The role of functional magnetic resonance imaging in brain surgery

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New functional neuroimaging techniques are changing our understanding of the human brain, and there is now convincing evidence to move away from the classic and clinical static concepts of functional topography. In a modern neurocognitive view, functions are thought to be represented in dynamic large-scale networks. The authors review the current (limited) role of functional MR imaging in brain surgery and the possibilities of new functional MR imaging techniques for research and neurosurgical practice. A critique of current clinical gold standard techniques (electrocortical stimulation and the Wada test) is given. (DOI: 10.3171/2009.12.FOCUS09251)

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Functional MR imaging can map the living brain in space and time. Because of its noninvasive nature and widespread availability, it has helped in revolutionizing cognitive neuroscience, and it has shed new light on the cerebral representation of functions. In a modern neuroscientific view, cognitive and behavioral functions are thought to be dynamically represented in large-scale networks that are hierarchically organized around cortical epicenters. Mesulam stated, “At least five large-scale networks can be identified in the human brain,” namely for spatial attention, language, memory-emotion, executive function, and face-and-object recognition. Such a network view largely opposes the dogmatic and static neurological models that are still used in clinical decision making. Key elements of these models are the almost invariant relationship between anatomy and function, and the strict subdivision of the brain either into eloquent areas (in which damage can lead to permanent neurological deficit, for example, the Broca area) or noneloquent areas (in which damage is not expected to have any neurological implications, for example, right prefrontal cortex).

There is now abundant evidence that contradicts this more classic view; important findings are the substantial variation in anatomical and functional topography that is already present in healthy individuals, and the fact that the neural representation of brain functions is constantly changing on microscopic and macroscopic levels. This plasticity is in fact a fundamental property of the brain, which permits normal physiological processes such as learning and memory. Under pathological conditions, the brain probably uses similar mechanisms to recover from functional loss whenever its networks are damaged. This explains why in some patients a brain tumor can grow to a considerable size without causing any obvious neurological deficits, or why children who had undergone a left hemispherectomy are able to walk and talk. In these cases, functions seem to have reorganized to perilesional or contralesional brain areas.

Because fMR imaging has good spatial resolution and can easily be integrated with anatomical images, it is frequently used for presurgical planning or as an adjunct to existing techniques for this purpose, such as the amobarbital test and ESM. In experienced hands, it is already able to replace these techniques in some patients. However, the technique and methodology of fMR imaging are complex. Studies that have compared fMR imaging brain maps with the results of the amobarbital test and ESM have found an incomplete match between these modalities. From this incongruity, it is usually concluded that fMR imaging cannot yet replace the existing techniques and that further research and refinement are needed to obtain that goal. However, it is very likely that fMR im-
aging findings will never completely agree with those from the amobarbital test and ESM because of fundamental differences in methods and outcome measures. More importantly, the techniques that are currently considered gold standards suffer from drawbacks and methodological flaws and need to be reevaluated for their purpose.

In the first part of this paper, we will review the pros and cons of fMR imaging and ESM as tools for localization of functional brain areas and as predictors of postoperative neurological function. We will conclude that the use of these techniques does indeed decrease the risk of postoperative neurological deficits as they are reliable predictors of immediate neurological outcome after surgery. However, they are not very sensitive tools to predict postoperative recovery or long-term functional outcome. Another drawback of current clinical techniques is that assessment of higher cognitive functions such as emotion or attention is very difficult or even impossible. In the second part of the paper, we will look at how new functional neuroimaging techniques are now beginning to elucidate the complex cortical and subcortical networks that sustain brain functions and their behavior under normal and pathological conditions. Arguments for a new network view of functional brain topography will be given, as well as clinical relevancy. Ultimately, functional neuroimaging techniques should become reliable clinical tools to model the long-term behavioral and cognitive effects of surgery in the individual patient. This will permit better presurgical risk assessment, will increase the efficacy of surgery, and can guide rehabilitation therapy.

Functional MR Imaging: a Short Introduction to Its Principles and Methods

Several articles and books are available that extensively review the technical, methodological, and practical aspects of clinical fMR imaging. We will therefore only briefly touch on the most relevant aspects here from a clinical point of view.

Functional MR imaging rests on the assumption that there is a relationship between brain function and cerebral blood dynamics. There are several fMR imaging methods available, but the one most widely used employs the effect of deoxyhemoglobin on MR imaging signals (the BOLD effect). Functional MR imaging maps reflect task-related local changes in the vascular response of brain tissue, and they are therefore an indirect measure of neural activity. The BOLD changes seem most closely related to changes in afferent input. Spatial resolution is high (typically between 1 and 5 mm), and submillimeter resolution of voxels is possible. There is a possible mismatch between the location of the BOLD signal and the actual site of neural activity that can be reduced to a maximum error of 3–6 mm with dedicated MR imaging and postprocessing techniques. Temporal resolution is generally low, as the hemodynamic BOLD response lags behind the neural response by several seconds. There are methods to increase temporal resolution to tens of milliseconds.

