two imaging modalities for spatiotemporal mapping of brain activity was strengthened in several publications (DALE and HALGREN 2001) and led to the co-integration of both techniques into presurgical protocols in specialized centers (GANSLANDT et al. 2002), especially in patients receiving epilepsy surgery (ASSAF et al. 2004; DUFFNER et al. 2003; KNAKE et al. 2004). It is useful to perform postprocessing of MEG and fMRI data in one software environment in that context to avoid potential methodologically based problems, as previously suggested (DALE et al. 2000). For that purpose of integration of fMRI, 3-D MRI and MSI in one unique coordinate frame, the activation achieved by fMRI analysis can be used as possible sites of current sources for the MEG source

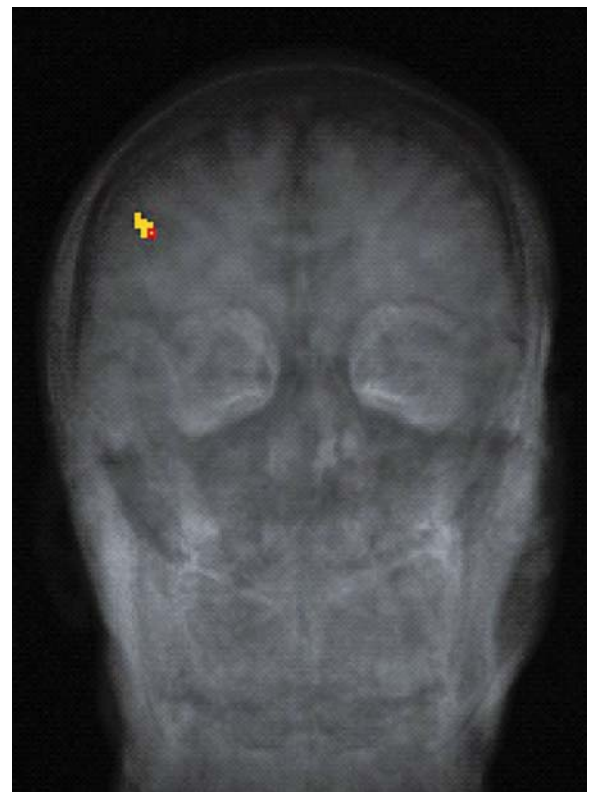


Fig. 8.6. fMRI and MSI co-localization (motor paradigm) within one unique coordinate plane (OMEGA) in a coronal glass brain view (MÜLLER et al. 2005). Yellow clusters of fMRI activation are used as possible sites of current sources for MEG source reconstruction (red dipole)

reconstruction as an elegant approach for multimodality integration which was suggested by the “Open Magnetic and Electric Graphic Analysis (OMEGA)” software (MÜLLER et al. 2005) (Fig. 8.6).

As a further continuation of the multimodal presurgical concept, information about the metabolic, hemodynamic and electrical activity of the brain and also the verification of one imaging modality with the other might be achieved by the combination of MEG/MSI and functional MRS (RAMON et al. 2004).

8.3

Advantages and Limitations of Multimodal Functional Neuroimaging

The combination of different non-invasive neuroimaging tools and their co-integration into frameless stereotaxy/neuronavigational systems after registration is an important and valuable element of presurgical diagnostics. Here, various technical approaches such as fMRI techniques, DTI, MRS, PET, SPECT, and MEG/MSI were reviewed together with options of useful combinations. It has to be kept in mind that additional techniques exist such as (multi-channel) EEG which is a major presurgical diagnostic element of epilepsy surgery but is rarely used for direct source coregistration with MRI and neuronavigation and was therefore not commented on, although in particular the spatio-temporal relationship between MSI and EEG in epileptic focus localization has been subject to several studies (LEIJTEN et al. 2003), as well as the combination of EEG and fMRI (LANTZ et al. 2001; cf. Chap. 5). Furthermore, the technique of functional transcranial magnetic stimulation might provide an additional tool to add presurgical information (KRINGS et al. 2001b).

The use of neuronavigational systems together with presurgical neuroimaging in surgical planning and realization has been shown to be a safe and reliable instrument (WINKLER et al. 2004), in particular in lesions which are hard to delineate or which are located adjacent to functionally important areas. Of course, the presurgically acquired data reflect only the status before the start of the intervention and may change intraoperatively, causing incongruence between neuroimaging results and situs. The surgeon has to be aware of this fact – alternatively, there

are solutions for real-time imaging for instance by the advanced but expensive implementation of intraoperative open MRI systems (NIMSKY et al. 2004, 2005a, d), either as a low-field or as a high-field (1.5 Tesla) system. Furthermore, immanent sources of error require continuous critical reevaluation, i.e. the exactness of the localization process itself and the postprocessing algorithms.

With respect to cost effectiveness and the burden of often time-consuming data acquisition procedures in critically ill patients, multimodality presurgical imaging does not necessarily mean “the more, the better”. Some options are complementary, such as techniques for the localization of eloquent cortex (fMRI or MSI, respectively) and techniques for the imaging of white matter fiber bundles (DTI). For the methods of imaging cortical areas it has to be held that fMRI can be performed on most regular clinical MRI scanners, whereas MSI, although it seems to be a promising technique, is still limited due to the low distribution of MEG devices which will most probably not much increase over the coming years. Nuclear medicine techniques in the sense of (multi-) ligand imaging are valuable tools in the delineation of cerebral neoplasms and may be complemented by MRS. Therefore, the particular information which is imperatively needed preoperatively in the individual patient should guide the clinician to choose from the available techniques. Will different neuroimaging modalities be used, one has to be aware that the fusion of the results of these techniques is possible after co-registration, but that equivalent co-localizations in the ideal neuroanatomical sense are very difficult to achieve and sometimes impossible due to different neurophysiological substrates, acquisition methods, and spatial resolution.

References

- Antel SB, Bernasconi A, Bernasconi N, Collins DL, Kearney RE, Shinghal R, Arnold DL (2002a) Computational models of MRI characteristics of focal cortical dysplasia improve lesion detection. *Neuroimage* 17:1755–1760
- Antel SB, Li LM, Cendes F, Collins DL, Kearney RE, Shinghal R, Arnold DL (2002b) Predicting surgical outcome in temporal lobe epilepsy patients using MRI and MRSI. *Neurology* 58:1505–1512
- Asano E, Chugani DC, Muzik O, Shen C, Juhasz C, Janisse J, Ager J, Canady A, Shah JR, Shah AK, Watson C, Chugani HT (2000) Multimodality imaging for improved detection of epileptogenic foci in tuberous sclerosis complex. *Neurology* 54:1976–1984

- Ashburner J, Csernansky JG, Davatzikos C, Fox NC, Frisoni GB, Thompson PM (2003) Computer-assisted imaging to assess brain structure in healthy and diseased brains. *Lancet Neurol* 2:79–88
- Ashburner J, Friston KJ (2000) Voxel-based morphometry – the methods. *Neuroimage* 11:805–821
- Assaf BA, Karkar KM, Laxer KD, Garcia PA, Austin EJ, Barbaro NM, Aminoff MJ (2004) Magnetoencephalography source localization and surgical outcome in temporal lobe epilepsy. *Clin Neurophysiol* 115:2066–2076
- Barker PB (2005) Fundamentals of MR spectroscopy. In: Gillard J, Waldman A, Barker P (eds.) *Clinical MR neuroimaging*. Cambridge University Press, vol 7, p 26
- Basser PJ, Jones DK (2002) Diffusion-tensor MRI: theory, experimental design and data analysis – a technical review. *NMR Biomed* 15:456–467
- Bergstrom M, Collins VP, Ehrin E, Ericson K, Eriksson L, Greitz T, Halldin C, von Holst H, Langstrom B, Lilja A (1983) Discrepancies in brain tumor extent as shown by computed tomography and positron emission tomography using [68Ga]EDTA, [11C]glucose, and [11C]methionine. *J Comput Assist Tomogr* 7:1062–1066
- Braun V, Dempf S, Tomczak R, Wunderlich A, Weller R, Richter HP (2000) Functional cranial neuronavigation. Direct integration of fMRI and PET data. *J Neuroradiol* 27:157–163
- Braun V, Dempf S, Weller R, Reske SN, Schachenmayr W, Richter HP (2002) Cranial neuronavigation with direct integration of (11)C methionine positron emission tomography (PET) data – results of a pilot study in 32 surgical cases. *Acta Neurochir (Wien)* 144:777–782
- Brett M, Johnsrude IS, Owen AM (2002) The problem of functional localization in the human brain. *Nat Rev Neurosci* 3:243–249
- Cendes F, Caramanos Z, Andermann F, Dubeau F, Arnold DL (1997) Proton magnetic resonance spectroscopic imaging and magnetic resonance imaging volumetry in the lateralization of temporal lobe epilepsy: a series of 100 patients. *Ann Neurol* 42:737–746
- Chenevert TL, Stegman LD, Taylor JM, Robertson PL, Greenberg HS, Rehemtulla A, Ross BD (2000) Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. *J Natl Cancer Inst* 92:2029–2036
- Chenevert TL, Meyer CR, Moffat BA, Rehemtulla A, Mukherji SK, Gebarski SS, Quint DJ, Robertson PL, Lawrence TS, Junck L, Taylor JM, Johnson TD, Dong Q, Muraszko KM, Brunberg JA, Ross BD (2002) Diffusion MRI: a new strategy for assessment of cancer therapeutic efficacy. *Mol Imaging* 1:336–343
- Chugani DC, Chugani HT, Muzik O, Shah JR, Shah AK, Canady A, Mangner TJ, Chakraborty PK (1998) Imaging epileptogenic tubers in children with tuberous sclerosis complex using alpha-[11C]methyl-L-tryptophan positron emission tomography. *Ann Neurol* 44:858–866
- Cizek J, Herholz K, Vollmar S, Klein J, Schrader R, Heiss WD (2004) Fast and robust registration of PET and MR images. *Neuroimage* 22:434–442
- Clark CA, Barrick TR, Murphy MM, Bell BA (2003) White matter fiber tracking in patients with space-occupying lesions of the brain: a new technique for neurosurgical planning? *Neuroimage* 20:1601–1608
- Coenen VA, Huber KK, Krings T, Weidemann J, Gilsbach JM, Rohde V (2005) Diffusion-weighted imaging-guided resection of intracerebral lesions involving the optic radiation. *Neurosurg Rev* 28:188–195
- Cross JH (2003) Functional neuroimaging of malformations of cortical development. *Epileptic Disord* 5(2):S73–S80
- Dale AM, Liu AK, Fischl BR, Buckner RL, Belliveau JW, Lewine JD, Halgren E (2000) Dynamic statistical parametric mapping: combining fMRI and MEG for high-resolution imaging of cortical activity. *Neuron* 26:55–67
- Dale AM, Halgren E (2001) Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. *Curr Opin Neurobiol* 11:202–208
- Duffner F, Freudenstein D, Schiffbauer H, Preissl H, Siekmann R, Birbaumer N, Grote EH (2003). Combining MEG and MRI with neuronavigation for treatment of an epileptiform spike focus in the precentral region: a technical case report. *Surg Neurol* 59:40–45
- Ebersole JS (1997) Magnetoencephalography/magnetic source imaging in the assessment of patients with epilepsy. *Epilepsia* 38(4):S1–S5
- Ericson K, Lilja A, Bergstrom M, Collins VP, Eriksson L, Ehrin E, von Holst H, Lundqvist H, Langstrom B, Mosskin M (1985) Positron emission tomography with ([11C]methyl)-L-methionine, [11C]D-glucose, and [68Ga]EDTA in supratentorial tumors. *J Comput Assist Tomogr* 9:683–689
- Firsching R, Bondar I, Heinze HJ, Hinrichs H, Hagner T, Heinrich J, Belau A (2002) Practicability of magnetoencephalography-guided neuronavigation. *Neurosurg Rev* 25:73–78
- Fischer MJ, Scheler G, Stefan H (2005) Utilization of magnetoencephalography results to obtain favourable outcomes in epilepsy surgery. *Brain* 128:153–157
- Ganslandt O, Steinmeier R, Kober H, Vieth J, Kassubek J, Romstock J, Strauss C, Fahlbusch R (1997) Magnetic source imaging combined with image-guided frameless stereotaxy: a new method in surgery around the motor strip. *Neurosurgery* 41:621–627
- Ganslandt O, Fahlbusch R, Nimsky C, Kober H, Moller M, Steinmeier R, Romstock J, Vieth J (1999) Functional neuronavigation with magnetoencephalography: outcome in 50 patients with lesions around the motor cortex. *J Neurosurg* 91:73–79
- Ganslandt O, Fahlbusch R, Kober H, Gralla J, Nimsky C (2002) [Use of magnetoencephalography and functional neuronavigation in planning and surgery of brain tumors]. *Nervenarzt* 73:155–161
- Ganslandt O, Buchfelder M, Hastreiter P, Grummich P, Fahlbusch R, Nimsky C (2004) Magnetic source imaging supports clinical decision making in glioma patients. *Clin Neurol Neurosurg* 107:20–26
- Ganslandt O, Stadlbauer A, Fahlbusch R, Kamada K, Buslei R, Blumcke I, Moser E, Nimsky C (2005) Proton magnetic resonance spectroscopic imaging integrated into image-guided surgery: correlation to standard magnetic resonance imaging and tumor cell density. *Neurosurgery* 56(Suppl):291–298
- Goldman S, Levivier M, Pirotte B, Brucher JM, Wikler D, Damhaut P, Dethy S, Brotchi J, Hildebrand J (1997) Regional methionine and glucose uptake in high-grade gliomas: a comparative study on PET-guided stereotactic biopsy. *J Nucl Med* 38:1459–1462
- Good CD, Ashburner J, Frackowiak RS (2001a) Computational neuroanatomy: new perspectives for neuroradiology. *Rev Neurol (Paris)* 157:797–806

- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001b) A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14:21–36
- Gossmann A, Helbich TH, Kuriyama N, Ostrowitzki S, Roberts TP, Shames DM, van Bruggen N, Wendland MF, Israel MA, Brasch RC (2002) Dynamic contrast-enhanced magnetic resonance imaging as a surrogate marker of tumor response to anti-angiogenic therapy in a xenograft model of glioblastoma multiforme. *J Magn Reson Imaging* 15:233–240
- Grosu AL, Lachner R, Wiedenmann N, Stark S, Thamm R, Kneschaurek P, Schwaiger M, Molls M, Weber WA (2003) Validation of a method for automatic image fusion (BrainLAB System) of CT data and 11C-methionine-PET data for stereotactic radiotherapy using a LINAC: first clinical experience. *Int J Radiat Oncol Biol Phys* 56:1450–1463
- Guye M, Ranjeva JP, Le Fur Y, Bartolomei F, Confort-Gouny S, Regis J, Chauvel P, Cozzzone PJ (2005) 1H-MRS imaging in intractable frontal lobe epilepsies characterized by depth electrode recording. *Neuroimage* 26:1174–1183
- Hamalainen M, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV (1993) Magnetoencephalography – theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev Mod Phys* 65:413–497
- Hendler T, Pianka P, Sigal M, Kafri M, Ben-Bashat D, Constantini S, Graif M, Fried I, Assaf Y (2003) Delineating gray and white matter involvement in brain lesions: three-dimensional alignment of functional magnetic resonance and diffusion-tensor imaging. *J Neurosurg* 99:1018–1027
- Herholz K, Reulen HJ, von Stockhausen HM, Thiel A, Ilmberger J, Kessler J, Eisner W, Yousry TA, Heiss WD (1997) Preoperative activation and intraoperative stimulation of language-related areas in patients with glioma. *Neurosurgery* 41:1253–1260
- Herholz K, Holzer T, Bauer B, Schroder R, Voges J, Ernestus RI, Mendoza G, Weber-Luxemburger G, Lottgen J, Thiel A, Wienhard K, Heiss WD (1998) 11C-methionine PET for differential diagnosis of low-grade gliomas. *Neurology* 50:1316–1322
- Hund M, Rezai AR, Kronberg E, Cappell J, Zonenshayn M, Ribary U, Kelly PJ, Llinas R (1997) Magnetoencephalographic mapping: basic of a new functional risk profile in the selection of patients with cortical brain lesions. *Neurosurgery* 40:936–942
- Huppertz HJ, Grimm C, Fauser S, Kassubek J, Mader I, Hochmuth A, Spreer J, Schulze-Bonhage A (2005) Enhanced visualization of blurred gray-white matter junctions in focal cortical dysplasia by voxel-based 3D MRI analysis. *Epilepsy Res* 67:35–50
- Jacobs AH, Kracht LW, Gossmann A, Ruger MA, Thomas AV, Thiel A, Herholz K (2005) Imaging in neurooncology. *NeuroRx* 2:333–347
- Juengling FD, Kassubek J (2002) [Nuclear medicine imaging in epilepsy diagnostics – I: perfusion and metabolism.]. *Nervenheilkunde* 21:420–425
- Juhasz C, Chugani DC, Muzik O, Shah A, Shah J, Watson C, Canady A, Chugani HT (2001) Relationship of flumazenil and glucose PET abnormalities to neocortical epilepsy surgery outcome. *Neurology* 56:1650–1658
- Juhasz C, Chugani DC, Muzik O, Shah A, Asano E, Mangner TJ, Chakraborty PK, Sood S, Chugani HT (2003) Alpha-methyl-L-tryptophan PET detects epileptogenic cortex in children with intractable epilepsy. *Neurology* 60:960–968
- Juhasz C, Chugani DC, Padhye UN, Muzik O, Shah A, Asano E, Mangner TJ, Chakraborty PK, Sood S, Chugani HT (2004) Evaluation with alpha-[11C]methyl-L-tryptophan positron emission tomography for reoperation after failed epilepsy surgery. *Epilepsia* 45:124–130
- Kagawa K, Chugani DC, Asano E, Juhasz C, Muzik O, Shah A, Shah J, Sood S, Kupsky WJ, Mangner TJ, Chakraborty PK, Chugani HT (2005) Epilepsy surgery outcome in children with tuberous sclerosis complex evaluated with alpha-[11C]methyl-L-tryptophan positron emission tomography (PET). *J Child Neurol* 20:429–438
- Kaplan AM, Bandy DJ, Manwaring KH, Chen K, Lawson MA, Moss SD, Duncan JD, Wodrich DL, Schnur JA, Reiman EM (1999) Functional brain mapping using positron emission tomography scanning in preoperative neurosurgical planning for pediatric brain tumors. *J Neurosurg* 91:797–803
- Kassubek J, Juengling FD, Otte A (2000) Improved interpretation of cerebral PET with respect to structural MRI changes using combined voxel-based statistical mapping. *Eur J Nucl Med* 27:880
- Kassubek J, Huppertz HJ, Spreer J, Schulze-Bonhage A (2002) Detection and localization of focal cortical dysplasia by voxel-based 3-D MRI analysis. *Epilepsia* 43:596–602
- Kassubek J, Juengling FD (2002) [Nuclear medicine imaging in epilepsy diagnostics – II: receptor diagnostics and functional imaging]. *Nervenheilkunde* 21:475–481
- Knake S, Grant PE, Stufflebeam SM, Wald LL, Shiraishi H, Rosenow F, Schomer DL, Fischl B, Dale AM, Halgren E (2004) Aids to telemetry in the presurgical evaluation of epilepsy patients: MRI, MEG and other non-invasive imaging techniques. *Suppl Clin Neurophysiol* 57:494–502
- Knowlton RC, Laxer KD, Ende G, Hawkins RA, Wong ST, Matson GB, Rowley HA, Fein G, Weiner MW (1997) Presurgical multimodality neuroimaging in electroencephalographic lateralized temporal lobe epilepsy. *Ann Neurol* 42:829–837
- Knowlton RC (2004) Multimodality imaging in partial epilepsies. *Curr Opin Neurol* 17:165–172
- Kober H, Moller M, Nimsky C, Vieth J, Fahlbusch R, Ganslandt O (2001a) New approach to localize speech relevant brain areas and hemispheric dominance using spatially filtered magnetoencephalography. *Hum Brain Mapp* 14:236–250
- Kober H, Nimsky C, Moller M, Hastreiter P, Fahlbusch R, Ganslandt O (2001b) Correlation of sensorimotor activation with functional magnetic resonance imaging and magnetoencephalography in presurgical functional imaging: a spatial analysis. *Neuroimage* 14:1214–1228
- Koepp MJ, Labbe C, Richardson MP, Brooks DJ, Van Paesschen W, Cunningham VJ, Duncan JS (1997) Regional hippocampal [11C]flumazenil PET in temporal lobe epilepsy with unilateral and bilateral hippocampal sclerosis. *Brain* 120:1865–1876
- Koepp MJ, Woermann FG (2005) Imaging structure and function in refractory focal epilepsy. *Lancet Neurol* 4:42–53
- Kracht LW, Friese M, Herholz K, Schroeder R, Bauer B, Jacobs A, Heiss WD (2003) Methyl-[11C]-l-methionine uptake as measured by positron emission tomography correlates to

- microvessel density in patients with glioma. *Eur J Nucl Med Mol Imaging* 30:868–873
- Kracht LW, Miletic H, Busch S, Jacobs AH, Voges J, Hoevels M, Klein JC, Herholz K, Heiss WD (2004) Delineation of brain tumor extent with [11C]L-methionine positron emission tomography: local comparison with stereotactic histopathology. *Clin Cancer Res* 10:7163–7170
- Krakow K, Wiesmann UC, Woermann FG, Symms MR, McLean MA, Lemieux L, Allen PJ, Barker GJ, Fish DR, Duncan JS (1999) Multimodal MR imaging: functional, diffusion tensor, and chemical shift imaging in a patient with localization-related epilepsy. *Epilepsia* 40:1459–1462
- Krings T, Schreckenberger M, Rohde V, Foltys H, Spetzger U, Sabri O, Reinges MH, Kemeny S, Meyer PT, Moller-Hartmann W, Korinth M, Gilsbach JM, Buell U, Thron A (2001a) Metabolic and electrophysiological validation of functional MRI. *J Neurol Neurosurg Psychiatry* 71:762–771
- Krings T, Foltys H, Reinges MH, Kemeny S, Rohde V, Spetzger U, Gilsbach JM, Thron A (2001b) Navigated transcranial magnetic stimulation for presurgical planning – correlation with functional MRI. *Minim Invasive Neurosurg* 44:234–239
- Lantz G, Spinelli L, Menendez RG, Seeck M, Michel CM (2001) Localization of distributed sources and comparison with functional MRI. *Epileptic Disord (Special Issue)*:45–58
- Le Bihan D, van Zijl P (2002) From the diffusion coefficient to the diffusion tensor. *NMR Biomed* 15:431–434
- Leijten FS, Huiskamp GJ, Hilgersom I, Van Huffelen AC (2003) High-resolution source imaging in mesiotemporal lobe epilepsy: a comparison between MEG and simultaneous EEG. *J Clin Neurophysiol* 20:227–238
- Leijten FS, Ramsey NF, Van Rijen PC (2004) Function localisation in neurosurgery: new tools, new practices? *Clin Neurol Neurosurg* 107:17–19
- Levivier M, Goldman S, Pirotte B, Brucher JM, Baleriaux D, Luxen A, Hildebrand J, Brotschi J (1995) Diagnostic yield of stereotactic brain biopsy guided by positron emission tomography with [18F]fluorodeoxyglucose. *J Neurosurg* 82:445–452
- Lounasmaa OV, Hamalainen M, Hari R, Salmelin R (1996) Information processing in the human brain: magnetoencephalographic approach. *Proc Natl Acad Sci USA* 93:8809–8815
- Marks WJ Jr (2004) Utility of MEG in presurgical localization. *Epilepsy Curr* 4:208–209
- Mazziotta JC (2000) Preoperative brain mapping. In: Mazziotta JC, Toga AW, Frackowiak RSJ (eds.) *Brain mapping: the disorders*. Academic Press, San Diego, pp 59–76
- Mehta S, Grabowski TJ, Trivedi Y, Damasio H (2003) Evaluation of voxel-based morphometry for focal lesion detection in individuals. *Neuroimage* 20:1438–1454
- Mori S, van Zijl PC (2002) Fiber tracking: principles and strategies – a technical review. *NMR Biomed* 15:468–480
- Moskkin M, Ericson K, Hindmarsh T, von Holst H, Collins VP, Bergstrom M, Eriksson L, Johnstrom P (1989) Positron emission tomography compared with magnetic resonance imaging and computed tomography in supratentorial gliomas using multiple stereotactic biopsies as reference. *Acta Radiol* 30:225–232
- Müller HP, DeCesaris I, DeMelis M, Marzetti L, Pasquarelli A, Erne SN, Ludolph AC, Kassubek J (2005) Open magnetic and electric graphic analysis. *IEEE Eng Med Biol Mag* 24:109–116
- Murphy MA, O'Brien TJ, Morris K, Cook MJ (2004) Multimodality image-guided surgery for the treatment of medically refractory epilepsy. *J Neurosurg* 100:452–462
- Muzik O, da Silva EA, Juhasz C, Chugani DC, Shah J, Nagy F, Canady A, von Stockhausen HM, Herholz K, Gates J, Frost M, Ritter F, Watson C, Chugani HT (2000) Intracranial EEG versus flumazenil and glucose PET in children with extratemporal lobe epilepsy. *Neurology* 54:171–179
- Muzik O, Pourabdollah S, Juhasz C, Chugani DC, Janisse J, Draghici S (2005) Application of an objective method for localizing bilateral cortical FDG PET abnormalities to guide the resection of epileptic foci. *IEEE Trans Biomed Eng* 52:1574–1581
- Nimsky C, Ganslandt O, Von Keller B, Romstock J, Fahlbusch R (2004) Intraoperative high-field-strength MR imaging: implementation and experience in 200 patients. *Radiology* 233:67–78
- Nimsky C, Ganslandt O, Fahlbusch R (2005a) 1.5 T: intraoperative imaging beyond standard anatomic imaging. *Neurosurg Clin N Am* 16:185–200, vii
- Nimsky C, Grummich P, Sorensen AG, Fahlbusch R, Ganslandt O (2005b) Visualization of the pyramidal tract in glioma surgery by integrating diffusion tensor imaging in functional neuronavigation. *Zentralbl Neurochir* 66:133–141
- Nimsky C, Ganslandt O, Hastreiter P, Wang R, Benner T, Sorensen AG, Fahlbusch R (2005c) Preoperative and intraoperative diffusion tensor imaging-based fiber tracking in glioma surgery. *Neurosurgery* 56:130–137
- Nimsky C, Ganslandt O, Hastreiter P, Wang R, Benner T, Sorensen AG, Fahlbusch R (2005d) Intraoperative diffusion-tensor MR imaging: shifting of white matter tracts during neurosurgical procedures – initial experience. *Radiology* 234:218–225
- O'Brien TJ, So EL, Cascino GD, Hauser MF, Marsh WR, Meyer FB, Shalhough FW, Mullan BP (2004) Subtraction SPECT coregistered to MRI in focal malformations of cortical development: localization of the epileptogenic zone in epilepsy surgery candidates. *Epilepsia* 45:367–376
- Ogawa T, Shishido F, Kanno I, Inugami A, Fujita H, Murakami M, Shimosegawa E, Ito H, Hatazawa J, Okudera T (1993) Cerebral glioma: evaluation with methionine PET. *Radiology* 186:45–53
- Orrison WW Jr (1999) Magnetic source imaging in stereotactic and functional neurosurgery. *Stereotact Funct Neurosurg* 72:89–94
- Ossenblok P, Leijten FS, de Munck JC, Huiskamp GJ, Barkhof F, Boon P (2003) Magnetic source imaging contributes to the presurgical identification of sensorimotor cortex in patients with frontal lobe epilepsy. *Clin Neurophysiol* 114:221–232
- Patarai E, Simos PG, Castillo EM, Billingsley RL, Sarkari S, Wheless JW, Maggio V, Maggio W, Baumgartner JE, Swank PR, Breier JI, Papanicolaou AC (2004) Does magnetoencephalography add to scalp video-EEG as a diagnostic tool in epilepsy surgery? *Neurology* 62:943–948
- Patarai E, Lindinger G, Deecke L, Mayer D, Baumgartner C (2005) Combined MEG/EEG analysis of the interictal spike complex in mesial temporal lobe epilepsy. *Neuroimage* 24:607–614
- Pirotte B, Goldman S, Salzberg S, Wikler D, David P, Vandestee A, Van Bogaert P, Salmon I, Brotschi J, Levivier

