FUNCTIONAL BRAIN MAPPING AND ITS APPLICATIONS TO NEUROSURGERY

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FUNCTIONAL BRAIN MAPPING may be useful for both preoperative planning and intraoperative neurosurgical decision making. "Gold standard" functional studies such as direct electrical stimulation and recording are complemented by newer, less invasive techniques such as functional magnetic resonance imaging. Less invasive techniques allow more areas of the brain to be mapped in more subjects (including healthy subjects) more often (including pre- and postoperatively). Expansion of the armamentarium of tools allows convergent evidence from multiple brain mapping techniques to bear on pre- and intraoperative decision making. Functional imaging techniques are used to map motor, sensory, language, and memory areas in neurosurgical patients with conditions as diverse as brain tumors, vascular lesions, and epilepsy. In the future, coregistration of high resolution anatomic and physiological data from multiple complementary sources will be used to plan more neurosurgical procedures, including minimally invasive procedures. Along the way, new insights on fundamental processes such as the biology of tumors and brain plasticity are likely to be revealed.

KEY WORDS: Brain mapping, Diffusion tension imaging, Functional magnetic resonance imaging, Preoperative planning, Transcranial magnetic stimulation

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The goal of neurosurgical resection of brain lesions is maximal excision with minimal permanent injury to the surrounding normal brain tissue and, more importantly, no resultant neurological deficit. A new deficit may be caused by damage to cortical areas immediately surrounding a lesion, as well as to the white matter at the depths of the lesion and to brain tissue involved in the surgical approach. Central to minimally morbid surgery is an understanding of the anatomic and physiological relationship of a lesion to surrounding eloquent brain tissue. Functional brain imaging provides information on the anatomic localization of a variety of brain functions, such as movement, sensation, speech and memory, as well as of white matter tracts connecting critical areas. Together with conventional imaging methods used to localize the lesion, functional imaging can be helpful in defining the relationship of the lesion to critical brain structures for operative planning. Although neurosurgeons have long used invasive brain mapping techniques, recent technological advances have led to several additional less invasive methods for mapping brain function. These methods differ not only in their methodology and physiological basis but also in their level of spatial and temporal resolution, their invasiveness, and their cost.

Conceptually, one may ascribe function to a given area of brain by observing it, blocking it, or stimulating it. Observational methods reveal increased electrical or metabolic activity in specific brain regions while a certain behavior, such as movement or speech, is performed. Such methods demonstrate involvement of various brain areas in a specific function, without demonstrating either necessity or sufficiency. Blocking (or inhibition) methods localize function by reversibly inhibiting neuronal functioning in specific brain areas and looking for a consequent reversible functional deficit. Inhibition methods demonstrate the necessity of a given area to a specific function and are useful in that they mimic the effect of surgical resection. However, inhibition methods cannot demonstrate sufficiency. For example, primary auditory pathways are necessary for the perception of speech, but they do not serve to decode speech. Stimulation or activation methods involve stimulation of a target brain area with the goal of eliciting a specific neurological response, such as movement of a specific body part. Stimulation demonstrates sufficiency and can mimic an activating lesion such as a seizure focus. Some techniques, such as electric cortical stimulation (ECS), may be used for both activation and inhibition. Given incomplete information inherent in any single technique, convergent information from multiple methods may be the most useful in operative planning. In this review, we will describe the various functional mapping techniques, their utility in assessing particular functions, and their application to neurosurgical disease processes.

TECHNIQUES

Observational

Positron Emission Tomography

In positron emission tomographic (PET) imaging, a radioactive tracer compound labeled with a positron-emitting isotope such as ^{15}O is administered. The patient is then imaged in a scanner containing rings of scintillation detectors that determine the position of the isotopes within the body. PET may be used to measure cerebral blood flow, cerebral glucose metabolism, and dopamine receptor occupancy, among other functions. $H_2{}^{15}O$ PET is used to measure cerebral blood flow. Hemodynamic changes thus measured may be used as a surrogate for neuronal cell activation. When $H_2{}^{15}O$ PET is used for functional brain mapping, the patient performs a task and cerebral blood flow, as quantified by the tracer, is measured. Blood flow under control conditions is then subtracted from blood flow during task performance to obtain regions of increased flow thought to subserve the task in question. When fluoro deoxyglucose (FDG)-PET is used for functional brain mapping, the patient performs a task and cerebral metabolism, as measured by FDG uptake, is measured and compared to uptake under control conditions (170).