The foremost advantage of fMR imaging is that any sensorimotor or cognitive function of interest can in principle be studied once appropriate experimental conditions are devised. It is therefore not limited to the regions of the brain that have been damaged or to the function that is disturbed. Another advantage is that individuals without neurological impairments can be studied, which allows modeling of brain processes in a population that is free from the effects of pathology and potential reorganization.
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Fig. 2. Images obtained in a patient with a right parietal low-grade glioma without neurological deficits. The results of a left-handed finger tapping fMR imaging experiment are shown in red. Two clusters of fMR imaging activation are seen, in the precentral and the postcentral gyrus. Green dots denote sites of electrical stimulation evoked motor responses. The anterior cluster of activation thus proved to be primary motor cortex. The posterior cluster probably represents sensory activation due to tactile feedback during the finger tapping experiment.

of function; this also permits study of individual differences in brain organization.

An fMR imaging experiment is conducted to test the investigator’s hypothesis of a particular brain function. This requires a task design that can extract the function of interest and has adequate detection power. Most fMR imaging experiments follow a block design in which 2 or more conditions are alternated over the course of the image. An fMR image can best be described as a series of MR images that are acquired like a movie (Fig. 1). Every few seconds, an image of the brain is acquired. During the procedure, the individual performs a carefully designed computerized task in which specific brain functions are invoked and alternated with periods of rest or a control task (see below). The movie of the brain images is analyzed as a time series, and each spatial element (volume element, or voxel) is assessed for a correlation with the alternating task. Only voxels in brain areas that are involved in the task—and that are switched on and off according to the task design—will correlate with the task. These are assessed for significance of the correlation and are then displayed as colored regions on top of an anatomical image acquired before or after the fMR imaging procedure.

Repeated stimuli are necessary to increase the contrast-to-noise ratio (that is, the ability to detect brain activity) and obtain statistically sound activation maps; the number of stimuli depends on experimental design and hardware. Ideally, one condition contains the function of interest, while another (control) condition involves a similar set of functions except for the one of interest. Experiments that use subtraction of conditions are fairly simple to implement, are robust, and have high statistical power. For these reasons they are most often used in clinical practice. However, subtraction of conditions relies on assumptions that are not always valid. One is the idea of pure insertion, where it is thought that a cognitive process can be added to a set of existing cognitive processes without affecting them. More complex task designs have been developed to target such methodological pitfalls or to analyze individual hemodynamic responses to stimuli; these designs involve multiple levels of task complexity (parametric design), measurements of single stimulus-related BOLD responses (event-related design), or multiple task-control conditions (for example, conjunction analyses).

Most MR imaging units today have software for real-time automatic analysis and display results during, or immediately after, imaging. The fMR imaging maps can be implemented in neuronavigational systems for intraoperative use. The fact that these automated software programs are available (either commercially or as freeware) does not imply that the resulting maps are always a reliable roadmap for surgery or that expert knowledge is no longer needed. Contrary to the suggestion that is sometimes made in the literature or in commercial advertisements, there are currently no standardized and user-independent fMR imaging protocols that can be easily and reliably used for surgical purposes, or even for simpler tasks such as localization of primary motor function.

The main reason for the lack of these protocols is the fact that interpretation of fMR imaging maps is not straightforward. It is very difficult to construct a task protocol that can extract only the function of interest and thereby differentiate between brain areas indispensable for that specific function and brain areas that are involved in task performance but are not truly indispensable. As an example, consider identification of primary hand motor cortex (M1), a common presurgical question. Constructing a task for this purpose seems not very difficult, as various simple motor tasks (for example, finger tapping or hand clenching) have shown reliable activation of M1. If the brain activation map shows a relatively large cluster of fMR imaging activation in the central region, this cluster is, in our experience, always located within the central sulcus and/or the posterior part of the precentral gyrus. In this case identification of M1 is straightforward. The problem is that there are usually several other activated areas, often in neighboring gyri, and this makes a priori identification of M1 with fMR imaging difficult. For an example of this, see Fig. 2, where 2 clusters of fMR imaging activation were found near a centrally located tumor. The challenge is to disentangle the M1 activation from activation in secondary motor or nonmotor areas. There are currently no fMR imaging protocols that can selectively activate only primary motor cortex, so additional information is needed from other modalities to increase reliability. What is often done in practice, as a first step, is to compare the location of fMR imaging activity with the expected location of M1 according to anatomical landmarks such as the handknob. Note that this is again a fallback to a static view of functional topography; in this classic view, control over different body parts is strictly somatotopically organized along the precentral gyrus.
which is also considered a synonym for the primary motor cortex area. As with any model, by definition, it is only a simplified reduction of reality. In the original stimulation studies by Penfield and Rasmussen (from which the model of the sensory and motor homunculus was created) it had been found that motor responses could not only be obtained from the precentral gyrus (80%) but also quite frequently from the postcentral gyrus (20%). A minor representation of somatic sensation was also found in the precentral gyrus (in 25% of stimulations that elicited sensory responses; the remainder were obtained from the postcentral gyrus). Animal studies with intracortical microstimulation and, more recently, human fMR imaging studies have yielded further arguments for a more complex view of primary somatosensorimotor representation, where the controlling neural populations for different fingers show considerable overlap in M1 and are represented in a more widespread cortical area than usually assumed. Studies have also shown that at least part of the primary motor cortex seems to code for movement rather than for a specific muscle or body part, with several sites, instead of one, for each functional representation. In addition, M1 has been postulated to participate not only in the executive but also the preparative motor phase. Additionally, pathological lesions may influence functional topography and lead to functional reshaping of motor areas, even on the level of M1. This all implies that unexpected activation on fMR imaging maps needs to be cautiously interpreted, whereby it is easily forgotten that we are often biased in our anatomically guided expectations. Abnormal fMR imaging activation can of course be truly false positive because of movement artifacts or a low statistical threshold, but it can also represent variations in normal anatomy (double precentral sulcus) and physiology (multiple representations) or reflect brain plasticity. Of course, things get even more complex when one is asked for the localization of cognitive functions such as working memory or language.

