Invited Review

Presurgical Planning for Tumor Resectioning

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Since the birth of functional magnetic resonance imaging (fMRI)—a noninvasive tool able to visualize brain function—now 15 years ago, several clinical applications have emerged. fMRI follows from the neurovascular coupling between neuronal electrical activity and cerebrovascular physiology that leads to three effects that can contribute to the fMRI signal: an increase in the blood flow velocity, in the blood volume and in the blood oxygenation level. The latter effect, gave the technique the name blood oxygenation level dependent (BOLD) fMRI. One of the major clinical uses is presurgical fMRI in patients with brain abnormalities. The goals of presurgical fMRI are threefold: 1) assessing the risk of neurological deficit that follows a surgical procedure, 2) selecting patients for invasive intraoperative mapping, and 3) guiding of the surgical procedure itself. These are reviewed here. Unfortunately, randomized trials or outcome studies that definitively show benefits to the final outcome of the patient when applying fMRI presurgically have not been performed. Therefore, fMRI has not yet reached the status of clinical acceptance. The final purpose of this article is to define a roadmap of future research and developments in order to tilt pre-surgical fMRI to the status of clinical validity and acceptance.

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THE GOAL OF SURGICAL TREATMENT of brain tumors is the complete removal of the abnormality, while minimizing the risk of inducing (permanent) neurological deficits. Resection of primary brain tumors improves survival, functional performance, and the effectiveness of adjuvant therapies, provided that surgically-induced neurological deficits can be avoided (1). Therefore, the proposed margin of the surgical resection should not violate functionally eloquent cortical areas. Mapping of these areas is traditionally achieved by invasive methods such as intraoperative cortical stimulation (ICS) in the awake patient, implantation of a subdural grid with extraoperative stimulation mapping, or operative sensory-evoked potential recordings. While accurate, these techniques are rather difficult to perform, place great stress on the awake patient, and often require a larger craniotomy than necessary for the removal of the tumor. Another major disadvantage of these techniques is that a surgical procedure itself is required before any functional information can be obtained. As a result, important patient management decisions must be made without complete knowledge of the anatomic relationship between the lesion borders and functionally eloquent cortex.

In contrast, functional magnetic resonance imaging (fMRI) can be obtained preoperatively and is completely noninvasive (2–4). Together with the high sensitivity of MRI for the visualization of brain lesions, fMRI can establish the relationship between the margin of the lesion and the functionally viable brain tissue. fMRI thus has the potential to predict possible deficits in cognitive, language, motor, and sensory perceptual functions due to treatment (e.g., surgery) or due to lesion growth (e.g., bleeding of arteriovenous malformation). This preoperative risk estimation would allow the physician and the patient to make a fully informed decision regarding the costs and benefits of the various treatment options. Having identified the exact location of a lesion, the first goal of presurgical fMRI is to assess the risk of neurological deficit that follows a therapeutic procedure. Yetkin et al (5) were the first to show that a distance of 2 cm between lesion border and functional representation precludes any deficit. The rate of neurological deficits increases with the decrease in distance to reach 50% when the distance is below 10 mm. In the latter case fMRI selects the patient for invasive intraoperative mapping, which is the second goal. A final third goal is the guidance of the surgical procedure itself. This goal is achieved by integration of the fMRI data into neuronavigation systems. Frameless stereotactic surgery, also known as neuronavigation, is widely applied in brain surgery and has become a standard procedure in most neurosurgical centers nowadays. The integration of fMRI activation maps into neuronavigation is often referred to as "functional neuronavigation," and allows the neurosurgeon to plan the safest route to and removal of the lesion.

Many articles describe the use of fMRI for these three goals, and we review them here.

The complete noninvasiveness and relative safety, the widespread availability of MRI in comparison to other imaging modalities, the good sensitivity—allowing individual subjects (or patients) to be studied, the ease of imaging underlying anatomy and pathology, and the

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explosive growth of its use in cognitive neuroscience have lead to the increased clinical use of fMRI in presurgical planning.

Unfortunately, no randomized trials or outcome studies have been performed that definitively show benefits to the final outcome of the patient when applying fMRI presurgically. Therefore, fMRI has not yet reached the status of clinical acceptance. This is due to numerous disadvantages and problems of fMRI. These include the lack of correct spatial localization, lack of reliable detection of electrical activity in the surrounding of tumors, lack of discrimination between essential and expendable brain regions, lack of standardized paradigms and postprocessing, and last-but-not-least, the lack of information about the underlying white matter structures and connections. Therefore the final purpose of this work is to define a roadmap of future research and developments in order to overcome these limitations and tilt fMRI to the status of clinical validity and acceptance.

THE FIRST GOAL OF PRESURGICAL FMRI: ASSESSMENT OF THE FEASIBILITY OF SURGICAL TREATMENT OF BRAIN TUMORS

The general idea here is that the assessment of the risk of inducing neurological deficits can be achieved by identifying the distance between the margin of the tumor resection and the eloquent or essential functional areas. Several authors (5,6) have described a "golden rule" that a minimal distance for feasible surgical resection is a distance of at least 10 to 15 mm between tumor margin and an essential structure. Yetkin et al (5) were the first to show a correlation between distance and risk of a subsequent neurological deficit that was statistically significant. Motor deficits occurred in 50% of the 12 patients in whom the distance between the lesion and the activation was <1 cm, in 33% of the six patients in whom that distance measured between 1 and 2 cm, and in none of the seven patients with more than 2 cm between the zone of activation and the lesion. More recently, others (5) showed that the risk of postoperative loss of function tested with fMRI was significantly lower when the distance between tumor periphery and BOLD activity was 10 mm or more.

In our opinion this "golden rule" is subject to criticism. First, a major point is the definition of "essential" functional areas: damage to certain cortical brain regions leads to profound neurological deficits, while damage to other 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 postoperatively. Second, the exact measurement of the distance is highly determined by technical factors, such as the used statistical threshold, the accuracy of fMRI localization and the effect of brain shift during craniotomy. Third, fMRI is sensitive to cortical changes, but provides no or only limited information about the relation of the tumor to white matter fiber tracts. Interruption of these fibers tracts can lead to major disruptions in neurological function, e.g., conduction aphasia. These topics will be discussed later in detail below.

Ignoring the criticism on the "golden rule" for a moment, three elements are important when trying to asses the relationship between a tumor and an eloquent cortical area.

Using Anatomical Landmarks to Identify the Location of Functional Areas

First, in case of undistorted anatomy, eloquent cortical areas may be identified using specific anatomical landmarks on conventional MRI sections. The use of fMRI in normal subjects has provided vital information for clinical pre-surgical fMRI by providing information on the locations of the neuronal networks involved in a variety of functions and their associated anatomical landmarks (7). Classically, the anatomic location of a lesion is defined using an elaborated system based on reliable anatomic landmarks (8–14), that takes into account variations of the location and the shape of these landmarks. Clear reliable landmarks exists that describe— among others—the location of the primary sensorimotor cortex (pre- and postcentral gyri; see Refs. 8–10,12 for a detailed description; see also Fig. 1), the location of the auditory cortex (transverse temporal gyrus or Heschl's gyrus; see Refs. 13 and 15 for a detailed description; Fig. 2), the location of the primary and secondary visual cortices (calcarine sulcus, see Refs. 8 and 16 for rapid retinotopic mapping of the visual areas) and the pars triangularis and opercularis of the inferior frontal gyrus (i.e., the location of the classical language production area of Broca [8,13]; Fig. 3).

Identifying Eloquent Areas in the Distorted Pathological Brain Using fMRI

While these anatomical landmarks are important in patients with undistorted cortical anatomy, they are of limited use. It has been shown that even in the normal brain there is a considerable variability between function and anatomy. Secondly, mass-effects associated with brain tumors can distort these common relations, making anatomy-based localization of function impossible. These anatomic landmarks may fail when a tumor and its surrounding edema cause a significant mass effect that efface gyri and sulci, distorting the cortical anatomy and thereby obviating the use of any anatomic landmarks. In these cases, fMRI can help in locating the eloquent areas by identifying the site of parenchymal activation.

Many stimulation paradigms have been used in order to assess the relationship between a tumor margin and eloquent cortical areas (1). The most commonly mapped functions include sensory functions such as auditory, tactile, and visual perception, motor function, and last-but-not-least language comprehension and production.

For mapping sensorimotor functions it is important to keep in mind the somatotopic representation of the primary motor and sensory cortex. Classically, the anterior bank of the central sulcus contains the primary motor cortex (M1; Brodmann's area 4), while the posterior bank contains the sensory cortex (S1; Brodmann's areas 3, 2, and 1). The pre- and postcentral gyri are

Figure 1. Landmarks localizing lesions with respect to the undistorted cortical anatomy of the perirolandic region (Adapted from Naidich TP, Blum JT, Firestone MI. The parasagittal line: an anatomic landmark for axial imaging. AJNR AMJ Neuroradiol 2001;22:885–895 © American Society of Neuroradiology with permission). **a**,**c**,**e:** schematic representation of major sulci visible on transversal sections through the brain (superior frontal sulcus, precentral sulcus, central sulcus, postcentral sulcus and intraparietal sulcus). The parasagittal line is a vertical line that can be drawn through the superior frontal sulcus and intraparietal sulcus . **b:** The central sulcus is not a "straight line"; the hand "knob" (114), i.e., the representation of the motor neurons in primary motor cortex involved in hand muscle movements, form a knob in the precentral gyrus, that has the shape of a Greek letter "epsilon," or an inverted letter "omega." **d:** Medially, the central sulcus (yellow arrow) hooks into the pars marginalis of the cingulate sulcus (green arrow). **f:** Mnemonic help for memorizing these landmarks: the vertically orientated superior frontal sulcus and the horizontal precentral sulcus often intersect, and form a capital letter "L," the intersecting intraparietal sulcus and postcentral sulcus, look like a "banana-shaped" structure; the pars marginalis can be remembered as a "moustache," into which the medial extent of the central sulcus hooks. **g**,**h:** Application to a patient with a perirolandic cavernous hemangioma reveals that the lesion is anatomically situated within the precentral gyrus.
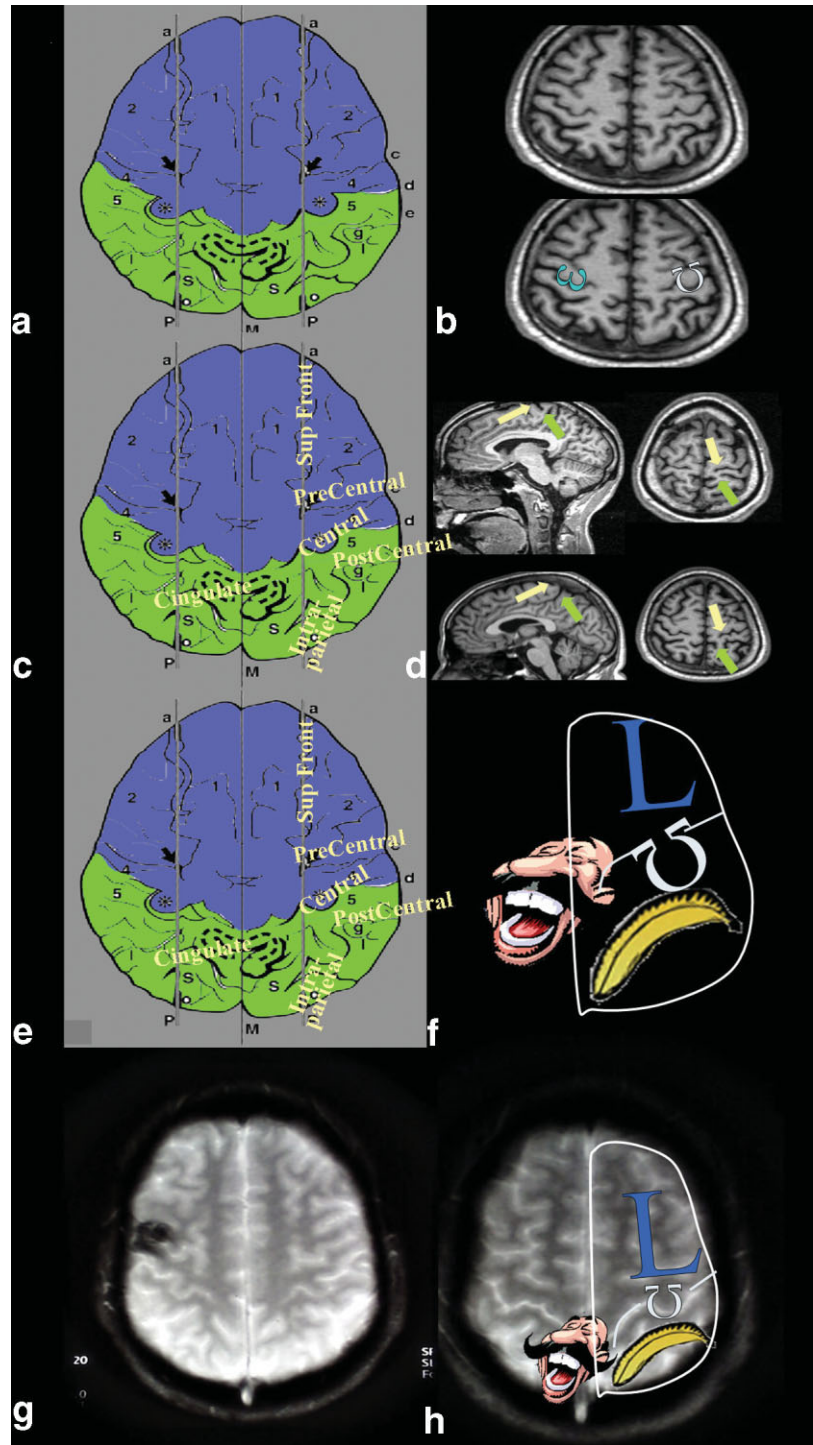
functionally organized according to a somatotopic organization (17). The following general organization is a constant finding in normal subjects: the lower extremity is located on the medial surface and the vertex of the hemisphere, the upper extremity is located on the superior portion of the hemisphere with a considerable area devoted to the hand function, and the face, tongue, and pharynx are located on the inferior portion of the lateral hemisphere (18) (Fig. 4). This somatotopy can be well reproduced in presurgical fMRI studies by asking patients to perform finger tapping (19–23), lip pouting (24,25), and extension/flexion movements of the toes (25–27). In patients with mild to severe motor–hand paresis, finger tapping can be replaced by hand clenching, or in the case of paralysis, indirect localization of M1 can be obtained through pure sensory mapping of S1 by rubbing, stroking, or brushing the body part under investigation (22,28) (Fig. 5).