One advantage of PET is its ability to study a wide range of functions: any brain function that can be called upon with a behavioral task can be studied by PET. Specificity of the PET image will be dependent on specificity of the behavioral and control task paradigm and implementation. Disadvantages of PET include a poor signal-to-noise ratio when compared with functional MRI (fMRI), only moderate spatial resolution (the best PET scanners have spatial resolution of 4 mm), and poor temporal resolution owing to imaging time and the temporal delay in measuring metabolic changes as a proxy for neuronal changes. Moreover, PET is relatively invasive as it involves administration of radioactive tracer, limiting the number of studies in any individual patient and excluding certain patient populations such as children. PET studies also require expensive, dedicated equipment and personnel and, ideally, access to a cyclotron for the production of tracers. Because it is hemodynamically based, PET is vulnerable to processes that uncouple neural and hemodynamic events. Like any observational technique, it has the disadvantage of not differentiating essential from participating areas.

PET has been used in preoperative planning, including motor and somatosensory mapping (158, 180). PET studies have also examined brain changes that are associated with neurological diseases such as Alzheimer's disease (108), as well as those that accompany functional recovery from neurological injury such as stroke (19). Perhaps the most common use of PET in neurosurgical planning is its utility in the localization of seizure foci (2, 34, 35, 171, 172). Technological developments in PET continue. In the future, PET imaging may be used to delineate areas of abnormal brain function or altered neurochemistry, thereby guiding resections or pinpointing functional targets.

fMRI

Like PET, fMRI measures change in cerebral blood flow as a surrogate for neuronal activity. The most commonly used fMRI method measures blood oxygen level-dependent (BOLD) changes in the magnetic resonance signal. Neuronal activity results in increased blood flow through local capillaries. The increased perfusion outstrips the increased demand, resulting in an increase in the ratio of oxyhemoglobin (oxy-Hb) to deoxyhemoglobin (deoxy-Hb) (39). The iron in deoxy-Hb is paramagnetic and reduces the T2 signal. The relative increase in oxy-Hb concentration with neuronal activity results in an increase in the T2 signal with neuronal activity, forming the basis of BOLD imaging (124). For each voxel, the BOLD signal during performance of a task is compared with that during the resting or control state. Unlike PET, BOLD signal change represents a ratio rather than an absolute physiological measure. The change in signal is small, on the order of 0.5 to 5% (6). To obtain an acceptable signal-to-noise ratio, the BOLD signal is averaged over multiple repeated trials and then subjected to statistical analysis. fMRI investigations are normally carried out according to one of two types of experimental paradigms: block design or event-related paradigms (28, 51). In block design, multiple trials of a task or stimulus presentations (a task block) are alternated with multiple trials or presentations of a control task (a control block). The fMRI signals from these two (or more) types of blocks, task versus control, are compared. This is a high sensitivity method but does not allow for analysis of data according to the subject's performance (e.g., speed or accuracy). The second type of fMRI protocol is the event-related protocol in which single trials of a task or tasks are compared. This allows analysis of fMRI data based on the subject's performance on the task but is a lower sensitivity technique (28, 51). Finally, the BOLD map is superimposed on the detailed neuroanatomy derived from the conventional structural magnetic resonance imaging (MRI). Perfusion imaging using arterial spin labeling (ASL), a second fMRI method in which magnetically labeled arterial blood water, delivered as a bolus, is used as a tracer, is a less commonly used technique.

There is evidence in humans and primates that the fMRI signal is proportional to the neuronal firing rate (61, 142) and to local field potentials (97). The same has been demonstrated in rodents (125, 191). fMRI has been validated against PET, transcranial magnetic stimulation (TMS), and ECS for localization of the motor cortex in patients with lesions displacing the central sulcus, demonstrating overlapping ($<$1 cm) maps in the majority of cases (88). The typical spatial resolution of fMRI is 2 to 5 mm, which is generally higher than PET (192). Advanced

MRI techniques, including higher field strengths (81, 133, 190) and parallel imaging (94, 164), can provide increased signal-to-noise ratios, increased spatial resolution, or shortened acquisition times. The latency of the observed signal change in BOLD imaging is several seconds, making the temporal resolution of fMRI poor when compared with techniques such as ECS or electroencephalography (EEG).