Another reason it is difficult to create standardized clinical fMR imaging protocols is that the parameters that are mostly used to interpret and judge fMR imaging maps (that is, the extent and the number of activated areas) are not a very reproducible measure of brain activation. When a patient undergoes imaging twice with the same protocol using the same imaging unit, the activation maps will not be exactly the same. Some of the factors that contribute to this variability are known, such as field-strength or imaging unit type and artifacts due to movements (for example, respiration and cardiovascular pulsation); these factors can to some extent be controlled in data analysis. Part of the test-retest variation is, however, caused by yet unknown factors. For clinical use of fMR imaging, there are some strategies to increase the reliability and detection power of brain activation maps.

Absence of activation is another important issue to consider. Failure to detect activity can be caused by several factors, some of which are difficult or impossible to control. They should at least be known so that fMR imaging maps are properly interpreted and possible false-negative results can be verified with other functional techniques. A tumor or vascular malformation can distort the brain or cause blood flow abnormalities that may alter or diminish the BOLD signal. Under these circumstances, absence of fMR imaging activation does not necessarily imply absence of relevant neural activity. On the other hand, fMR imaging activity within tumor borders is not necessarily false positive and can be functionally relevant, as was confirmed with ESM.

Other confounding factors can be experimentally controlled for, but this requires radiological personnel and clinicians who are familiar with all stages of the fMR imaging experiment, as errors often go unnoticed in inexperienced hands; it also requires a continuous feedback from surgical practice so that fMR imaging protocols can be validated and optimized. A factor that needs to be controlled is task performance. We think that optimal task performance requires a practice session prior to the imaging session in which the patient is acquainted with the setting and the stimulus presentation. Patients with a paresis or cognitive impairments may suffer from a limited attention span or early fatigue; in these cases task design should be adapted. If task performance is not monitored, the investigator is left with uncertainty about the cause of poor results, that is, is brain function impaired or did the patient fail to perform the task as required? The effects of impaired performance due to brain damage on brain activation maps are a known problem that is very difficult to solve with task-driven fMR imaging. Examples are studies in patients with poststroke aphasia in whom baseline measures are obviously not available. New MR imaging techniques (notably resting state functional connectivity mapping) eliminate the effects of impaired task performance on activation maps but are not yet reliable on an individual level.

In conclusion, all stages of an fMR imaging experiment are tightly interwoven and slight changes in MR hardware, task design, task performance, or data analysis can significantly change the resulting brain activation maps. As of today there are no fMR imaging protocols that are invariant to such changes and that provide the surgeon with a roadmap that unambiguously shows only “go” and “no-go” areas. This variability can also account for the significant differences that are often reported between different studies or institutions. This hinders validation of fMR imaging results (as it is difficult to pool and compare data across different institutions) and development of user-independent clinical protocols. We think, therefore, that every institution that uses fMR imaging for neurological planning should have clinicians who are trained for this purpose. The fMR imaging maps should be used as an adjunct to existing clinical techniques and be compared with ESM and, in particular, with patient outcome for continuous optimization of fMR imaging protocols.

A Critique of Clinical Gold Standard Techniques

Electrocortical Stimulation Mapping

Electrocortical stimulation mapping remains the gold standard for localization of eloquent brain areas. Electrocortical stimulation mapping has a good track record in...
neurosurgery, and most surgeons consider it a valuable technique to safely maximize tumor resection.\textsuperscript{20,30} Electro cortical stimulation mapping relies on the principle that a particular brain area can be functionally disabled for several seconds during electrical stimulation. At first glance, the technique seems very intuitive and valid. When a particular area is stimulated and the patient has difficulty performing a task, there must be a close and essential relationship between that brain area and the disturbed function. Consequently, areas in which ESM is positive are considered to be indispensable for normal function and are not included in the resection. However, such a straightforward inference is not justified. For example, when the posterior part of the SMA proper is electrically stimulated, this will often elicit involuntary motor responses in a patient. As expected, resection results in immediate postoperative neurological deficits (hemiparesis, akinesia, and mutism). However, these deficits typically resolve in several weeks or months. Thus, the fact that an area is tested positively with ESM does not necessarily imply that it this indispensable (that is, eloquent) for that particular function (note that in this case an eloquent area is defined as an area that when damaged leads to permanent deficits). This finding calls into question the clinical usefulness and even the validity of ESM for its purpose, as ESM seems unable to account for functional reorganization after surgery. Stated otherwise, ESM is not predictive of permanent loss of function. What probably happened in the patients with SMA resections is that contralateral secondary motor areas partially compensated for the loss of function. Indeed, such unmasking of new motor areas has been demonstrated when fMR imaging results. Also, assessment of higher-order cognitive functions such as emotion or discourse is currently not possible.