For the mapping of the primary and secondary auditory cortices different kinds of auditory stimuli can be used, as long as the interference of the MR gradient
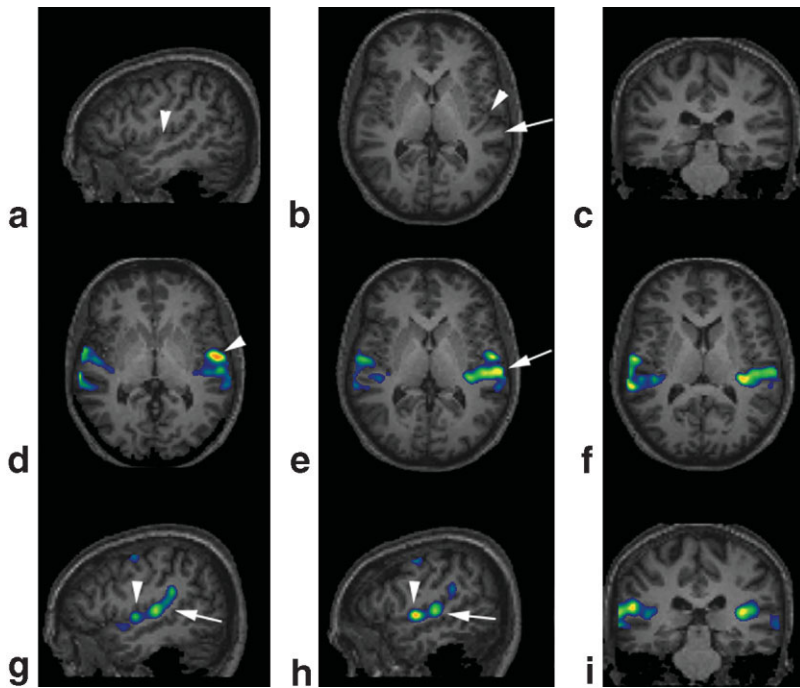
Figure 2. Functional anatomy of the primary and secondary auditory cortex in healthy subject. Anatomical T1-weighted sagittal (**a**), transversal (**b**), and coronal (**c**) cuts, depicting the anatomical landmarks of Heschl's gyrus (arrowhead) and the planum temporale (arrow). fMRI activation obtained during binaural musical stimulation versus no stimulation acquired with a sparse temporal sampling fMRI acquisition scheme, overlaid on transverse (**d**–**f**), sagittal (**g**,**h**), and coronal (**i**) cuts. Both primary auditory cortex (Heschl's gyrus; arrowhead) and secondary auditory cortices (arrowhead) are activated bilaterally. (Adapted from Sunaert S. Functional MR imaging of hearing. In: Lemmerling M, Kollias SS, editors. Radiology of the petrous bone, 1st edition. 2003. p 223–235 with permission of Springer Science and Business Media.)

generated noise is dealt with (for a review of this topic see Ref. 15).

Language can be mapped using comprehension and expression tasks (Fig. 6). For depicting language expression, a task involving Broca proper (pars triangularis and opercularis of the inferior frontal gyrus) and other expressive language areas within the middle and superior frontal gyri, word generation tasks (22,29,30) are used. Most of the time, patients are instructed to perform covert language production tasks, as words spoken aloud would induce artifactual gross head movements. These word generation tasks include pic-
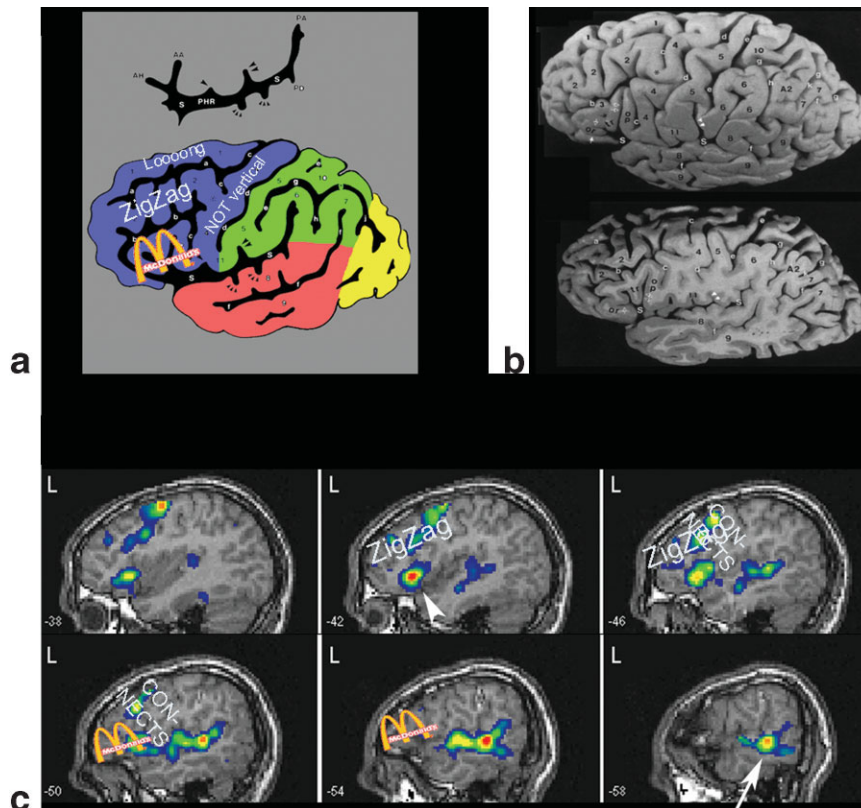

Figure 3.

ture naming, verbal fluency, and verb-to-noun generation. Wernicke's area can be mapped by tasks requiring language comprehension (19,21). Most commonly, semantic judgement tasks are used to that purpose. If these tasks are too difficult in severely ill (cognitively slowed-down patients), listening to spoken language or reading written language may be a (less optimal) alternative.

Using visual stimuli, such as flashing lights or flickering checkerboards, occipital activity can be obtained. A more detailed mapping of primary and higher order visual areas (V1, V2, V3, V3A, V4, and hMT/V5) can be rapidly mapped using wedge shape alternating checkerboards placed on the vertical and horizontal visual field meridians (16).

The value of fMRI with respect to the above mentioned items, is illustrated by the case depicted in Fig. 7. In this patient, who presented with a large perirolandic glioblastoma multiforme, the left central sulcus and the location of the left motor hand knob can be clearly identified in the healthy left hemisphere on axial MR scans. Due to the distortion of the anatomical landmarks in the lesioned right hemisphere, similar identification was impossible. If one assumes that left and right hemispheres are more or less symmetrical, one would probably conclude that the right motor hand knob would be either adjacent or even involved within the lesion. However, when the actual localization of the hand motor area was derived from an fMRI in which the motor neurons were activated with a finger-tapping task, it became clear that the motor area had been displaced anteriorly by the mass effect of the lesion. Furthermore, the radiological margin of the glioblastoma multiforme was situated >15 mm posterior from the primary sensory-motor cortex, a distance that was, in this particular case, considered to be large enough for a safe total surgical removal. Postoperatively this patient indeed had an intact motor function.

Relocation of Function (Plasticity)

Finally, in response to pathology, function may be relocated to other areas in the brain, thereby altering the normal relationship between function and anatomy. Such a relocation of function is different from "shift" in function by mechanical displacement of a region, a phenomenon already explained above. True relocation of function may be designated as cortical reorganization or plasticity, and this anatomic relocation must be differentiated from the displacement of the anatomic structure caused by the space-occupying lesion that can simulate a relocation of function. Cerebral reorganization (plasticity) is defined as the capacity of remaining areas to assume functions that are normally assumed by the damaged brain. It was found that a true relocation of function is often associated with a functional impairment such as a paresis (47). The information about the cerebral reorganization in the damaged brain could be an important decisional factor for surgical treatment.

Alkadhi et al. (32) have 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) (intrahemispheric reorganization), activation of the ipsilateral M1 (interhemispheric reorganization), and function taken over by nonprimary motor areas. The different patterns of reorganization may reflect possible differences in the timings of the occurrence of the lesions in the brain. In the case of early brain lesions (as is typically the case for vascular malformations and cortical dysplasias), the reorganization may be interhemispheric, while in case of lesions occurring later in life, the reorganization is more likely to be intrahemispheric. Inter- or intrahemispheric primary motor or premotor reorganization does not seem to depend on the type of lesion (33). Carpentier et al. (34) proposed a classification scheme of plasticity with 6 grades based on interhemispheric 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

Figure 3. Landmarks identifying the typical location of Broca's area in the left inferior frontal gyrus (pars triangularis and opercularis). **a,b:** Schematic representation of the lateral convexity of the brain. Sagittal sections of anatomic specimens and MR images display the individual gyri and sulci well along the low-middle convexity. Those familiar with the typical pattern and with the common normal variations will be able to use sagittal MRI to correctly localize lesions by identifying: (a) the five major rami of the sylvian fissure; the subdivision of the triangular inferior frontal gyrus (3) into the M-shaped ("Mc-Donalds"-shaped) partes orbitalis (or), triangularis (tr), and opercularis (op) by the anterior horizontal (AH) and anterior ascending (AA) rami of the sylvian fissure; the zigzag shape of the middle frontal gyrus (2), which characteristically angles sharply and inferiorly to connect with the anterior surface of the precentral gyrus (4); T-shaped bifurcation of the posterior end of the inferior frontal sulcus to form the inferior precentral sulcus; separation of the central sulcus from the sylvian fissure by union of the opercular ends of the precentral (4), and postcentral (5) gyri to form the subcentral gyrus inferior to the central sulcus; narrower sagittal dimension of the postcentral (5) gyrus than the precentral (4) gyrus; horseshoe shape of the supramarginal gyrus (6) perched atop the posterior ascending ramus of the sylvian fissure; (h) similar horseshoe shape of the angular gyrus (7) perched atop the posterior end of the superior temporal sulcus. When used as described, they prove helpful in correctly localizing pathology and in planning a surgical approach to lesions that may be difficult to localize on the basis of axial or coronal plane magnetic resonance images. (Adapted from Naidach TP, Valavanis AG, Kubic S. Anatomic relationships among the low-middle convexity: Part 1. Normal specimens and magnetic-resonance-imaging. Neurosurgery 1995;36:517–532, with permission of Lippincott Williams & Wilkins.) **c:** Activation map in response to a verb-to-noun generation task vs. tone-listening, overlaid on sagittal section through the left hemisphere of a normal volunteer. Note the location of Broca's area (arrow point) in the pars triangularis and opercularis of the inferior frontal gyrus (The "Mc-Donalds"-shaped gyrus). Additional expressive language areas can be seen within the frontal lobe in the medial and superior frontal gyri. Wernicke's area is denoted by an arrow.