- M (2003) Combined positron emission tomography and magnetic resonance imaging for the planning of stereotactic brain biopsies in children: experience in 9 cases. *Pediatr Neurosurg* 38:146–155
- Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Koepp MJ, Duncan JS (2005) MR tractography predicts visual field defects following temporal lobe resection. *Neurology* 65:596–599
- Ramon C, Haueisen J, Richards T, Maravilla K (2004) Multimodal imaging of somatosensory evoked cortical activity. *Neurol Clin Neurophysiol* 2004:96
- Reinges MH, Krings T, Meyer PT, Schreckenberger M, Rohde V, Weidemann J, Sabri O, Mulders EJ, Buell U, Thron A, Gilsbach JM (2004) Preoperative mapping of cortical motor function: prospective comparison of functional magnetic resonance imaging and [15O]-H₂O-positron emission tomography in the same co-ordinate system. *Nucl Med Commun* 25:987–997
- Ribom D, Eriksson A, Hartman M, Engler H, Nilsson A, Langstrom B, Bolander H, Bergstrom M, Smits A (2001) Positron emission tomography ¹¹C-methionine and survival in patients with low-grade gliomas. *Cancer* 92:1541–1549
- Richardson MP, Friston KJ, Sisodiya SM, Koepp MJ, Ashburner J, Free SL, Brooks DJ, Duncan JS (1997) Cortical grey matter and benzodiazepine receptors in malformations of cortical development. A voxel-based comparison of structural and functional imaging data. *Brain* 120:1961–1973
- Rohde V, Spangenberg P, Mayfrank L, Reinges M, Gilsbach JM, Coenen VA (2005) Advanced neuronavigation in skull base tumors and vascular lesions. *Minim Invasive Neurosurg* 48:13–18
- Ryvlin P, Bouvard S, Le Bars D, De Lamerie G, Gregoire MC, Kahane P, Froment JC, Mauguire F (1998) Clinical utility of flumazenil-PET versus [18F]fluorodeoxyglucose-PET and MRI in refractory partial epilepsy. A prospective study in 100 patients. *Brain* 121:2067–2081
- Sinha S, Bastin ME, Whittle IR, Wardlaw JM (2002) Diffusion tensor MR imaging of high-grade cerebral gliomas. *AJNR Am J Neuroradiol* 23:520–527
- Sporns O, Tononi G, Edelman GM (2000) Connectivity and complexity: the relationship between neuroanatomy and brain dynamics. *Neural Netw* 13:909–922
- Stefan H, Hummel C, Scheler G, Genow A, Druschky K, Tilz C, Kaltenhauser M, Hopfengartner R, Buchfelder M, Romstock J (2003) Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases. *Brain* 126:2396–2405
- Stippich C, Freitag P, Kassubek J, Soros P, Kamada K, Kober H, Scheffler K, Hopfengartner R, Bilecen D, Radu EW, Vieth JB (1998) Motor, somatosensory and auditory cortex localization by fMRI and MEG. *Neuroreport* 9:1953–1957
- Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Thieme, New York
- Tang L, Mantle M, Ferrari P, Schiffbauer H, Rowley HA, Barbaro NM, Berger MS, Roberts TP (2003) Consistency of interictal and ictal onset localization using magnetoencephalography in patients with partial epilepsy. *J Neurosurg* 98:837–845
- Thiel A, Herholz K, von Stockhausen HM, van Leyen-Pilgram K, Pietrzyk U, Kessler J, Wienhard K, Klug N, Heiss WD (1998) Localization of language-related cortex with 15O-labeled water PET in patients with gliomas. *Neuroimage* 7:284–295
- Toga AW, Ojemann GA, Ojemann JG, Cannestra AF (2000) Intraoperative brain mapping. In: Mazziotta JC, Toga AW, Frackowiak RSJ (eds) *Brain mapping: the disorders*. Academic Press, San Diego, pp 77–105
- Trabesinger AH, Meier D, Boesiger P (2003) In vivo ¹H NMR spectroscopy of individual human brain metabolites at moderate field strengths. *Magn Reson Imaging* 21:1295–1302
- Tuch DS, Reese TG, Wiegell MR, Wedeen VJ (2003) Diffusion MRI of complex neural architecture. *Neuron* 40:885–895
- Turkington TG, Hoffman JM, Jaszczak RJ, MacFall JR, Harris CC, Kilts CD, Pelizzari CA, Coleman RE (1995) Accuracy of surface fit registration for PET and MR brain images using full and incomplete brain surfaces. *J Comput Assist Tomogr* 19:117–124
- Ulmer JL, Salvan CV, Mueller WM, Krouwer HG, Stroe GO, Aralasmak A, Prost RW (2004) The role of diffusion tensor imaging in establishing the proximity of tumor borders to functional brain systems: implications for preoperative risk assessments and postoperative outcomes. *Technol Cancer Res Treat* 3:567–576
- Vigneron D, Bollen A, McDermott M, Wald L, Day M, Moyher-Noworolski S, Henry R, Chang S, Berger M, Dillon W, Nelson S (2001) Three-dimensional magnetic resonance spectroscopic imaging of histologically confirmed brain tumors. *Magn Reson Imaging* 19:89–101
- Vinas FC, Zamorano L, Mueller RA, Jiang Z, Chugani H, Fuerst D, Muzik O, Mangner TJ, Diaz FG (1997) [15O]-water PET and intraoperative brain mapping: a comparison in the localization of eloquent cortex. *Neurol Res* 19:601–608
- Vollmar S, Cizek J, Sue M, Klein J, Jacobs A, Herholz K (2004) VINCI – Volume Imaging in Neurological Research, Co-Registration and ROIs included. In: Kremer K, Macho V (eds) *Forschung und wissenschaftliches Rechnen 2003*. Göttingen: Gesellschaft für wissenschaftliche Datenverarbeitung, pp 115–131
- Vollmar S (2006) Integration of functional imaging (PET) to surgery planning in brain tumors. PhD thesis, University of Cologne
- Wiest R, Kassubek J, Schindler K, Loher TJ, Kiefer C, Mariani L, Wissmeyer M, Schroth G, Mathis J, Weder B, Juengling FD (2005) Comparison of voxel-based 3-D MRI analysis and subtraction ictal SPECT coregistered to MRI in focal epilepsy. *Epilepsy Res* 65:125–133
- Winkler D, Strauss G, Hesse S, Goldammer A, Hund-Georgiadis M, Richter A, Sabri O, Kahn T, Meixensberger J (2004) [Preoperative imaging as the basis for image-guided neurosurgery]. *Radiologe* 44:723–732
- Witwer BP, Moftakhar R, Hasan KM, Deshmukh P, Haughton V, Field A, Arfanakis K, Noyes J, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, Badie B (2002) Diffusion-tensor imaging of white matter tracts in patients with cerebral neoplasm. *J Neurosurg* 97:568–575

Brain Plasticity and fMRI

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9.1 Introduction

Throughout the entire lifespan the brain exhibits the remarkable capacity to change and adapt in response to its own needs as well as in response to novel experiences and environmental factors (for an extensive recent review see PASCUAL-LEONE et al. 2005). Distributed neuronal networks can be reshaped in order to obtain a more efficiently functioning system. The adaptation of the neural networks can be accomplished by different molecular and struc-

KEY POINTS

Plasticity is the collective term used for a number of mechanisms that lead to molecular and/or structural alterations of an organism. These changes occur throughout life during learning processes, novel experiences as well as in response to injury. This chapter consists of a review of functional magnetic resonance imaging findings on plasticity phenomena occurring in response to brain injury, epilepsy, and congenital lesions. First, in a brief introduction to the phenomenon ‘plasticity’, a number of factors influencing plasticity phenomena and recovery from brain injury are discussed. Next, we discuss the occurrence of plasticity phenomena in a number of diseases. In the section on plasticity phenomena in patients with brain Tumors, both preoperative and postoperative plastic changes are considered, with a focus on the motor system. The section on plasticity phenomena in patients with epilepsy is mainly focused on the lateralization (or dominance) of language in these patients. In the section on developmental disorders it is demonstrated that plastic changes can occur to a large extent, especially in children. In the last part of the chapter it is shown that plasticity does not always lead to advantageous changes of the brain, as plastic changes may also be the cause of disease.

tural alterations and the mechanisms involved in this process are often termed with the common denominator “plasticity”. The capacity of the brain to modulate neural networks allows an organism to learn, develop and retain memories and is elicited by every sensory input, motor act, association, reward signal and action plan that organism experiences. Therefore, plasticity is not an occasional state of the nervous system; rather, it is the normal continuously

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ongoing state of the nervous system throughout life. In the brain, changes can be induced in both the functional grey matter units and the white matter connections between different cortical areas at different levels, including the molecular level (expression of genes), the cellular level (cell proliferation and differentiation) and the local level (cortical units and their connections) and the system level (development of the entire brain). The effects of plastic changes may either be short or long-term. Short-term changes might be induced by the unmasking of latent pathways, which is not an actual adaptive change but rather a consequence of the change of the equilibrium of inhibitory and excitatory input that a specific cortical area receives (MANTO et al. 2006). More long-term changes include the strengthening of existing cortical connections between cortical areas outside the lesion, and might even include adult neurogenesis (KEMPERMANN et al. 2004; LLEDO et al. 2006; MALENKA 2003; CHEN et al. 2002).

Aside from the learning and developmental capacities of the brain, intriguing adaptations can occur in reaction to injuries inflicted on the brain (ELBERT and ROCKSTROH 2004; PASCUAL-LEONE et al. 2005; JOHNSTON 2004; MARTINO 2004). These changes will be made in order to compensate for the loss of function and/or to optimize remaining functions.

The dynamics of such remodeling of the brain have been studied widely (for a review see LEE and VANDONKELAAR 1995) and functional MR imaging (fMRI) and perhaps also diffusion tensor imaging (DTI) may provide appropriate techniques to visualize the functional reorganization occurring both in normal development as well as in pathological context. Magnetic resonance imaging allows to visualize structural as well as functional characteristics of the human brain and the combination of different types of imaging (such as the combination of fMRI and DTI) can offer detailed insights in underlying pathologies, as has already been demonstrated. Plasticity phenomena have been demonstrated using fMRI, with stroke being the most extensively studied disease (ELBERT and ROCKSTROH 2004; KRAKAUER 2005; RIJNTJES 2006; WEILLER et al. 2006; SAUR et al. 2006; FEYDY et al. 2002; GERLOFF et al. 2006; TEASELL 2003; THIRUMALA et al. 2002; WARD et al. 2002; ZEMKE et al. 2003; CRAMER et al. 1997). Understanding of the mechanisms involved in plasticity and their temporal characteristics may open up new avenues for therapeutic intervention for clinical populations, both at pharmacological/genetic level and behavioral levels.

This review will focus on plasticity phenomena occurring in response to brain injury and epilepsy. The mechanisms for such plasticity will be briefly addressed and a description of plasticity phenomena occurring in patients with Tumoral lesions, epilepsy, and neurodevelopmental disease will be discussed in more detail.

9.2

Plasticity Phenomena in Brain Injury

The past decade there has been a vastly growing interest in the concept of plasticity and the notion of plasticity has been implied in very diverse biochemical and biological processes (such as long-term potentiation, axonal sprouting,...). The term "plasticity" is thus not limited to one typical phenomenon, but it rather covers a wide range of phenomena that occur in the continuously developing and changing brain.

As the scope of this review is the description of plasticity phenomena in brain injury we will limit the discussion on the different possible mechanisms of plasticity to those occurring in the recovery of brain injuries. In case of brain injury, the brain will try to adapt over time in such manner that cognitive, sensory or motor impairments will gradually diminish or are eliminated. The acute or chronic deficits may disappear spontaneously, but these can also be reduced by pharmacologic, physiologic, surgical or behavioral treatments. Recovery can also imply that patients change their behavioral strategies in order to maintain the functions impaired by the lesion. This is a form of compensation or adaptation to the deficit, resulting in an extensive reorganization of the brain. From this point of view, the remaining healthy brain tissue would modulate its physiologic activities, thereby taking over the functions of tissue lost or destroyed by the injury.

A first possibly occurring plasticity phenomenon in brain injury might be the increase in the activation of cortical areas that were already involved in the task, which represents the recruitment of parallel cortical circuits. For example, it has been demonstrated that in stroke patients in whom the location of the stroke was the primary motor cortex, there was an expansion of activity in both contralateral as well as ipsilateral motor areas (premotor cortex, supplementary motor area) (FEYDY et al. 2002;

WARD et al. 2002). Furthermore, it is possible that cortical areas which were not previously involved in the specific function become active during the performance of task that utilize impaired functional areas or networks. Shifts of activation in functional areas have also been observed. However, it should be noted that a shift in the location of activation can be induced simply by the mass effect of the lesion and does not represent an actual plasticity phenomenon. Therefore, one should be very cautious when interpreting results of functional neuroimaging.

Plasticity phenomena may also be evoked by a mechanism called “dynamic diaschisis”, as has been proposed by Price and colleagues (FRISTON and PRICE 2001; PRICE et al. 2001). In this theory, it is stated that the environmental context and the locus of damage can play a role in the functional outcome of a lesion. The basic idea of dynamic diaschisis is that aberrant neuronal responses are generated by an otherwise viable cortical region when those responses depend on interactions with a damaged region, as normal responses in any given region depend on excitatory and inhibitory inputs from and reciprocal interactions with many other regions. This might explain why in some cases, regions at a large distance from the lesion can exhibit ‘unusual’ responses in case of brain injury.

The above-mentioned possible mechanisms of plasticity phenomena only summarize some of the mechanisms that have been proposed in an abundant literature on plasticity, but it is clear that the brain can employ many different strategies in order to retain its functionality in case of brain injury.

9.2.1

Factors for Recovery from Brain Injury

There seems to be a number of factors affecting the final outcome in recovery.

First, the time of occurrence of the injury throughout life might be one of the key factors for the prognosis of recovery. However, no straightforward relation between time of occurrence and recovery can be established. There have been reports that provide strong substantiation that early brain damage is associated with long-term deficits and diminished intellectual impairments in later life (ANDERSON et al. 2000; MURDOCH and HALL 1990). In contrast, other studies show support for “the Kennard principle” (FINGER and WOLF 1988) – stating that early brain lesions lead to much more sparing of functions

than when the same type of injury occurs when the organism is more mature (PRINS and HOVDA 2001; TRUDEAU et al. 2000). Regarding the timing of occurrence of the lesion, there seems to exist a very specific, critical period for plasticity such that injury in very early development may lead to much worse outcomes than is the case when the injury is inflicted weeks or months later (COHEN et al. 1999; KOLB and CIOE 2000).

At a later age, it might be that anatomically distinct areas of the brain have the capacity to mediate a rather wide variety of disparate functions. This is often referred to as the “equipotentiality of cerebral areas” and it would allow a greater chance of recovery at a more mature age. The idea that even the mature brain retains a certain number of redundant subsystems that are involved in the takeover of function is described by the concept “neural vicariation” (SLAVIN et al. 1988). The underlying mechanisms for this adaptation, however, have not yet been clearly described and remain subject of an ongoing discussion.

The type of lesion may also play a role in the occurrence of plasticity phenomena and its relation to the degree of recovery. Slow growing lesions may not evoke the same severity of clinical symptoms compared to an acute lesion of the same extent (STEIN et al. 1983; DUFFAU 2005).

Apart from the above-mentioned factors and their role in recovery from brain injury, the degree of functional recovery will also depend on the individual anatomical and functional connections.

It is clear that the functional outcome of brain injury cannot be predicted by assessing some standard parameters, but that the final outcome will highly depend on the subject-specific characteristics as well as personal experiences and environmental factors.

At present, functional MRI only plays a minor role in the unraveling of mechanisms of brain plasticity after injury. Many of the studies so far – as is the case for those described below – are based on observations in a few patients only, and they contain a considerable part of speculation due to the still limited evidence on this topic. Furthermore, there are no large prospective fMRI trials that have proven that the functional reorganization observed in patients with altered brain activity after injury contributes to the effective recovery (One prospective study exists, but encompasses only data from six patients (REINGES et al. 2005)). In fact, one might argue that the measured changes in brain activa-

tion are nothing else than a reaction of the brain to pathological changes, but do not actually contribute to the recovery of function. However, we hope to demonstrate – with caution – that some observed changes do indeed correlate (but it is impossible to prove a causal relationship) to functional recovery.

9.2.2

Brain Plasticity in Patients with Tumoral Lesions

Functional imaging in patients harbouring brain Tumors aims to maximise the amount of Tumor resection while reducing the risk of functional deficits to eloquent cortical areas (for reviews see, e.g., SUNAERT 2006; DUFFAU 2005). In addition to risk estimation, functional imaging provides the possibility to study reorganization and plastic change, by repeated pre- and post-surgical scanning and by comparison with known functional anatomy in healthy subjects (REINGES et al. 2005; ALKADHI et al. 2000; KRINGS et al. 2001, 2002; WEILLER and RIJNTJES 1999). The patterns of reorganization in patients with brain Tumors may vary depending on the time of imaging and distinction can be made between functional reorganization induced by lesions pre- and post-operatively (DUFFAU 2005).

9.2.2.1

Preoperative Plasticity

Preoperative plasticity needs to be differentiated from a ‘shift’ in function that merely occurs just by mechanical displacement of a functional region by the mass-effect of the Tumor. Evidence also exists that function can still exist within the Tumor itself (SCHIFFBAUER et al. 2001). Both of these patterns are not part of plastic reorganization. True plastic functional reorganization relies on the mechanisms of plasticity described above and results in an intrinsic reorganization within injured brain tissue and/or recruitment of some remote areas within the same hemisphere as the Tumor and/or solicitation of the contralateral homologues brain regions (DUFFAU 2001, 2005; CARPENTIER et al. 2001; DUFFAU et al. 2004; ELBERT and ROCKSTROH 2004; REINGES et al. 2005; ALKADHI et al. 2000; KRINGS et al. 2002). One of the first studies describing such plastic changes was ALKADHI et al. (2000) who suggested three different patterns of cerebral reorganization in patients presenting with arteriovenous malformations (AVMs)

situated in motor areas: functional displacement within the contralateral primary motor area (M1) (intra-hemispheric reorganization), activation of the ipsilateral M1 (inter-hemispheric reorganization) and function taken over by non-primary motor areas. More recently, CARPENTIER et al. (2001) proposed a classification scheme of plasticity with six grades based on inter-hemispheric pixel asymmetry and displacement of activation. Grade 1 represents the normal activation pattern, grade 2 appears to reflect a mass effect, grade 3 reflects the impact of the lesion on the activation (interface disorder) with no clear evidence of plasticity, grade 4 represents possible local plasticity, whereas grade 5 represents definite ipsilateral plasticity, and the grade 6 pattern represents definite contralateral plasticity. As designed, the classification categories, ranging from grades 1 to 6, correspond to levels of reorganization ranging from none to highly reorganized patterns of motor function. A case with grade 6 plasticity is presented in Fig. 9.1.

The different patterns of reorganization may reflect possible differences in the timing of the occurrence of the lesion in the life. In case of early brain lesions (as is typically the case for vascular malformations and cortical dysplasias), the reorganization may be inter-hemispheric, while in case of lesions occurring later in life, the reorganization is more likely to be intra-hemispheric (COHEN et al. 1999; HERTZ-PANNIER et al. 2002; LIEGEOIS et al. 2004). Initially it was argued that inter- or intra-hemispheric reorganization does not seem to depend on the type of lesion (BACIU et al. 2003). However, clear evidence exists that inter-hemispheric reorganization especially occurs within patients with slow growing Tumors (DUFFAU 2005). This reorganization is thought to explain why slow infiltrative low-grade gliomas near or in eloquent motor or language areas do often not induce detectable neurological deficits (DUFFAU 2005).

Patients with brain Tumors exhibit a wide range of functional deficits, going from no noticeable deficit to severe paresis or speech impairment. They also differ in the degree to which plasticity phenomena have already occurred pre-operatively. To understand the relationship between preoperative plasticity and the degree of functional deficits in patients harbouring Tumoral lesions, one needs to consider lesion location in addition to the timing of occurrence of the lesion and the lesion type (slow vs fast growing). The location of the lesion is important, with respect to the relation to essential eloquent

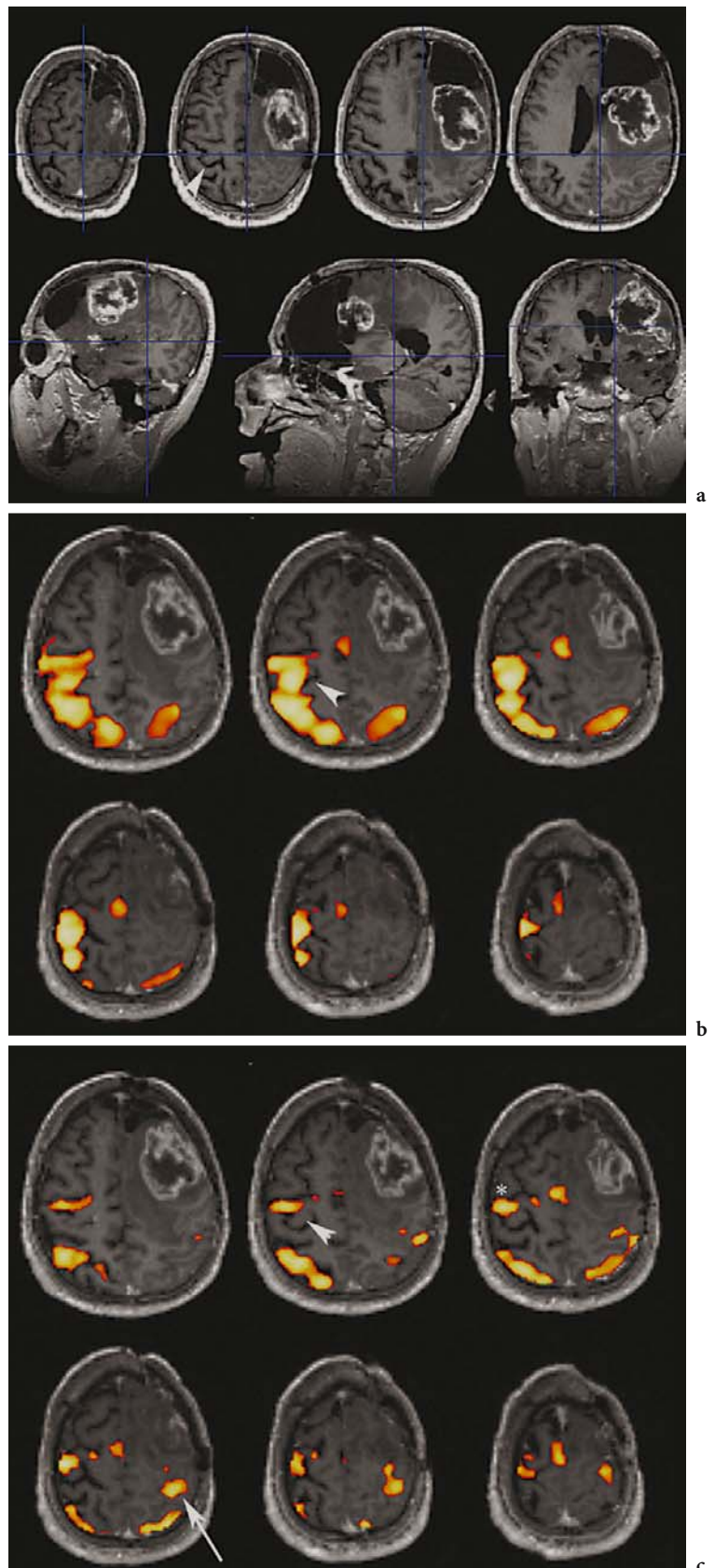


Fig. 9.1a–c. Cortical reorganization of the motor system in a patient with a recurrent glioblastoma multiforme three years after resection of a glioma grade 2 in the right frontal lobe. **a** T1w post-contrast anatomical images. **b** Activation pattern in response to repetitive left hand clenching vs rest. **c** Activation pattern in response to right hand clenching. Arrowheads indicate the position of the right primary motor cortex (M1). The arrow points to the presumed location of the left primary motor cortex. Note the normal pattern of brain activity in **b**, with contralateral activation of the right M1, PMC, and bilateral activation pattern of the SMA and parietal proprioceptive regions. The activation pattern in **c** should be the symmetric of **b**, but this is not the case. There is some residual activity in the left M1 (arrow), but ipsilateral activation in the right primary motor and premotor cortices is clearly present

structures compared to more redundant cortical areas. "Essential" functional areas are those areas in which lesions lead to profound neurological deficits, while damage to non-essential regions of the brain seems to induce only minor deficits, or deficits that resolve completely in the majority of patients in a matter of weeks. For example, the cingulate gyrus exhibits activation in a large number of neuroimaging experiments, including those involving language production, but damage to this structure does not have the devastating consequences on speech that are caused by damage to Broca's area. Similarly, a lesion to the primary motor cortex (M1) leads to long-lasting profound motor paresis, while a lesion to the supplementary motor area (SMA) or premotor cortex (PMC) leads to a less profound deficit, which completely recovers in the majority of patients after 1–3 months. Further study is necessary to understand why recovery of function, and associated plasticity seems to occur more or better when lesions are situated in hierarchically higher order regions (such as SMA) than in primary 'essential' areas (such as M1). For the motor system, one could speculate that this is due to the fact that M1 has a direct execution function, which can not be taken over easily by other areas, and because of the high unilateral connectivity of M1 to the spine (which makes it difficult for the ipsilateral M1 to take over function). On the contrary, SMA and PMC, that are both involved in higher order motor functions, such as planning of action, coordination and timing of voluntary action, can take over each other's function. This might be due to the fact that these regions are highly interconnected (even to their contralateral homologue) and that they have closely related functions.

Even though perhaps not completely understood at present, the information about the cerebral reorganization in the damaged brain could be an important decisional factor for surgical treatment.

9.2.2.2

Postoperative Plasticity

Immediately postoperatively, patients with (partially) resected lesions can either functionally worsen or improve. The latter improvement can be due to diminishment of the compression of eloquent structures by the Tumor mass and/or reduction of the concomitant edema. It might also be due to immediate plasticity phenomena. Using electrostimulation, DUFFAU (2001) documented that motor sites in the vicinity of the Tumor, that were initially silent,

started to induce clear motor responses immediately postoperatively. This is thought to be due to local acute changes in the balance of excitatory and inhibitory connections between different components of the neural network.

The functional reshaping induced by surgery can also be studied using postoperative functional imaging, either immediately after surgery, or longitudinally. Clear evidence for post-operative motor system plasticity has been documented by KRAINIK et al. (2001a, b, c, 2004) for patients with resection of the SMA. In patients in whom there was already some degree of preoperative reorganization of SMA activation towards the contralateral healthy hemisphere, resection of a tumoral mass involving the SMA was performed. The preoperative plasticity was not sufficient to prevent the occurrence of post-operative neurological motor deficit, but it was associated with a faster recovery. After final recovery, SMA activation was almost exclusively located in the healthy hemisphere and there was an additional recruitment of the PMC in the same hemisphere (Fig. 9.2). The recruitment of both PMC and SMA in the healthy hemisphere increased as the extent of tumoral infiltration in the SMA (and of the area of SMA resection) increased.