In conclusion, ESM seems a reliable technique to assess the immediate functional consequences of removal of part of the brain and is currently the best technique available for this purpose. It cannot, however, predict whether perilesional or distant neural networks are able to compensate for any loss of function after operation (that is, there is a risk of false-positive results). It also has limited potential to test different or more complex cognitive functions. For this, new techniques need to be developed. To do so, as a first step theories need to be further developed to explain and model the new concepts of functional topography.

The Amobarbital (or Wada) Test

The amobarbital test (or Wada test, named after its inventor Juhn Wada) is widely used in epilepsy surgery and occasionally in tumor surgery to probe whether a single hemisphere is capable of normal language (and memory) function.\textsuperscript{97} It uses an ultra–short acting barbiturate that is injected into an internal carotid artery, effectively disabling a large part of that hemisphere for approximately 5 minutes. During this period, the contralateral hemisphere is examined for language and other functional capacities. While the patient is asked to perform a series of language tasks (object-naming, reading, picture-describing, and so on), he or she is monitored for aphasic errors. Validity of the test is based on 2 assumptions. First, the injected amobarbital can reach and anesthetize all brain areas in the ipsilateral hemisphere that are involved in language function. Second, during the testing period (that is, the time that the amobarbital is effective) there is no substitution of language function by nonanesthetized ipsilateral or contralateral brain areas.

There are several factors that may confound interpretation of the Wada test.\textsuperscript{53} At times, agitation or somnolence make determination of language dominance problematic. Inadequate anesthetization of brain regions may also lead to false-negative results on laterality of function. For instance, as the temporoparietal region receives blood from the middle and/or the posterior cerebral artery, the amobarbital that is injected via the carotid system may not always adequately deactivate some of the temporoparietal areas involved in speech comprehension. Another possible confounder is that the amobarbital may cross over to the other hemisphere via variations in vasculature; this can be monitored with angiography.
Among different clinical centers, there is no standardized set of parameters in terms of which language functions are evaluated during the test. This accounts for at least some of the considerable variability in the reported incidences of typical (that is, left-sided) and nontypical (that is, right-sided or bilateral) language dominance. Most groups use naming or responses to verbal commands, but others have predominantly relied on the duration of speech arrest as an important parameter for hemispheric language dominance.4,5,9 There is some concern that the Wada test underestimates the incidence of bilateral language dominance, as inconsistencies have been reported with clinical outcome or the findings of ESM.5,6 These arguments favor the notion that the Wada test may not be a highly independent measure of language dominance.

The Current Role of fMR Imaging in Brain Surgery

Brain mapping in neurosurgery is predominantly performed for planning surgery of motor and language areas. The main questions are the location of primary sensorimotor areas (occasionally also the location of the motor part of the SMA), assessment of the language-dominant hemisphere, and location of language areas. Other cognitive functions are seldom asked for and are only occasionally mapped by neurosurgeons with a special interest in functional mapping. Examples are calculation, writing, spatial attention, and working memory.24,78,89 This is probably for 2 reasons. First, it is common neurosurgical opinion that these functions are not easily damaged after surgery and that they are therefore not as localized and vulnerable as motor and language functions. However, more recent studies have clearly shown that when patients are tested with dedicated neuropsychological tests, cognitive deficits are far more common than previously assumed on the basis of clinical impression and observation, both before and after surgery.28,89,90 Second, in the classic studies of lesions, a firm anatomical basis for most cognitive functions was never established, with the incorrect exception of language functions. We now know that the static neurological models that resulted from these postmortem studies of patients with brain lesions, first formulated at the end of the 19th century by Wernicke and Lichtheim,10 have several severe shortcomings that make them unsuitable for use in the individual neurosurgical patient. More recent alternative models have proposed a more dynamic network view, where multiple regions are interconnected and serve specific functions. Given the inherent individual and pathology-driven variability of these areas and interconnections, functional mapping techniques are necessary to identify each individual's critical epicenters to optimize surgical treatment. To do so, techniques other than fMR imaging are additionally required to visualize critical subcortical connections. A review of the advantages and limitations of these techniques (notably DT imaging) is beyond the scope of this paper.81,108