Figure 4. Somatotopic organization of the primary motor cortex mapped using fMRI in a healthy subject, performing one of four tasks that were compared with rest: flexion-extension of the foot (blue), finger tapping (yellow), lip pouting (red), and tongue movements (green).

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. 8.

Furthermore, the stronger involvement of the premotor cortex 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 a primary motor function.

Another explanation may be the reinforcement of the premotor origin of the pyramidal tract. Fandino et al (35) compared the fMRI results with those obtained during intra-operative cortical stimulation in pa-

tients with tumors situated close to or involving the primary motor area. In some patients, two or more activation sites were demonstrated on fMRI, which were considered to reflect a consequence of reorganization of the motor cortex. This reorganization concerned the contralateral primary motor area, the contralateral premotor area, the ipsilateral primary motor area, and the ipsilateral premotor area. These authors have suggested 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.

However, the results of a possible cerebral reorganization in patients presenting with lesions of motor cortices have to be carefully interpreted. As will be discussed below, artifactually decreased or even absent fMRI signal, caused by disruption of the neurovascular
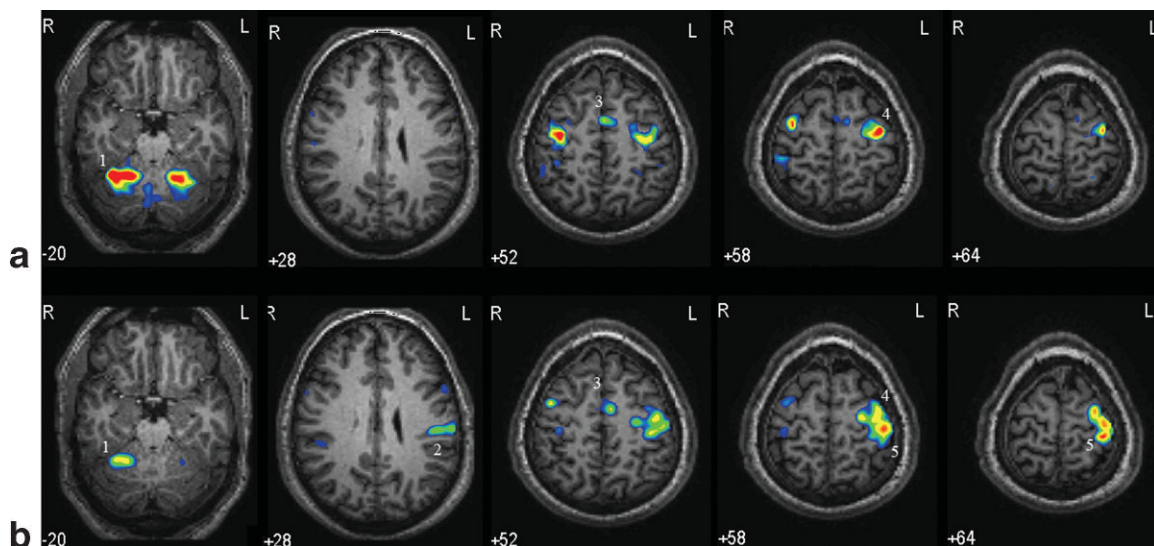

Figure 5. Comparison of bilateral finger-tapping (**a**) and left hand brushing (**b**) in a normal volunteer. Bilateral finger tapping activates primary motor cortex (M1, label = 4), supplementary motor area (SMA, label = 3), and cerebellum (label = 1). In comparison, left hand brushing activates mainly the primary sensory cortex (S1, label = 5), but also, due to afferent input, M1 (4), SMA (3) and cerebellum (1); an additional site of activation corresponds to the secondary sensory cortex (S2, label = 2).
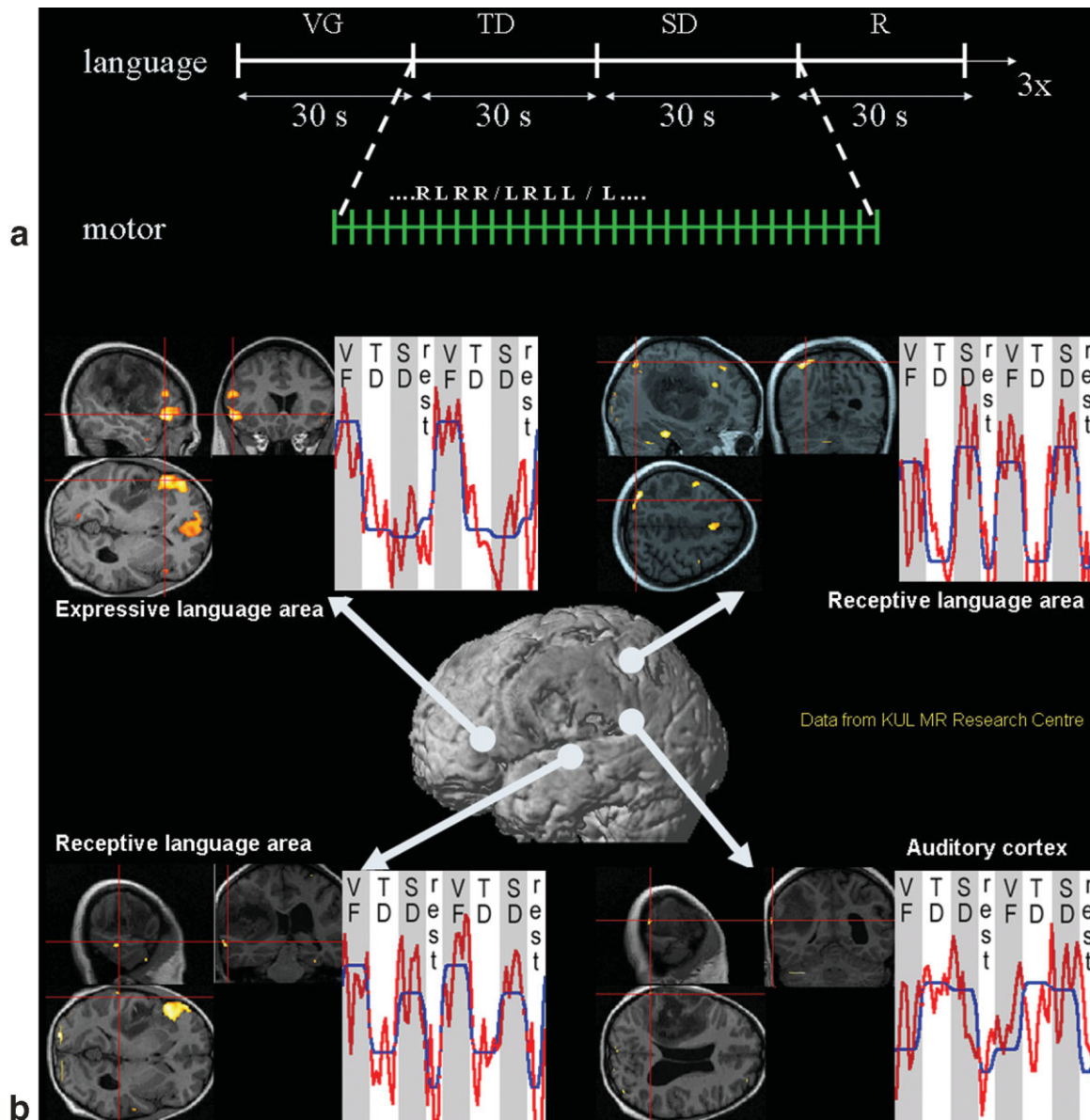
Figure 6. **a**: Language paradigm consisting of a covert verb-to-noun generation (VG; e.g., auditorily presented noun "car," and patient covertly responds "drive"), tone discrimination (TD; discrimination of tone pitch), semantic discrimination (SD; e.g., patient makes distinction between objects and animals), and rest (R). **b**: Right-handed patient with a very large fronto-parieto-temporal tumor in the left hemisphere. The mass-effect of the lesion effaces typical anatomical landmarks. The change in MR signal in response to the different tasks compared to rest is used to identify the nodes of the language network: in the auditory cortex the response is the highest during the execution of the TD task; in the receptive language areas the activity is the highest during the SD-task; in the left inferior frontal region, there is only an increase in MR signal during the execution of the covert verb-to-noun generation task, thus this area corresponds to the classical Broca's expressive language area. Note the lateralization of Broca's area to the left hemisphere in this right handed patient.

coupling, may lead to the false interpretation of inter-hemispheric relocation of function (36).

THE SECOND GOAL OF PRESURGICAL FMRI: SELECT PATIENTS FOR INTRAOPERATIVE CORTICAL STIMULATION (ICS)

A problematic feature of certain brain tumors is the inclusion of active brain tissue. Activation has been demonstrated within tumors or at the radiological tumor boundary (21,37,38). In the event that fMRI identified activity adjacent to or within a clearly essential cortical area, such as the hand representation of the primary motor cortex (a lesion within the precentral gyrus), an aggressive resection is likely to cause a longstanding profound functional deficit. In this case the patient would be better served with a more conservative approach, such as biopsy and radiation, gamma-knife ablation, or chemotherapy. In this respect fMRI is a useful tool for assessing brain function in advance of the surgery.

However, another treatment option might be to perform a subtotal resection, trying to eradicate most of the
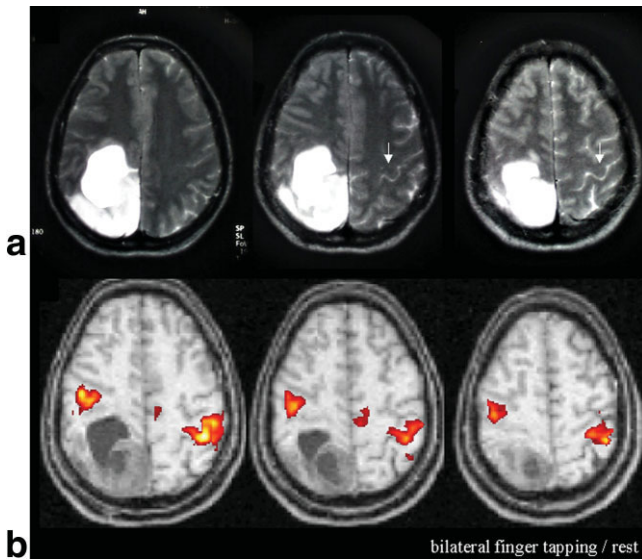
Figure 7. a: T2-weighted axial sections of a patient with a right parietal glioblastoma multiforme. Note the location of the central sulcus and the motor hand knob (arrow) in the left cerebral hemisphere. This localization of the central sulcus is impossible in the right hemisphere due to the faintness of central sulcus landmarks. Based on these conventional images, it was concluded that the lesion was inoperable. **b:** Functional MRI activation during bilateral finger tapping, superimposed onto T1 weighted axial sections at identical location as in A. The primary sensorimotor cortex of the hand is located in pre- and postcentral gyrus. The activation in the left hemisphere is located where it is expected based on the anatomical landmarks. In the right hemisphere, the primary sensorimotor cortex has been displaced anteriorly.

Figure 8. Cortical reorganization of the motor system in a patient with a recurrent glioblastoma multiforma three years after resection of a glioma grade 2 in the right frontal lobe. **a:** T1w postcontrast anatomical images. **b:** Activation pattern in response to repetitive left hand clenching vs. rest. **c:** In response to right hand clenching. Arrowheads indicate the position of the right primary motor cortex. 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, PM, 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.

tumor mass, while minimizing the resulting functional deficit. In the latter case, the neurosurgeon will in most cases use ICS, in order to identify the exact resection margin during the surgery itself.