Similar observations have been made for lesions to the primary motor cortex. The stronger involvement of the SMA and/or PMC during a motor exercise involving the damaged brain may be explained either because the motor act must be better planned and programmed or because the premotor cortex takes over the primary motor function. The latter may be the case, because of the premotor origin of the pyramidal tract. FANDINO et al. (1999) compared the post-operative fMRI results with those obtained during intra-operative cortical stimulation in patients with Tumors situated close to or involving the primary motor area. Functional reorganization was seen in the contralateral primary motor area, the contralateral premotor area, the ipsilateral primary motor area and the ipsilateral premotor area. It is clear that cortical reorganization patterns of motor areas may explain the differences in motor function and the diversity of postoperative motor function among patients with central Tumors.

More study is needed to understand the temporal characteristics of functional reorganizations, as too few studies have followed the development of plastic changes over time. Within the auditory system, BILECEN et al. (2000) had the rare opportunity to repeatedly measure fMRI signals in response to

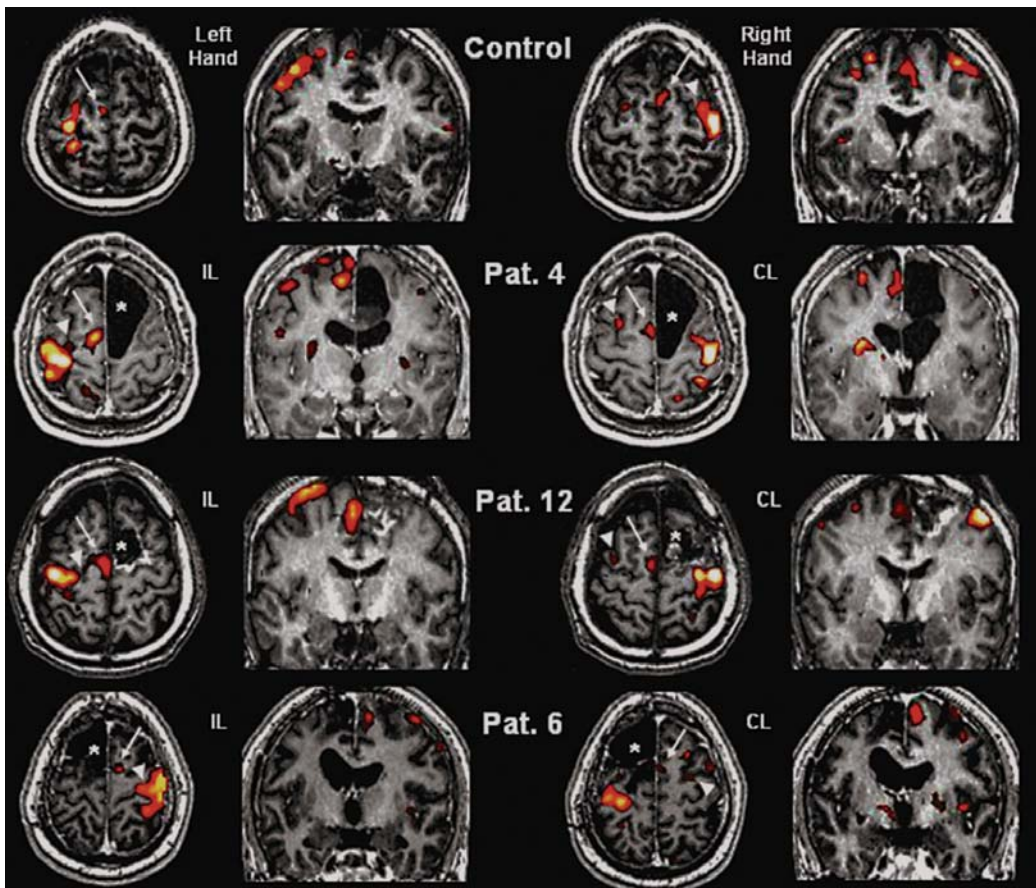
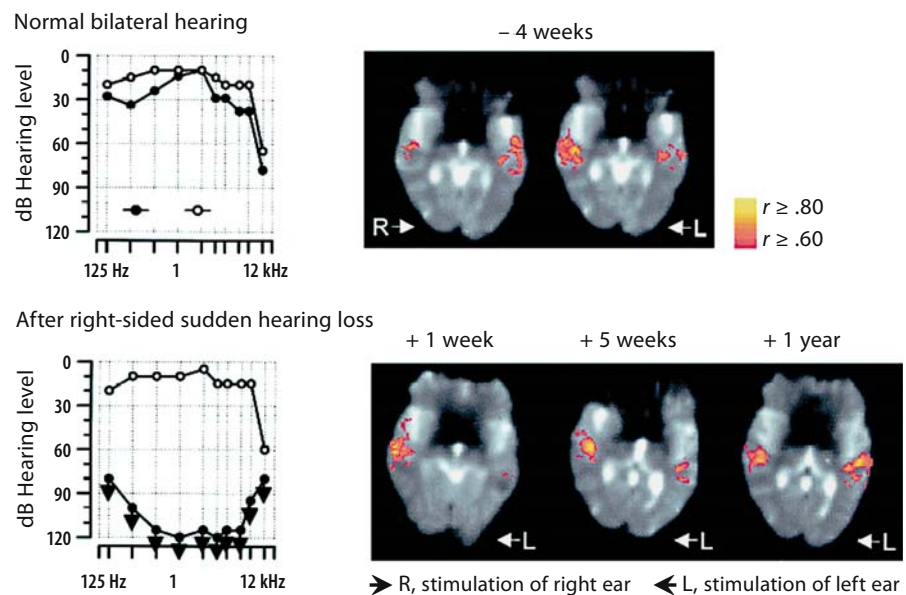


Fig. 9.2. Anatomic and functional MRI in one representative control and in patients 4, 6, and 12 of the study of KRAINIK et al. (2004) (with permission) during ipsilesional (IL) and contralesional (CL) movements after surgery. In controls and in patients during IL movements, supplementary motor area (SMA) (arrow) and premotor cortex (PMC) (arrowhead) activation predominated in the hemisphere contralateral to the moving hand. In patients during CL movements, SMA activation was located in the healthy hemisphere and PMC activation became more important in the ipsilateral healthy hemisphere

Fig. 9.3. Pure tone audiometry 1 week before and 3 months after acoustic nerve resection. FMRI activity in the primary auditory cortex after stimulation with a 1 kHz sine tone at 95 dB SPL. Before surgery, a chiefly contralateral response was found. After surgery, progressively balanced bilateral rather than contralateral fMRI response pattern. From BILECEN et al. 2000, with permission



auditory stimulation in an initially normal-hearing subject who had lost hearing after an acoustic neurinoma resection (Fig. 9.3). This patient had been studied 1 month before surgery (at that time normal-hearing) and 1, 5 and 55 weeks after surgery (then unilaterally deaf). One week after surgery, unilateral stimulation of the intact left ear yielded a response that was strongly contralateral (left/right ratio: 1/4.8). Five weeks after surgery less disparity was found (left/right ratio: 1/3.6), and 1 year later the response was almost bilaterally balanced (left/right ratio: 1/1.3). This progressive balancing of activity was largely a result of increasing ipsilateral activity rather than decreasing contralateral activity. A progressing compensatory reorganization with bilateral representation of unilateral acoustic stimulation was thus observed over a period of approximately 1 year. The exact mechanism and sites of this reorganization are largely unknown but might be due to the abundant presence of ipsilateral connections in the ascending auditory pathway. These ipsilateral connections, which are normally suppressed, might become disinhibited when contralateral inhibitory inputs are removed.

9.2.3 Reorganization of Language Function in Epilepsy

In more than 94% of healthy subjects language functions are strongly lateralized to the left (SPRINGER et al. 1999; KNECHT et al. 2000). This left-sided (or “typical”) language dominance is more intrinsic for healthy right-handers, but it also can be found in the majority of left-handers (SATZ 1979). A recently published voluminous functional MRI study of 100 healthy right-handed volunteers demonstrated that only 6% had an atypical language representation (SPRINGER et al. 1999).

Early damage to the left hemisphere can result in atypical, i.e. bilateral or right-lateralized, representation of language (RASMUSSEN and MILNER 1977; SPRINGER et al. 1999; STAUDT et al. 2002). Several studies (LIEGEOIS et al. 2004; SATZ 1979; STAUDT et al. 2002; WOERMANN et al. 2003; RAUSCH and WALSH 1984) provide evidence that left temporal lobe pathology is more often associated with atypical language lateralization. In temporal lobe epilepsy (TLE), BRÁZDIL et al. (2003) demonstrated that hemispheric language dominance, as determined by intracarotid short-acting barbiturate injections (Wada testing), was atypical (right or bilateral) in

13.6% of patients with temporal lobe epilepsy. Moreover, a significantly higher rate of deviance from complete left hemisphere dominance was observed in left TLE (23.1%) than in right TLE (0%). The Wada test has been the reference procedure “gold standard” for identifying lateralization of language and memory functions in TLE patients, but it is invasive and therefore carries risk. fMRI offers a promising non-invasive alternative approach (ADCOCK et al. 2003; SUNAERT 2006), and several recent studies (WOERMANN et al. 2003; BINDER et al. 1996) reported a good cross-validation comparing language dominance determined by both fMRI and Wada, even in patients with TLE (WOERMANN et al. 2003). For details see Chapter 7.

Recently the findings reported using Wada test were confirmed using fMRI. An illustrative case of a right handed patient suffering from left hemispheric epilepsy with atypical right lateralized fMRI language lateralization, confirmed by Wada testing, can be seen in Figure 9.4. BERL et al. (2005) found lower asymmetry indices in left hemisphere focus patients within the inferior and middle frontal gyri (expressive language areas) and Wernicke’s area compared to healthy controls. These authors state that this reflects increased recruitment of homologous right hemisphere areas for language processing. Greater right hemisphere activation may reflect greater cognitive effort in patient populations, the effect of epilepsy, or an effect of its treatment.

Furthermore, in a study by JANSZKY et al. (2006) higher left-sided spike frequency in MTLE was associated with a left–right shift of speech representation, suggesting that chronic frequent interictal activity may induce a reorganization of speech lateralization (see Fig. 9.5).

The question arises whether plastic shifts of language just occur in the symmetrical counterparts (homologues) of Broca’s and Wernicke’s areas, or whether this plastic remodelling is more complex in nature. Few studies have anatomically characterized the specific right hemisphere structures engaged. VOETS et al. (2006) used functional MRI with verbal fluency tasks in 12 right-handed patients with left temporal lobe epilepsy (LTLE) and 12 right-handed healthy controls to localize language-related activity in the right inferior frontal gyrus (RIFG). During the phonemic task, LTLE patients activated a significantly more posterior region of the right anterior insula/frontal operculum than healthy controls. Activation of the left inferior frontal gyrus (LIFG) did not differ significantly between the two groups.

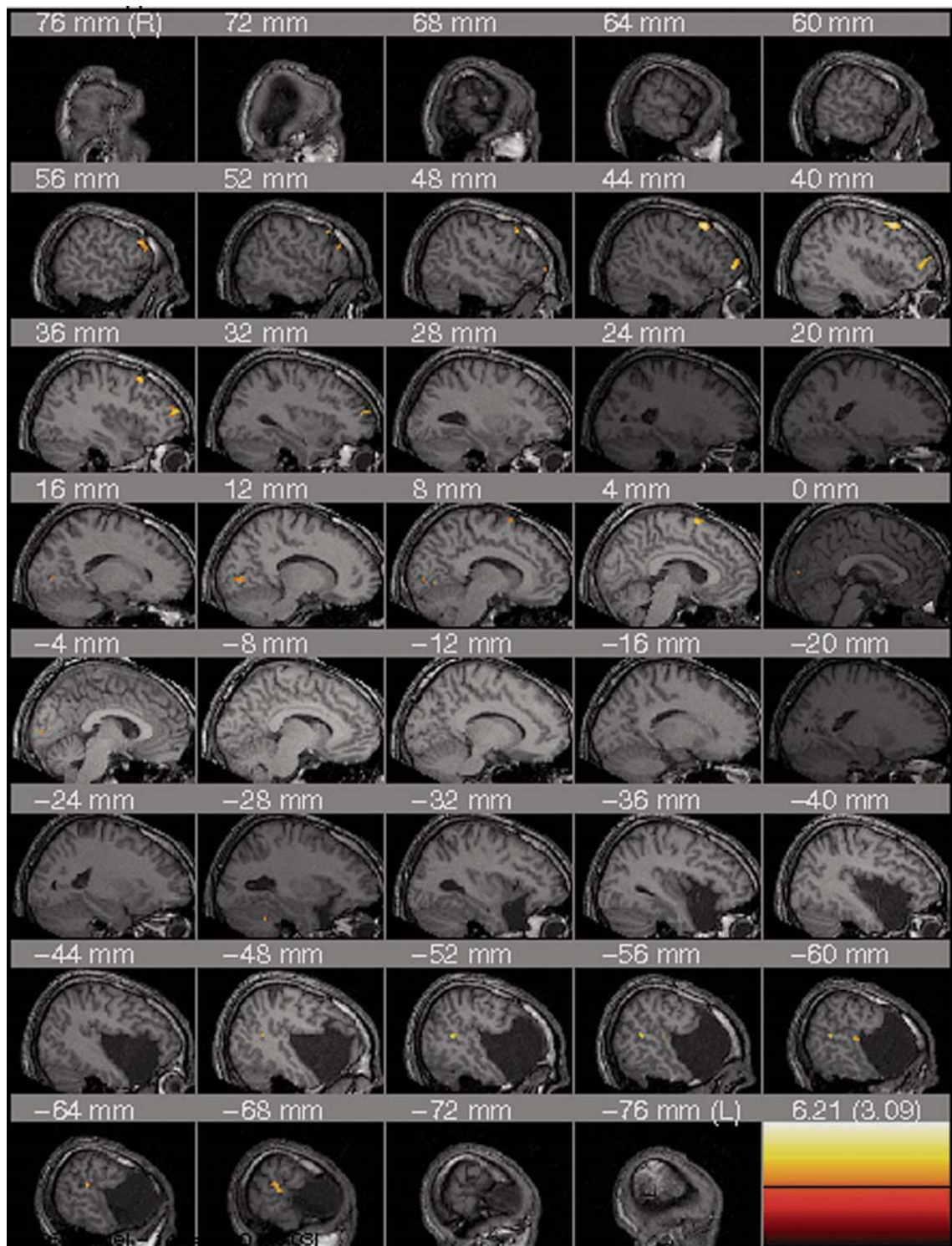


Fig. 9.4. Crossed language lateralization in a strongly right-handed patient (Oldfield scale $>+0.8$) with right frontal reorganization of expressive language areas. fMRI activation foci in response to a verb-to-noun generation task vs rest are shown on sagittal sections (L = left hemisphere, R = right hemisphere, numbers denote distance of slice from midline). The seizures are believed to originate from the left frontal lobe, where a relatively large arachnoidal cyst can be found. During the partial complex seizures, and post-ictally there is no significant speech impairment. This can be explained by the shift of language function to the non-lesioned right hemisphere

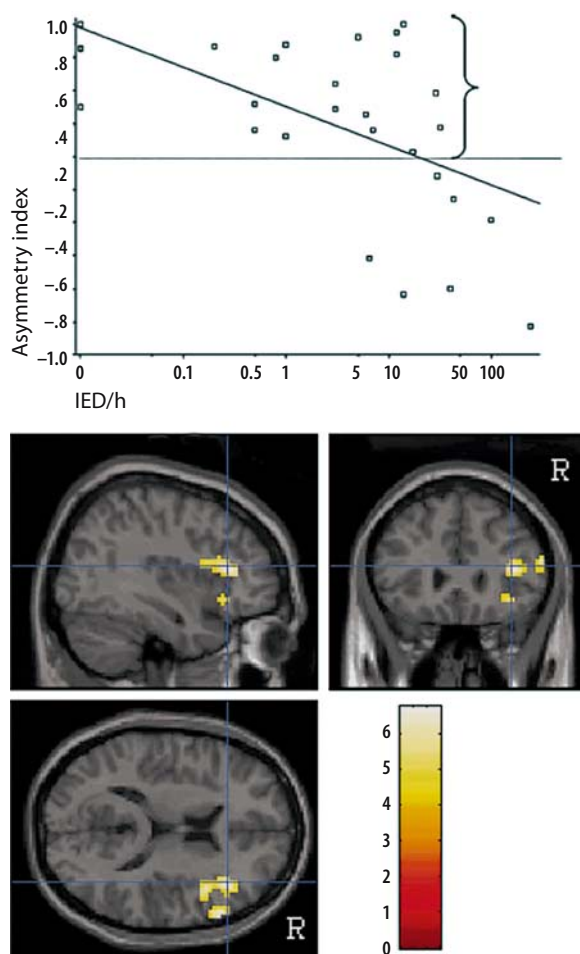


Fig. 9.5. The relation between the speech lateralization and frequency of interictal epileptic discharges: the above panel shows that patients with a higher interictal epileptic discharges (IED) frequency in left-sided mesial temporal lobe have a 'atypical' asymmetry index (AI): a frequent left-sided spiking was associated with a right shift of speech lateralization. The SPM below shows a group comparison with an increase of right-sided fMRI activity during word generation in patients with left-sided mesial temporal lobe epilepsy (MTLE) and frequent left-sided interictal epileptic discharges (IEDs) compared with a low IED frequency (adapted from JANSZKY et al. 2006)

This suggests that, following left hemisphere injury, language-related processing in the right hemisphere differs from that within a functionally normal left hemisphere. The localization of activation in the left and right inferior frontal gyri was determined with respect to the anatomical sub-regions pars opercularis (Pop), pars triangularis (Ptr) and pars orbitalis (Por). In the LIFG, both healthy controls and LTLE patients engaged primarily Pop during phonemic

fluency. Activations in the RIFG, however, were located mostly in the anterior insula/frontal operculum in both healthy controls and LTLE patients, albeit in distinct regions. Mapping the locations of peak voxels in relation to previously obtained cytoarchitectonic maps of Broca's area confirmed lack of homology between activation regions in the left and right IFG.

The type of lesion causing TLE does not seem to be of influence on the development of language shift. In a study by BRIELLMANN et al. (2005) patients with hippocampal sclerosis, a lesion that can be understood as an early, acquired lesion, were compared to patients with developmental Tumors, which are thought to originate in utero. When they assessed whether language lateralization differed between these groups of TLE patients, language lateralization was shown to be not different between patients with presumably acquired lesions compared with patients with developmental pathology. This suggests that the nature of the temporal lobe lesion does not influence overall language lateralization.

Conversely, the lobar location of the lesion seems to be important. The hypothesis that shifts in language dominance are particularly likely when epileptic lesions are located in close vicinity to the so-called language-eloquent areas rather than in more remote brain regions such as the hippocampus has been challenged by WEBER et al. (2006). In this recent study the effect of lesions in different parts of the left hemisphere was investigated in 84 adult patients with drug-resistant focal epilepsy with structural lesions and 45 healthy control subjects with an established functional MRI language paradigm. Out of the 84 patients 43 had left hippocampal sclerosis, 13 a left frontal lobe lesion and 28 a left temporal-lateral lesion. All these lesions were likely to have been present during the first years of life during language acquisition. Patients with left hippocampal sclerosis showed significantly more 'atypical' language lateralization than all other groups of subjects (Fig. 9.6). This effect was independent of the factor of region, indicating that language lateralization was generally affected by a left hippocampal sclerosis. Thus, the hippocampus seems to play an important role in the establishment of language dominance.

Assessment of lateralization of language by functional MRI becomes also more readily available to the pediatric population, allowing the study of language plasticity in children with epilepsy (DUBOIS

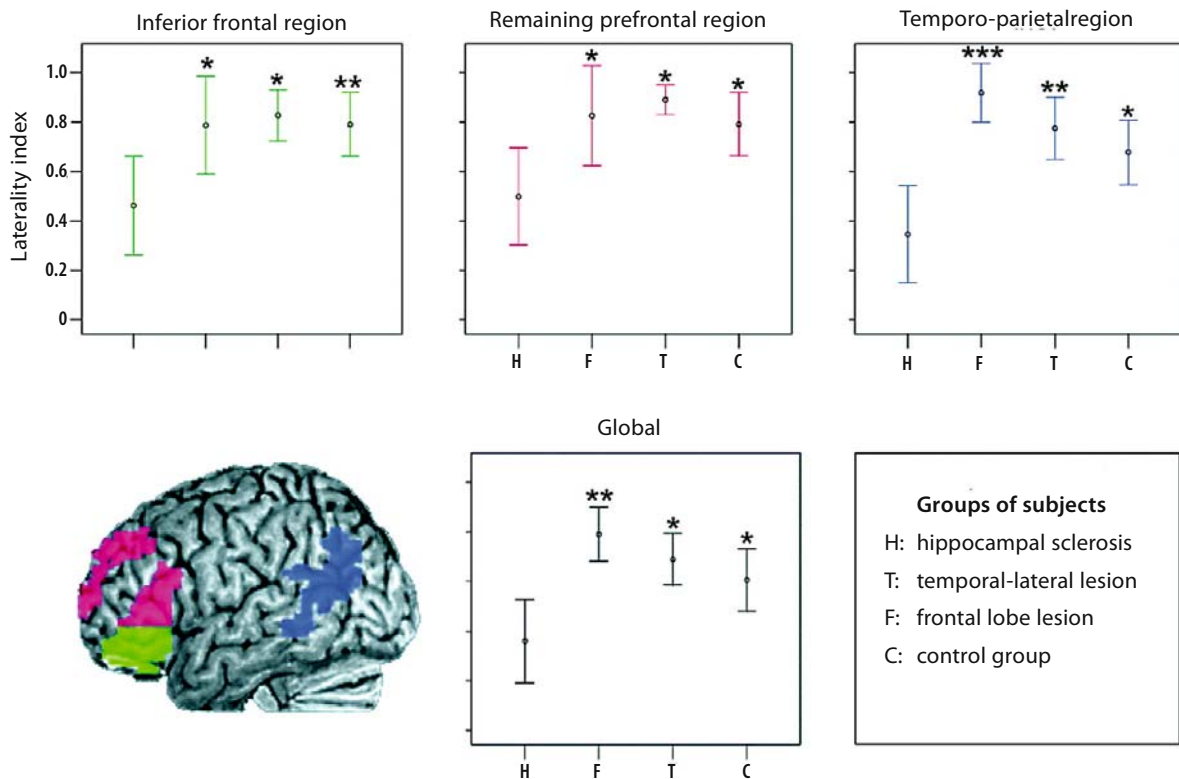


Fig. 9.6. Influence of lesion location on the development of language plasticity in epilepsy patients: laterality indices and their standard deviations computed in the four regions of interest are scaled from -1.0 (complete right lateralization) to $+1.0$ (complete left lateralization). The hippocampal location of origin of epilepsy seems to play the most important role in the establishment of language dominance (with permission from WEBER et al. 2006)

et al. 2006; DEHAENE-LAMBERTZ et al. 2002; HERTZ-PANNIER et al. 2001, 2002). A recent study by YUAN et al. (2006), shows that epilepsy during childhood is associated with neuroplasticity and reorganization of language function, similar to adults. A dramatic difference was observed in the percentage of children with epilepsy (77.8%) that had atypical lateralization index (LI) (right-hemispheric or bilateral, $LI < 0.1$) when compared with the age-gender-handedness matched group (11.1%). In the case of Rasmussen's encephalitis, depicted in Fig. 9.7, with extremely frequent seizures (up to 20 attacks per day) that are refractory to treatment and originate from the left hemisphere, a complete shift to the right hemisphere could be demonstrated using fMRI.

The mechanism underlying the higher incidence of atypical language dominance associated with left-hemispheric pathologies is not very well understood. The convolution of epilepsy and development, combined with other factors, makes it

extremely difficult to distinguish the actual impact of epilepsy on the neural substrates of language based solely on language function distribution patterns observed in functional imaging studies. Due to limitations in the control of experimental conditions in clinical fMRI research, the question of cause and effect remains. Does repeated seizure activity in epilepsy cause the reorganization of language in the developing brain, or, does epilepsy result from underlying neuropathology, which, although invisible by neuroimaging, causes early redistribution of language? The study of JANSZKY et al. (2006), showing increased right language dominance with increased interictal activity, as well as animal studies suggest the first question is closer to the answer. There is evidence showing that seizures in developing mouse brain can cause immediate neural cell loss, synaptic circuitry reorganization, as well as long-term neurological consequences such as lowering of seizure threshold, impaired learning capacity, and cognitive deficit in

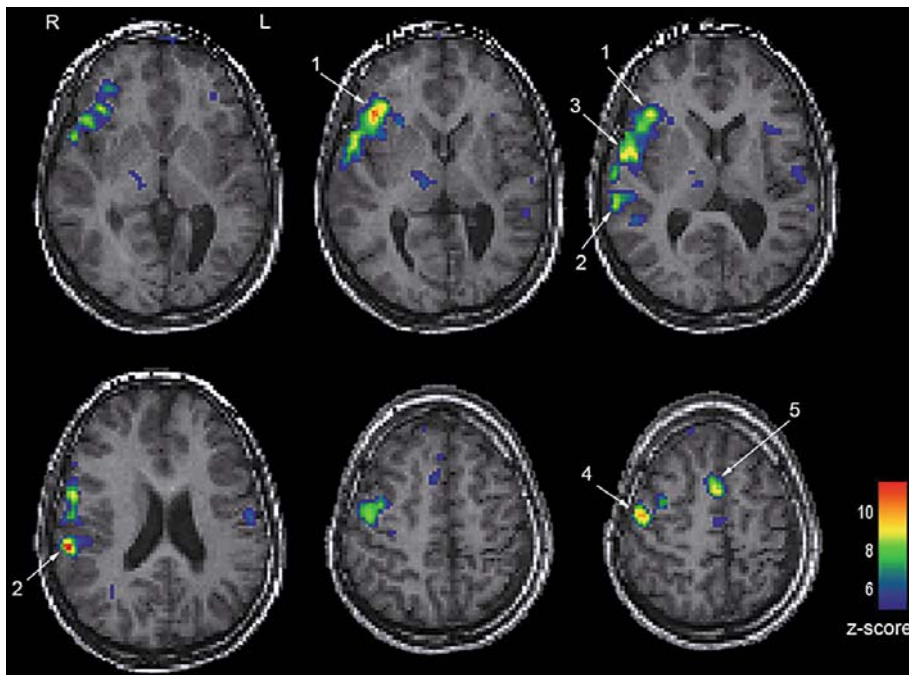


Fig. 9.7. Twelve-year-old boy suffering from Rasmussen's encephalitis with left refractory epilepsy. fMRI using a verb-to-noun generation task demonstrates clear right lateralized language (the right sided homologues of Broca's and Wernicke's area are indicated by labels '1' and '2' respectively; additional activation was observed in right primary and secondary auditory cortices [label '3'], right premotor cortex [label '4'] and supplementary motor area [label '5']). Hemispherotomy was performed, without language disturbance post-operatively, and much improved seizure control

later life (HOLMES et al. 1998; KUBOVA et al. 2001; LIU et al. 1999; WEBER et al. 2006).