Localization of Primary Motor Areas

In the absence of anatomical variations or functional reorganization, it is probably safe to assume that the primary motor cortex (M1) is located in the precentral gyrus. Various anatomical landmarks have been described that help to identify the central sulcus and the precentral gyrus. On MR images, there are at least 6 of these landmarks, the handknob being the most robust one. In fact, this landmark was discovered because of consequent fMR imaging activation within this area.103 These landmarks are obviously less reliable under pathological conditions in which a lesion can distort or destroy anatomical and functional topography. Lehéricy et al.41 found that in 8 of 60 patients with a centrally located brain tumor, it was not possible to reliably identify the precentral gyrus using only anatomical landmarks. With help of fMR imaging or ESM, identification was 100%. According to their study, "There was a good agreement between fMR imaging and intraoperative mappings," with 92% of ESM areas located at the margins of the fMR imaging area; the remaining ESM sites were within 15 mm of fMR imaging areas. Bizzì et al. reported sensitivity and specificity of 88 and 87%, respectively, when hand motor function on fMR imaging was compared with ESM (both modalities were considered to match if fMR imaging activation was present within 1 cm of a positive ESM site). With similar criteria, Roessler et al.25 found 100% agreement in 17 patients with low- or high-grade gliomas. They were able to detect fMR imaging activation in the handknob region in all patients. As this significantly exceeds the detection power for fMR imaging activation in other studies, Roessler et al. speculated that this might be related to the use of high-field fMR imaging (3 T) in their study. Various other studies have shown good but suboptimal agreement between fMR imaging and ESM; unfortunately, many studies have methodological flaws and/or judged the correlation in a qualitative manner or in small patient series.68,102

Studies have also tried to establish the surgical relevance of fMR imaging activation patterns by looking at the distance between the resection border and fMR imaging activation.29 Not surprisingly, this distance was found to be inversely related to the occurrence of postoperative motor deficits; a safe margin of 1–2 cm was mentioned in these studies.29 However, many other factors can contribute to the presence or absence of postoperative deficits, and these factors are generally not accounted for in the few studies that compared fMR imaging with functional outcome. An important confounder is proximity to the corticospinal tract. Despite these limitations, displacement of brain activation or an asymmetrical activation pattern often reliably reflects the anatomical and functional impact of a lesion (Fig. 3).87

Other previously discussed confounders are disturbance of the neurovascular coupling due to brain lesions and impaired task performance due to sensorimotor deficits or cognitive problems. The latter can have a profound influence on the resulting brain activation maps. In a series of 110 patients with centrally located brain tumors, Krings et al.42 found that, with an increasing degree of paresis, activation decreased in the primary motor area, whereas activation increased in secondary motor areas. Although these findings suggest brain plasticity, one needs to be cautious; as with task-driven fMR imaging,
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these changes may also be related to an increase in effort and reflect the result (rather than the cause) of impaired performance.

In conclusion, there is general consensus in the literature that fMR imaging is a valuable tool for localization of the primary motor cortex and assessment of presurgical risks. However, several methodological and practical questions remain to be answered, and there is currently no standardized protocol for surgical use of motor fMR imaging.

Our strategy for clinical use of motor fMR imaging is as follows. First, the hand motor area on the primary motor cortex is determined according to anatomical and fMR imaging results. Then, the following margins are determined: the distance between the primary motor cortex and the cortical tumor border, and the distance between the corticospinal tract and the subcortical tumor border. The corticospinal tract is visualized using DT imaging. We advise using ESM if the cortical margin is less than 1 gyms or the subcortical margin is less than 15 mm. In these cases, fMR imaging results are implemented in the surgical navigation system to guide ESM. We believe that this increases the efficiency and safety of our procedure.32 Note that we use fMR imaging protocols that have been validated with ESM at our own institutions. We are currently assessing the exact accuracy of DT imaging fiber tracks compared with subcortical neurosurgical stimulation in awake patients for use in the neuronavigation system during surgery.

Localization of Secondary Motor Areas

Krainik et al.41 published an important paper in which they were able to show that resection of fMR imaging activation in the posterior part of the SMA (the SMA proper) predicted an SMA syndrome. Patients in their series had a low-grade glioma in or near the SMA. In a follow-up paper, the authors showed that, in these patients, there was already preoperative reorganization in ipsilateral and contralateral premotor cortex activations (including SMA). Although this reorganization could not prevent the temporary deficits, postoperative recovery was faster and was associated with increased activity in secondary motor areas in the healthy hemisphere. There are no other studies that have systematically validated motor-related fMR imaging activation in medial or lateral premotor areas with ESM or patient outcome.

Assessment of the Language-Dominant Hemisphere

To begin, there is no unique definition of language, and there is no definite neurobiological substrate for its various functions. Lack of anatomical and functional definitions makes development of clinical fMR imaging protocols and comparison with existing techniques very difficult as there is no agreement on outcome measures. Historically, neurosurgeons use a rather restrictive but practical definition of language based on clinical assessment. This means that subtler language functions or potential right-hemisphere language functions are normally not tested.