Functional MRI is noninvasive and, therefore, repeatable, both for many runs in a single session (unlike Wada testing) and on multiple occasions to follow patients over time. Because of its noninvasiveness and safety, fMRI is suitable for use in children. Unlike Wada testing, fMRI can provide localization and not merely lateralization of critical functions such as language and memory. Finally, fMRI is able to demonstrate functional activations in the depths of cortical sulci, not just at the cortical surface, an advantage over the "gold standard" electrocortical stimulation (ECS). Disadvantages of fMRI include sensitivity to motion-related artifacts, including those arising from the heartbeat, breathing, and head motion. This has proven particularly problematic for language mapping, generally precluding the use of tasks involving overt spoken language. Furthermore, the technique is sensitive to signal from large draining veins, although this is less prevalent at higher field strengths (45). fMRI also does not have the proven clinical track record of Wada testing or intraoperative mapping.

Neurosurgical applications of fMRI include preoperative localization of primary motor and sensory cortices. As with any emerging technique, validation against standard techniques is a requirement for adoption into mainstream use. Many groups have now examined the validity of fMRI in localizing motor (101, 149, 151), somatosensory (101), and visual (63) areas versus ECS. fMRI has also been used to determine hemispheric language lateralization, and correlates well with Wada findings (27). Although fMRI may soon be substituted for Wada testing for the preoperative determination of language lateralization, and may indeed offer many advantages (discussed below), the technique is has not yet been well correlated with ECS in finer language localization studies (150); thus, its use remains an adjunct as experimental efforts to improve its agreement with standard techniques continue. Several groups have also used fMRI to determine memory lateralization in patients with medically refractory medial temporal lobe (MTL) epilepsy and have also demonstrated good agreement with Wada testing (14, 30, 48). Asymmetric MTL activation has also been shown to be increased contralateral to the side of the seizure focus (9, 48, 72), as well as to be predictive of postoperative memory deficits after mesial temporal resection (71). Spike-triggered fMRI has also been used to localize seizure foci for surgical resection in intractable epilepsy (29, 65, 156, 157).

Anisotropic Diffusion Tensor Imaging

Although not strictly a functional study, diffusion tensor imaging (DTI) is able to demonstrate white matter tracts by using MRI to measure the direction of diffusion of water molecules as a marker for the axis of these tracts. The technique is based on the restriction of diffusion of water by axonal membranes and myelin. Water diffusion in axon tracts is direction-dependent, or anisotropic. For physiological reasons that are incompletely understood, water will diffuse least in a direction perpendicular to fiber tracts and most in a direction parallel to them (114). In DTI, magnetic field gradients are applied in multiple orientations. The diffusion tensor is a matrix (mathematical model) that is used to estimate the direction of maximum diffusivity of water molecules based upon MRI data for every voxel. This direction of maximum diffusivity corresponds to the axis of white matter tracts in that voxel (73). Typical spatial resolution in DTI is a voxel size of $2 \times 2 \times 5$ mm^3, although this is improving quickly (69). An advantage of DTI is that it specifically examines white matter, which is poorly imaged by other functional techniques. One limitation is that it offers little specific information on the functional status or substrates of these tracts. The technique also suffers from poor signal-to-noise ratio (69) and is vulnerable to artifact from air spaces. Other difficulties include imaging crossing tracts, although acquisition and computational advances are continuously being made, providing solutions to these and other issues. *Figure 1* presents a preoperative DTI tractography image incorporating fiber clustering algorithms (123) and demonstrating the relationship of the tumor to adjacent tracts.

DTI may be used to visualize major white matter tracts, including the cingulum, superior and inferior occipitofrontal fasciculi, uncinate fasciculus, arcuate fasciculus, occipitotemporal fasciculus, the corticospinal, corticobulbar and corticopontine tracts, the optic radiations, corpus callosum, and anterior commissure (73). The same authors report occasional but inconsistent visualization of the optic tract, fornix, and tapetum (73). DTI has been used to image the effect of neoplasms on the integrity and trajectory of white mater tracts (187). Four patterns of anisotropy have been observed: normal signal with altered position or direction, corresponding to tract displace-