Additional evidence comes from the observation that plastic changes observed in epilepsy patients can become undone when the epilepsy is brought under control. Indeed, in left mesial temporal lobe epilepsy, where eloquent cortex is not directly involved, it is a matter of debate to which degree atypical language dominance is driven not only by morphological lesions but also by epileptic dysfunction, and whether atypical dominance is hardwired or not. Taking this as the background, HELMSTAEDTER et al. (2006) evaluated the hypothesis that epilepsy driven atypical dominance might be reversible when seizures are successfully controlled. This was evaluated in patients with left mesial temporal lobe epilepsy, who were atypically language dominant by means of language fMRI before surgery, and became seizure free after left selective amygdalo-hippocampectomy. Postoperative follow-up language fMRI indicated reversal of right into left dominance in one patient along with unexpected losses in verbal memory performance. The data thus provide supporting evidence that atypical language dominance can indeed be functionally driven and moreover, that at least in some patients, right hemispheric language can shift-back to the left hemisphere when the driving factor (i.e. seizures) becomes successfully controlled.

9.3

Brain Plasticity in Congenital (Developmental) Lesions

As mentioned above, the age at which a lesion occurs is an important factor in the process of brain plasticity. The brain seems to undergo plastic changes to a much larger extent when a lesion occurs in the early development of the brain. This seems logical since redundancy of brain circuitry is larger at that stage.

Stroke does not have to lead to profound language disturbances, if it occurs at birth, as was the case in a patient with kern icterus due to rhesus incompatibility, which is depicted in Figure 9.8. Functional MRI using a verb-to-noun generation task depicts a right hemispheric language shift, which is more striking than that observed in the majority of patients with TLE described above.

The extent to which brain plasticity may occur at early age can be illustrated by the case shown in Fig. 9.9. This normally developing child suffered a traumatic brain injury at the age of two. Before the trauma, her language functions were normal to advanced – she was able to speak three-word sentences at that age. She suffered extensive damage to her left hemisphere close to the presumed locations of Broca's area and Wernicke's area. Post-trauma she was completely aphasic, suggesting that lan-

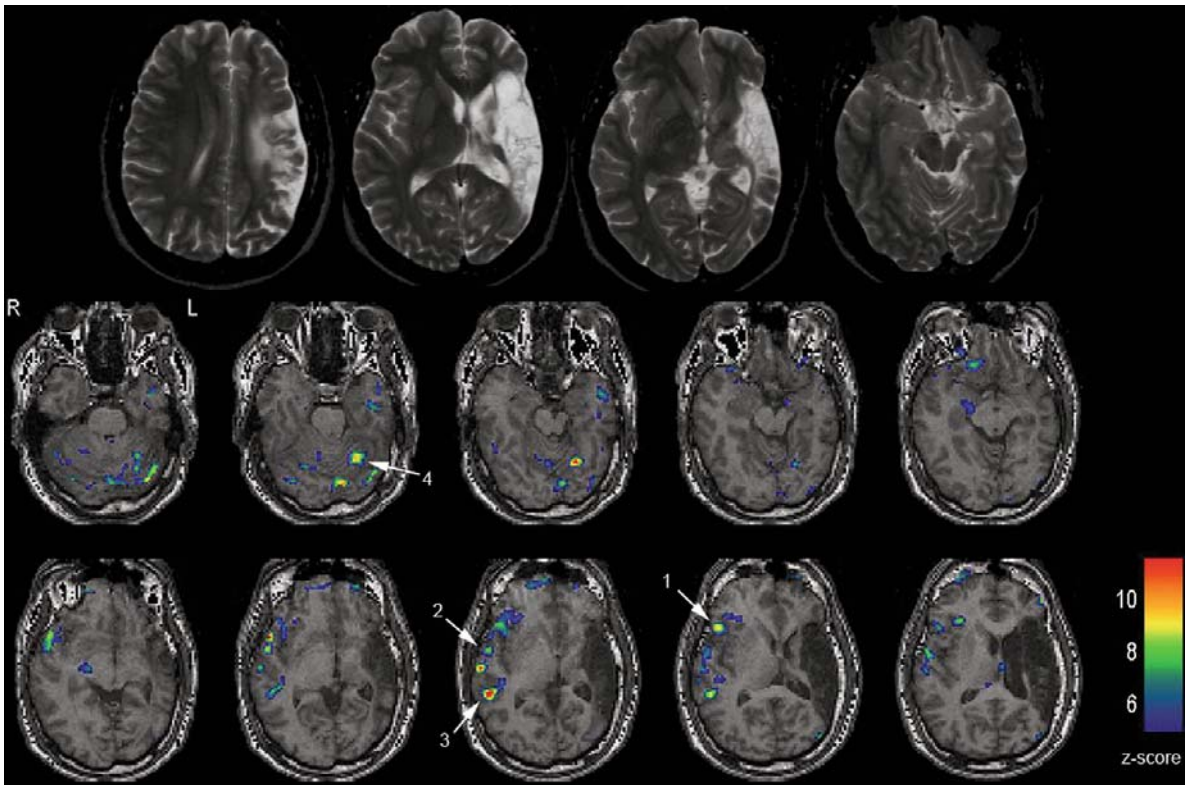


Fig. 9.8. Thirty-five-year-old patient with a congenital stroke in the left ACM territory, suffering from right hemiparesis, but who has normal language skills. fMRI demonstrates clear right hemispheric shift of language function (Right sided homologues of Broca's area (label '1'), Wernicke's area (label '3') in addition to right primary and secondary auditory cortex (label '2'), accompanied by a left cerebellar shift (activation labelled '4')

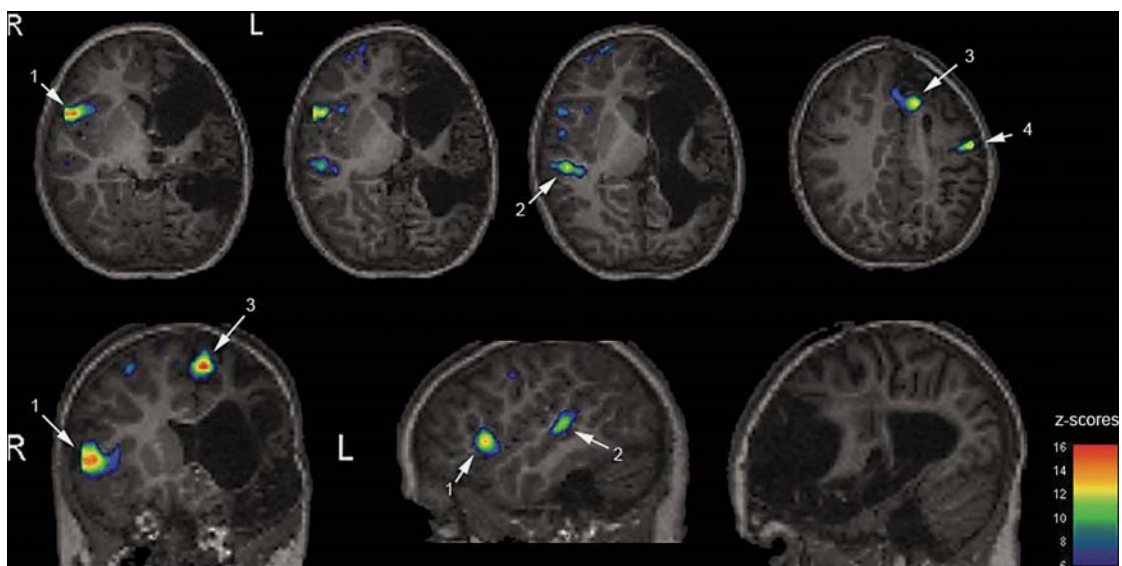


Fig. 9.9. Six-year-old girl who suffered a traumatic brain injury at the age of two. A verb-to-noun generation task results in activity in the right superior temporal gyrus (right sided homologue of Wernicke's area labelled with '2'), right inferior frontal gyrus (right sided homologue of Broca's area labelled with '1'), left superior frontal gyri (supplementary motor area, labelled '3') and the left precentral / middle frontal gyrus (premotor cortex, labelled '4')

guage was originally in the left hemisphere. However, from the age of three she started to develop language skills again and at the age of six, her language functions were almost as good as normal children at that age. An fMRI experiment conducted at the age of six, using a covert verb-to-noun generation task (Fig. 9.9) showed activation in the right homologue of Broca and Wernicke, suggesting a 're-appearing' of language functions on the right side of the brain. Surprisingly, the premotor cortex, which is known to be involved in such a task (preparation of a motor plan to speak out words), was still located in the left hemisphere, presumably the original location.

Extended plastic changes can also be found within the motor system, as depicted by another case shown in Figure 9.10. This thirteen-year-old girl presented with bilateral frontoparietal polymicrogyri and a left Rolandic schizencephaly (Fig. 10a). These lesions, occurring in mid-embryologic development, resulted clinically in mild bilateral paresis and hypertonia, most pronounced within the left lower limb. Right hand movements (Fig. 10c) activated contralateral left primary sensorimotor cortex (SM1 – pre-/post-central gyri), which is the normal pattern of activation, except for the fact that part of the activation could be found within the abnormal gray matter of the polymicrogyri. Movement of the left hand resulted in a more bilateral activation of SM1. More striking are the patterns observed during lower limb movements. Right toe movement (Fig. 10e) resulted in left contralateral SM1 activation, which was somatotopically located more laterally than expected from normal subjects. However, the movement of the left toes (Fig. 10d) resulted in activation within the ipsilateral SM1, corresponding exactly to the same location in SM1 as during right toe movement. It seems that the patient performs movements of the muscles of both lower limbs from the left hemisphere only. Clinically this might explain the strong 'mirror' movements that occur when the child is moving her left toes: she uncontrollably mirrors the movements in the right lower limb. Therefore, another explanation might be that the above described ipsilateral motor activity is solely due to the mirror movements in the right leg. We additionally performed a sensory (brushing) stimulation of the skin of the plantar side of the feet. Again, during left sensory stimulation (Fig. 10f), only ipsilateral left activation within the primary sensory cortex could be observed. This is additional evidence that in this

child, motor and sensory functions of the left lower leg are plastically reorganized within the ipsilateral left hemisphere. Finally, a diffusion tensor imaging fiber tractography of the corticospinal tracts (CSTs) was performed. The fiber tractography suggests that the right CST is congenitally underdeveloped. It exists of far less fiber tractography streamlines, and has a lower mean fractional anisotropy (FA) compared to the left CST (Fig. 10h). These diffusion tensor imaging results are in good agreement with the fMRI data, suggesting a larger impairment of the right CST, with subsequently a reorganization of function to the left hemisphere.

9.4

White Matter Plasticity?

As depicted by the above case, one can question whether plasticity only involves the gray matter of the brain. The available evidence suggests that in the recruitment and reorganization, white matter structures also play a pivotal role. THOMAS et al. (2005) have recently shown that the ipsilateral pyramidal tract fibers in the brainstem reorganize in children with spastic hemiparesis. Furthermore, functional recovery after demyelinating episodes in diseases like multiple sclerosis (MS) may be partly due to gray and white matter plasticity. However it must be noted that, the mechanisms and relative contributions of the white matter plasticity of human brain are much less understood at present.

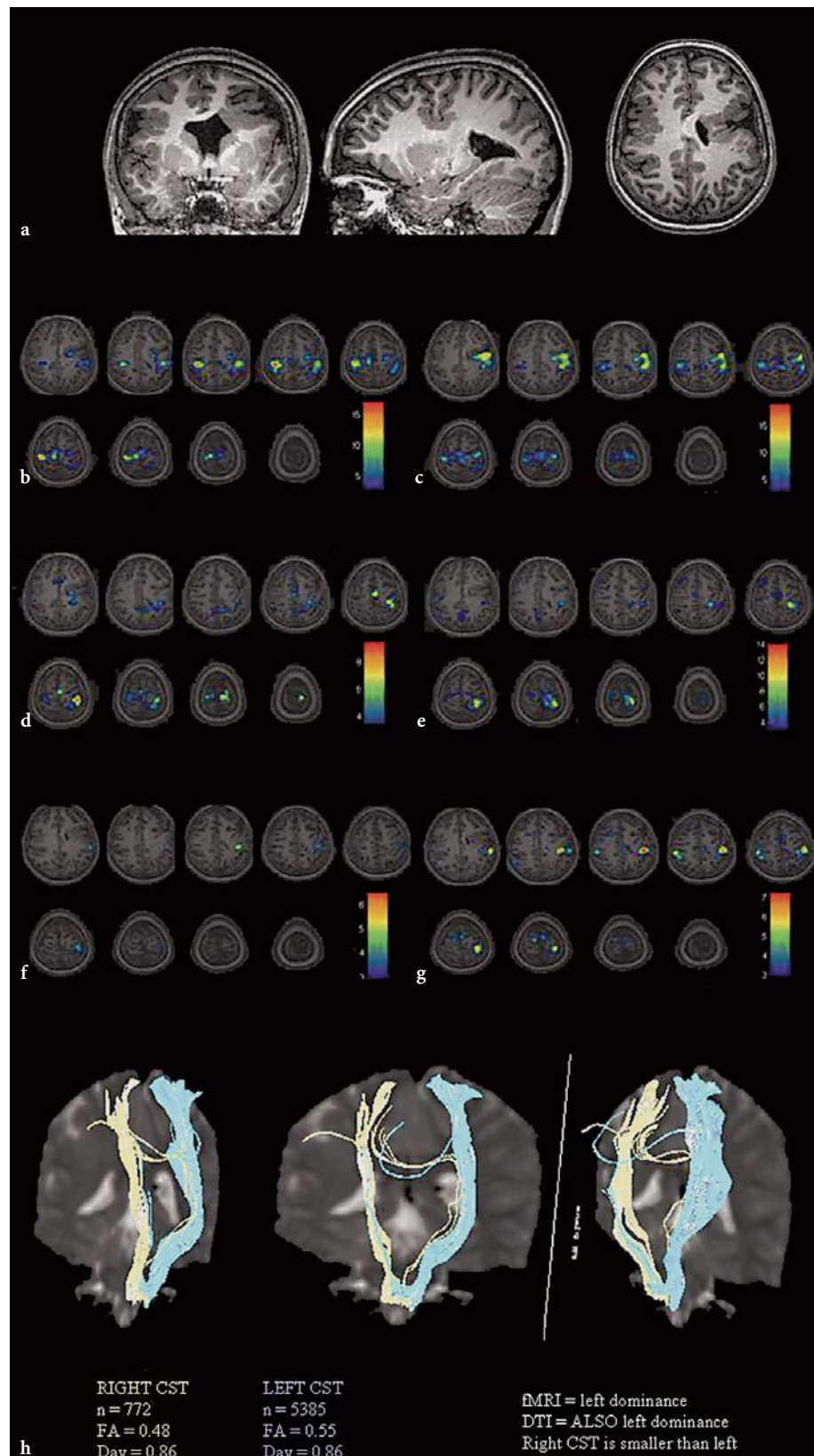
9.5

When Plasticity Goes Wrong

Brain plasticity does not always lead to recovery of function (in the case of brain injury) or to improved function (in the case of plasticity of learning and development). Sometimes plasticity itself can be the origin of diseases.

A first example is focal hand dystonia in musicians, also termed "musician's cramp" (HALLETT 1998). This illness is a sensorimotor disorder characterized by a loss of control over individual finger movements, especially during specific actions related to playing a given musical instrument. Hand

Fig. 9.10a–h. Plastic changes in a child with bilateral polymicrogyria and a left schizencephaly, clinically resulting in bilateral paresis and hypertonia, which is most pronounced on the right side of the body. When moving the right upper or lower extremity mirror movements in the opposite limb are present. Coronal, sagittal and transversal T1w sections (a) depicting the abnormalities. fMRI activation maps during left (b) and right (c) motor hand clenching task, left (d) and right (e) motor toe movement task, and left (f) and right (g) sensory stimulation (brushing) of the toes. Diffusion tensor imaging (h) with fiber tractography was performed of the cortico-spinal tracts (CST), and shows a considerable larger left CST as compared to right CST



dystonia seems to be caused or at least related to the excessive performance of repetitive activities. Animal models have shown that repeated and prolonged use of the contralateral hand results in 'maladaptive' changes in the functional organization of the motor (NUDO 2003) and the primary sensory cortex (WANG et al. 1995).

Another disease which might be the consequence of maladaptive plastic brain changes is non-pulsatile tinnitus. Tinnitus, the perception of sound when no external sound is present, is a distressing symptom afflicting 15% of the population. Recent findings have provided a physiological measure of tinnitus and support the view that non-pulsatile tinnitus is caused by an abnormally functioning and reorganized auditory system (MUHLNICKEL et al. 1998). Any lesion along the auditory tract, influencing its normal function, can generate non-pulsatile tinnitus. Alteration of the normal sensory input, or especially, deprivation of input, can lead to reorganization of the entire auditory pathways including the cerebral cortex. For example, in a frequency selective cochlear lesion, e.g., a high frequency lesion caused by ototoxic antibiotics, the tonotopic map in the auditory cortex and brainstem nuclei can reorganize such that cortical neurons that are deprived of their usual afferent input become supersensitive and now respond to tone frequencies adjacent to the frequency range damaged by the lesion, leading to the symptom of tinnitus.

9.6

Conclusion

We have reviewed functional neuroimaging findings on plasticity phenomena occurring in response to brain injury, epilepsy, and congenital lesions. Many of the studies and data described above do show clear patterns of reorganization of functional networks that occur either fast or slow in response to brain injury. In some cases, such as the recovery of language in early brain injury, it is not hard to believe that the observed altered brain activity contributes to the actual functional recovery. However, many of the other reviewed data are based on observations in a few patients only, and they contain a considerable part of speculation due to the still limited evidence on this topic, demanding further prospective study.

References

- Adcock JE, Wise RG, Oxbury JM, Oxbury SM, Matthews PM (2003) Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. *Neuroimage* 18:423–438
- Alkadhi H, Kollias SS, Crelier GR, Golay X, Hepp-Reymond MC, Valavanis A (2000) Plasticity of the human motor cortex in patients with arteriovenous malformations: a functional MR imaging study. *Am J Neuroradiol* 21:1423–1433
- Anderson VA, Catroppa C, Rosenfeld J, Haritou F, Morse SA (2000) Recovery of memory function following traumatic brain injury in pre-school children. *Brain Injury* 14:679–692
- Baciu M, Le Bas JF, Segebarth C, Benabid AL (2003) Presurgical fMRI evaluation of cerebral reorganization and motor deficit in patients with tumors and vascular malformations. *Eur J Radiol* 46:139–146
- Berl MM, Balsamo LM, Xu B, Moore EN, Weinstein SL, Conry JA, Pearl PL, Sachs BC, Grandin CB, Frattali C, Ritter FJ, Sato S, Theodore WH, Gaillard WD (2005) Seizure focus affects regional language networks assessed by fMRI. *Neurology* 65:1604–1611
- Bilecen D, Seifritz E, Radu EW, Schmid N, Wetzel S, Probst R, Scheffler K (2000) Cortical reorganization after acute unilateral hearing loss traced by fMRI. *Neurology* 54:765–767
- Binder JR, Swanson SJ, Hammeke TA, Morris GL, Mueller WM, Fischer M, Benbadis S, Frost JA, Rao SM, Haughton VM (1996) Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology* 46:978–984
- Brazdil M, Zakopcan J, Kuba R, Fanfrdlova Z, Rektor I (2003) Atypical hemispheric language dominance in left temporal lobe epilepsy as a result of the reorganization of language functions. *Epilepsy Behav* 4:414–419
- Briellmann RS, Labate A, Harvey AS, Saling MM, Lillywhite L, Abbott DF, Jackson GD (2005) Language lateralisation is no different between patients with temporal lobe developmental tumours and hippocampal sclerosis. *Epilepsia* 46:334–335
- Carpentier AC, Constable RT, Schlosser MJ, de Lotbiniere A, Piepmeier JM, Spencer DD, Awad IA (2001) Patterns of functional magnetic resonance imaging activation in association with structural lesions in the rolandic region: a classification system. *J Neurosurg* 94:946–954
- Chen R, Cohen LG, Hallett M (2002) Nervous system reorganization following injury. *Neuroscience* 111:761–773
- Cohen LG, Weeks RA, Sadato N, Celnik P, Ishii K, Hallett M (1999) Period of susceptibility for cross-modal plasticity in the blind. *Ann Neurol* 45:451–460
- Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, Kennedy DN, Finklestein SP, Rosen BR (1997) A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke* 28:2518–2527
- Dehaene-Lambertz G, Dehaene S, Hertz-Pannier L (2002) Functional neuroimaging of speech perception in infants. *Science* 298:2013–2015
- Dubois J, Hertz-Pannier L, Dehaene-Lambertz G, Cointepas Y, Le Bihan D (2006) Assessment of the early organization and maturation of infants' cerebral white matter

- fiber bundles: a feasibility study using quantitative diffusion tensor imaging and tractography. *Neuroimage* 30:1121–1132
- Duffau H (2001) Acute functional reorganisation of the human motor cortex during resection of central lesions: a study using intraoperative brain mapping. *J Neurol Neurosurg Psychiatry* 70:506–513
- Duffau H (2005) Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol* 4:476–486
- Duffau H, Gatignol P, Mandonnet E, Denvil D, Sichez N, Leroy M, Lopes M, Taillandier L, Bitar A, Sichez JP, Van Effenterre R, Capelle L (2004) Functional recovery after surgical resection of eloquent brain areas invaded by low-grade gliomas: the use of cerebral plasticity. *Neurosurgery* 55:468
- Elbert T, Rockstroh B (2004) Reorganization of human cerebral cortex: the range of changes following use and injury. *Neuroscientist* 10:129–141
- Fandino J, Kollias SS, Wieser HG, Valavanis A, Yonekawa Y (1999) Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumors involving the primary motor cortex. *J Neurosurg* 91:238–250
- Feydy A, Carlier R, Roby-Brami A, Bussel B, Cazalis F, Pierot L, Burnod Y, Maier MA (2002) Longitudinal study of motor recovery after stroke – recruitment and focusing of brain activation. *Stroke* 33:1610–1617
- Finger S, Wolf C (1988) The Kennard effect before Kennard – the early history of age and brain-lesions. *Arch Neurol* 45:1136–1142
- Friston KJ, Price CJ (2001) Generative models, brain function and neuroimaging. *Scand J Psychol* 42:167–177
- Gerloff C, Bushara K, Sailer A, Wassermann EM, Chen R, Matsuoaka T, Waldvogel D, Wittenberg GF, Ishii K, Cohen LG, Hallett M (2006) Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. *Brain* 129:791–808
- Hallett M (1998) The neurophysiology of dystonia. *Arch Neurol* 55:601–603
- Helmstaedter C, Fritz NE, Gonzalez Perez PA, Elger CE, Weber B (2006) Shift-back of right into left hemisphere language dominance after control of epileptic seizures: evidence for epilepsy driven functional cerebral organization. *Epilepsia Res* (in press)
- Hertz-Pannier L, Chiron C, Vera P, Van de Mortelee PF, Kaminska A, Bourgeois M, Hollo A, Ville D, Cieuta C, Dulac O, Brunelle F, LeBihan D (2001) Functional imaging in the work-up of childhood epilepsy. *Child Nerv Syst* 17:223–228
- Hertz-Pannier L, Chiron C, Jambaque I, Renaux-Kieffer V, Van de Moortele PF, Delalande O, Fohlen M, Brunelle F, Le Bihan D (2002) Late plasticity for language in a child's non-dominant hemisphere – a pre- and post-surgery fMRI study. *Brain* 125:361–372
- Holmes GL, Gairsa JL, Chevassus-Au-Louis N, Ben-Ari Y (1998) Consequences of neonatal seizures in the rat: morphological and behavioral effects. *Ann Neurol* 44:845–857
- Janszky J, Mertens M, Janszky I, Ebner A, Woermann FG (2006) Left-sided interictal epileptic activity induces shift of language lateralization in temporal lobe epilepsy: an fMRI study. *Epilepsia* 47:921–927
- Johnston MV (2004) Clinical disorders of brain plasticity. *Brain Devel* 26:73–80
- Kempermann G, Wiskott L, Gage FH (2004) Functional significance of adult neurogenesis. *Curr Opin Neurobiol* 14:186–191
- Knecht S, Dräger B, Deppe M, Bobe L, Lohmann H, Floel A, Ringelstein EB, Henningsen H (2000) Handedness and hemispheric language dominance in healthy humans. *Brain* 123(12):2512–2518
- Kolb B, Cioe J (2000) Recovery from early cortical damage in rats, VIII. Earlier may be worse: behavioural dysfunction and abnormal cerebral morphogenesis following perinatal frontal cortical lesions in the rat. *Neuropharmacology* 39:756–764
- Krainik A, Lehericy S, Duffau H, Cornu P, Capelle L, Menu Y, Le Bihan D, Marsault C (2001a) Functional recovery following lesion of the Supplementary Motor Area: a fMRI study. *Neuroimage* 13:S1206
- Krainik A, Lehericy S, Duffau H, Cornu P, Nence Y, Marsault CJ (2001b) Functional recovery after lesion of the supplementary motor area: an fMRI study. *Radiology* 221:132
- Krainik A, Lehericy S, Duffau H, Vlaicu M, Poupon F, Capelle L, Cornu P, Clemenceau S, Sahel M, Valery CA, Boch AL, Mangin JF, Le Bihan D, Marsault C (2001c) Role of the supplementary motor area in motor deficit following medial frontal lobe surgery. *Neurology* 57:871–878
- Krainik A, Duffau H, Capelle L, Cornu P, Boch AL, Mangin JF, Le Bihan D, Marsault C, Chiras J, Lehericy S (2004) Role of the healthy hemisphere in recovery after resection of the supplementary motor area. *Neurology* 62:1323–1332
- Krakauer JW (2005) Arm function after stroke: from physiology to recovery. *Semin Neurol* 25:384–395
- Krings T, Reinges MHT, Thiex R, Gilsbach JM, Thron A (2001) Functional and diffusion-weighted magnetic resonance images of space-occupying lesions affecting the motor system: imaging the motor cortex and pyramidal tracts. *J Neurosurg* 95:816–824
- Krings T, Topper R, Willmes K, Reinges MHT, Gilsbach JM, Thron A (2002) Activation in primary and secondary motor areas in patients with CNS neoplasms and weakness. *Neurology* 58:381–390
- Kubova H, Druga R, Lukasiuk K, Suchomelova L, Haugvicova R, Jirmanova I, Pitkanen A (2001) Status epilepticus causes necrotic damage in the mediodorsal nucleus of the thalamus in immature rats. *J Neurosci* 21:3593–3599
- Lee RG, Vandonkelaar P (1995) Mechanisms underlying functional recovery following stroke. *Can J Neurol Sci* 22:257–263
- Liegeois F, Connelly A, Cross JH, Boyd SG, Gadian DG, Vargha-Khadem F, Baldeweg T (2004) Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. *Brain* 127:1229–1236
- Liu Z, Yang Y, Silveira DC, Sarkisian MR, Tandon P, Huang LT, Stafstrom CE, Holmes GL (1999) Consequences of recurrent seizures during early brain development. *Neuroscience* 92:1443–1454
- Lledo PM, Alonso M, Grubb MS (2006) Adult neurogenesis and functional plasticity in neuronal circuits. *Nature Rev Neurosci* 7:179–193
- Malenka RC (2003) Synaptic plasticity and AMPA receptor trafficking. *Glutamate Disorders Cognit Motiv* 1003:1–11