From a clinical perspective, most people are considered left-hemisphere dominant for language, as lesions that cause aphasia are usually located in the left hemisphere. Language dominance is considered a discrete variable, that is, language is either present or absent in a hemisphere. Aphasia develops in 20–30% of left-handed individuals after right-hemisphere damage (in right-handed individuals the incidence is <2%), illustrating that most individuals (whether right- or left-handed) are therefore left-hemisphere dominant for language. These data are comparable to results in Wada-tested patients and fMR imaging studies in healthy volunteers.14,90 Atypical language organization (right-sided or bilateral) is more often found in patients with structural or functional damage to the left hemisphere. In these cases, the right hemisphere has partially taken over.34,91 In general, recovery is more successful if the injury has slowly evolved.15,54

The clinical gold standard for assessment of language dominance remains the amobarbital test, although this technique can be disputed on methodological and practical grounds. Several fMR imaging (and PET) studies have tried to match outcome of the amobarbital test. To do this, most studies have calculated an LI to quantify the proportion of activation in both hemispheres; this LI varies from −100 (all activation in the right hemisphere) to 100 (all activation in the left hemisphere). A cutoff value of the LI is then chosen to determine whether patients have typical or atypical language dominance. Unfortunately, the variability in the reported LIs across fMR imaging studies is
so large that every study has defined its own criteria for assessment of language dominance; there is no consensus about an optimal fMR imaging protocol or cutoff values for the LI. In general, a good correlation has been reported in the literature between fMR imaging and the amobarbital test, but no protocol has been able to obtain complete agreement between the methods. Combining multiple fMR imaging language tasks is currently the best strategy and yields reproducible and reliable results. Use of only a single task is less reliable in particular for identification of the one atypical patient among the majority of typical patients. When atypical language dominance is suspected, activation maps should be inspected for possible mixed dominance, as frontal and temporoparietal areas can be located in different hemispheres. Only a few studies have compared fMR imaging and the amobarbital test to the true gold standard: patient outcome. Sasevitz et al. showed that preoperative fMR imaging predicted naming decline after left anterior temporal lobectomy. Somewhat paradoxically, in this study ESM was used to tailor the extent of the resection.

There are several fundamental issues that need to be resolved and that hinder straightforward interpretation of any currently available monitoring technique for language. First, since neuropsychological studies began to study language functions in greater detail, it is realized that the so-called nondominant right hemisphere also has an important language contribution, in particular for functions such as prosody, kinesics, and understanding of nonliteral content (for example, jokes or metaphors). This explains at least part of the activation that is usually seen in the nondominant hemisphere with fMR imaging. Second, some authors have found evidence for a continuous distribution of language functions across hemispheres. For instance Springer et al. observed a gaussian-like distribution of fMR imaging–derived LI values in healthy volunteers and patients with epilepsy. This could implicate a degree of equipotentiality between hemispheres with respect to language processing that is also supported by some of the amobarbital studies.

Third, discrepancies among ESM, the amobarbital test, and patient outcome have been reported and need to be clarified. Hunter et al. reported on a patient with a 6-month postoperative aphasia after left-sided temporal lobectomy where the amobarbital test showed right-hemisphere language dominance. Wyllie et al. found language areas in the left hemisphere with ESM in 2 of 9 patients in whom the amobarbital test had previously found right-hemisphere dominance. Kho et al. found a discrepancy between the amobarbital test (right) and ESM (left); in this case, fMR imaging yielded bilateral frontal language areas. We agree with the conclusion of Wyllie et al. that when right-hemisphere dominance is found with the amobarbital test, these results need to be validated by other techniques.

In our assessment, we perform a combined analysis of 3 fMR imaging tasks for language. If brain activation is strongly left lateralized, surgery in the right hemisphere is considered safe with regard to language problems, and additional invasive testing is not deemed necessary. From previous studies we calculated a cutoff value of the LI of 75 (note that these values are protocol and hardware specific). If the LI is less than 75, there is possible involvement of the right hemisphere in language. In these cases we rely on ESM when language areas are judged to be close to the surgical area of interest.

Localization of Language Areas

From historical lesion studies, the phrenological view was that language processing is performed in the areas of Broca and Wernicke in the left hemisphere. Contemporary neurological textbooks still often show a cartoon of 2 relatively large areas that are connected by the arcuate fasciculus, despite abundant evidence that language processing depends on a network of many other subcortical and cortical areas (Fig. 3B). Contrary to the general clinical assumption, there are no clear functional or anatomical definitions of the areas of Broca and Wernicke. Although the Broca area is generally denoted as the posterior part of the left inferior frontal gyrus, damage to this area alone yields only a transient decrease of speech output and not Broca aphasia. The Wernicke area is often defined as “the region which causes Wernicke’s aphasia when damaged.” The view that there are no well-defined language areas is strongly supported by the many functional neuroimaging studies that have identified widespread and overlapping networks for phonological, semantic, orthographic, and syntactic processing.

Recent MR imaging–based analyses of dysphasic patients with brain lesions confirm a wide area of potential language cortex in the left hemisphere with different frontal and temporal epicenters than classically formulated. The ESM and fMR imaging studies show that these critical language epicenters are smaller than generally thought (<1–2 cm2) with multiple representations in frontal and temporoparietal areas.