An important element why patients should be referred for ICS during surgery is the limited accuracy of the spatial localization of the fMRI activations, due to the nature of the BOLD contrast: this originates from hemodynamic changes in the vasculature, slightly offset toward the venous compartment and thus not exactly localizing the electrically active neurons. The spatial specificity that can be achieved with fMRI and how well the activation location corresponds to the actual sites of neuronal (electrical) activity has been shown to be technique dependent. Several authors have raised the concern that fMRI exams at 1.5-T field strength image predominantly large draining veins. Spatial specificity can also be a problem when single slice, large flip angle, and short TR gradient echo sequences are used (39,40), since this can enhance the contribution of partially suppressed signal from arterial blood when flow increases. Gao et al (41) have shown that fMRI images weighted towards the microcirculation may be obtained at 1.5 T if the pulse sequence is designed for minimizing inflow effects and maximizing BOLD contribution. This can be achieved by acquiring multislice, long TR, single-shot echo-planar images (41). However, using gradient-echo (GE) fMRI sequences one is still most sensi-
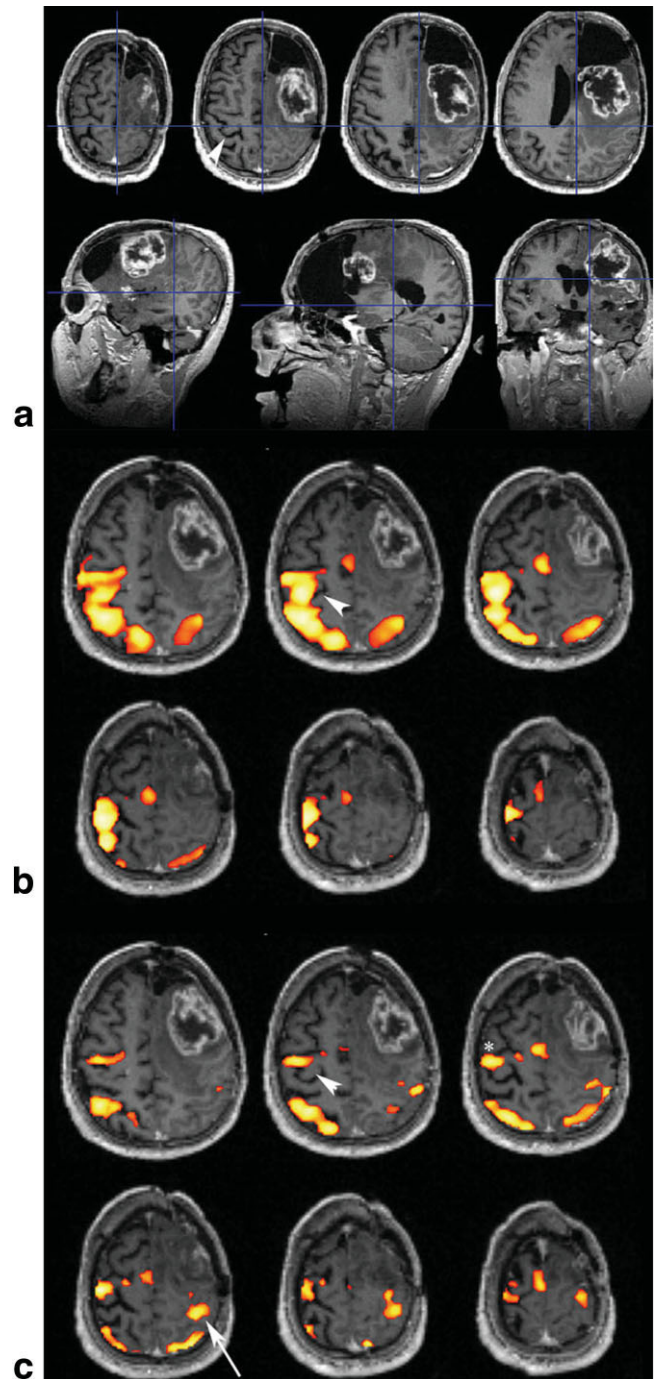
tive to vascular structures with deoxyhemoglobin, which is more in the venous compartment than in the capillaries. Using spine-echo (SE) sequences one is sensitive to the extravascular contribution and better localized to the capillaries, especially when using a higher main magnetic field strength (e.g., 3 T). Recent experiments (42) using diffusion-weighted GE EPI have suggested that intravoxel incoherent motion (IVIM) weighting can selectively attenuate contributions from large blood vessels, thereby revealing activation in capillaries in close spatial proximity to the activated neuronal tissue. Implementation of imaging parameters confining the fMRI signal toward the site of neuronal activity should thus be a prerequisite when conducting clinical fMRI exams. Recently, using optimal techniques, the spatial uncertainty from this draining vein effect was estimated to be no larger than 5 mm (43), suggesting that accuracy of fMRI is good enough for presurgical fMRI. However, in lesions adjacent to eloquent areas, the verification intraoperatively by ICS is still warranted.

Even more importantly, ICS is essential for discriminating essential versus expendable cortical regions. Behavioral tasks can evoke changes in activation in a number of cortical and subcortical structures, but many of these structures are not necessary for task performance (7). For example, the cingulate gyrus exhibits activation in a large number of neuroimaging experiments (44), 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. This example illustrates the fact that the brain may exhibit a complex pattern of activation, but not all of these activations may be necessary for performance of the behavior in question. This has clinical implications especially when fMRI is intended to substitute for other methods that directly test the necessity of a brain region for a given task. It should be noted that fMRI and ICS start from different approaches for assessing function (7). ICS begins by reversibly disrupting brain function, effectively removing those regions from the neuronal circuitry. One can then observe the effects this has on behavior, thereby directly testing the necessity of these regions for a given function. In contrast, an fMRI procedure begins with behavior, consisting of performance a particular task. One can then measure the resulting changes in brain function. These two approaches may not necessarily yield identical conclusions, and an fMRI study could in fact exhibit a number of regions that are correlated with, but are not necessary for, language behavior per se. Because of this possibility, ICS is still regarded as a "gold standard," with a lesser adjuvant role for fMRI as a means to discriminate essential from expendable brain regions.

THE THIRD GOAL OF PRESURGICAL FMRI: FUNCTIONAL NEURONAVIGATION

In recent years, image-guided systems have been used for intraoperative navigation based on preoperatively acquired computed tomography (CT) and/or MR imaging documented structural information (45). This offers the possibility of adding functional information to these systems, allowing for "functional neuronavigation." Thus, the surgeon can rely on intraoperative structural data (location of the lesion) and functional data (location of indispensable functional areas) (46–48). It is based on the registration of fMRI maps, obtained preoperatively in a first session, with MR or CT high resolution anatomical datasets acquired immediately preoperatively, and with the physical space of the patient's brain in the operating theatre. The merits of this new technology are obvious: the greatest advantage would be that functional information is more readily available and can be used in general neurosurgical practice, where it may be used to avoid unnecessary intrusions into the eloquent cortex and avoid undesirable limited resections of tumors (Fig. 9). The disadvantage however, is the uncertainty between fMRI data-maps and the actual localization of the brain tissue during surgery, due to the "brain shift" that results from craniotomy. After craniotomy, a certain amount of brain shift occurs, up to 20 mm according to Hartkens et al (49). This very important factor can severely reduce the usability and efficacy of functional neuronavigation, which is dependent on the correct registration of the brain tissue to the fMR image set. Efforts are undertaken to correct for this brain shift during the craniotomy and subsequent surgery, e.g., by estimation of the amount of brain shift using three-dimensional sonography of the brain. Unfortunately, reliable prediction of brain shift remains impossible (50).

A derived application of functional neuronavigation is the implantation of epidural or intrasulcal electrodes, guided by fMRI, in the treatment of pain syndromes (51,52), and more recently nonpulsatile tinnitus (Fig. 10) (53). In these cases, fMRI is used in order to depict the location of (sub)cortical brain regions involved in the central perception of the (phantom) pain or sound. These regions do not necessarily correspond to the classical areas of sensory (pain/sound) perception, and are identified in the individual patients by paradigms eliciting the perception of the specific pain (or phantom sound) percept of the patient in question. They then form the target for the electrode implantation. In this application, brain shift is less problematic, since for the implantation of an electrode, in most cases, only a small bore hole is necessary in contrast to a larger craniotomy.

CAVEATS OF FMRI IN THE CLINICAL SETTING OF PRESURGICAL EVALUATION

fMRI, even in normal subjects, suffers from a number of technical problems and pitfalls, such as gross head movement, ghosting, instability of the MR systems, etc. These fall beyond the scope of this aritcle (for a review see e.g., Jezzard and Clare [54]).

Here we address the specific caveats of fMRI in the clinical application of brain tumor surgery.

Technical Success Rate of Presurgical fMRI

A survey of literature shows that the success rate of presurgical fMRI is about 80% to 85% (6,28,55). Tech-
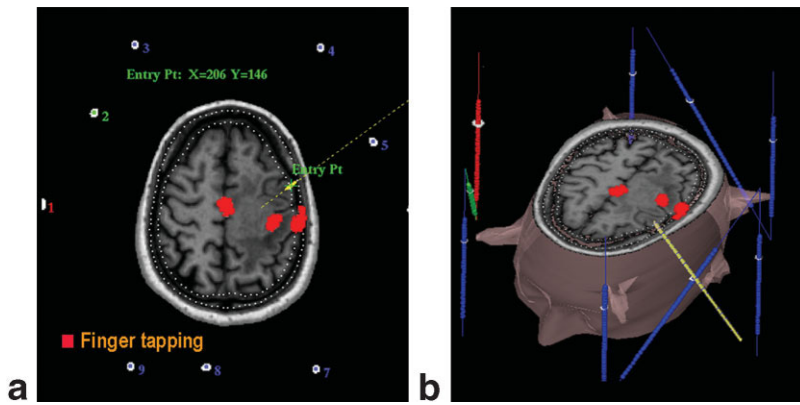
Figure 9. Functional neuronavigation: intraoperative approach to a left perirolandic tumor using the coregistered neuronavigation T1w anatomical and fMRI (right finger-tapping vs. rest) datasets.
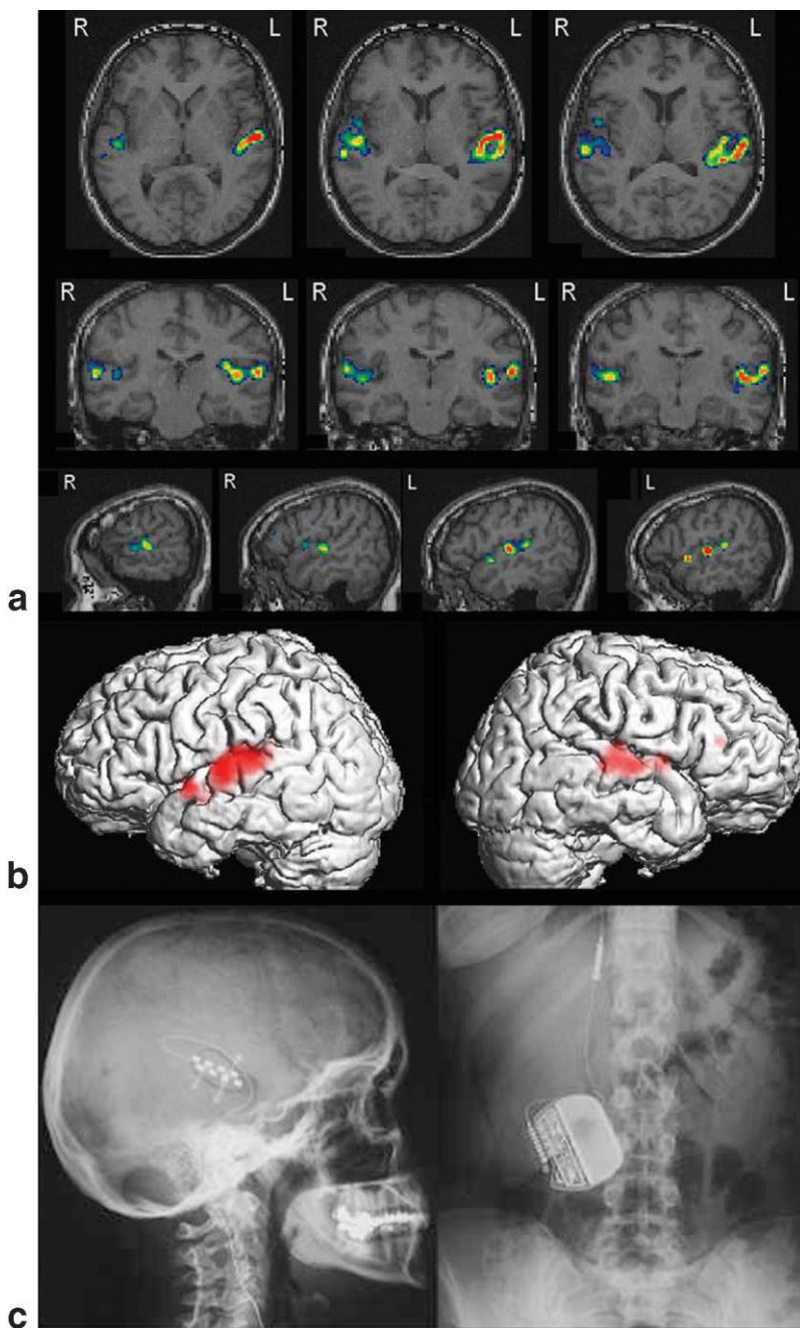