- Manto M, ben Taib NO, Luft AR (2006) Modulation of excitability as an early change leading to structural adaptation in the motor cortex. *J Neurosci Res* 83:177–180
- Martino G (2004) How the brain repairs itself: new therapeutic strategies in inflammatory and degenerative CNS disorders. *Lancet Neurol* 3:372–378
- Muhlcnickel W, Elbert T, Taub E, Flor H (1998) Reorganization of auditory cortex in tinnitus. *Proc Natl Acad Sci USA* 95:10340–10343
- Murdoch J, Hall R (1990) Brain protection – physiological and pharmacological considerations. Part 1. The physiology of brain injury. *Can J Anaesth-J Can Anesth* 37:663–671
- Nudo RJ (2003) Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. *J Rehab Med* 35:7–10
- Pascual-Leone A, Amedi A, Fregni F, Merabet LB (2005) The plastic human brain cortex. *Annu Rev Neurosci* 28:377–401
- Price CJ, Warburton EA, Moore CJ, Frackowiak RSJ, Friston KJ (2001) Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions. *J Cognit Neurosci* 13:419–429
- Prins ML, Hovda DA (2001) Mapping cerebral glucose metabolism during spatial learning: interactions of development and traumatic brain injury. *J Neurotrauma* 18:31–46
- Rasmussen T, Milner B (1977) The role of early left-brain injury in determining lateralization of cerebral speech functions. *Ann N Y Acad Sci* 299:355–369
- Rausch R, Walsh GO (1984) Right-hemisphere language dominance in right-handed epileptic patients. *Archiv Neurol* 41:1077–1080
- Reinges MHT, Krings T, Rohde V, Hans FJ, Willmes K, Thron A, Gilsbach JM (2005) Prospective demonstration of short-term motor plasticity following acquired central pareses. *Neuroimage* 24:1248–1255
- Rijntjes M (2006) Mechanisms of recovery in stroke patients with hemiparesis or aphasia: new insights, old questions and the meaning of therapies. *Curr Opin Neurol* 19:76–83
- Satz P (1979) Test of some models of hemispheric speech organization in the left-handed and right-handed. *Science* 203:1131–1133
- Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M, Weiller C (2006) Dynamics of language reorganization after stroke. *Brain* 129:1371–1384
- Schiffbauer H, Ferrari P, Rowley HA, Berger MS, Roberts TPL (2001) Functional activity within brain tumors: a magnetic source imaging study. *Neurosurgery* 49:1313–1320
- Slavin S, Laurence S, Stein DG (1988) Another look at vicariation. In: Finger S, LeVere TE, Almli CR, Stein DG (eds) *Brain injury and recovery: theoretical and controversial issues*. Plenum Press, New York, pp 165–178
- Springer JA, Binder JR, Hammeke TA, Swanson SJ, Frost JA, Bellgowan PSF, Brewer CC, Perry HM, Morris GL, Mueller WM (1999) Language dominance in neurologically normal and epilepsy subjects – a functional MRI study. *Brain* 122:2033–2045
- Staudt M, Lidzba K, Grodd W, Wildgruber D, Erb M, Krageloh-Mann I (2002) Right-hemispheric organization of language following early left-sided brain lesions: functional MRI topography. *Neuroimage* 16:954–967
- Stein DG, Finger S, Hart T (1983) Brain-damage and recovery – problems and perspectives. *Behav Neural Biol* 37:185–222
- Sunaert S (2006) Presurgical planning for tumor resectioning. *J Magn Reson Imaging* 23:887–905
- Teasell R (2003) Stroke recovery and rehabilitation. *Stroke* 34:365–366
- Thirumala P, Hier DB, Patel P (2002) Motor recovery after stroke: lessons from functional brain imaging. *Neurol Res* 24:453–458
- Thomas B, Eyssen M, Peeters R, Molenaers G, Van Hecke P, De Cock P, Sunaert S (2005) Quantitative diffusion tensor imaging in cerebral palsy due to periventricular white matter injury. *Brain* 128:2562–2577
- Trudeau N, Poulin-Dubois D, Joannette Y (2000) Language development following brain injury in early childhood: a longitudinal case study. *Intl J Lang Commun Disorders* 35:227–249
- Voets NL, Adcock JE, Flitney DE, Behrens TEJ, Hart Y, Stacey R, Carpenter K, Matthews PM (2006) Distinct right frontal lobe activation in language processing following left hemisphere injury. *Brain* 129:754–766
- Wang XQ, Merzenich MM, Sameshima K, Jenkins WM (1995) Remodeling of hand representation in adult cortex determined by timing of tactile stimulation. *Nature* 378:71–75
- Ward NS, Thompson AJ, Frackowiak RSJ (2002) Spontaneous reorganization of the motor system after stroke: a longitudinal functional magnetic resonance imaging study. *Ann Neurol* 52:S86–S87
- Weber B, Wellmer J, Reuber M, Mormann F, Weis S, Urbach H, Ruhlmann J, Elger CE, Fernandez G (2006) Left hippocampal pathology is associated with atypical language lateralization in patients with focal epilepsy. *Brain* 129:346–351
- Weiller C, Rijntjes M (1999) Learning, plasticity, and recovery in the central nervous system. *Exp Brain Res* 128:134–138
- Weiller C, May A, Sach M, Buhmann C, Rijntjes M (2006) Role of functional imaging in neurological disorders. *J Magn Reson Imaging* 23:840–850
- Woermann FG, Jokeit H, Luerding R, Freitag H, Schulz R, Guertler S, Okujava M, Wolf P, Tuxhorn I, Ebner A (2003) Language lateralization by Wada test and fMRI in 100 patients with epilepsy. *Neurology* 61:699–701
- Yuan WH, Szaflarski JP, Schmithorst VJ, Schapiro M, Byars AW, Strawsburg RH, Holland SK (2006) fMRI shows atypical language lateralization in pediatric epilepsy patients. *Epilepsia* 47:593–600
- Zemke AC, Heagerty PJ, Lee C, Cramer SC (2003) Motor cortex organization after stroke is related to side of stroke and level of recovery. *Stroke* 34:E23–E26

Clinical BOLD fMRI:

Artifacts, Tips and Tricks

RONALD PEETERS and STEFAN SUNAERT

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KEY POINTS

BOLD-fMRI is prone to different *artifacts* and *sources of error*. These *artifacts* can have a technical origin, like *susceptibility artifacts* in specific brain regions, but they can also be related to brain physiology such as activation in *draining veins* that may occur in the vicinity of functionally active regions or *flow artifacts*. There are also several specific effects related to pathology that can effect clinical fMRI and therefore can lead to medical misinterpretation, e.g. *alterations or absence of BOLD-signals* induced by various brain lesions. The same holds true for *pharmacological effects* on BOLD-imaging in patients receiving medication. *Reduced cooperation* of the patients during scanning or *marked head motion* are practical problems in clinical neuroimaging and especially in fMRI. Therefore the success of clinical fMRI depends considerably on the clinician’s/technician’s ability to recognize and cope with these technical, physiological and patient-induced artifacts and sources of error.

Introduction

The fMRI technique suffers from many different types of *artifacts* (ZEFFIRO 1996). Some of these artifacts have a purely technical origin (e.g. spikes in EPI images), others may be related to physiology (e.g. cardiac related physiologic brain motion) and – last but not least – there are also pathology induced artifacts, which can lead to false interpretation of clinical fMRI maps. Clinical fMRI, which is nowadays mostly performed at a field strength of 1.5 Tesla or higher, is a rather insensitive technique since signal intensity changes induced by neuronal activity are typically in the order of a few percent, i.e. in the order of magnitude of noise (AGUIRRE et al. 1998; BOXERMAN et al. 1995). Many artifacts will therefore be related to the low signal-to-noise ratio in fMRI.

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This low signal-to-noise ratio and various possible artifacts limit the *success rate* of clinical fMRI. Also *claustrophobia and patient cooperation*, especially in more difficult tasks such as cognitive or language tasks, hinder the use of fMRI in severely ill patients. Nonetheless, the reported success rate in literature of pre-surgical fMRI is about 80–85% (HABERG et al. 2004; KRINGS et al. 2001a; LEE et al. 1999). This reported rate is probably overestimated since most patients undergoing fMRI have already undergone selection by the referring clinician, and not all patients with brain pathology are referred for pre-surgical fMRI. Head movement artifacts are the most frequent cause for fMRI failure, followed by low signal-to-noise ratio. The overall success rate is, however, also highly dependent on the scanning technique used.

The success rate of clinical fMRI is clearly related to the clinician's/technician's ability to recognize and cope with the low signal-to-noise ratio and technical, physiological and patient-induced artifacts. But there are tips and tricks how to detect and minimize these artifacts and to distinguish real brain activation from false activation.

10.1

Artifacts Related to the BOLD fMRI Signal

As discussed in Chapter 2, the neurovascular coupling between neuronal activation and cerebrovascular physiology leads to three effects that can contribute to the fMRI signal: an increase in regional blood flow velocity (rCBF), in regional blood volume (rCBV) and in local blood oxygenation level. According to the latter effect, the most widely used fMRI technique has been called “blood oxygenation level dependent (BOLD) fMRI” (OGAWA and LEE 1990; TURNER et al. 1993; RAO et al. 1993; YANG et al. 1997).

All imaging modalities that extrapolate changes in neuronal activity from changes in hemodynamic parameters produce functional maps that have passed through a “vascular filter”. This means that the regional sensitivity of the imaging modality for detecting functional changes following neuronal activation depends upon the vascular baseline state and the vascular density in and around the activated neurons. Due to the contrast mechanism of the BOLD technique – exploiting changes in deoxyhemoglobin

concentration – this also holds true for fMRI experiments (LOGOTHETIS 2002; MENON and KIM 1999; MANDEVILLE et al. 2001). Thus the observed area of signal change in the BOLD images is larger than and can be displaced relative to the actually activated neuronal population. These intrinsic effects of the BOLD mechanism limit the temporal and spatial resolution of fMRI, independently of the acquisition protocol used (ENGEL et al. 1997; MENON et al. 1998).

10.1.1

Artifacts in Spatial Localization of Brain Activity (Brain or Vein)

Spatial specificity of activated patches obtained with fMRI and how well the activation location corresponds to the actual sites of neuronal (electrical) activity have been shown to be acquisition technique dependent (LOGOTHETIS 2000; KIM et al. 2000; DUONG et al. 2004). Several authors have raised the concern that BOLD fMRI exams performed at 1.5 T may detect predominantly large draining veins, not necessarily directly adjacent to the activated area (FRAHM et al. 1994).

In order to recognize BOLD-signals that arise from veins draining the excess of blood from activated areas (MENON 2002; KANSABU et al. 1998) one can use the principles described below.

Voxel-clusters that indicate activation in draining veins are usually small, contiguous on several adjacent slices and tubulus-like following the (often intrasulcal) path of the vein through different slices, whereas the activated functional area tends to appear more expansive inside the brain parenchyma (GATI et al. 1997; KRINGS et al. 2001a).

By coregistration (overlay) of fMRI activation maps with anatomical T1-weighted contrast enhanced images – that visualize the contrast filled larger draining veins – it is possible to check for position and possible overlap of BOLD-clusters with the draining vessels. The additional coregistration of a venous MR-angiogram is also supportive to distinguish intravenous BOLD-signals from parenchymal brain activation (BAUDENDISTEL et al. 1998).

Analyzing the BOLD-signal time course, there are also differences observable between signals that originate from activated parenchyma or from draining veins. Because the draining veins are fed by venules and arterioles of the activated brain area the signal change can be expected to have a later

onset as compared to the parenchyma (KANSAKU et al. 1998; HALL et al. 2002), which is reflected by a later onset of contrast change in the timecourse of the MR-signal for the draining vein. However, this difference in temporal offset between the microvasculature in the activated parenchyma and the draining macrovasculature, is not very large, namely in the order of 1–2 s which is the time necessary for the blood to pass the smaller veins and reach larger vessels (LEE et al. 1995). Consequently, this effect is almost never observable in the standard clinical fMRI acquisition protocol with a typical temporal resolution of around 3 s, which is too coarse to detect this time difference robustly. On the other hand the relative BOLD-signal change observed in the draining vein is considerably larger as compared to that of the parenchyma (typically twice as large on a 1.5-T scanner) in a gradient echo pulse sequence. This is the result of several different effects (GATI et al. 1997). The magnetic susceptibility effects and the resulting percent signal change are enhanced around large draining veins. As the microvessels occupy a considerable smaller volume in a voxel as compared to the large draining veins the partial volume effect will also increase the percent signal change in the voxels containing the draining veins as compared to those containing the parenchymal venules/arterioles. Inflow effects are also less pronounced in the randomly oriented microvasculature as compared to the large tubuli-like draining veins (KRINGS et al. 2001a).

Thus in general the activated areas observed in functional BOLD imaging studies can be divided in two different types of appearance on the basis of high-resolution T_2^* -weighted and T_1 -weighted images. The “venous” type is highly localized, tends to be sulcal and tubulus-like and accounts for higher percentage BOLD contrast changes upon stimulation. High resolution anatomical images demonstrate that areas with the most intense stimulation-related signal intensity changes correlate with dark spots or lines on T_2^* -weighted images, and with fissures in T_1 -weighted images arising from macroscopic venous blood vessels. The latter observation is consistent with the fact that the relatively large blood vessels are located on cortical surfaces rather than within the brain tissue itself (YAMADA et al. 1997). Besides these “venous hot-spots” of activation, however, the parenchymal stimulation/activation related BOLD-signals spread more diffuse and are not at all associated with any obvious large venous vessel on anatomical images. This “parenchymal”

type accounts for most of the spatial extension of the BOLD-activation.

10.1.1.1

How to Minimize the Contribution of Draining Veins?

Contribution to fMRI signals from large draining veins is especially present when single slice, large flip angle and short TR gradient echo sequences are used (DUYN et al. 1994; HAACKE et al. 1994; YOUSRY et al. 1996), since this enlarges the contribution of the increase in blood flow and blood volume (inflow-effect). GAO et al. (1996) have demonstrated that fMRI images are more sensitive towards the microcirculation in the brain parenchyma at 1.5 T when the pulse sequence is designed to minimize inflow effects and to maximize the BOLD contribution. This can be achieved by acquiring multi-slice, long TR, heavily T_2^* -weighted single shot echo-planar images (GAO et al. 1996). Implementation of these imaging parameters, maximizes the fMRI signal towards the site of neuronal activity and thus should be a prerequisite when conducting clinical fMRI exams. Doing so, several studies have shown a good correlation between the BOLD fMRI signal and intra-operative mapping, suggesting that the functional-anatomical specificity is adequate for presurgical mapping, given that an appropriate acquisition technique was used (KRINGS et al. 2001b; NITSCHKE et al. 1998; TOMCZAK et al. 2000; STIPPICH et al. 2003).

The use of a higher main magnetic field strength will also decrease the effect of draining veins (GATI et al. 1997). The decrease in draining vein influence in increasing field strengths is a result of the field dependence on the alteration in T_2^* -values due to susceptibility induced gradients around blood vessels which depends on the diffusional averaging. Thus, the change in T_2^* is a function of the motion of protons in the brain tissue as well as of the magnitude of field gradients encountered by the tissue protons. The latter is dependent on the size of the blood vessels and the orientation of these vessels relative to the main magnetic field direction. This effect has been modeled into an equation by OGAWA et al. 1993:

$$1/T_2^* = \alpha [\gamma \Delta\chi B_0] b_L + \beta [\gamma \Delta\chi B_0]^2 (b_s)^q p$$

with b_L and b_s the blood volume fractions for respectively large (venules and larger veins) and small blood vessels (capillaries) in a given voxel. α , β are

constants, p is the fraction of active capillary vessels so that b_v is the blood volume when the entire capillary bed in the voxel has been recruited. B_0 is the strength of the main magnetic field, γ the gyromagnetic ratio for protons, and $\Delta\chi$ the susceptibility difference between blood vessel and surrounding tissue, a value which is linearly related to the amount of deoxyhemoglobin in the blood (OGAWA and LEE 1990). This equation predicts therefore that the overall effect of susceptibility difference on a T_2^* -sensitive imaging technique will be somewhere between linear and quadratic depending on the main magnetic field. It also reveals that at high magnetic fields the contribution of small vessels is more pronounced than at low fields (MENON et al. 1995). Thus, with respect to signal intensity changes induced by susceptibility alterations of the blood vessels secondary to neuronal activity, this effect will increase more than linearly with magnetic field strength, with a larger contribution of the more desired small vessel effect and therefore resulting in advantages towards higher fields (UGURBIL et al. 1999) for distinguishing parenchymal activation. However, higher fields are also more sensitive to other artifacts such as susceptibility induced image deformations in EPI (see Section 10.3.1 Susceptibility Artifacts in this chapter), larger influences of scanner instability (COHEN and DuBOIS 1999) and physiological effects (WEISSKOFF 1996), which will be discussed below.

BOLD functional activation maps can also be obtained by using the spin echo based T_2 -contrast rather than the gradient echo based T_2^* -contrast (DUONG et al. 2003). However, the observed BOLD effect is smaller on the T_2 -relaxation parameter making this technique less sensitive and decreasing the SNR of the activated brain regions. On the other hand, the use of the T_2 -effect can be preferable if one wants to avoid spurious activation in large veins (LOWE et al. 2000) since spin echo sequences have a high specificity for microvessels and are less sensitive to susceptibility effects around the larger blood vessels (OJA et al. 1999). For further elucidation about the spatial specificity of gradient echo and spin echo sequences we like to refer to Chapter 7 where this topic is discussed in more detail.

Another technique to maximize parenchymal activation compared to venous activation has been demonstrated by COHEN et al. (2004) where hypercapnic normalization of the BOLD activation maps with the aid of CO_2 inhalation was used to normalize the BOLD activated areas making them indepen-

dent of the resting state CBV in the voxels (COHEN et al. 2004). Maximizing the fMRI signal towards the site of neuronal activity can also be achieved by optimizing the mode of stimulation. A study by LE RUMEUR et al. (2000) has shown that different types of sensory stimulation are capable of differentiating primary sensory cortex from the venous draining network. Discontinuous stimulation of a limited skin area elicited activity in the microvasculature of the sensory cortex only, whereas robust continuous stimulation of a large skin area gives access to the functional area as well as the venous network. The authors claimed that the discontinuous stimulation paradigm induced less effective summation of the hemodynamic responses, and thus less migration of BOLD contrast to the venous network. Also if the activated region has a rather small surface area ($<100 \text{ mm}^2$) the oxygenation state in the vein draining that area will extend in that vein without dilution only up to 4–5 mm beyond the edge of the activated region (TURNER 2002), minimizing the influence of the draining vein signal on the presurgical BOLD maps, when only small activated regions are present.

Practical tip – in preoperative fMRI the impact of spurious venous signals will be important as to know which distance to keep clear of when removing a lesion. In this context we also refer to Chap. 4. Within the brain parenchyma it is not clear, yet, which distance to a functional activation is safe for resection. This important issue requires further study based on standardized functional neuroimaging, intraoperative use of functional data and detailed pre- and postoperative assessment of clinical parameters. Due to the current knowledge resection borders cannot be delineated reliably from BOLD-fMRI as the clustersize changes with the statistical threshold. However, the center of gravity of a BOLD-cluster precisely identifies the part of the anatomical structure (gyrus) that is relevant for the corresponding brain function and needs to be preserved during surgery. For venous vessels this is not the case as this is not a real activated region and one only has to keep clear of the large draining veins. Practically it is advised to always acquire anatomical high resolution images of the patient, preferably contrast enhanced, to pinpoint blood vessels and to coregister the fMRI activation images with these anatomical images in order to distinguish ‘activation’ in anatomically visible vessels and in brain parenchyma. In general localization errors up to 5 mm should be taken into account that may arise

from inaccuracies in the overlay of the distorted functional EPI-images on the morphological images. When small very intense activated patches are observed it is also advised to compare these time courses with those of the more diffuse paranchymal regions to distinguish both types of regions.

10.1.2

The Influence of Brain Lesions on BOLD fMRI

An important aspect of functional MRI validity for clinical purposes that has not been resolved yet is the significance of absent, reduced or artificial BOLD-activation. Here it is important to know, whether absent or reduced BOLD-signal also reflects absent or reduced neuronal activation and whether BOLD-signals in hyperperfused tissue (e.g. nearby or in the boundaries of highly vascularized tumors and metastasis) or in areas with altered hemodynamic properties (e.g. AVMs) truly represent functional neuronal activation. Until now the knowledge on these issues is very limited as is the information on their prevalence. The different phenomena have been described anecdotally, but investigators using fMRI preoperatively should be aware of their existence. As pointed out in an editorial by Bryant, these “negative results” deserve further study (BRYANT and JACKSON 1998). Therefore future studies of the underlying pathophysiological processes are mandatory to correctly interpret BOLD-fMRI in the clinical context.

10.1.2.2

Absent or Reduced BOLD Signals

Different pathological conditions could dampen the hemodynamic response that is the source of the BOLD-fMRI signals. Brain tumor vessels typically lack cerebral autoregulation. Their vasculature is less responsive than that of surrounding normal tissue. Intracranial space-occupying lesions could alter some different properties; they induce proliferation of pathologic vessels in the adjacent tissue (neovascularisation), thus altering density, size, and topography of vessels and increasing the blood volume. The blood-brain barrier may break down within the tumor mass itself as well as in the surrounding tissue. The mass effect of the lesion and the peritumoral vasogenic edema changes the apparent diffusion coefficient and therefore could also produce mechanical vascular compression. If, how-

ever, the brain's ability to autoregulate the flow of blood is lost in the local brain tissue proximal to the tumor, which is still functioning, then this area may not respond to increased neural activity by a corresponding increase in blood flow and subsequent BOLD signal (HOLODNY et al. 2000; LUDEMANN et al. 2000). The biochemical environment (adenosine 59-triphosphate, pH, glucose, lactate, etc.) and the cortical levels of neurotransmitters in and around gliomas are altered. Specifically, the release of nitric oxide by reactive astrocytes and macrophages at the brain-glioma interface may increase the ‘resting state’ regional cerebral blood flow and thus alter the physiological hemodynamic response (FUJIWARA et al. 2004; HUND-GEORGIADIS et al. 2003; SCHREIBER et al. 2000). Similarly, therapeutic drugs administered to the patients may also interact with hemodynamic autoregulation (SEIFRITZ et al. 2000; BRAUS and BRASSEN 2005). In regions more distant from the gliomas where tumor vasculature is not present, the release of nitric oxide by reactive astrocytes and macrophages at the brain-glioma interface results in luxury perfusion and a reduced oxygen extraction fraction, resulting also in a reduced BOLD contrast enhancement (SCHREIBER et al. 2000).

10.1.2.2.1

Case of a Patient Showing an Inverted BOLD Signal Change

It is of utmost importance to realize that the absence of fMRI activity in a particular brain region *does NOT mean* that electrical neuronal activity within this area is non-existing, and thus that it is safe to surgically remove this region. We will demonstrate this important point using the following case report, illustrated in Figure 10.1. fMRI activity during bilateral finger-tapping vs rest in a patient with a left Rolandic tumor (glioma WHO grade II in the postcentral gyrus also extending through the central sulcus into the “hand knob” of the precentral gyrus). In the non-lesioned right hemisphere fMRI activity is observed within the right sensorimotor cortex (SM1; pre- and postcentral gyri), the right premotor cortex (PM), and right parietal cortex (PP). In contrast, in the lesioned left hemisphere fMRI activation is only observed anterior to the tumor in the left premotor cortex (PM). While this fMRI activation map might be interpreted as an absence of electrical neuronal activity within the left SM1 and PP areas (e.g. due to plastic changes and take-over of motor function within the ipsilateral

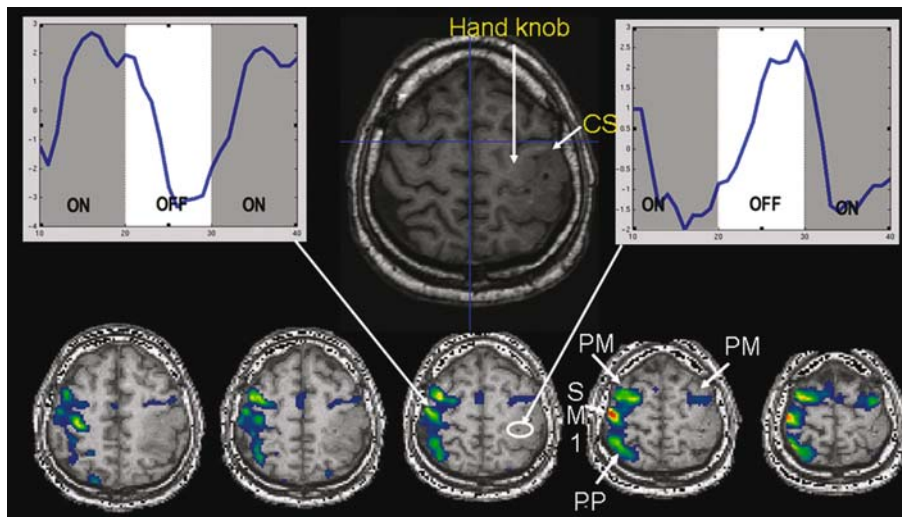


Fig. 10.1. Case study of a patient showing an inverted BOLD signal in the neighborhood of a lesion

non-lesioned hemisphere), the signal time courses clearly show that this is a false conclusion. In the left, tumor-infiltrated SM1 hand representation, the BOLD signals decrease during performance of the motor task, and increase during the baseline condition (rest); i.e. an *inverse* BOLD MR signal change as compared to the physiological activation. This finding may result from lesion-induced neurovascular uncoupling, where oxygen extraction (cause of the initial dip of the BOLD signal) occurs without increase in regional cerebral blood flow and volume (rCBF and rCBV), resulting in a steady decrease of fMRI signals despite increased electrical neuronal activity driving the actual movements. As pointed out in a editorial by BRYAN and KRAUT (1998), these “negative results” deserve further study (SUNAERT et al. 1998). One may speculate that – depending on the lesion induced hemodynamic changes in different patients – there could be continuous alterations of BOLD-signals from “normal” via “absent” to “inverse”. Possible BOLD-alterations should be taken into account when functional lateralization is determined using fMRI as they may lead to incorrect interpretation of clinical fMRI data.

10.1.2.2

BOLD-Signals in Contrast Enhancing Parts of Brain Malignancies

In some patients with gliomas, BOLD-signal changes can be observed inside contrast enhancing parts of the tumors which are believed to not contain functional tissue. In addition these areas have a blood brain barrier disruption and neovascularity and they

may contain necrotic areas – all pathologies that are known to interfere with BOLD-imaging. Therefore an exclusion of artifacts that may alter the BOLD-signals would be most welcome, but is not available yet. This issue has been studied using electrophysiological measures of brain activation, but not BOLD-fMRI (SKIRBOLL et al. 1996; GANSLANDT et al. 1999; SCHIFFBAUER et al. 2001). From these studies using magnetic source imaging (which is a combination of magnetoencephalography with anatomical MRI) it can be concluded that real functional activity might be located within or at the margins of tumors in a considerable body of patients (e.g. 25% in a study of Schiffbauer) so that only partial resection was possible. The interpretation of sources at the tumor margin remains ambiguous; cortex has either been “displaced” by the growing tumor or is “on the point of” being invaded by infiltrative tumor. Therefore it is not always the case that these activated areas in the tumor tissue are artifacts, but could be real functionally active tissue which is infiltrated by the gliomas. If, in doubt of the real or artificial nature of the activations, it is advisable to combine different techniques that measure brain activation indirectly (e.g. fMRI) and directly (e.g. MEG) to pinpoint better the real nature of the BOLD signal change. More information on multimodality functional neuroimaging is provided in Chap. 8.

10.1.2.3

BOLD-Signals in Patients with Brain AVMs

Arteriovenous malformations (AVM) can produce widespread vascular steal effects beyond their nidus,

that preclude a normal hemodynamic response (for details see Chap. 7). However, cerebral blood flow reductions do not necessarily cause cerebral dysfunction, as suggested in previous reports. Alterations of microvascular architecture are prone to exist in the neighborhood of vascular malformations and neovascularization is characteristic for malignant brain tumors and for brain metastases of different malignancies, resulting in a change in the observed BOLD-signal in these brain pathologies. Also several studies have been published in different patient populations with AVMs reporting a shift of the functionally active regions in the neighbourhood of the AVMs. Vascular malformations are believed to form during gestation, and the development of these lesions and the associated brain damage due to hemorrhage or ischemia could lead to reorganization of not only the local anatomy but also the functional cortex (LEHERICY et al. 2002). This can result in cortical reorganization where the real functionally active region has been shifted in previously other functionally defined regions (FANDINO et al. 1999; MALDIJAN et al. 1996). For more information on brain plasticity see Chapter 9.