Only a few studies have meticulously compared fMR imaging and ESM for the purpose of language localization. General findings from these studies are as follows: 1) Functional MR imaging is able to identify most of the language areas that are found with ESM. To achieve optimal detection power, the results from multiple fMR imaging tasks need to be combined (a minimum of 3 tasks seems necessary). In practice, this means that fMR imaging can very reliably predict the absence of positive ESM sites (that is, fMR imaging has a very high negative predictive value). 2) Functional MR imaging finds more areas than ESM (up to 50%), and consequently the positive predictive value is limited. 3) There is a significant variability of fMR imaging data across patients, tasks, and statistical methods, and this makes generalization of results or development of a standard protocol currently impossible.

There are several possible explanations for the observed discrepancies between fMR imaging and ESM. One explanation for the observed differences in the language maps is the fundamental differences in methodology between the techniques. Functional MR imaging potentially shows all areas that are involved in language processing, including various supportive functions such as attention or verbal memory. The main difficulty is to design an fMR imaging protocol that can selectively
identify only the critical language sites. Although different cognitive functions may be easily separated on theoretical grounds, this is not the case in practice, and it is questionable whether brain mapping techniques will ever be able to show only critical language areas.

Most surgical teams that use intraoperative ESM use a single language task, most often visual object naming. This task is chosen because naming errors are common to most aphasic syndromes, the task is simple to apply, and it yields good correlation with postoperative language outcome. However, by performing only a single language task, one implicitly assumes that any critical language area is involved in all aspects of language processing. A more likely view is that different language functions are in part supported by different critical areas. This is strongly supported by results from both fMR imaging and ESM studies. This would also imply that the match between the two modalities can be further optimized when multiple tasks are used during ESM. There are, of course, practical problems and constraints in doing this intraoperatively. Language can operate in different modalities (reading, writing, speaking, and gesturing), and many patients do speak more than one language. Should all these modalities be monitored to ensure safe surgery, and in what detail? Even if one were to consider this clinically relevant (and there is currently not much evidence for this), it would take too much time during surgery as patient cooperation during surgery is time limited.

In our practice, we use fMR imaging intraoperatively as guidance for ESM. We do not plan surgery solely on the basis of fMR imaging results when language areas are judged to be close to the surgical area of interest.

In conclusion, much more data are required to answer these questions. The multiple-task approach can be addressed in patients who have temporarily implanted grid electrodes and in whom extraoperative ESM is possible. Questions regarding the sensitivity and validity of the various brain mapping techniques can only be investigated when information in large patient series is collected and when results are compared with patient outcome (the true gold standard). This can only be achieved in multicenter studies.

New Concepts of Functional Topography

There is convincing evidence to move away from the classic concept of a static brain with fixed functional areas and to adapt the new and dynamic view in which functions are thought to be represented in large-scale networks that are organized around cortical epicenters. The advent of functional neuroimaging and its ability to visualize brain functions has been a profound contribution to the advance of an ongoing paradigm shift that is, however, yet to be accepted in general clinical practice.

These new insights in functional topography are grounded in animal studies where it has been found that information processing for a given modality (for example, vision) is performed in a highly distributed and hierarchically organized system of different brain areas. In the macaque monkey, 32 cortical areas were found that relate to visual processing, and 305 connections have been reported between the different areas. Motor and language systems operate in similarly distributed networks. Such a network model explains the existence of selective neurological impairments such as prosopagnosia, akinetopsia, or transcortical motor aphasia. Because of the parallel design and the numerous reciprocally connected areas, it is practically impossible to exactly localize a function. So in effect, when a neurosurgeon wants to know whether a brain area is functionally relevant, he or she in fact wants to know whether the particular area is crucial for normal functioning of the network. To answer this question, the behavior of the modified network (that is, the network minus the planned area of resection) should be known.

The one important factor that was never accounted for in the older clinical models is time and the concept of a plastic functional brain topography. Continuous modifications in neuronal networks are a sine qua non for the brain to store and update information, to acquire new skills, to optimize and automate information processing, and to adapt to structural changes (for example, aging or a brain tumor). This automatically implies interindividual variability. One of the big advantages of fMR imaging is that it can provide information about both the spatial and temporal aspects of neural activity. The spatial extent of activation ranges from millimeters (firing patterns of groups of neurons) to centimeters (interaction between cortical regions). In a similar manner, temporal processes can be represented on a scale from milliseconds (firing patterns of groups of neurons, synchronization, and cognitive processes) to weeks and months (for example, recovery from loss of brain function due to stroke or surgery) and to years (for example, functional reshaping due to growth of a low-grade glioma). We will give several examples to illustrate the potential relevance for neurosurgery and the abilities of current fMR imaging techniques to assess these processes.

Although there is a time lag of several seconds between the onset of the neural event and the BOLD response, the relative timing between the onset of the hemodynamic responses in different brain areas seems to be preserved. This can be used to study the temporal order of activation within a network. For example, Lee et al. tracked the temporal activation of primary and secondary motor areas in an event-related motor task. Within the SMA, temporal profiles were different for the anterior and posterior parts. These differences in latencies can be used to monitor and characterize networks, and possibly differentiate normal from pathological behavior. However, this method has significant practical limitations as differences in timing can only be detected with fMR imaging when areas are activated in a sequential manner. When areas behave as coupled high-frequency oscillators, they will appear as parallel activated areas with fMR imaging. Interestingly, even when the brain is at “rest” there is a vast amount of spontaneous neuronal activity that is coupled between different regions that form a functional network. This temporal synchronization between brain areas defines the concept of functional connectivity, and is currently investigated with fMR imaging, electroencephalography, and MEG. Resting-state fMR imaging
has already proven to yield maps of networks without requiring individuals to perform a task (see below).