Figure 10. Functional neuronavigation for the guided implantation of an epidural electrode in a patient with left unilateral tinnitus. **a:** Auditory cortical activation in response to binaural musical stimulation; the right primary auditory cortex has less differential activity, due to the spontaneous high level of electrical activity in the right auditory cortex, which causes the (phantom) percept of unilateral left tinnitus. **b:** Same activation represented on three-dimensional surface reconstruction of the brain of the patient. **c:** Postoperative X-ray showing the location of the epidural electrode projected on the skull (left panel) and of the location of the pacemaker (right panel). (Adapted from De Ridder D, De Mulder G, Walsh V, Muggleton N, Sunaert S, Moller A. Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus [Case report]. J Neurosurg 2004; 100:560–564, with permission.)

nical and physiologic factors, discussed below, result in noninterpretative fMRI studies, but also claustrophobia and patient cooperation, especially in more difficult tasks such as cognitive or language task, hinder the use of fMRI in severely ill patients. The 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 presurgical fMRI. In a recent study by Krings et al (55) using multisection scanning techniques, the success rate of the fMRI was 85% of 194 fMRI studies in 103 patients on the representation of motor functions. Head movement artifacts were the most frequent cause for fMRI failure, followed by low signal-to-noise ratio. Motion artifacts were correlated with the degree of paresis and with the functional task. Tasks involving more proximal muscles led to significantly more motion artifacts when compared with tasks that primarily involved distal muscles. In an earlier study by Lee et al (28) the technical success rate of fMRI in identifying the functional central sulcus in the hemisphere of surgical interest in a group of 46 patients was reported to be 70%. This overall success rate, was however also highly dependent on the scanning technique that was used. Whereas the initial success rate was only 42% with a single slice scanning technique, this increased to almost 90% when they used a multisection echo-planar imaging technique covering the central sulcus to a larger extent. The need for a multisection scanning technique is emphasized by the aforementioned effects of the presence of a lesion on the cortical representation of a given function: the functional area can decrease/increase in size, can shift in location, and additional functional areas can be recruited.

The Influence of Tumors on the BOLD fMRI Signal—Reduced or Absence of fMRI Activation

Accumulating evidence seems to indicate that the BOLD response in the vicinity of certain tumors does not reflect the electrical neuronal activity as accurately as it does in healthy brain tissue (36,56–58). Recent data indicate that cortical BOLD activation can be reduced near glial tumors, both at the edge of the tumor and in normal vascular territories somewhat removed from the tumor (58). Loss of regional cerebral vasoactivity near these tumors has been suggested to be a contributing factor (56,58). At the interface of tumors and normal brain, astrocytes and macrophages can continuously release nitric oxide that leads to a regionally increased cerebral blood flow (rCBF) and decreased oxygen extraction fraction (59) during basal metabolism, which may result in a decreased BOLD signal intensity difference (58) following activation. Tumor-induced changes in regional tissue pH and glucose, lactate, and adenosine triphosphate levels have been documented (60,61), although such effects on BOLD-neuronal coupling are not clear. Glial tumors can induce abnormal vessel proliferation in adjacent brain, altering regional CBF, regional cerebral blood volume (rCBV), vasoactivity, and potentially, BOLD contrast.

Other factors, including vasogenic edema and tumoral hemorrhage, could contribute to the observed decrease in near-lesion BOLD contrast. Despite the theoretical consequences of vasogenic edema induced dilutional and tissue pressure changes on neurovascular coupling, evidence for a substantial impact on BOLD contrast is lacking in a small number of patients studied. The true impact of vasogenic edema awaits further investigation in larger patient populations with a range of tumor types. Microhemorrhages associated with intraparenchymal tumors could hinder the detection of changing susceptibility gradients that provide BOLD contrast, but confirmation of this effect requires verification with histological correlation. Metabolic changes in some brain tumors could induce, e.g., tissue pH changes, which may again eliminate the physiological hemodynamic response (62,63). Finally, alterations of microvascular architecture are also prone to exist in the neighborhood of vascular malformations (vascular steal effects).

It is of utmost importance to realize that an absence of fMRI activity in a particular brain region does *not* mean that electrical activity within this area is nonexistent, and thus that it is safe to surgically remove this region. We will demonstrate this important point using the following case report, illustrated in Fig. 11. fMRI activity during bilateral finger-tapping vs. rest in a patient with a Rolandic tumor (glioma grade 2 within the postcentral gyrus but extending within the "hand knob" of the precentral gyrus). In the nonlesioned 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, activation is only observed anterior from 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 takeover of motor function within the ipsilateral nonlesioned hemisphere), the time traces of the MR signal changes clearly show that this is a false conclusion. Within the left, tumor-invaded hand, represented in SM1, the MR signal decreases during performance of the motor task, and increases during the rest baseline condition; i.e., the inverse of the BOLD MR signal change expected in normal volunteers. This phenomenon can be explained as a complete 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 MR signal during the increased electrical neuronal activity.

To our knowledge, the existence and prevalence of these artifacts is only anecdotal, and still not well studied. As pointed out in a 1998 editorial by Bryan and Kraut (64), these "negative results" deserve further study (18,64).

Finally, it is also important to realize that the BOLD signal can also be influenced by various pharmacological agents. There are indications that antihistamines reduce the BOLD response; caffeine is a known booster of the BOLD response (65). It is not unlikely that many more pharmacological agents influence the BOLD response, and patients harboring brain tumors may receive such medication.
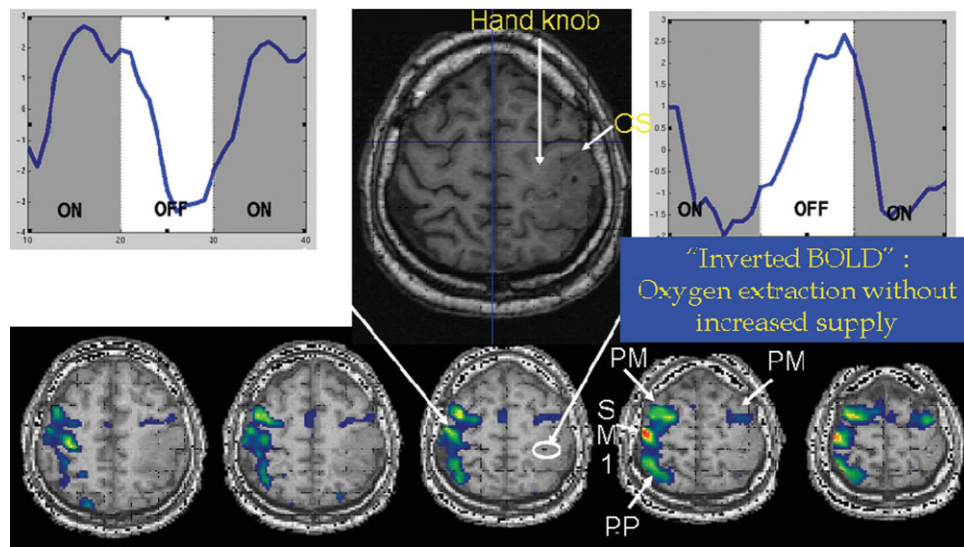
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Signal Dropouts in GE-EPI Images

Almost all BOLD fMRI acquisitions have been performed with multislice single-shot GE-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 this high susceptibility sensitivity and resulting high T2*-weighting and the long readout time during which the entire k-space of a single slice is acquired (66). In most (nonclinical) fMRI studies these drawbacks are generally overlooked relative to the advantages offered in other areas of the brain for the sensitivity of the EPI technique. But the susceptibility related signal drop in those brain areas, which are located near the skull base and in the neighborhood of large air cavities like the orbitofrontal cortex and the

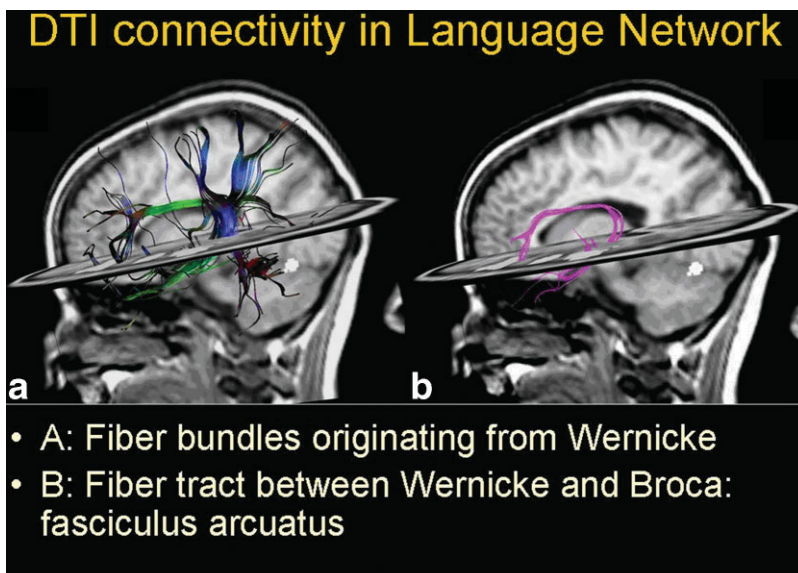**Figure 12.** Combined fMRI and DTI in a normal subject. **a:** Fiber bundles originating from a region-of-interest (ROI) corresponding to the activation site of Wernicke's area: Wernicke's area is anatomically interconnected with the temporal pole, cerebellum, parietal lobe, perirolandic region, and frontal areas. **b:** DTI fiber tracking between Wernicke's and Broca's regions: depiction of the classical direct arcuate fasciculus.

anterior and medial temporal cortex, pose a problem for fMRI experiments expecting brain activation in the those areas (66–69). In patients, this effect will also be observed in the neighborhood of a metallic implant or certain types of lesions (such as arteriovenous malformations, cavernous hemangioma, in necrotic tumors with intratumoral bleeding) in which the susceptibility difference between the lesion and the surrounding brain tissue is large (6). Furthermore, if patients previously underwent brain surgery, there is a possibility of residual metal from a skull drill, which may induce severe image signal dropouts.

Geometric distortion in the vicinity of air–tissue boundaries and in the neighborhood of lesions can give a false idea of the real position of the activated region. This is an extra factor contributing to the poor spatial localization of fMRI activations, in addition to the above described factors. It has been shown that field inhomogeneities could lead to displacements in functional GE-EPI vs. high-resolution anatomical images by up to 10–20 mm (70–72). With the current trend of using increasing static magnetic field strength, this effect of local signal loss and image distortion is even more pronounced (73). These misalignments are not corrected for by standard postprocessing packages, and may cause serious errors, when activation data from functional images are just superimposed on anatomical datasets. The take-home message here is that one should carefully examine the original GE-EPI functional images for such artifacts, and not only report fMRI activations superimposed on anatomical images.