10.1.3

The Effect of Different Pharmaceuticals on the BOLD fMRI Signal

Chemicals and pharmaceuticals can have an effect on different aspects of brain physiology and/or hemodynamic coupling (SEIFRITZ et al. 2000; BRAUS and BRASSEN 2005). The next paragraph introduces some known effects of substances on BOLD signals.

10.1.3.1

Caffeine

The effect of caffeine – a vasoconstrictor – on BOLD-signals has been studied by several researchers (LAURIENTI et al. 2003; PARRISH et al. 2001). In an experiment to determine the hemodynamic response function, volunteers have been presented a short visual flash to activate primary visual areas and triggering a finger to thumb opposition. They were scanned in two consecutive sessions: before and after drinking three cups of coffee. The observed hemodynamic response function before and after administration of caffeine demonstrate a large increase (up to 50%) of BOLD signals for the ses-

sion after caffeine intake as compared to the control session (Fig. 10.2a). The explanation for this effect may rely on the different properties of caffeine, it modulates neural activity and neurovascular tone. The influence on the neurovascular tone decreases the resting state CBF. As a result the increase in rCBF and the relative BOLD signal change during stimulation is much higher after intake of caffeine. Caffeine also has an excitatory action on neurons through blockade of A1 adenosine receptors increasing the resulting neural activity following stimulation (PARRISH et al. 2001; LAURIENTI et al. 2002).

10.1.3.2

Alcohol

The effect of alcohol on BOLD-signals is shown in Figure 10.2b. A similar experiment as the one described above has been conducted in volunteers before and after the consumption of three glasses of beer (about 34 ml of alcohol). The graph demonstrates that alcohol has an adverse effect as compared to caffeine on the hemodynamic response. The effect of alcohol is twofold: first, alcohol is a vasodilator which increases the resting state CBF resulting in a lower increase of rCBF following stimulation and hence a reduction in relative BOLD-signal increase (SEIFRITZ et al. 2000; LEVIN et al. 1998). Second, alcohol also decreases attention to the task the subjects have to perform and therefore the neuronal activation of the stimulated brain areas, whereas caffeine increases attention.

10.1.3.3

Other Chemicals

Finally, it is also important to notice, that various pharmacological agents may potentially alter BOLD signals. Cocaine, for example, has effects on neuronal connectivity (LI et al. 2000), neuronal activation and on the resting state cerebral blood flow (BREITER et al. 1997; LEE et al. 2003); however BOLD signals remained unaffected after cocaine administration (GOLLUB et al. 1998). The absence of an effect on the BOLD signal change may be interpreted as follows. The 14% decrease in CBF measured contributed less to the changes in BOLD signal intensity than do changes in oxygenation level. A concomitant decrease in glucose metabolism after acute cocaine infusion offset the decrease in BOLD signal intensity caused by the decreased CBF, with the result that matching changes in blood flow and

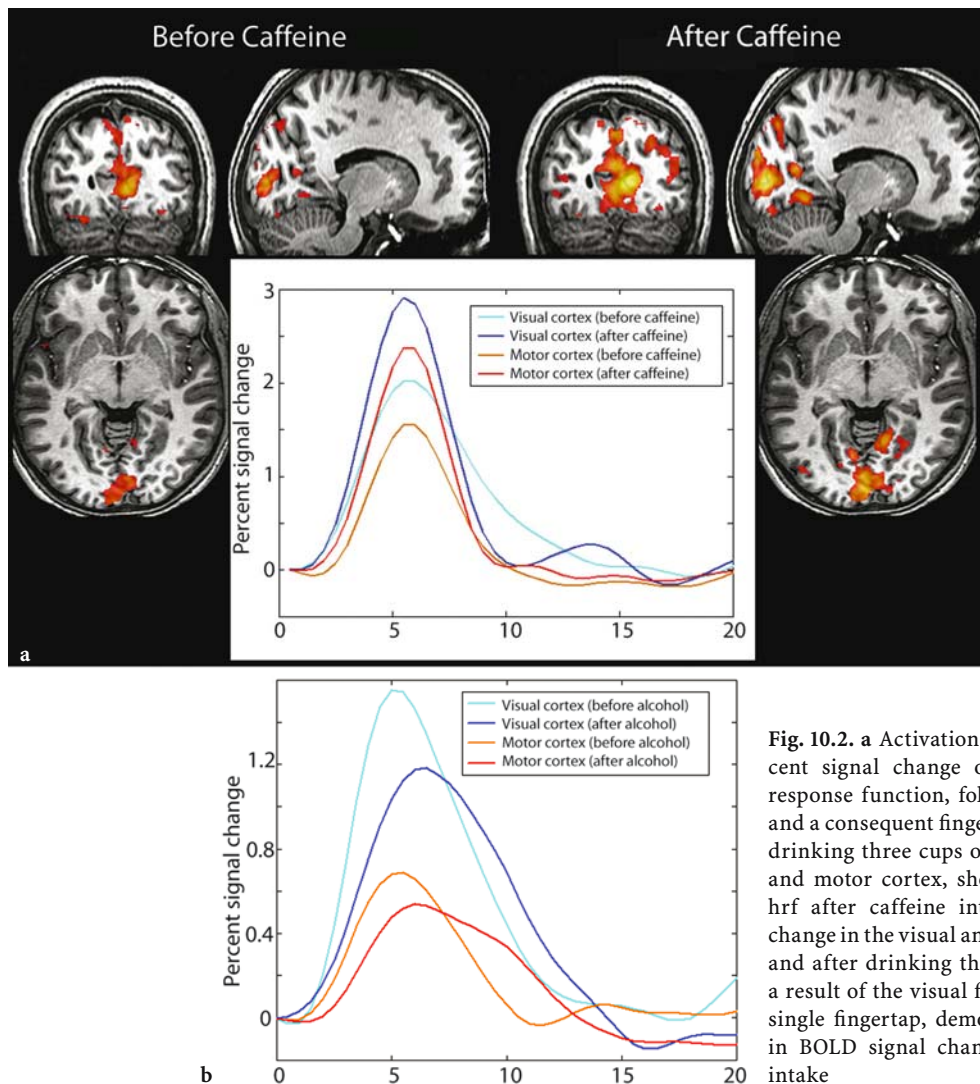


Fig. 10.2. a Activation maps and mean percent signal change of the hemodynamic response function, following a visual flash and a consequent fingertap, before and after drinking three cups of coffee, in the visual and motor cortex, showing an increase in hrf after caffeine intake. **b** Mean signal change in the visual and motor cortex before and after drinking three glasses of beer as a result of the visual flash stimulation with single fingertap, demonstrating a decrease in BOLD signal change following alcohol intake

oxygen consumption left the hemoglobin oxygen saturation nearly unchanged. Theophylline was shown to increase BOLD signals in the rat primary motor cortex (MORTON et al. 2002), a finding also observed in patients with hyposmia where theophylline increased odor induced BOLD responses (LEVY et al. 1998). The decreased resting cerebral blood flow due to the vasoconstrictor response might possibly account for the increased BOLD response after theophylline use. Theophylline also has known neuroexcitatory properties – it is an antagonist of the inhibitory neurotransmitter adenosine. With this neuroexcitatory effect, theophylline could increase the number of neurons that are activated in response to a given stimulus, increasing the observed BOLD response. On the other hand nicotine – a drug without effects on local brain hemodynamics as dem-

onstrated in a simple visual task (JACOBSEN et al. 2002) – has been demonstrated to increase attention to cognitive tasks both in schizophrenics and normal smokers (KUMARI et al. 2003; JACOBSEN et al. 2004). It is important to notice that many pharmacological agents, which have not yet been tested in this respect, may influence the BOLD response, and patients harboring brain tumors may receive such medication.

10.1.3.4 CO₂

Several studies report on the effects of CO₂ on the resting state BOLD signal and on the BOLD response during activation while inhaling CO₂. CO₂ is a potent vasodilator increasing BOLD signals.

Breathing a mixture of air with 5% CO₂ increases the measured BOLD signal by 10 % (KASTRUP et al. 1998). This effect can have consequences in patient studies as well. A change in breathing rate during the task, as a result of excitement and stress at the beginning of the experiment can occur in some patients. This change in breathing rate changes the oxygen supply to the brain and the CO₂ content in the blood effecting the vasodilatation and thus the global BOLD signal in the brain. This can interfere with the task-related BOLD response. When

a volunteer is asked to change his breathing rate from normal breathing to hyperventilation and vice versa, the time course of the BOLD signals displays clearly the large effect of hyperventilation on the resting state fMRI signal (Fig. 10.3). In order to minimize effects of anxiousness and the change in breathing rate in clinical fMRI studies, it is therefore very important to instruct and comfort the patients comprehensively and allow them to accommodate to the scanner environment before the start of the experiment.

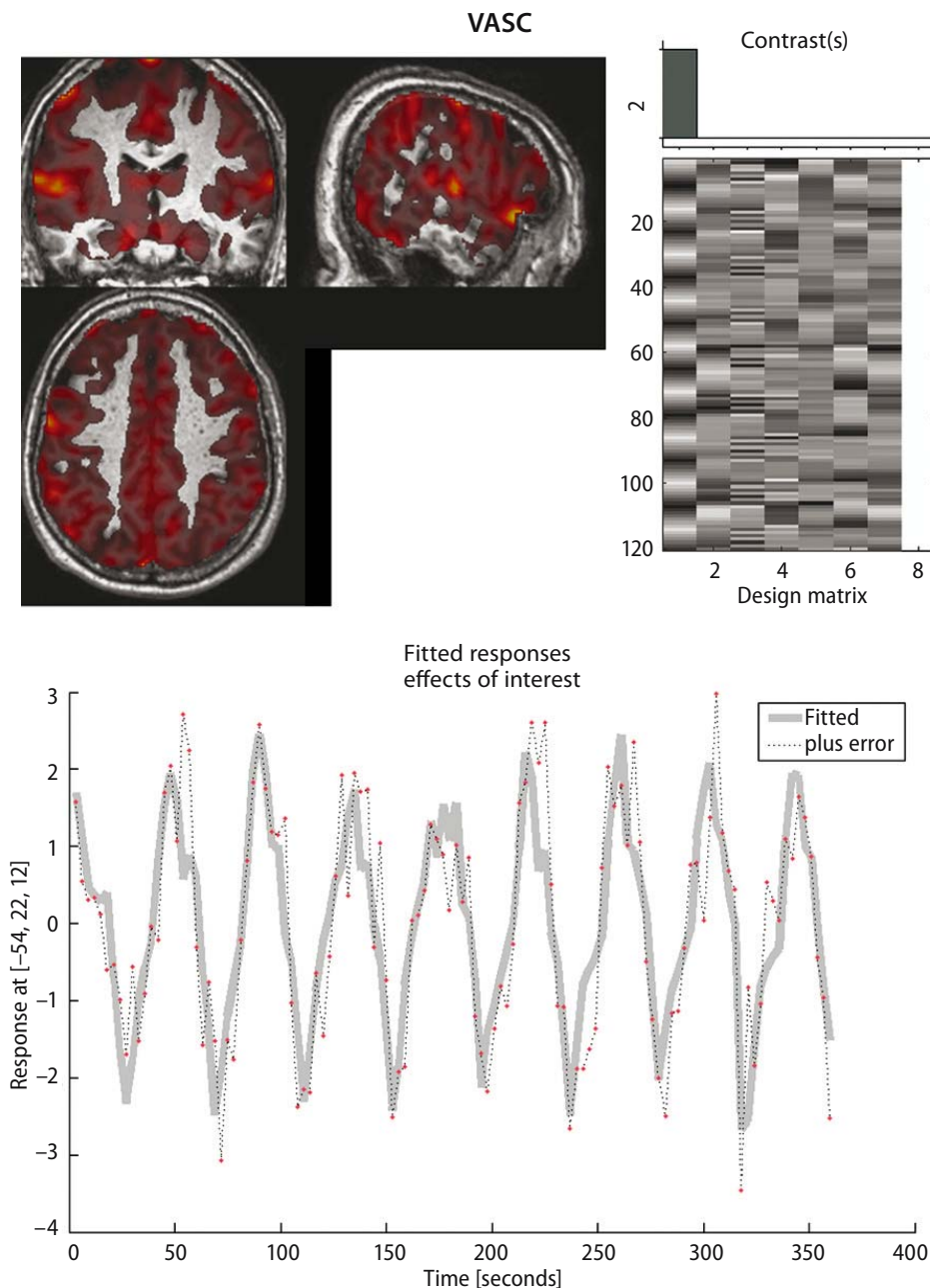


Fig. 10.3. Effect of hyperventilation on the BOLD resting state signal. During this scanning session the volunteer switched from hyperventilation periods to breath-hold periods of 24 s. The activation map shows MR signal change following the breathhold/hyperventilation paradigm in the entire cortex of the volunteer. The MR signal timetrace in the bottom of the figure clearly demonstrates the signal fluctuation for a random voxel in the cortex

10.2
Patient Related Artifacts and Physiological Noise

10.2.1
Flow and Pulsation Artifacts

Flow artifacts result from the pulsating in- and out-flow of blood perpendicular to the imaging slices, introducing signal changes in different slices. At 1.5 T these artifacts are observed especially in pathological flow conditions such as AVMs. However, with the trend towards using higher magnetic field strengths

(3T and above) flow and pulsation artifacts become more prominent (BISWAL et al. 1996; SRIVASTAVA et al. 2005). These artifacts may appear as slowly varying signal changes with a sinusoidal rhythm, which is the result of the undersampling of the real underlying blood pulsation. In Figure. 10.4a a pulsation artifact is demonstrated in an fMRI experiment acquired in a 3-T scanner without any specific brain activation demonstrating several tubular shaped regions which have a signal intensity behaving in a sinusoidal fashion. If the stimulation paradigm has a period similar to the period of this sine (in this case a period of 100 s), these areas will light up as false positives (DAGLI et al. 1999).

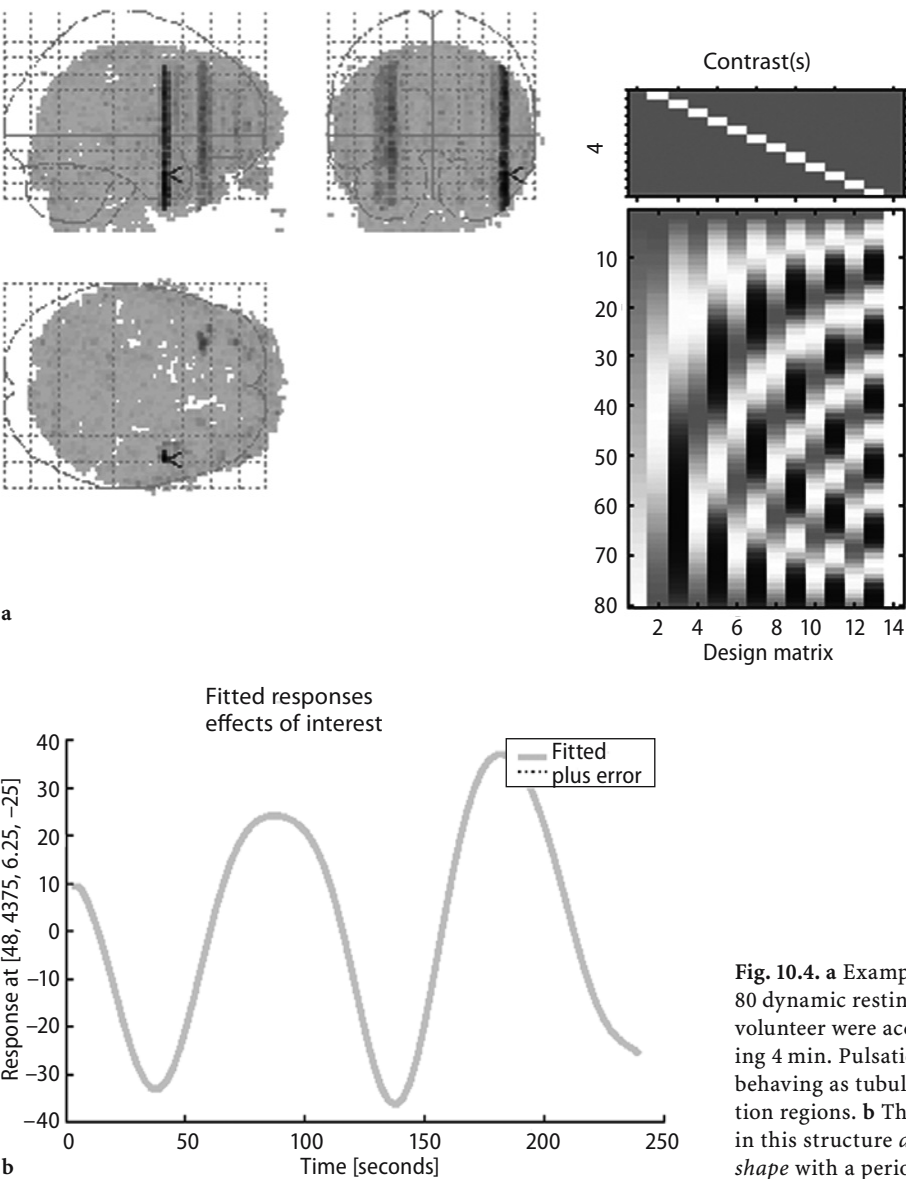


Fig. 10.4. a Example of a pulsation artifact: 80 dynamic resting state BOLD scans of a volunteer were acquired with a TR of 3 s during 4 min. Pulsation artifacts are observed behaving as tubuli-like BOLD fMRI activation regions. b The time course of the signal in this structure demonstrating a sinusoidal shape with a period of 100 s

10.2.2

Artifacts from Bulk Head Motion

The small intensity changes typically observed in fMRI images (ranging from a fraction of a percent signal change to a few percent) can easily be contaminated by a variety of sources. In clinical fMRI the major contribution to signal artifacts comes from bulk head motion during the acquisition of the functional data series (SETO et al. 2001), another minor contribution comes from physiological brain motion (pulsation of the brain, overlying vessels and cerebrospinal fluid) driven by cardiac pulsations (DAGLI et al. 1999; WINDISCHBERGER et al. 2002). Thus, the primary reason for most failed clinical fMRI examinations is head motion. In the study of KRINGS et al. (2001a) the most frequent cause for the failure of 15% of their clinical exams was due to the presence of head movement artifacts.

The motion and its effect occurring during an fMRI time series acquisition can be divided into two separate categories: Intra-image motion is generally a very fast and sudden motion (i.e. at a time scale smaller than the image acquisition time) and inter-image motion on a time scale between a couple of seconds to minutes is a slow movement of the subject (i.e. at a time scale larger than the time necessary to acquire a single image volume). These two sub-categories of motion have quite different effects on the acquired image and functional map properties. The intra-image motion which is typically induced

by sudden head movement results in blurring and ghosting in older GE based acquisition sequences, but is less often detectable in single shot echo-planar imaging in which all data for an image are collected in under 100 ms (DUERK and SIMONETTI 1991). However, if present this sudden motion can have the following effects on the resulting EPI images: if the motion is very fast (<100 msec), it can still result in ghosting artifacts in several slices of the acquired volumes; slower longer lasting motion can also change the image contrast. This is especially true if the motion occurs perpendicular to the acquisition plane. Such through plane head motion will result in a change of the apparent repetition time for the acquisition of the same slice in the different volumes (Fig. 10.5) which changes the T1 weighting of the tissue for the different slices and thus the signal intensity of the tissue. In other words the tissue has experienced a different “spin history” (FRISTON et al. 1996b).

Motion on a time-scale larger than the image acquisition time leads to a misregistration of the images within the time series and makes activation foci undetectable or, even worse, induces artificial activation when the motion is temporally correlated to the stimulus (HAJNAL et al. 1994) (Fig. 10.6). This will especially have an effect in those brain regions that show steep image intensity gradients (e.g. at the edges of the brain or in patients at the border of a T2 hyperintense lesion) which are very prone to these artifacts. The effect of this inter-image motion has

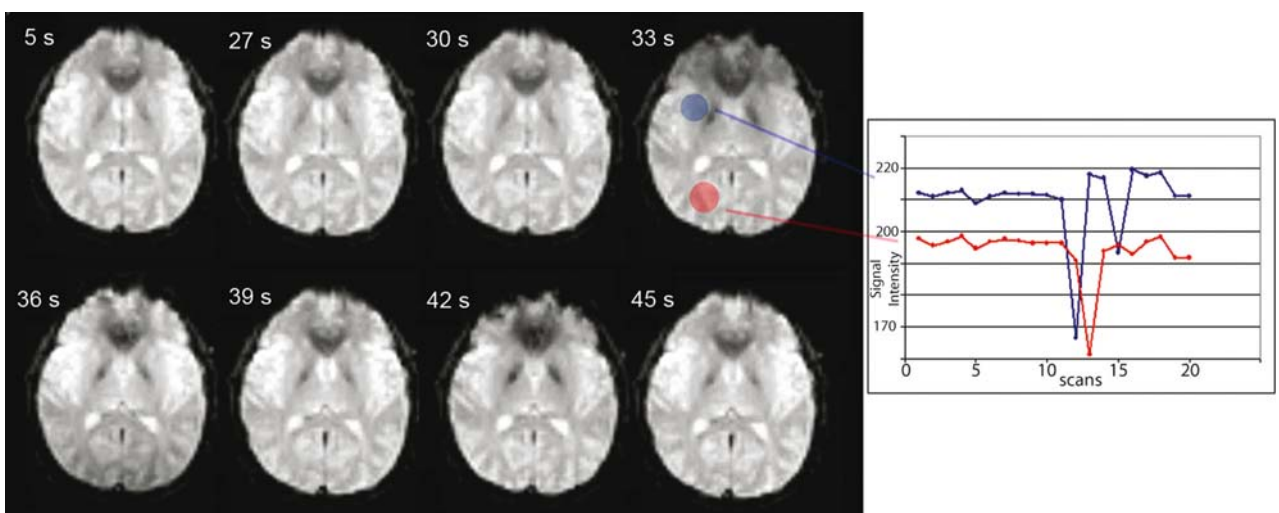


Fig. 10.5. Different time points in a fMRI series (TR=3) of a volunteer. During the scan he moved his head through the plane of acquisition. The time trace shown on the right displays the signal intensity change of the voxels in the filled regions, a large motion induced signal drop is apparent resulting from this through plane motion at around 30 s

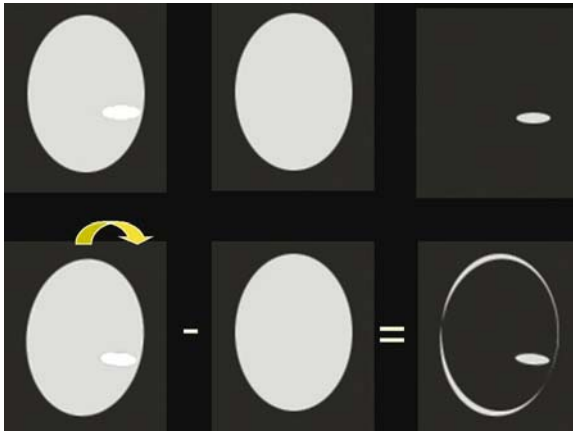


Fig. 10.6. Simulation of the effect of head motion between different states of activation on the observed activation in a subtraction map. *In the top row* without motion only the real activated region is discerned, *in the bottom row* on the other hand motion between both images is introduced and a rim of false activation appears in the subtraction map

been shown to be particularly problematic in clinical examinations. Results from HILL et al. (2000) indicate that head motion occurs with a greater magnitude in a group of epilepsy patients than in a group of healthy volunteers undergoing the same examination.

10.2.2.1

Minimizing and Correcting for Motion

Several solutions exist to correct for or to minimize inter-image motion which have been proposed by several groups. Head movement during the acquisition phase can be restricted by fixation of the head with molds and straps (DEBUS et al. 1996; FITZSIMMONS et al. 1997; EDWARD et al. 2000), which provide an intermediate level of head fixation. The use of a “bitebar” (Fig. 10.7) – a custom molded dental fixation, regularly used in our institution to restrain head motion while imaging volunteers – provides a highly rigid fixation, but its usability is limited in patients (DYMARKOWSKI et al. 1998). The presence of dental prosthesis interferes, and not all patients tolerate this kind of fixation. Furthermore, safety precautions preclude its use in those patients who are at risk of having epileptic seizures during imaging (JIANG et al. 1995; FREIRE and MANGIN 2001).

Another solution is the use of motion correction algorithms in data postprocessing which are integrated into most fMRI analysis softwares. Motion correction is typically achieved by rigid realign-

ment of the consecutively acquired images in the data series with the first image (or an arbitrary other image) (FRISTON et al. 1995, 1996b; MAES et al. 1997). If the patient moved with a frequency unrelated to the frequency of the applied stimulation paradigm, this realignment post-processing can successfully separate this motion from true activation (Fig. 10.8). As most motion correction algorithms are intensity based it is also possible that a false motion could be observed in the time series which is actually the result of a large activation at a specific brain region shifting the center of intensity to a certain direction following the activation paradigm (BISWAL and HYDE 1997)

However, most patient motion will be correlated with the applied stimulus (HILL et al. 2000), which is certainly true if the patient is performing different motor paradigms (e.g. the patient is moving the head at the start of the task to look at the fingers performing the task); this is an effect that cannot be easily separated from the real functional activation due to their synchronicity (HAJNAL et al. 1994).

The problem of patient motion could be further reduced in a number of ways. First, stimulation paradigms can be optimized to induce less patient head motion, an issue that is currently under investigation (see also Chap. 4). Much attention is given to the differences in anatomico-functional information that can be obtained from active versus passive tasks which inherently will induce less motion (GASSER et al. 2004).

As described earlier, the effect of through plane motion is a combination of misregistration of the different subsequent BOLD images and the T1-slice effect changing the signal intensity resulting from the change in TR. Therefore it is advisory to adapt the scanning planes in such a way that the highest motion would be parallel to the acquisition plane, e.g. if one expects head nodding from left to right, axial slices should be acquired, if head motion is expected from front to back acquisition of sagittal slices would be preferable. There also exist techniques to correct for the spin history effects due to through plane motion (MURESAN et al. 2005).