Several different frequencies have been described in the brain, which are related to particular regions or pathological conditions. For instance, alpha waves (8–12 Hz) are measured over the posterior regions of the brain and are attenuated with closure of the eyes or relaxation. Similar low-frequency waves can be measured over sensorimotor areas (mu waves), and these are influenced by movement of, for instance, the hand or fingers. This leads to so-called event-related desynchronization, and this is considered an electrophysiological correlate of activated or excited cortical neurons. Higher frequencies (> 30 Hz, gamma waves) are a particularly promising index of cortical activation. In a study using electrocorticography, Sinai et al. found reasonable agreement between areas with language-related changes in the gamma band and positive sites found with ESM. Recently, Hirata et al. used MEG and event-related desynchronization to map language areas for use in neurosurgery. Although these are still experimental studies, it seems a promising new way to look at localized brain function.

Temporal correlations in activity can also be used to study the interaction between different cortical regions. With MEG, significant differences in functional connectivity were found between patients with brain tumors and healthy controls, and an association with cognitive functions was reported. Somewhat paradoxically, functional connectivity can also be studied using fMR imaging but only at very low frequencies (0.01–0.1 Hz). With data obtained from individuals in a resting state, several of the known networks have been identified. A recent exploratory study reported that the motor regions that were localized based on the correlation of spontaneous fMR imaging measurement were quite similar to the regions that were defined with actual movements and with cortical stimulation in these patients. The main advantage of this functional connectivity MR imaging is that the resulting brain maps are independent of the actual motor or cognitive status of the patient. This means that a neurological deficit does not confound the brain maps because of impaired performance. Another advantage is that multiple brain systems can be determined with a single resting-state image.

Functional MR imaging has been used to study recovery from acute lesions (most often stroke). There is a large amount of data showing evidence for functional reorganization to brain areas close to or distant from the lesion. With acute lesions, recovery is often incomplete, and task-related brain activation studies such as fMR imaging are confounded by this impaired performance and by a lack of baseline measurements. It is unclear whether for instance (unmasked) activation that is seen in contralateral homolog areas is truly related to language processing. Techniques such as transcranial magnetic stimulation may help clarify these issues. Kralinik et al. performed one of the few studies that compared fMR imaging maps before and after surgery. They demonstrated that recovery from a motor SMA syndrome correlated with increased postoperative activity in the healthy hemisphere. In patients with slow-growing lesions, such as a low-grade glioma, functional compensation can be impressive, and deficits are generally less severe than in patients with acute-onset lesions. Despite large lesions most of these patients with low-grade gliomas have a normal social and professional life. Benzagnmout et al. demonstrated that in patients without aphasia, a low-grade glioma in the classic area of Broca can be resected without permanent language or cognitive deficits, and even with improvement in the quality of life. Patterns of reorganization appear to differ between patients. As of yet, these patterns have not been mapped out comprehensively, but the increasing use of fMR imaging, coupled with functional outcome, may prove particularly informative in the coming years. To do so, multicenter studies need to increase patient numbers. This is one of the motivations of the European Low Grade Glioma Network, a platform for clinical and scientific collaboration (refer to http://www.brain tumours.eu/).

Conclusions

It is clear that new functional neuroimaging techniques are changing our understanding of the human brain. New insights into networks that serve brain functions, notably language and motor systems, improve our understanding of effects of both pathology and surgical lesions on behavior. However, these have had little impact yet on most of the surgical procedures that are still often based on the classic static view of functional organization. As insight into the mechanisms of brain functions is still evolving, the effects on current neurosurgical practice are understandably limited.

This warrants several new strategies. We think fMR imaging and DT imaging should be used routinely as presurgical functional localization techniques, and that there should be a bolder approach toward resection of lesions in so-called eloquent cortex. To prove that the effects of brain plasticity can have major influence on surgical decision making, multicenter studies are needed in which brain lesions, surgical therapy, and functional outcome are studied. In these studies, outcome should be thoroughly assessed with dedicated behavioral and neuropsychological test batteries. Multicenter studies should also be started to develop evidence-based standard fMR imaging and DT imaging protocols. Longitudinal studies are important to study network behavior and monitor the effects of brain plasticity.

Ultimately, long-term effects of surgery should be predicted with functional neuroimaging techniques prior to surgery to optimize survival and quality of life for each patient.

We envision that several other areas of research will benefit surgical practice in the near future, for instance development of techniques to promote reorganization of brain function away from the surgical area of interest, or patient-specific rehabilitation therapy. Overall, neurosurgery not only benefits but can also make vital contributions to the advancing field of brain function research.

Disclosure

The authors report no conflict of interest concerning the mate-
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rials or methods used in this study or the findings specified in this paper.

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