In order to reduce image distortion and signal dropouts, new strategies have been proposed including the use of other acquisition sequences like multishot EPI sequences, spin-echo EPI sequences, and flash sequences (74), but these sequences are also less sensitive to the BOLD contrast (75). On the other hand different ingenious image processing methods also have been proposed to recover the local signal and reduce image distortions from the EPI images. But the recovery of signal, using these other sequences and recovery techniques, always comes at the expense of temporal resolution, temporal stability, spatial resolution, and/or contrast/signal-to-noise ratio, and are very difficult to use in patients with abnormal brain anatomy. Other examples of methods proposed to decrease local signal loss in the EPI sequences are decreasing the slice thickness of the acquired images minimizing slice induced susceptibility artifacts (76), local shimming to decrease local magnetic field inhomogeneity (77), maximizing the readout bandwidth in order to minimize the length of the EPI echo train, which decreases the T2* decay and thus susceptibility effects, but also increases the noise in the images.

Recently, promising work has come from another development, notably the use of parallel imaging techniques (78,79). 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 that suffer from susceptibility artifacts in the standard single-shot BOLD fMRI experiments (80). In these methods receiver coil arrays using a combination of a number of receive coils (ranging from two to 32 elements) (81,82) 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 (78,79). As a result, this reduces acquired phase encoding steps and leads to a diminution of measurement time. 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 the parallel imaging techniques has been demonstrated in several studies at 1.5 T and 3 T (80,83), where they demonstrated the potential of the sensitivity encoding (SENSE) technique at 1.5 T with different reduction factors and spatial resolutions for fMRI purposes (80).

ROADMAP TOWARD CLINICAL ACCEPTANCE OF PRESURGICAL FMRI

Despite its successful application, preoperative fMRI has not yet reached the status of an established clinical diagnostic procedure. Many of the above mentioned technical and physiological limitations contribute to this—justified—lack of acceptance. In the next paragraphs we propose lines of future research and development that would bring presurgical fMRI closer to its ultimate goal: improving the outcome of a patient with a brain tumor.

Disentangling Essential vs. Expendable Brain Regions

As mentioned before fMRI lacks the ability to discriminate essential from expendable regions within a network of activations involved in a particular function. Expendable areas could be defined as regions within the network that correlate with the performance of a given neurological function, but that are not essential for the correct execution of this function. Intraoperative cortical stimulation—given its ability to reversibly locally disrupt brain function—can be used to interrogate whether a certain region is critical for the neurological function. Similarly, the intraarterial amobarbital procedure, also referred to as the Wada test, is commonly employed for assessing hemispheric language and memory dominance. For this procedure, the patient receives an injection of sodium amobarbital in each carotid artery, anesthetizing one hemisphere at a time. During the approximately 10-minute anesthetization, language and/or memory functions are assessed. Since this is again a local (one hemisphere) knockout of function, one can assess whether the activations observed within the language or memory network are crucial or not to the correct execution.

However, both ICS and the Wada test are highly invasive and difficult to perform. Both are very unpleasant to the patient, who experiences unilateral paralysis, the inability to speak, and the inability to understand speech; both are expensive, costing nearly as much as the surgery itself. In addition, the Wada test does not provide information about the

localization of language within the hemisphere. Furthermore, ICS requires a surgical procedure itself, before any functional information can be obtained.

The combination of fMRI and focal transcranial magnetic stimulation (TMS) might be an interesting alternative for ICS and/or Wada testing. TMS is a noninvasive technique able to produce focal, transient, and fully-reversible disruption of cortical network function during the performance of cognitive, sensory, or motor tasks (84). Effectively, TMS utilizes an electromagnet to cause a very temporary disruption in the firing of neurons at the site of stimulation. TMS has a relatively high spatial resolution and recent advances in image processing (85) allow further refinement of TMS by combining MRI modalities with TMS using a neuronavigation system to measure the position of the stimulating coil and map this position onto a MRI data set, so that it is possible to pinpoint very specific areas of cortex for transcranial magnetic stimulation. Where fMRI cannot tell us whether an area is necessary for the task we are investigating, in contrast, stimulating the same area with TMS and observing the effects of the stimulation on behavior can tell us if that area is required for the task. The combination of fMRI and TMS might also be used to study cortical plasticity in response to the presence of tumors and other lesions (cortical dysplasia, stroke, etc.) (86). There are, however, also limitations of TMS. It has a limited efficacy in disrupting deeper brain structures, or cortical areas that are difficult to reach due to the skull shape (e.g., posterior fossa due to neck, temporal lobe due to interposition of the ears). Furthermore, in the reachable areas of the cortex, the knockout can be limited in space and intensity, making it quite difficult to interpret a negative response by TMS. Nonetheless, the combination of fMRI and TMS deserves more research attention.

The Brain Is Composed of Gray and White Matter

The major goal of presurgical fMRI is the risk assessment of surgical removal of brain tumors by identifying the distance between the margin of the tumor resection and the eloquent or essential functional areas. Many authors have described a "golden rule" that a minimal distance for feasible surgical resection is a distance of at least 10 to 15 mm between tumor margin and an essential structure.

As mentioned above, this "golden rule" is subject to criticism. The major being the fact that fMRI is sensitive to cortical changes, but provides no or only limited information about the relation of the tumor to white-matter fiber tracts. Interruption of these fiber tracts can lead to major neurological disfunction. There is a need to improve the risk assessment of treatment of tumors by combining fMRI with techniques that provide information about the white matter.

Diffusion-tensor imaging (DTI) is a modification of the MRI technique that is sensitive to Brownian motion of water molecules in biological tissues (87,88); it is a new clinical method that can demonstrate the orientation and integrity of white matter fibers in vivo (89). Within cerebral white matter water molecules diffuse more freely along the direction of axonal fascicles than across them, arising from the restriction of free-water diffusion

by the axonal membrane, axonal microtubule, and the axonal myelin sheath (90–92). Such directional dependence of diffusivity is termed anisotropy. An integrated MR measure of water diffusion in at least six noncollinear directions is used to calculate the diffusion tensor (D), from which fractional anisotropy (FA; the amount of anisotropy) and the directionally averaged mean diffusivity (Dav) can be derived (93). By combining anisotropy data with the directionality it is possible to obtain estimates of fiber orientation. This has lead to fiber tractography (FT) in which three-dimensional pathways of white-matter tracts are reconstructed by sequentially piecing together discrete and shortly-spaced estimates of fiber orientation to form continuous trajectories (94–96).

The power of the combined use of fMRI and DTI is the fact that both techniques can be performed using the same MR machine, in a single imaging session. Valuable information about the major white-matter connections can be obtained through FT, using the fMRI-activated regions as starting points for the FT algorithm. Doing so, corticospinal and corticobulbar tracts, arcuate, uncinate, inferior and superior longitudinal fasciculi, corpus callosum, and cerebellar peduncles, are some of the major fiber bundles that can be readily depicted (89,97). An example of the tracking of the arcuate fasciculus, the classical direct pathway between Broca's and Wernicke's language regions (98), in a normal subject can be seen in Fig. 12.

DTI has been proposed as a technique suitable for presurgical planning in brain tumor patients (99–107). It has the potential to establish spatial relationships between eloquent white matter and tumor borders, provide information essential to preoperative planning, and improve the accuracy of preoperative surgical risk assessments. Several recent studies (99,100,102) showed that the combined use of fMRI and DTI can provide a better estimation of the proximity of tumor borders to eloquent brain systems subserving language, speech, vision, motor, and premotor functions. In the study of Ulmer et al (99) twice as many eloquent structures were localized to within 5 mm of tumor borders when DTI and fMRI were utilized for preoperative planning, compared to that afforded by fMRI alone. Additionally, a low regional complication rate of surgery (4%) observed in this series suggests that preoperative planning with these combined techniques may improve surgical outcomes compared to that previously reported in the literature.

We would like to emphasize this point by the illustrative case shown in Fig. 13. This 31-year-old right-handed patient with a low grade glioma in the left supramarginal and angular gyri underwent an fMRI with verbal fluency tasks in order to assess the language network. The fMRI activity in Broca's and Wernicke's areas were at a larger than 20 mm distance from the radiological tumor border, and applying the "golden rule" here, would lead to the (false) conclusion that it is safe to remove the tumor. DTI with fiber-tracking depicting the arcuate bundle between Wernicke and Broca shows that the bundle seems to be displaced medially by the mass effect of the lesion and its middle part is adjacent to the tumor border. It is likely that a
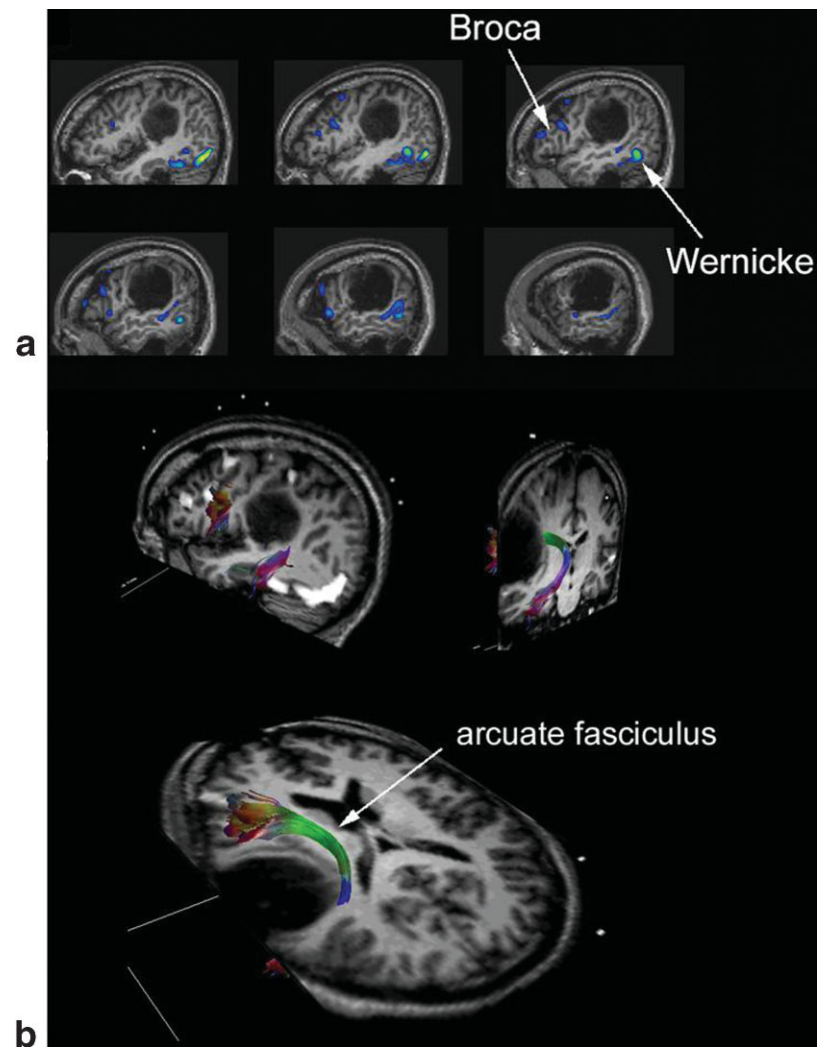
Figure 13. A 31-year-old, male, right-handed patient presenting with seizures. MR imaging revealed a low-grade tumoral mass in the left supramarginal and angular gyri. **a:** fMRI during a verbal fluency task depicts a left lateralized language, with Wernicke's area in the middle temporal gyrus and Broca in the inferior frontal gyrus. Both eloquent areas are some distance of the lesion. **b:** Diffusion tensor imaging with fiber-tracking depicting the arcuate bundle between Wernicke and Broca. The bundle seems to be displaced medially by the mass effect of the lesion and its middle part is adjacent to the tumor border.

resection of the tumor would lead to an injury of the arcuate fasciculus, which functionally would result in a severe conduction aphasia.

Larger studies specifically designed to establish the accuracy and predictive value of combined fMRI-DTI in brain tumor patients are warranted to substantiate our preliminary observations. One has to realize that DTI fiber tracking also has its limitations and artifacts (for a review see, e.g., Ref. 103), especially in areas of the brain with pathological signal changes. Fiber tracking might be enhanced by multitensor evaluation, Q-ball imaging, etc. (104), but these are quite time consuming—both in terms of data acquisition as well as postprocessing—and might be difficult to perform in a clinical setting. Nonetheless, it is our conviction that the single use of fMRI without knowledge of the white matter connections will prove to be unethical in the nearby future.