Recently adapted acquisition sequences have been presented that prospectively change the position of the acquired EPI volume in order to match for the motion of the subject. To achieve this subject motion has to be calculated online between two consecutive acquired volumes and this information can be used to predict the position of the head for the following (third) acquisition. This technique uses a prospec-

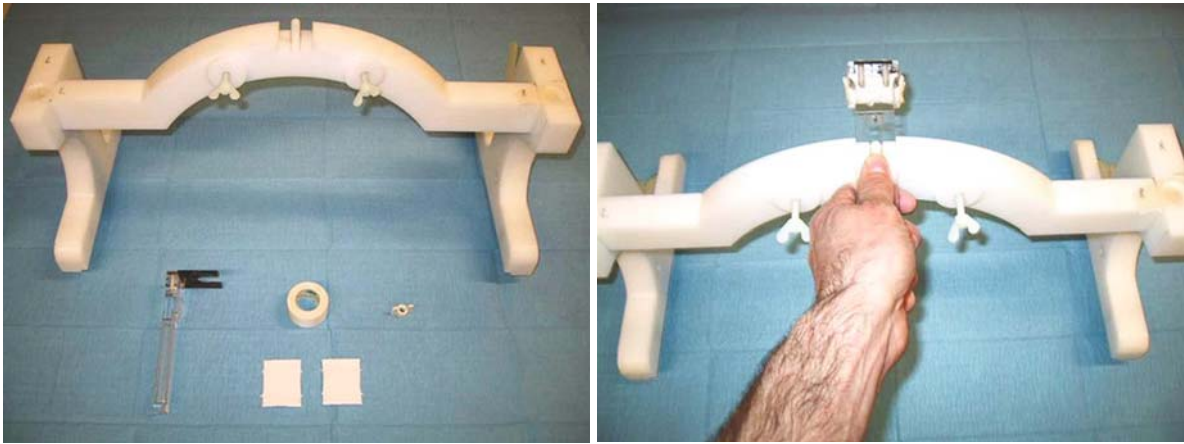


Fig. 10.7. Pictures of a custom build bite-bar system used to minimize patient motion during the fMRI experiment, consisting of a plastic bridge which is positioned over the subject's shoulder and a small detachable piece which the subject puts in his mouth

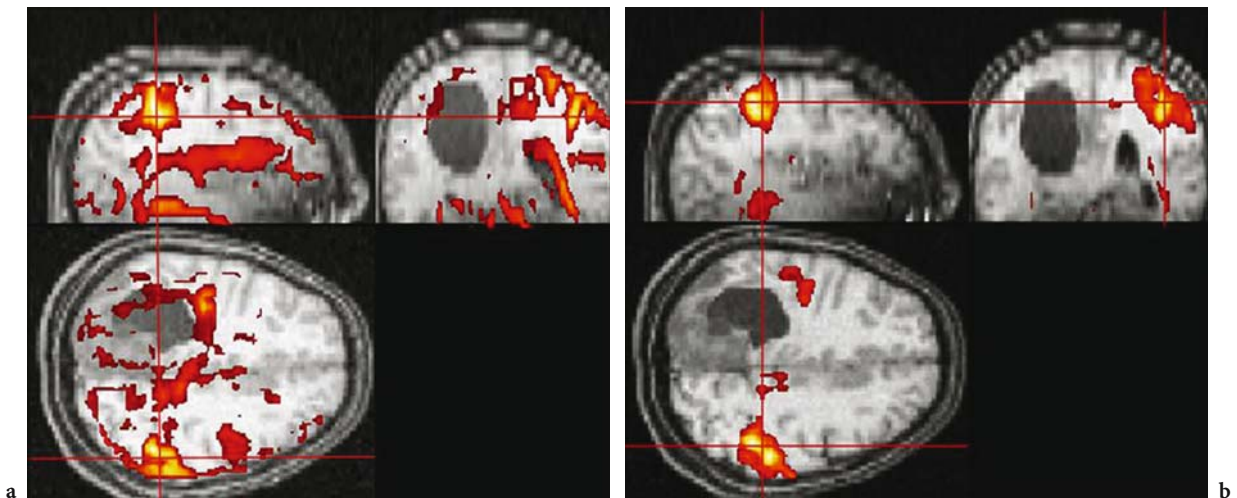


Fig. 10.8a,b. Effect of subject motion on the resulting fMRI activation map of a patient (a) and the effect of the correction of this motion (b) on the observed real and false motion induced activation in the calculated fMRI map

tive motion correction algorithm in contrast to the retrospective motion correction techniques used in former fMRI postprocessing software tools. As the scan planes are adapted to the motion the T1 slice effect is also diminished (WARD et al. 2000; THESEN et al. 2000).

If the motion artifacts still persist in the resulting BOLD activation maps, there is an option in most software packages to incorporate the motion parameters calculated in the preprocessing step in the statistical calculation of functional activation (e.g. using the general linear model (GLM)). By doing so the signal variability in the voxels, correlating with these motion parameters will be described in this contrast decreasing the influence of the motion

induced signal changes in the other contrasts of interest of the stimulation paradigm. Although this will effectively remove motion induced “false” activations it can also remove or decrease the real activation correlated with the motion. For more details see Chapter 2.

10.2.2.2

How to Distinguish Real Activation from Motion Induced False Activation

If it was not possible to completely eliminate motion during image acquisition and data processing (e.g. in the case of paradigm related motion), motion artifacts need to be identified in the activation maps.

This paragraph provides some practical tips to distinguish motion induced “false activations” from the real activation induced BOLD signals. Most of motion induced “false activations” are localized at the borders of different structures which show large signal intensity gradients (WEISSKOFF 1995; ORCHARD and ATKINS 2003). The motion induced signal changes at these borders typically have a ring like spatial appearance at their boundaries, in other words they are observed as a thin rim of hyperactivation in the neighborhood of large image intensity gradients (Figs. 10.6 and 10.8). The BOLD hemodynamic response curve typically increases 4 s after the onset of stimulation and reaches its maximum after 6–8 s. If the movement follows the paradigm, the onset of the movement will be at the same time as the onset of the paradigm. Movement related signal changes will follow the movements instantaneously. Therefore the temporal profile of the movement related “false activations” will be shifted forwards compared to the real activation temporal profile (which has typically a delay of approximately 2–4 s related to the hemodynamic changes in the functional area) and coincide with the external profile,

the signal intensity change will also be more abrupt compared to the more gradual activation induced BOLD signal intensity change. Movement related signal changes tend to display much higher signal intensity changes as compared to the physiological BOLD signal changes (Fig. 10.9).

10.2.3 Cooperation of Patient

Cooperation of the patient during the fMRI exam is very important; therefore control of task performance during the scanning is a prerequisite in clinical functional MRI. In an active motor task, cameras are very handy to inspect whether the patient understands and performs the task correctly. In patients with limited ability to cooperate, direct instruction plus direct supervision of proper task performance by the investigator standing next to the scanner is strongly recommended. In visual experiments it is important to monitor eye movements using an eye tracking camera. Figure 10.10 displays the difference in activation maps between a fixating and a

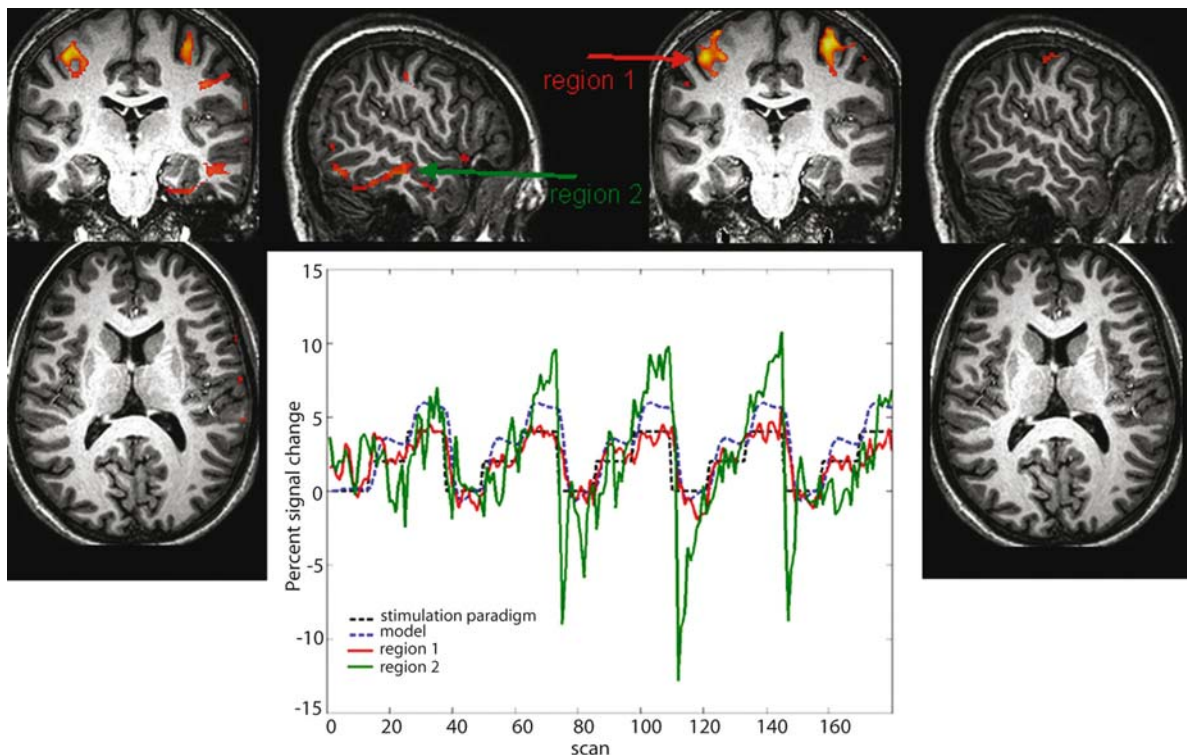


Fig. 10.9. fMRI activation map of a volunteer who moved (*left*) and did not move (*right*). Signal time traces in a motion related region (*green*) and a real activation region (*red*) demonstrate the temporal mismatch between both signal traces and between the motion related signal change and the model of activation

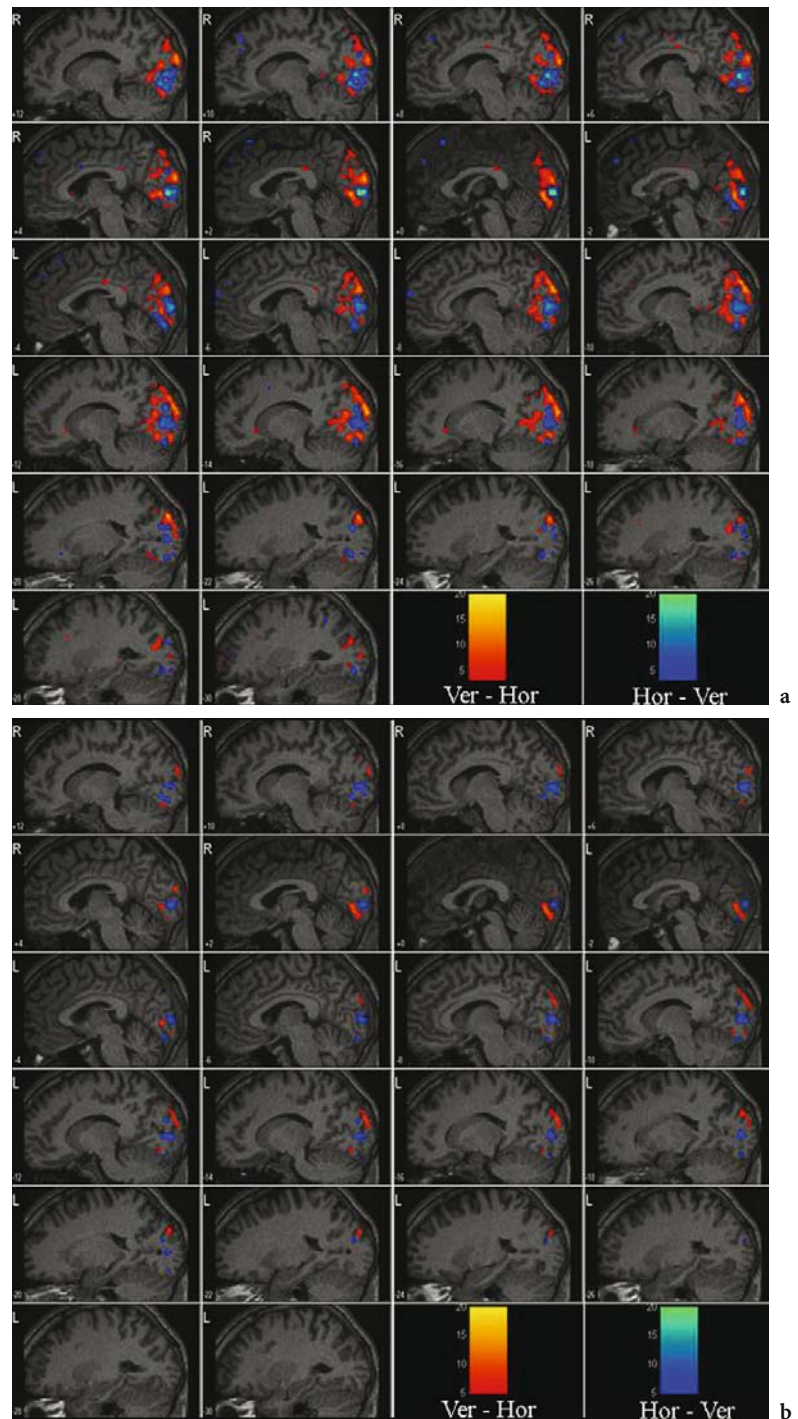


Fig. 10.10a,b. Effect when the subject is not cooperating during the fMRI exam: **a** a retinotopic map of a subject fixating to the middle of the visual stimulus (alternating horizontal and vertical wedges); **b** retinotopic map of the same subject looking around (i.e. not fixating) during the fMRI exam

non-fixating subject in a visual retinotopy experiment. In cognitive and language tasks an indirect control can be implemented to the paradigm. Cognitive paradigms can be devised in such a way that the patient has to respond by pressing a response button. These responses can be logged during the scanning and controlled afterwards for correctness.

Precisely informing the patients about what you want them to do before scanning is very important. Real time fMRI analysis tools enable for direct control of experimental success such that a failed functional session can be repeated immediately, which is much less time demanding than asking the patient to come back after a couple of days for an extra scanning session.

10.3

Technically Related Artifacts

10.3.1

Susceptibility Artifacts

Almost all BOLD fMRI acquisitions are performed with multislice single shot EPI acquisition sequences. These techniques have a very high temporal resolution and are very sensitive to the BOLD effect which manifests itself as a change in susceptibility in the activated regions. But these single shot EPI sequences also suffer from distortion and susceptibility artifacts as a result of their high sensitivity to susceptibility and the resulting high T2*-weighting (DEVLIN et al. 2000). In most fMRI studies these drawbacks are of minor importance and don't weigh up to the advantages of the EPI techniques to both detect and localize brain activation. However the susceptibility related signal drop in brain areas which are located near the skull base or near to large air cavities like the orbitofrontal cortex and the anterior and medial temporal cortex pose a problem for fMRI studies that measure activation in adjacent parts of the brain (O'DOHERTY et al. 2000; FRISTON et al. 1996a; SMALL et al. 2004; DEVLIN et al. 2000). In clinical fMRI this poses a problem both for studies searching for activated regions in the orbitofrontal cortex (like taste and smell related regions, emotional processing) (DEICHMANN et al. 2003; SMITS et al. 2007) or anterior temporal cortex (regions responsible for object recognition) (DEVLIN et al. 2000). This problem also exists for brain areas containing metal implants or certain types of lesions (e.g. lesions containing deoxyhemoglobin or hemosiderine) where the susceptibility difference between lesion and surrounding brain tissue is large (HABERG et al. 2004). With the current trend of using higher static magnetic field strengths, this effect of local signal loss and image distortion is even more pronounced (ABDULJALIL and ROBITAILLE 1999).

10.3.1.1

Methods to Decrease Susceptibility Related Artifacts

Different new strategies for experiments in susceptibility prone regions have been proposed including the use of other less susceptibility sensitive acquisition sequences like multi shot EPI sequences, spin echo EPI sequences or flash sequences

(MENON et al. 1997), but these sequences are also less sensitive to the BOLD contrast (SONG et al. 2000). On the other hand various image processing methods have been developed to recover the local signal and to reduce image distortions from EPI images, albeit the gain of signal using these other sequences and recovery techniques always comes to the expense of reducing temporal resolution, temporal stability, spatial resolution and/or contrast/signal to noise ratio. Other methods proposed to reduce local signal loss in EPI sequences are decreasing the slice thickness of acquired images, minimizing slice induced susceptibility artifacts (HOOGENRAAD et al. 2000), local shimming to decrease local magnetic field inhomogeneity (DEICHMANN et al. 2003), maximizing the read-out bandwidth in order to minimize the length of the EPI echo train, which decreases the T2* decay and thus susceptibility effects but also increases noise in the images. Another solution is the use of parallel imaging techniques (PRUESSMANN et al. 1999; SODICKSON and MANNING 1997). The advent of parallel acquisition techniques which have the potential to decrease the problems inherent to single shot EPI imaging sequences, makes it possible to perform fMRI studies in those brain areas which suffer from large susceptibility artifacts in the standard single shot BOLD fMRI experiments (PREIBISCH et al. 2003). In these methods receiver coil arrays consisting of a combination of a number of receiving coils (ranging from 2 to 32 elements) (DE ZWART et al. 2002; WEIGER et al. 2002) are used. The spatial inhomogeneity and sensitivity of the separate elements is employed to decrease the number of acquired phase encoding steps for every separate coil element, by combining the different resulting images or raw data to one new reconstructed image (PRUESSMANN et al. 1999; SODICKSON and MANNING 1997). As a result, this reduces acquired phase encoding steps and thus EPI read-out train length. In BOLD fMRI experiments this decrease in the number of phase encoding steps during a single readout step results in a decline of the susceptibility related artifacts. Recently the potential of parallel imaging techniques has been demonstrated in several studies at 1.5T and 3T (PREIBISCH et al. 2003; SCHMIDT et al. 2002), where the potential of the SENSE technique at 1.5T with different reduction factors and spatial resolutions for fMRI purposes was demonstrated (PREIBISCH et al. 2003). The advantage of parallel imaging techniques is shown in Figure 10.11, demonstrating the

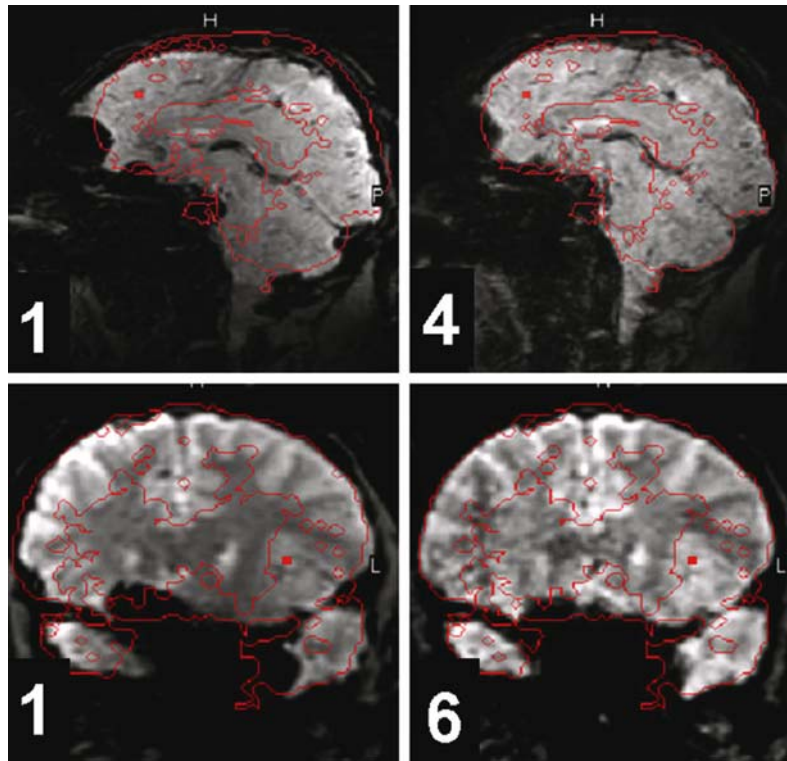


Fig. 10.11. Comparison of the geometrical distortion of both NO-SENSE (without parallel imaging) and SENSE (with parallel imaging) images acquired in the sagittal (*top row*) and coronal plane (*bottom row*). The *red border lines* delineate the boundaries of the anatomical 3D T1 image, demonstrating the large improvement of geometric compliance using parallel imaging. The *number* on the images represents the SENSE acceleration factor

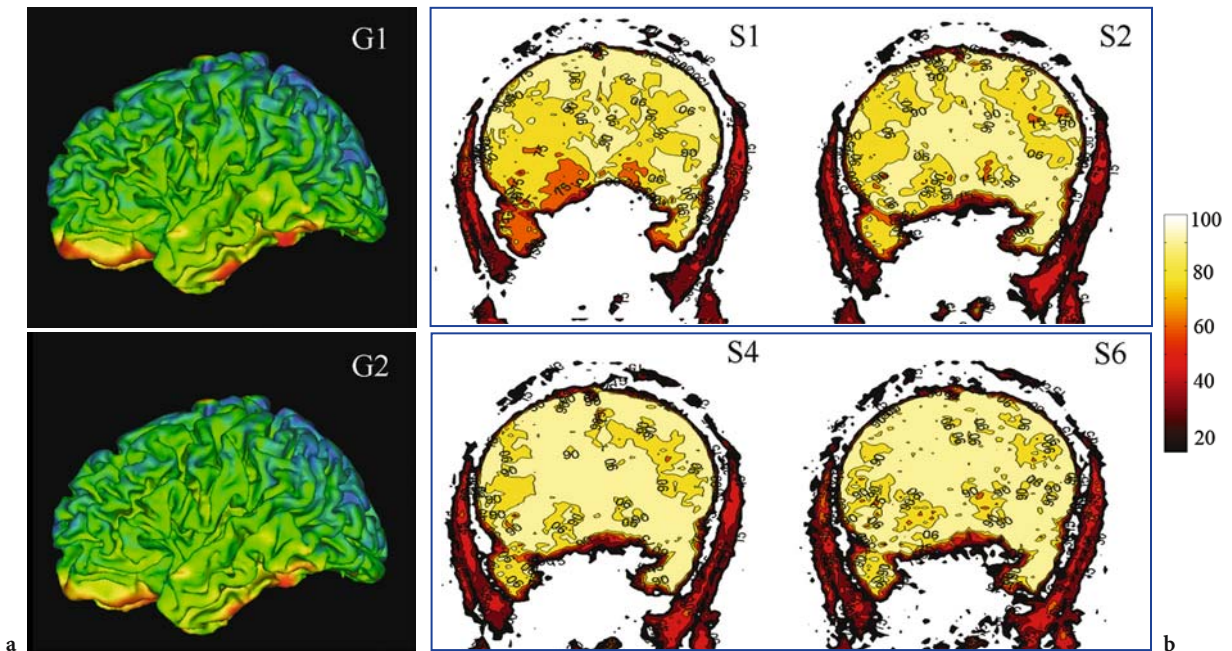


Fig. 10.12. a Signal loss maps on a rendered brain of an EPI acquisition without (*above*) and with GRAPPA acquisition (*below*). The *regions in red* are those which suffer the largest signal intensity loss, note the difference between the grappa factor 2 (*smaller, less intense red areas*) and non-grappa images (*large red regions*). b Percentage signal intensity in two different coronal EPI slices acquired with different SENSE factors compared to the mean brain signal intensity of the same slice. The *dark (orange/red) areas* in the slices suffer a signal loss higher than 40%. The maps demonstrate that images acquired without SENSE (S1) display a larger and a more inhomogeneous signal loss as compared to the scans with a high parallel imaging factor in the susceptibility sensitive areas. The *number next to the images* represents the SENSE factor used

gain of geometric correctness by using higher parallel imaging factors. In Figure 10.12 the loss of signal intensity is calculated and represented for images acquired with different parallel imaging factors. The drawback of the use of high SENSE factors is the increase of noise in the images especially in the central regions which is clearly visible when using very high parallel imaging factors (Fig. 10.11). Therefore it is recommended to only use very high SENSE factors when this is really necessary, e.g. when looking for orbitofrontal or anterior temporal activated regions.

Acquisition related susceptibility effects can mimic activation where in reality is none – often in unexpected anatomical localisation – or they can extinguish activation where in reality is one – often in expected anatomical localisation. Possible ways to overcome this problem are firstly to look at the original (not postprocessed) images where one can already observe, if there is BOLD signal in that region or not and secondly to acquire a B0 field map, which can be automatically generated on most recent MR-imagers. In such a B0 field map two different scans with a different echo time (TE) are combined to give a measure of the local T2* decay and thus pinpointing regions with high susceptibility. This field map can then be used to mask the fMRI activation maps to visualize only artifact free functional areas.

10.3.2 Sensitivity of the EPI Sequence to Spikes

Spikes in MR images arise from external interferences and can generate large signal changes (ZHANG et al. 2001). If there is a suspicion of spikes, one has to carefully analyze the signal time course of the activated regions, since spikes will typically change the signal in the order of tens of percent and are also easily observable in the original images. To eliminate spikes in the images one should always check, if the Faraday cage was closed and intact during image acquisition; scanning with an open door is asking for trouble (Fig. 10.13 shows the effect of opening the door of the Faraday cage during an fMRI scan). Sometimes spikes can arise from an external device in the scanner room, therefore it is recommended to switch off electrical devices or better to remove them from the scanner room. Alternatively, spikes can be scanner related and then you should contact the service.

10.4

Statistical Post-Processing “Artifacts”

Generation of functional activation maps in an fMRI experiment requires independent statistical analysis at each of the 100,000 or more voxels of the brain. The hypothesis that is tested at each voxel is that there is no effect of the task compared to the baseline condition, and statistical analysis involves making a decision as to whether or not this null hypothesis is true or false. A Type I error constitutes a false positive, i.e., a decision that the voxel shows a difference in activation during the task of interest when in reality it does not. A Type II error represents a false negative, i.e., a decision that there is no activation at that voxel when in reality there is.

In basic neuroscience studies the statistical analysis is essentially designed to prevent false positives: the colored activation maps show where one is confident that there is activation. Since fMRI measurements are intrinsically noisy, this always leads to a relative high number of false negatives: areas with real neuronal activation but large physiological and/or technique depended noise will not show up on the activation maps. For clinical applications of fMRI, one must consider whether false positives or false negatives have more deleterious consequences for the patient. For example, in the pre-surgical planning for removing pathologic brain regions, false positives (Type I errors) may bias the surgeon to avoid areas that may not be important to avoid. This could result in incomplete removal of the brain abnormality. In contrast, false negatives (Type II errors) may bias the surgeon to remove too much tissue, possibly leading to an irreversible deficit in function. Therefore, clinical fMRI data should be analyzed differently from how basic neuroscience data is analyzed. More research is warranted into a new method for clinical fMRI analysis which allows to assess both type I and type II errors. For example, one can imagine testing each voxel that has not reached significance to ask whether an fMRI response of a certain magnitude (such as 0.5% MR signal change) would have reached significance, if the signal to noise ratio in that voxel would have been higher. This would lead to a separate color map that shows voxels with low signal change as well as noisy voxels, and also show areas where artifacts or signal dropouts would make potential activation undetectable. More information on statistical processing of fMRI data are provided in Chapter 2, a standard evaluation for clinical fMRI in Chapter 4.

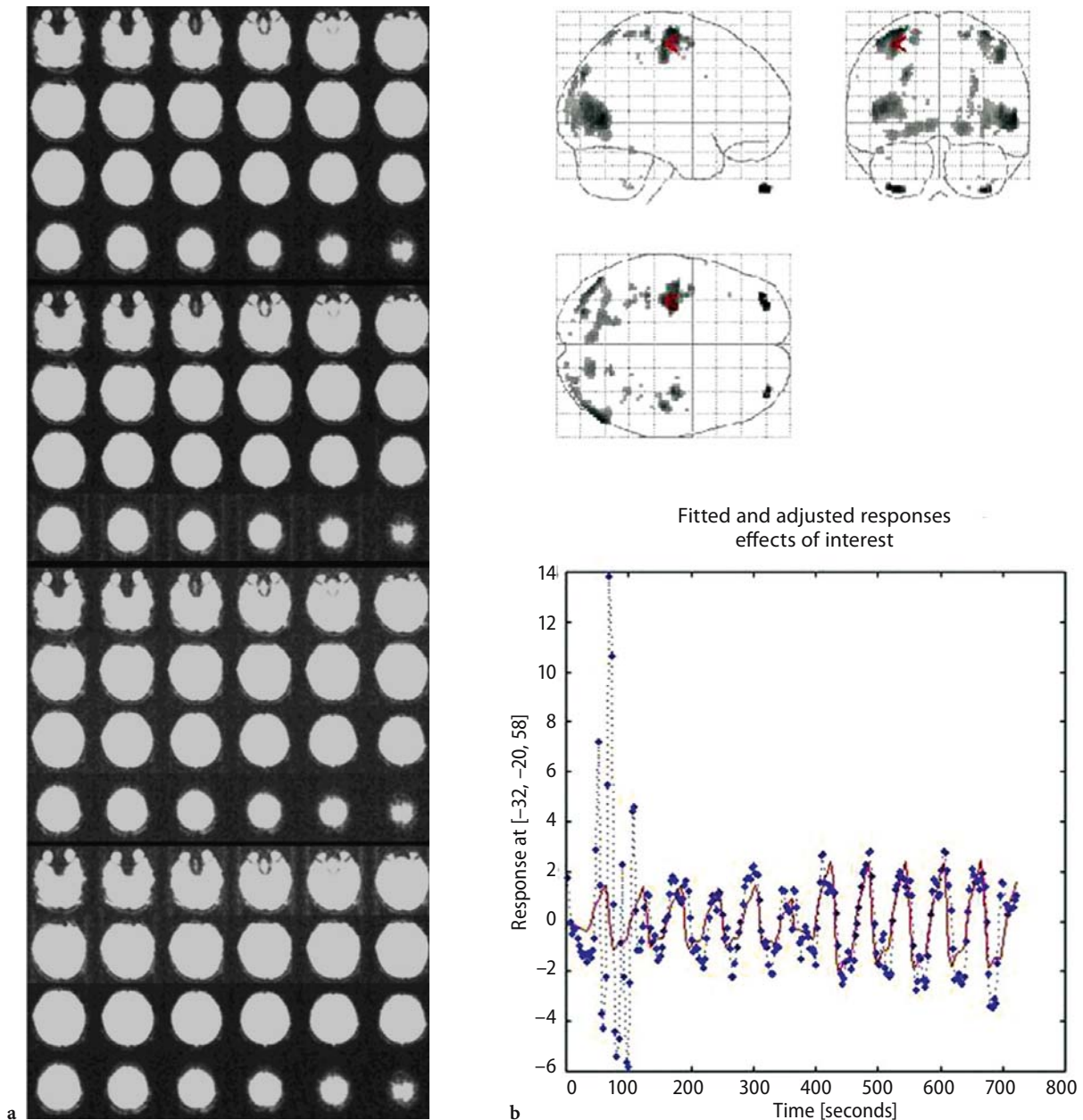


Fig. 10.13. **a** Spikes apparent in the fMRI time trace induced by opening the door of the Faraday cage during the acquisition of an fMRI exam. **b** The signal changes induced by the spikes is around 20% and much higher compared to the motor task induced signal change (red circle).

References

- Abduljalil AM, Robitaille PM (1999) Macroscopic susceptibility in ultra high field MRI. *J Comput Assist Tomogr* 23:832–841
- Aguirre GK, Zarahn E, D’Esposito M (1998) The variability of human, BOLD hemodynamic responses. *Neuroimage* 8:360–369
- Baudendistel KT, Reichenbach JR, Metzner R, Schroeder J, Schad LR (1998) Comparison of functional MR-venography and EPI-BOLD fMRI at 1.5 T. *Magn Reson Imaging* 16:989–991
- Biswal BB, Hyde JS (1997) Contour-based registration technique to differentiate between task-activated and head motion-induced signal variations in fMRI. *Magn Reson Med* 38:470–476
- Biswal B, DeYoe AE, Hyde JS (1996) Reduction of physiological fluctuations in fMRI using digital filters. *Magn Reson Med* 35:107–113

- Boxerman JL, Bandettini PA, Kwong KK, Baker JR, Davis TL, Rosen BR, Weisskoff RM (1995) The intravascular contribution to fMRI signal change – Monte-Carlo modeling and diffusion-weighted studies *n-vivo*. *Magn Reson Med* 34:4–10
- Braus DF, Brassen S (2005) Functional magnetic resonance imaging and antipsychotics. Overview and own data. *Radiologe* 45:178–185
- Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE (1997) Acute effects of cocaine on human brain activity and emotion. *Neuron* 19:591–611
- Bryan RN, Kraut M (1998) Functional magnetic resonance imaging: you get what you (barely) see. *Am J Neuroradiol* 19:991–992
- Bryant CA, Jackson SH (1998) Functional imaging of the brain in the evaluation of drug response and its application to the study of aging. *Drugs Aging* 13:211–222
- Cohen ER, Rostrup E, Sidas K, Lund TE, Paulson OB, Ugurbil K, Kim SG (2004) Hypercapnic normalization of BOLD fMRI: comparison across field strengths and pulse sequences. *Neuroimage* 23:613–624
- Cohen MS, DuBois RM (1999) Stability, repeatability, and the expression of signal magnitude in functional magnetic resonance imaging. *J Magn Reson Imaging* 10:33–40
- Dagli MS, Ingeholm JE, Haxby JV (1999) Localization of cardiac-induced signal change in fMRI. *Neuroimage* 9:407–415
- de Zwart JA, van Gelderen P, Kellman P, Duyn JH (2002) Application of sensitivity-encoded echo-planar imaging for blood oxygen level-dependent functional brain imaging. *Magn Reson Med* 48:1011–1020
- Debus J, Essig M, Schad LR, Wenz F, Baudendistel K, Knopp MV, Engenhart R, Lorenz WJ (1996) Functional magnetic resonance imaging in a stereotactic setup. *Magn Reson Imaging* 14:1007–1012
- Deichmann R, Gottfried JA, Hutton C, Turner R (2003) Optimized EPI for fMRI studies of the orbitofrontal cortex. *Neuroimage* 19:430–441
- Devlin JT, Russell RP, Davis MH, Price CJ, Wilson J, Moss HE, Matthews PM, Tyler LK (2000) Susceptibility-induced loss of signal: comparing PET and fMRI on a semantic task. *Neuroimage* 11:589–600
- Duerk JL, Simonetti OP (1991) Theoretical aspects of motion sensitivity and compensation in echo-planar imaging. *JMRI–J Magn Reson Imaging* 1:643–650
- Duong TQ, Yacoub E, Adriany G, Hu X, Ugurbil K, Kim SG (2003) Microvascular BOLD contribution at 4 and 7 T in the human brain: gradient-echo and spin-echo fMRI with suppression of blood effects. *Magn Reson Med* 49:1019–1027
- Duong TQ, Yacoub E, Adriany G, Hu XP, Andersen P, Vaughan JT, Ugurbil K, Kim SG (2004) Spatial specificity of high-resolution, spin-echo BOLD, and CBF fMRI at 7 T. *Magn Reson Med* 51:646–647
- Duyn JH, Moonen CTW, Vanyperen GH, Deboer RW, Luyten PR (1994) Inflow versus deoxyhemoglobin effects in bold functional MRI using gradient echoes at 1.5 T. *NMR Biomed* 7:83–88
- Dymarkowski S, Sunaert S, Van Oostende S, Van Hecke P, Wilms G, Demaerel P, Nuttin B, Plets C, Marchal G (1998) Functional MRI of the brain: localisation of eloquent cortex in focal brain lesion therapy. *Eur Radiol* 8:1573–1580
- Edward V, Windischberger C, Cunningham R, Erdler M, Lanzenberger R, Mayer D, Endl W, Beisteiner R (2000) Quantification of fMRI artifact reduction by a novel plaster cast head holder. *Hum Brain Mapp* 11:207–213
- Engel SA, Glover GH, Wandell BA (1997) Retinotopic organization in human visual cortex and the spatial precision of functional MRI. *Cerebral Cortex* 7:181–192
- Fandino J, Kollias SS, Wieser HG, Valavanis A, Yonekawa Y (1999) Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumors involving the primary motor cortex. *J Neurosurg* 91:238–250
- Fitzsimmons JR, Scott JD, Peterson DM, Wolverson BL, Webster CS, Lang PJ (1997) Integrated RF coil with stabilization for fMRI human cortex. *Magn Reson Med* 38:15–18
- Frahm J, Merboldt KD, Hancic W, Kleinschmidt A, Boecker H (1994) Brain or vein-oxygenation or flow – on signal physiology in functional MRI of human brain activation. *NMR Biomed* 7:45–53
- Freire L, Mangin JF (2001) Motion correction algorithms may create spurious brain activations in the absence of subject motion. *Neuroimage* 14:709–722
- Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SC, Frackowiak RS, Turner R (1995) Analysis of fMRI time-series revisited. *Neuroimage* 2:45–53
- Friston KJ, Holmes A, Poline JB, Price CJ, Frith CD (1996a) Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage* 4:223–235
- Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R (1996b) Movement-related effects in fMRI time-series. *Magn Reson Med* 35:346–355
- Fujiwara N, Sakatani K, Katayama Y, Murata Y, Hoshino T, Fukaya C, Yamamoto T (2004) Evoked-cerebral blood oxygenation changes in false-negative activations in BOLD contrast functional MRI of patients with brain tumors. *Neuroimage* 21:1464–1471
- Ganslandt O, Fahlbusch R, Nimsch C, Kober H, Moller M, Steinmeier R, Romstock J, Vieth J (1999) Functional neuronavigation with magnetoencephalography: outcome in 50 patients with lesions around the motor cortex. *J Neurosurg* 91:73–79
- Gao JH, Miller I, Lai S, Xiong J, Fox PT (1996) Quantitative assessment of blood inflow effects in functional MRI signals. *Magn Reson Med* 36:314–319
- Gasser TG, Sandalcioglu EI, Wiedemayer H, Hans V, Gizevski E, Forsting M, Stolke D (2004) A novel passive functional MRI paradigm for preoperative identification of the somatosensory cortex. *Neurosurg Rev* 27:106–112
- Gati JS, Menon RS, Ugurbil K, Rutt BK (1997) Experimental determination of the BOLD field strength dependence in vessels and tissue. *Magn Reson Med* 38:296–302
- Gollub RL, Breiter HC, Kantor H, Kennedy D, Gastfriend D, Mathew RT, Makris N, Guimaraes A, Riorden J, Campbell T, Foley M, Hyman SE, Rosen B, Weisskoff R (1998) Cocaine decreases cortical cerebral blood flow but does not obscure regional activation in functional magnetic resonance imaging in human subjects. *J Cereb Blood Flow Metab* 18:724–734
- Haacke EM, Hopkins A, Lai S, Buckley P, Friedman L, Meltzer H, Hedera P, Friedland R, Klein S, Thompson L, Detterman D, Tkach J, Lewin JS (1994) 2D and 3D high-

- resolution gradient-echo functional imaging of the brain – venous contributions to signal in motor cortex studies. *NMR Biomed* 7:54–62
- Haberg A, Kvistad KA, Unsgard G, Haraldseth O (2004a) Pre-operative blood oxygen level-dependent functional magnetic resonance imaging in patients with primary brain tumors: clinical application and outcome. *Neurosurgery* 54:902–914
- Hajnal JV, Myers R, Oatridge A, Schwieso JE, Young IR, Bydder GM (1994) Artifacts due to stimulus correlated motion in functional imaging of the brain. *Magn Reson Med* 31:283–291
- Hall DA, Goncalves MS, Smith S, Jezard P, Haggard MP, Kornak J (2002) A method for determining venous contribution to BOLD contrast sensory activation. *Magn Reson Imaging* 20:695–706
- Hill DLG, Smith ADC, Simmons A, Maurer CR, Cox TCS, Elwes R, Brammer M, Hawkes DJ, Polkey CE (2000) Sources of error in comparing functional magnetic resonance imaging and invasive electrophysiological recordings. *J Neurosurg* 93:214–223
- Holodny AI, Schuller M, Liu WC, Wolko J, Maldjian JA, Kalnin AJ (2000) The effect of brain tumors on BOLD functional MR imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery. *AJNR Am J Neuroradiol* 21:1415–1422
- Hoogenraad FG, Pouwels PJ, Hofman MB, Rombouts SA, Lavini C, Leach MO, Haacke EM (2000) High-resolution segmented EPI in a motor task fMRI study. *Magn Reson Imaging* 18:405–409
- Hund-Georgiadis M, Mildner T, Georgiadis D, Weih K, von Cramon DY (2003) Impaired hemodynamics and neural activation? A fMRI study of major cerebral artery stenosis. *Neurology* 61:1276–1279
- Jacobsen LK, Gore JC, Skudlarski P, Lacadie CM, Jatlow P, Krystal JH (2002) Impact of intravenous nicotine on BOLD signal response to photic stimulation. *Magn Reson Imaging* 20:141–145
- Jacobsen LK, D'Souza DC, Mencl WE, Pugh KR, Skudlarski P, Krystal JH (2004) Nicotine effects on brain function and functional connectivity in schizophrenia. *Biol Psychiatry* 55:850–858
- Jiang AP, Kennedy DN, Baker JR, Weisskoff RM, Tootell RBH, Woods RP, Benson RP, Kwong KK, Brady TJ, Rosen BR, Belliveau JW (1995) Motion detection and correction in functional MR imaging. *Hum Brain Mapping* 3:224–235
- Kansaku K, Kitazawa S, Kawano K (1998) Sequential hemodynamic activation of motor areas and the draining veins during finger movements revealed by cross-correlation between signals from fMRI. *Neuroreport* 9:1969–1974
- Kastrup A, Li TQ, Takahashi A, Glover GH, Moseley ME (1998) Functional magnetic resonance imaging of regional cerebral blood oxygenation changes during breath holding. *Stroke* 29:2641–2645
- Kim DS, Duong TQ, Kim SG (2000) High-resolution mapping of iso-orientation columns by fMRI. *Nat Neurosci* 3:164–169
- Krings T, Reinges MH, Erberich S, Kemeny S, Rohde V, Spetzger U, Korinth M, Willmes K, Gilsbach JM, Thron A (2001a) Functional MRI for presurgical planning: problems, artefacts, and solution strategies. *J Neurol Neurosurg Psychiatry* 70:749–760.
- Krings T, Schreckenberger M, Rohde V, Foltys H, Spetzger U, Sabri O, Reinges MH, Kemeny S, Meyer PT, Moller-Hartmann W, Korinth M, Gilsbach JM, Buell U, Thron A (2001b) Metabolic and electrophysiological validation of functional MRI. *J Neurol Neurosurg Psychiatry* 71:762–771
- Kumari V, Gray JA, ffytche DH, Mitterschiffthaler MT, Das M, Zachariah E, Vythelingum GN, Williams SC, Simmons A, Sharma T (2003) Cognitive effects of nicotine in humans: an fMRI study. *Neuroimage* 19:1002–1013
- Laurienti PJ, Field AS, Burdette JH, Maldjian JA, Yen YF, Moody DM (2002) Dietary caffeine consumption modulates fMRI measures. *Neuroimage* 17:751–757
- Laurienti PJ, Field AS, Burdette JH, Maldjian JA, Yen YF, Moody DM (2003) Relationship between caffeine-induced changes in resting cerebral perfusion and blood oxygenation level-dependent signal. *AJNR Am J Neuroradiol* 24:1607–1611
- Le Rumeur E, Allard M, Poiseau E, Jannin P (2000) Role of the mode of sensory stimulation in presurgical brain mapping in which functional magnetic resonance imaging is used. *J Neurosurg* 93:427–431
- Lee AT, Glover GH, Meyer CH (1995) Discrimination of large venous vessels in time-course spiral blood-oxygen-level-dependent magnetic-resonance functional neuroimaging. *Magn Reson Med* 33:745–754
- Lee CC, Ward HA, Sharbrough FW, Meyer FB, Marsh WR, Raffel C, So EL, Cascino GD, Shin CS, Xu YC, Riederer SJ, Jack CR (1999) Assessment of functional MR imaging in neurosurgical planning. *Am J Neuroradiol* 20:1511–1519
- Lee JH, Telang FW, Springer CS Jr, Volkow ND (2003) Abnormal brain activation to visual stimulation in cocaine abusers. *Life Sci* 73:1953–1961
- Lehericy S, Biondi A, Sourour N, Vlaicu M, du Montcel ST, Cohen L, Vivas E, Capelle L, Faillot T, Casasco A, Le BD, Marsault C (2002) Arteriovenous brain malformations: is functional MR imaging reliable for studying language reorganization in patients? Initial observations. *Radiology* 223:672–682
- Levin JM, Ross MH, Mendelson JH, Kaufman MJ, Lange N, Maas LC, Mello NK, Cohen BM, Renshaw PF (1998) Reduction in BOLD fMRI response to primary visual stimulation following alcohol ingestion. *Psychiatry Res-Neuroimaging* 82:135–146
- Levy LM, Henkin RI, Lin CS, Hutter A, Schellinger D (1998) Increased brain activation in response to odors in patients with hyposmia after theophylline treatment demonstrated by fMRI. *J Comput Assist Tomogr* 22:760–770
- Li SJ, Biswal B, Li Z, Risinger R, Rainey C, Cho JK, Salmeron BJ, Stein EA (2000) Cocaine administration decreases functional connectivity in human primary visual and motor cortex as detected by functional MRI. *Magn Reson Med* 43:45–51
- Logothetis N (2000) Can current fMRI techniques reveal the micro-architecture of cortex? *Nat Neurosci* 3:413–414
- Logothetis NK (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos Trans R Soc Lond B Biol Sci* 357:1003–1037
- Lowe MJ, Lurito JT, Mathews VP, Phillips MD, Hutchins GD (2000) Quantitative comparison of functional contrast from BOLD-weighted spin-echo and gradient-echo echoplanar imaging at 1.5 Tesla and H2 15O PET in the whole brain. *J Cereb Blood Flow Metab* 20:1331–1340

- Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P (1997) Multimodality image registration by maximization of mutual information. *IEEE Trans Med Imaging* 16:187–198
- Maldjian J, Atlas SW, Howard RS, Greenstein E, Alsop D, Detre JA, Listerud J, D'Esposito M, Flamm ES (1996) Functional magnetic resonance imaging of regional brain activity in patients with intracerebral arteriovenous malformations before surgical or endovascular therapy. *J Neurosurg* 84:477–483
- Mandeville JB, Jenkins BG, Kosofsky BE, Moskowitz MA, Rosen BR, Marota JJA (2001) Regional sensitivity and coupling of BOLD and CBV changes during stimulation of rat brain. *Magn Reson Med* 45:443–447
- Menon RS (2002) Postacquisition suppression of large-vessel BOLD signals in high-resolution fMRI. *Magn Reson Med* 47:1–9
- Menon RS, Kim SG (1999) Spatial and temporal limits in cognitive neuroimaging with fMRI. *Trends Cogn Sci* 3:207–216
- Menon RS, Ogawa S, Ugurbil K (1995) High-temporal-resolution studies of the human primary visual-cortex at 4 T – teasing out the oxygenation contribution in FMRI. *Intl J Imaging Systems Technol* 6:209–215
- Menon RS, Thomas CG, Gati JS (1997) Investigation of BOLD contrast in fMRI using multi-shot EPI. *NMR Biomed* 10:179–182
- Menon RS, Gati JS, Goodyear BG, Luknowsky DC, Thomas CG (1998) Spatial and temporal resolution of functional magnetic resonance imaging. *Biochem Cell Biol* 76:560–571
- Morton DW, Maravilla KR, Meno JR, Winn HR (2002) Systemic theophylline augments the blood oxygen level-dependent response to forepaw stimulation in rats. *AJNR Am J Neuroradiol* 23:588–593
- Muresan L, Renken R, Roerdink JBTM, Duifhuis H (2005) Automated correction of spin-history related motion artefacts in fMRI: Simulated and phantom data. *IEEE Trans Biomed Eng* 52:1450–1460
- Nitschke MF, Melchert UH, Hahn C, Otto V, Arnold H, Herrmann HD, Nowak G, Westphal M, Wessel K (1998) Preoperative functional magnetic resonance imaging (fMRI) of the motor system in patients with tumours in the parietal lobe. *Acta Neurochir (Wien)* 140:1223–1229
- O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. *Neuroreport* 11:893–897
- Ogawa S, Lee TM (1990) Magnetic resonance imaging of blood vessels at high fields: in vivo and in vitro measurements and image simulation. *Magn Reson Med* 16:9–18
- Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Ugurbil K (1993) Functional brain mapping by blood oxygenation level-dependent contrast magnetic-resonance-imaging – a comparison of signal characteristics with a biophysical model. *Biophys J* 64:803–812
- Oja JM, Gillen J, Kauppinen RA, Kraut M, Van Zijl PC (1999) Venous blood effects in spin-echo fMRI of human brain. *Magn Reson Med* 42:617–626
- Orchard J, Atkins MS (2003) Iterating registration and activation detection to overcome activation bias in fMRI motion estimates. In: Ellis R, Peters T, eds.: *Medical Image Computing and Computer-Assisted Intervention (MICCAI'03)*. Volume 2879 of LNCS., Montreal 886–893
- Parrish T, Mulderink T, Gitelman D, Mesulam M (2001) Caffeine as a BOLD contrast booster. *Neuroimage* 13:S1001
- Preibisch C, Pilatus U, Bunke J, Hoogenraad F, Zanella F, Lanfermann H (2003) Functional MRI using sensitivity-encoded echo planar imaging (SENSE-EPI). *Neuroimage* 19:pp 412–421.
- Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P (1999) SENSE: sensitivity encoding for fast MRI. *Magn Reson Med* 42:952–962
- Rao SM, Binder JR, Bandettini PA, Hammeke TA, Yetkin FZ, Jesmanowicz A, Lisk LM, Morris GL, Mueller WM, Estkowski LD (1993) Functional magnetic resonance imaging of complex human movements. *Neurology* 43:2311–2318
- Schiffbauer H, Ferrari P, Rowley HA, Berger MS, Roberts TP (2001) Functional activity within brain tumors: a magnetic source imaging study. *Neurosurgery* 49:1313–1320
- Schmidt CF, Pruessmann KP, Jaermann T, Lamerichs R, Boesiger P (2002) High resolution fMRI using SENSE at 3.0 Tesla. In: *Proc Intl Soc Magn Reson Med* 2002 May 15:125
- Schreiber A, Hubbe U, Ziyeh S, Hennig J (2000) The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement. *AJNR Am J Neuroradiol* 21:1055–1063
- Seifritz E, Bilecen D, Hanggi D, Haselhorst R, Radu EW, Wetzel S, Seelig J, Scheffler K (2000) Effect of ethanol on BOLD response to acoustic stimulation: implications for neuropharmacological fMRI. *Psychiatry Res* 99:1–13
- Seto E, Sela G, McIlroy WE, Black SE, Staines WR, Bronskill MJ, McIntosh AR, Graham SJ (2001) Quantifying head motion associated with motor tasks used in fMRI. *Neuroimage* 14:284–297
- Skirboll SS, Ojemann GA, Berger MS, Lettich E, Winn HR (1996) Functional cortex and subcortical white matter located within gliomas. *Neurosurgery* 38:678–684
- Small DM, Voss J, Mak YE, Simmons KB, Parrish T, Gitelman D (2004) Experience-dependent neural integration of taste and smell in the human brain. *J Neurophysiol* 92:1892–1903
- Smits M, Peeters RR, Van Hecke P, Sunaert S (2007) A 3T event-related functional magnetic resonance imaging (fMRI) study of primary and secondary gustatory cortex localization using natural tastants. *Neuroradiology* 49:61–71
- Sodickson DK, Manning WJ (1997) Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radio-frequency coil arrays. *Magn Reson Med* 38:591–603
- Song AW, Popp CA, Mao J, Dixon WT (2000) fMRI: methodology – acquisition and processing. *Adv Neurol* 83:177–185
- Srivastava G, Crottaz-Herbette S, Lau KM, Glover GH, Menon V (2005) ICA-based procedures for removing ballistocardiogram artifacts from EEG data acquired in the MRI scanner. *Neuroimage* 24:50–60
- Stippich C, Kress B, Ochmann H, Tronnier V, Sartor K (2003) Preoperative functional magnetic resonance tomography (fMRI) in patients with rolandic brain tumors: Indication, investigation strategy, possibilities and limitations of clinical application. *Rofo-Fortschritte Auf dem Gebiet der Röntgenstrahlen und der Bildgebenden Verfahren* 175, pp 1042–1050

- Sunaert S, Dymarkowski S, Van Oostende S, Van Hecke P, Wilms G, Marchal G (1998) Functional magnetic resonance imaging (fMRI) visualises the brain at work. *Acta Neurologica Belgica* 98:8–16
- Thesen S, Heid O, Mueller E, Schad LR (2000) Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. *Magn Reson Med* 44:457–465
- Tomczak RJ, Wunderlich AP, Wang Y, Braun V, Antoniadis G, Gorich J, Richter HP, Brambs HJ (2000) fMRI for pre-operative neurosurgical mapping of motor cortex and language in a clinical setting. *J Comput Assist Tomogr* 24:927–934
- Turner R, Jezzard P, Wen H, Kwong KK, Le Bihan D, Zeffiro T, Balaban RS (1993) Functional mapping of the human visual cortex at 4 and 1.5 tesla using deoxygenation contrast EPI. *Magn Reson Med* 29:277–279
- Turner R (2002) How much cortex can a vein drain? Downstream dilution of activation-related cerebral blood oxygenation changes. *Neuroimage* 16:1062–1067
- Ugurbil K, Hu X, Chen W, Zhu XH, Kim SG, Georgopoulos A (1999) Functional mapping in the human brain using high magnetic fields. *Philos Trans R Soc Lond B Biol Sci* 354:1195–1213
- Ward HA, Riederer SJ, Grimm RC, Ehman RL, Felmlee JP, Jack CR Jr (2000) Prospective multiplanar motion correction for fMRI. *Magn Reson Med* 43:459–469
- Weiger M, Pruessmann KP, Osterbauer R, Bornert P, Boesiger P, Jezzard P (2002) Sensitivity-encoded single-shot spiral imaging for reduced susceptibility artifacts in BOLD fMRI. *Magn Reson Med* 48:860–866
- Weisskoff RM (1995) Functional MRI: are we all moving towards artifactual conclusions? Or fMRI fact or fancy? *NMR Biomed* 8:101–103
- Weisskoff RM (1996) Simple measurement of scanner stability for functional NMR imaging of activation in the brain. *Magn Reson Med* 36:643–645
- Windischberger C, Langenberger H, Sycha T, Tschernko EA, Fuchsjager-Mayerl G, Schmetterer L, Moser E (2002) On the origin of respiratory artifacts in BOLD-EPI of the human brain. *Magn Reson Imaging* 20:575–582
- Yamada K, Naruse S, Nakajima K, Furuya S, Morishita H, Kizu O, Maeda T, Takeo K, Shimizu K (1997) Flow velocity of the cortical vein and its effect on functional brain MRI at 1.5T: preliminary results by cine-MR venography. *J Magn Reson Imaging* 7:347–352
- Yang X, Hyder F, Shulman RG (1997) Functional MRI BOLD signal coincides with electrical activity in the rat whisker barrels. *Magn Reson Med* 38:874–877
- Yousry TA, Schmid UD, Schmidt D, Hagen T, Jassoy A, Reiser MF (1996) The central sulcal vein: a landmark for identification of the central sulcus using functional magnetic resonance imaging. *J Neurosurg* 85:608–617
- Zeffiro T (1996) Clinical functional image analysis: artifact detection and reduction. *Neuroimage* 4:S95–100
- Zhang X, Van de Moortele PF, Pfeuffer J, Hu X (2001) Elimination of k-space spikes in fMRI data. *Magn Reson Imaging* 19:1037–1041

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