Need for Standardization of Paradigms

As mentioned earlier several reliable fMRI paradigms have been developed—based on neuropsychological principles—in order to visualize brain activity in response to sensory, motor, and cognitive tasks. However there is a lack of consensus for obtaining and interpreting brain activation maps. If presurgical fMRI is to be clinically valuable, standardization of scanning procedures, task administration, and standardized image analysis procedures will be needed in order to obtain meaningful and objective information.

Obtaining normative fMRI data in healthy subjects is a first step in the development of clinically useful paradigms. However paradigms need to be adopted for the patient population; e.g., it makes no sense to ask a patient with hemiparesis to perform a motor task with the paretic limbs. Parameters, such as task difficulty and duration of scanning, that are most suitable for clinical populations, but that do not sacrifice image integrity, need to be determined. Certain tasks may require practice outside the scanner to ensure the patient's understanding of what is required of them and the task itself. A criterion for performance prior to scanning for each task needs to be established. Standardized instructions should also be provided. As we are comparing individual differences instead of group differences in the clinical population, brain activations may be more sensitive to stimuli presentation based on equipment setup. Thus, standardized setup may also

be required. Studies have shown that the control task used for condition comparisons can influence activation results of language lateralization (105) and semantic processing (106), further emphasizing the need for task standardization.

In presurgical, fMRI activation paradigms are usually selected on the basis of lesion localization, and both neurosurgeon and neuroradiologist can be involved in this decision. Another approach, used in an increasing number of studies, is the use of fMRI task batteries (23,107–109). The use of such a battery in conjunction with real-time image analysis techniques is thought to enhance the precision of neurosurgical interventions (110–113) and is the next logical step in developing fMRI for clinical use.

Toward Standardized Statistical Postprocessing

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 we are 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-dependent 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 presurgical 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 we analyze basic neuroscience data. More research is warranted into a new method for clinical fMRI analysis that 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 had been higher. This would lead to a separate color map that shows voxels with low signal change as well as noisy voxels, and also shows areas where artifacts or signal dropouts would make potential activation undetectable.

Need for Hands-On Training

Historically, radiology is concerned with anatomy and so is the majority of the training and education provided to radiologists. Even for neuroradiologists, after a decade of functional neuroimaging, the complexity of the function of the human brain forms a hard barrier to overcome. The interpretation of fMRI activations, especially in the pathological brain, remains challenging. Furthermore, the clinical use of fMRI—as pointed out above—is highly demanding on the knowledge of (f)MRI physics, neurophysiology, neurology, and statistics. There is an urgent need for advanced training in clinical fMRI. Initiatives are necessary, not only publications such as these, but hands-on training. To that purpose, we, and others, organize clinical fMRI hands-on training, where attendees are given the possibility to learn hands-on scanning of different fMRI paradigms on real presurgical cases, as well as training in postprocessing, and case-image interpretation.

CONCLUSIONS

In conclusion, presurgical fMRI in patients with brain tumors is a promising clinical application with added value. In well-trained hands, and realizing its limitations—especially the lack of differentiating essential from expendable brain areas, and reduced or absent fMRI signal that anecdotally occurs in some patients—it allows assessment of the risk of therapeutic interventions, selection of patients for intraoperative mapping, and guides brain surgery itself. However, fMRI has not yet reached the status of clinical acceptance. Combining presurgical fMRI with other techniques such as DTI and TMS should give it that status in the near future.

ACKNOWLEDGMENTS

REFERENCES

1. Vlieger EJ, Majoie CB, Leenstra S, den Heeten GJ. Functional magnetic resonance imaging for neurosurgical planning in neurooncology. Eur Radiol 2004;14:1143–1153.
2. Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS. Time course EPI of human brain-function during task activation. Magn Reson Med 1992;25:390–397.
3. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic-resonance-imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 1990;87:9868–9872.
4. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation—functional brain mapping with magnetic-resonance-imaging. Proc Natl Acad Sci USA 1992; 89:5951–5955.
5. Yetkin FZ, Ulmer JL, Mueller W, Cox RW, Klosek MM, Haughton VM. Functional magnetic resonance imaging assessment of the risk of postoperative hemiparesis after excision of cerebral tumors. Int J Neuroradiol 1998;4:253–257.
6. Haberg A, Kvistad KA, Unsgard G, Haraldseth O. Preoperative blood oxygen level-dependent functional magnetic resonance imaging in patients with primary brain tumors: clinical application and outcome. Neurosurgery 2004;54:902–914.

7. Desmond JE, Chen SHA. Ethical issues in the clinical application of fMRI: Factors affecting the validity and interpretation of activations. Brain Cogn 2002;50:482–497.

8. Naidich TP, Valavanis AG, Kubik S. Anatomic relationships along the low-middle convexity .1. Normal specimens and magnetic-resonance-imaging. Neurosurgery 1995;36:517–532.

9. Naidich TP, Blum JT, Firestone MI. The parasagittal line: an anatomic landmark for axial imaging. AJNR Am J Neuroradiol 2001; 22:885–895.

10. Naidich TP, Hof PR, Yousry TA, Yousry I. The motor cortex—anatomic substrates of function. Neuroimaging Clin N Am 2001; 11:171–193.

11. Naidich TP, Hof PR, Gannon PJ, Yousry TA, Yousry I. Anatomic substrates of language—emphasizing speech. Neuroimaging Clin N Am 2001;11:305–341.

12. Fesl G, Moriggl B, Schmid UD, Naidich TP, Herholz K, Yousry TA. Inferior central sulcus: variations of anatomy and function on the example of the motor tongue area. Neuroimage 2003;20:601–610.

13. Naidich TP, Kang E, Fatterpekar GM, et al. The insula: anatomic study and MR Imaging display at 1.5 T. AJNR Am J Neuroradiol 2004;25:222–232.

14. Gati JS, Menon RS, Ugurbil K, Rutt BK. Experimental determination of the BOLD field strength dependence in vessels and tissue. Magn Reson Med 1997;38:296–302.

15. Sunaert S. Functional MR imaging of hearing. In: Lemmerling M, Kollias SS, editors. Radiology of the petrous bone, 1st edition. New York: Springer Verlag; 2003. p 223–235.

16. Sunaert S, Van Hecke P, Marchal G, Orban GA. Attention to speed of motion, speed discrimination, and task difficulty: an fMRI study. Neuroimage 2000;11:612–623.

17. Penfield W, Rasmussen T. The cerebral cortex of man. New York: Macmillan Publishing Co., 1950, 468 p.

18. Sunaert S, Dymarkowski S, Van Oostende S, Van Hecke P, Wilms G, Marchal G. Functional magnetic resonance imaging (fMRI) visualises the brain at work. Acta Neurol Belg 1998;98:8–16.

19. Maldjian J, Atlas SW, Howard RS, et al. Functional magnetic resonance imaging of regional brain activity in patients with intracerebral arteriovenous malformations before surgical or endovascular therapy. J Neurosurg 1996;84:477–483.

20. Latchaw RE, Hu XP, Ugurbil K, Hall WA, Madison MT, Heros RC. Functional magnetic-resonance-imaging as a management tool for cerebral arteriovenous-malformations. Neurosurgery 1995;37: 619–625.

21. Atlas SW, Howard RS, Maldjian J, et al. Functional magnetic resonance imaging of regional brain activity in patients with intracerebral gliomas: Findings and implications for clinical management. Neurosurgery 1996;38:329–337.

22. Dymarkowski S, Sunaert S, Van Oostende S, et al. Functional MRI of the brain: localisation of eloquent cortex in focal brain lesion therapy. Eur Radiol 1998;8:1573–1580.

23. Hirsch J, Ruge MI, Kim KHS, et al. An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery 2000;47:711–721.

24. Yetkin FZ, Mueller WM, Morris GL, et al. Functional MR activation correlated with intraoperative cortical mapping. Am J Neuroradiol 1997;18:1311–1315.

25. Lehericy S, Duffau H, Cornu P, et al. 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 2000;92:589–598.

26. Sabbah P, Foehrenbach H, Dutertre G, et al. Multimodal anatomic, functional, and metabolic brain imaging for tumor resection. Clin Imaging 2002;26:6–12.

27. Roux FE, Ibarrola D, Tremoulet M, et al. Methodological and technical issues for integrating functional magnetic resonance imaging data in a neuronavigational system. Neurosurgery 2001; 49:1145–1156.

28. Lee CC, Ward HA, Sharbrough FW, et al. Assessment of functional MR imaging in neurosurgical planning. AJNR Am J Neuroradiol 1999;20:1511–1519.

29. Rutten GJM, van Rijen PC, van Veelen CWM, Ramsey NF. Language area localization with three-dimensional functional magnetic resonance imaging matches intrasulcal electrostimulation in Broca's area. Ann Neurol 1999;46:405–408.

30. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, Lesage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: Correlation with direct cortical stimulation. Neurosurgery 2003;52:1335–1345.

31. Bittar RG, Olivier A, Sadikot AF, Andermann F, Reutens DC. Cortical motor and somatosensory representation: effect of cerebral lesions. J Neurosurg 2000;92:242–248.

32. Alkadhi H, Kollias SS, Crelier GR, Golay X, Hepp-Reymond MC, Valavanis A. Plasticity of the human motor cortex in patients with arteriovenous malformations: a functional MR imaging study. AJNR Am J Neuroradiol 2000;21:1423–1433.

33. Baciu M, Le Bas JF, Segebarth C, Benabid AL. Presurgical fMRI evaluation of cerebral reorganization and motor deficit in patients with tumors and vascular malformations. Eur J Radiol 2003;46: 139–146.

34. Carpentier AC, Constable RT, Schlosser MJ, et al. Patterns of functional magnetic resonance imaging activation in association with structural lesions in the Rolandic region: a classification system. J Neurosurg 2001;94:946–954.

35. Fandino J, Kollias SS, Wieser HG, Valavanis A, Yonekawa Y. Intraoperative validation of functional magnetic resonance imaging and cortical reorganization patterns in patients with brain tumors involving the primary motor cortex. J Neurosurg 1999;91: 238–250.

36. Ulmer JL, Krouwer HG, Mueller WM, Ugurel MS, Kocak M, Mark LP. Pseudo-reorganization of language cortical function at fMR imaging: a consequence of tumor-induced neurovascular uncoupling. AJNR Am J Neuroradiol 2003;24:213–217.

37. Skirboll SS, Ojemann GA, Berger MS, Lettich E, Winn HR. Functional cortex and subcortical white matter located within gliomas. Neurosurgery 1996;38:678–684.

38. Schiffbauer H, Ferrari P, Rowley HA, Berger MS, Roberts TPL. Functional activity within brain tumors: a magnetic source imaging study. Neurosurgery 2001;49:1313–1320.

39. Duyn JH, Moonen CTW, Vanyperen GH, Deboer RW, Luyten PR. Inflow versus deoxyhemoglobin effects in BOLD functional MRI using gradient echoes at 1.5 T. NMR Biomed 1994;7:83–88.

40. Haacke EM, Hopkins A, Lai S, et al. 2D and 3D high-resolution gradient-echo functional imaging of the brain - venous contributions to signal in motor cortex studies. NMR Biomed 1994;7:54–62.

41. Gao JH, Miller I, Lai S, Xiong TJ, Fox PT. Quantitative assessment of blood inflow effects in functional MRI signals. Magn Reson Med 1996;36:314–319.

42. Song AW, Woldorff MG, Gangstead S, Mangun GR, McCarthy G. Enhanced spatial localization of neuronal activation using simultaneous apparent-diffusion-coefficient and blood-oxygenation functional magnetic resonance Imaging. Neuroimage 2002;17:742–750.

43. Turner R. How much cortex can a vein drain? Downstream dilution of activation-related cerebral blood oxygenation changes. Neuroimage 2002;16:1062–1067.

44. Cabeza R, Nyberg L. Imaging cognition: an empirical review of PET studies with normal subjects. J Cogn Neurosci 1997;9:1–26.

45. Schneider JP, Schulz T, Schmidt F, et al. Gross-total surgery of supratentorial low-grade gliomas under intraoperative MR guidance. AJNR Am J Neuroradiol 2001;22:89–98.

46. Cosgrove GR, Buchbinder BR, Jiang H. Functional magnetic resonance imaging for intracranial navigation. Neurosurg Clin N Am 1996;7:313–322.

47. Nimsky C, Ganslandt O, von Keller B, Romstock J, Fahlbusch R. Intraoperative high-field-strength MR imaging: Implementation and experience in 200 patients. Radiology 2004;233:67–78.

48. Schulder M, Maldjian JA, Liu WC, et al. Functional image-guided surgery of intracranial tumors located in or near the sensorimotor cortex. J Neurosurg 1998;89:412–418.

49. Hartkens T, Hill DLG, Castellano-Smith AD, et al. Measurement and analysis of brain deformation during neurosurgery. IEEE Trans Med Imaging 2003;22:82–92.

50. Nimsky C, Ganslandt O, Hastreiter P, Fahlbusch R. Intraoperative compensation for brain shift. Surg Neurol 2001;56:357–364.

51. Sol JC, Casaux J, Roux FE, et al. Chronic motor cortex stimulation for phantom limb pain: Correlations between pain relief and functional imaging studies. Stereotact Funct Neurosurg 2001;77: 172–176.

52. Pirotte B, Brotchi J. SonoWand, an ultrasound-based neuronavigation system [Comment]. Neurosurgery 2000;47:1380.

53. De Ridder D, De Mulder G, Walsh V, Muggleton N, Sunaert S, Moller A. Magnetic and electrical stimulation of the auditory cortex for intractable tinnitus [Case report]. J Neurosurg 2004;100: 560–564.

54. Jezzard P, Clare S. Sources of distortion in functional MRI data. Hum Brain Mapp 1999;8:80–85.

55. Krings T, Reinges MHT, Erberich S, et al. Functional MRI for presurgical planning: problems, artefacts, and solution strategies. J Neurol Neurosurg Psychiatry 2001;70:749–760.

56. Holodny AI, Schulder M, Liu WC, Wolko J, Maldjian JA, Kalnin AJ. 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 2000;21:1415–1422.

57. Ulmer JL, Hacein-Bey L, Mathews VP, et al. Lesion-induced pseudo-dominance at functional magnetic resonance imaging: Implications for preoperative assessments. Neurosurgery 2004; 55:569–579.

58. Schreiber A, Hubbe U, Ziyeh S, Hennig J. The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement. AJNR Am J Neuroradiol 2000;21: 1055–1063.

59. Whittle IR, Collins F, Kelly PAT, Ritchie I, Ironside JW. Nitric oxide synthase is expressed in experimental malignant glioma and influences tumour blood flow. Acta Neurochir (Wien) 1996;138:870–875.

60. Hossmann KA, Linn F, Okada Y. Bioluminescence and fluoroscopic imaging of tissue pH and metabolites in experimental brain-tumors of cat. NMR Biomed 1992;5:259–264.

61. Linn F, Seo K, Hossmann KA. Experimental transplantation gliomas in the adult cat brain. 3. Regional biochemistry. Acta Neurochir (Wien) 1989;99:85–93.

62. Hund-Georgiadis M, Mildner T, Georgiadis D, Weih K, von Cramon DY. Impaired hemodynamics and neural activation? A fMRI study of major cerebral artery stenosis. Neurology 2003 11;61:1276–1279.

63. Fujiwara N, Sakatani K, Katayama Y, et al. Evoked-cerebral blood oxygenation changes in false-negative activations in BOLD contrast functional MRI of patients with brain tumors. Neuroimage 2004;21:1464–1471.

64. Bryan RN, Kraut M. Functional magnetic resonance imaging: you get what you (barely) see. Am J Neuroradiol 1998;19:991–992.

65. Laurienti PJ, Field AS, Burdette JH, Maldjian JA, Yen YF, Moody DM. Dietary caffeine consumption modulates fMRI measures. Neuroimage 2002;17:751–757.

66. Devlin JT, Russell RP, Davis MH, et al. Susceptibility-induced loss of signal: comparing PET and fMRI on a semantic task. Neuroimage 2000;11:589–600.

67. Friston KJ, Williams S, Howard R, Frackowiak RSJ, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med 1996;35:346–355.

68. O'Doherty J, Rolls ET, Francis S, et al. Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 2000;11:399–403.

69. Small DM, Voss J, Mak YE, Simmons KB, Parrish T, Gitelman D. Experience-dependent neural integration of taste and smell in the human brain. J Neurophysiol 2004;92:1892–1903.

70. Jezzard P, Balaban RS. Correction for geometric distortion in echo-planar images from B-0 field variations. Magn Reson Med 1995;34:65–73.

71. Zaitsev M, Hennig J, Speck O. Point spread function mapping with parallel imaging techniques and high acceleration factors: fast, robust, and flexible method for echo-planar imaging distortion correction. Magn Reson Med 2004;52:1156–1166.

72. Zeng HR, Constable RT. Image distortion correction in EPI: comparison of field mapping with point spread function mapping. Magn Reson Med 2002;48:137–146.

73. Abduljalil AM, Robitaille PML. Macroscopic susceptibility in ultra high field MRI. J Comput Assist Tomogr 1999;23:832–841.

74. Menon RS, Thomas CG, Gati JS. Investigation of BOLD contrast in fMRI using multi-shot EPI. NMR Biomed 1997;10:179–182.

75. Song AW, Wolff SD, Balaban RS, Jezzard P. The effect of off-resonance radiofrequency pulse saturation on fMRI contrast. NMR Biomed 1997;10:208–215.

76. Hoogenraad FGC, Pouwels PJW, Hofman MBM, et al. High-resolution segmented EPI in a motor task fMRI study. Magn Reson Imaging 2000;18:405–409.

77. Deichmann R, Gottfried JA, Hutton C, Turner R. Optimized EPI for fMRI studies of the orbitofrontal cortex. Neuroimage 2003;19: 430–441.

78. Sodickson DK, Manning WJ. Simultaneous acquisition of spatial harmonics (SMASH): Fast imaging with radiofrequency coil arrays. Magn Reson Med 1997;38:591–603.

79. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. Magn Reson Med 1999;42:952–962.

80. Preibisch C, Pilatus U, Bunke R, Hoogenraad F, Zanella F, Lanfermann H. Functional MRI using sensitivity-encoded echo planar imaging (SENSE-EPI). Neuroimage 2003;19:412–421.

81. Weiger M, Pruessmann KP, Osterbauer R, Bornert P, Boesiger P, Jezzard P. Sensitivity-encoded single-shot spiral imaging for reduced susceptibility artifacts in BOLD fMRI. Magn Reson Med 2002;48:860–866.

82. de Zwart JA, van Gelderen P, Kellman P, Duyn JH. Reduction of gradient acoustic noise in MRI using SENSE-EPI. Neuroimage 2002;16:1151–1155.

83. Schmidt CF, Degonda N, Luechinger R, Henke K, Boesiger P. Sensitivity-encoded (SENSE) echo planar fMRI at 3T in the medial temporal lobe. Neuroimage 2005;25:625–641.

84. Epstein CM, Figiel GS, McDonald WM, mazon-Leece J, Figiel L. Rapid rate transcranial magnetic stimulation in young and middle-aged refractory depressed patients. Psychiatr Ann 1998;28: 36–39.

85. Krings T, Chiappa KH, Foltys H, Reinges MHT, Cosgrove GR, Thron A. Introducing navigated transcranial magnetic stimulation as a refined brain mapping methodology. Neurosurg Rev 2001;24: 171–179.

86. Rutten GJM, Ramsey NF, van Rijen PC, Franssen H, van Veelen CWM. Interhemispheric reorganization of motor hand function to the primary motor cortex predicted with functional magnetic resonance imaging and transcranial magnetic stimulation. J Child Neurol 2002;17:292–297.

87. Lebihan D. Diffusion, perfusion and functional magnetic-resonance-imaging. J Mal Vasc 1995;20:209–14.

88. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Mag Reson B 1996;111:209–219.

89. Wakana S, Jiang HY, Nagae-Poetscher LM, van Zijl PCM, Mori S. Fiber tract-based atlas of human white matter anatomy. Radiology 2004;230:77–87.

90. Lebihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Lavaljeantet M. MR imaging of intravoxel incoherent motions - application to diffusion and perfusion in neurologic disorders. Radiology 1986;161:401–407.

91. Moseley ME, Cohen Y, Kucharczyk J, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central-nervous-system. Radiology 1990;176:439–445.

92. Pierpaoli C, Jezzard P, Basser PJ, Barnett A, DiChiro G. Diffusion tensor MR imaging of the human brain. Radiology 1996;201:637–648.

93. Basser PJ, Pierpaoli C. A simplified method to measure the diffusion tensor from seven MR images. Magn Reson Med 1998;39: 928–934.

94. Mori S, Crain BJ, Chacko VP, van Zijl PCM. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 1999;45:265–269.

95. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. Magn Reson Med 2000;44:625–632.

96. Mori S, Kaufmann WE, Davatzikos C, et al. Imaging cortical association using diffusion-tensor-based tracts in the human brain axonal tracking. Magn Reson Med 2002;47:215–223.

97. Bejoy T, Eyssen M, Peeters RR, et al. Quantitative diffusion tensor imaging in cerebral palsy due to periventricular white matter injury. Brain 2005;128:2562–2577.

98. Catani M, Jones DK, Ffytche DH. Perisylvian language networks of the human brain. Ann Neurol 2005;57:8–16.

99. Ulmer JL, Salvan CV, Mueller WM, et al. 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 2004;3:567–576.

100. Hendler T, Pianka P, Sigal M, et al. Delineating gray and white matter involvement in brain lesions: three-dimensional alignment of functional magnetic resonance and diffusion-tensor imaging. J Neurosurg 2003;99:1018–1027.

101. Wilms G, Demaerel P, Sunaert S. Intra-axial brain tumours. Eur Radiol 2005;15:468–484.

102. Parmar H, Sitoh YY, Yeo TT. Combined magnetic resonance tractography and functional magnetic resonance imaging in evaluation of brain tumors involving the motor system. J Comput Assist Tomogr 2004;28:551–556.

103. Thomas B, Sunaert S. Diffusion tensor imaging: technique, clinical and research applications. Rivista di Neuroradiologia 2005; 18:419–435.

104. Tuch DS, Reese TG, Wiegell MR, Wedeen VJ. Diffusion MRI of complex neural architecture. Neuron 2003;40:885–895.

105. Hund-Georgiadis M, Lex U, von Cramon DY. Language dominance assessment by means of fMRI: contributions from task design, performance, and stimulus modality. J Magn Reson Imaging 2001;13:668–675.

106. Binder JR, Frost JA, Hammeke TA, Bellgowan PSF. Superior temporal sulcus (STS) responses to speech and nonspeech auditory stimuli. J Cogn Neurosci 1999;99.

107. Papke K, Hellmann T, Renger B, et al. Clinical applications of functional MRI at 1.0 T: motor and language studies in healthy subjects and patients. Eur Radiol 1999;9:211–220.

108. Roux FE, Boulanouar K, Ibarrola D, Berry I. Routine contribution of functional MRI in neurosurgery. Neurochirurgie 2000; 46:11–22.

109. Stippich C, Kapfer D, Hempel E, et al. Robust localization of the contralateral precentral gyrus in hemiparetic patients using the unimpaired ipsilateral hand: a clinical functional magnetic resonance imaging protocol. Neurosci Lett 2000 12;285:155–159.

110. Fried I, Nenov VI, Ojemann SG, Woods RP. Functional MR and PET imaging of Rolandic and visual cortices for neurosurgical planning. J Neurosurg 1995;83:854–861.

111. Jack CR, Thompson RM, Butts RK, et al. Sensory-motor cortex—correlation of presurgical mapping with functional MR-imaging and invasive cortical mapping. Radiology 1994;190:85–92.

112. Krings T, Buchbinder BR, Butler WE, et al. Functional magnetic resonance imaging and transcranial magnetic stimulation: Complementary approaches in the evaluation of cortical motor function. Neurology 1997;48:1406–1416.

113. Pujol J, Conesa G, Deus J, et al. Presurgical identification of the primary sensorimotor cortex by functional magnetic resonance imaging. J Neurosurg 1996;84:7–13.

114. Yousry TA, Schmid UD, Alkadhi H, et al. Localization of the motor hand area to a knob on the precentral gyrus—a new landmark. Brain 1997;120:141–157.