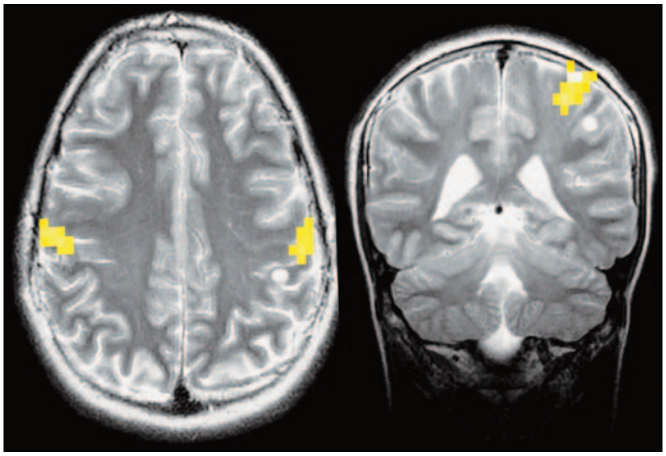

FIGURE 1. *Functional MRI study of a 17-year-old patient with a low grade tumor (DNET) in the primary motor cortex region. Left panel shows an axial view of activation associated with tongue movement. Right panel shows a coronal view of activation associated with finger tapping. These results demonstrate the usefulness of fMRI to study multiple functions in a single sitting as well as to display results in various planes.*

ment; decreased but present signal with normal direction and location, thought to correspond to vasogenic edema; decreased signal with disrupted direction maps, thought to correspond to infiltration; and loss of anisotropic signal corresponding to fiber tract obliteration or destruction (73). Histopathological studies for validation are still lacking, however, owing to the difficulty in performing such studies. Information on white matter tracts may be useful in operative planning to assist in the avoidance of displaced tracts and those affected by edema or tumor and to allow the surgeon greater confidence when working in areas of brain where critical white matter tracts might be expected but where DTI reveals preexisting tract destruction. There is also some evidence that low-grade tumors may contain white matter tracts within the boundaries of the tumor (163).

Tummala et al. (173) have used DTI of the optic radiations to facilitate complete resection of tumors with no postoperative visual field deficit in two pediatric patients. Berman et al. (13) have combined motor ECS with DTI of motor fiber tracts to visualize motor areas as well as their descending axons in patients with gliomas. This approach could be generalized to sensory and language mapping in awake craniotomies. A few groups have described the use of DTI with fMRI to evaluate the motor cortex and its descending tracts in patients with tumors near the motor cortex (76, 89, 113, 130, 187). Reliable integration of DTI datasets into standard neuronavigation systems by coregistration with fiber tract data with standard anatomic data will greatly facilitate the routine use of this technology. Nimsky et al. have described such integration of DTI data into a standard intraoperative neuronavigation system (119, 122). The authors have recently used this technique to visualize the pyramidal tracts and optic radiations during surgery in 16 patients with space-occupying lesions residing in the vicinity of the above-mentioned tracts (119). Combining DTI with fMRI allows imaging of a particular functional area as well as its connections to other areas, noninvasively, before surgery.

Electrocorticography and Electroencephalography

Electrocorticography is the direct recording of electrical potentials associated with brain activity from the cerebral cortex. A widely used application of electrocorticography is the localization of the central sulcus by means of phase reversal of somatosensory evoked potentials (SSEP-PR) (189). The EEG is a recording of the summed post-synaptic potentials of populations of cortical neurons. The EEG waveform assumes certain characteristic shapes in different states of arousal, with seizure activity, during the inter-ictal period, and in various disease states. The EEG may be recorded by means of extracranial (scalp) electrodes or intracranial electrodes (depth electrodes or subdural grids and strips). To pursue intracranial electrode placement, there must be sufficient evidence to limit the possible sites of epileptogenesis because clinical considerations necessarily limit coverage with these invasively placed electrodes. On the basis of the scalp EEG and other data, sites are selected for implantation with either depth or subdural electrodes. Depth electrodes are implanted using stereotactic guidance and are most commonly used to monitor the medial temporal lobe structures. Subdural electrodes, arranged in grids and strips, may be used to record from larger areas of cortex including intrahemispheric or subtemporal locations. Each technique has its strengths and limitations in terms of risk, brain coverage, and ease of placement; therefore, individualized determination of the appropriate method is important (57). In both cases, the electrodes can be used to stimulate and record, thereby allowing extraoperative functional mapping (115). Because of the necessity of an additional operative session and risks of hemorrhage, infection, or cerebral edema in 1 to 4% of patients (175), this technique has limited indications. In addition, the need for intracranial recording has declined as other, less invasive, preoperative studies that allow more patients to proceed directly to resective surgery without this step have been developed and validated. Like scalp EEG, intracranial EEG is characterized by excellent temporal resolution; because it does not suffer from distortion from the scalp and cranium, intracranial EEG has much better spatial resolution than scalp EEG. Because intracranial EEG is much more invasive than scalp EEG, it has found use only in limited situations, primarily in epilepsy surgery. Invasive recordings from the human brain can provide unique opportunities to study fundamental processes at fine temporal and spatial resolution (33).

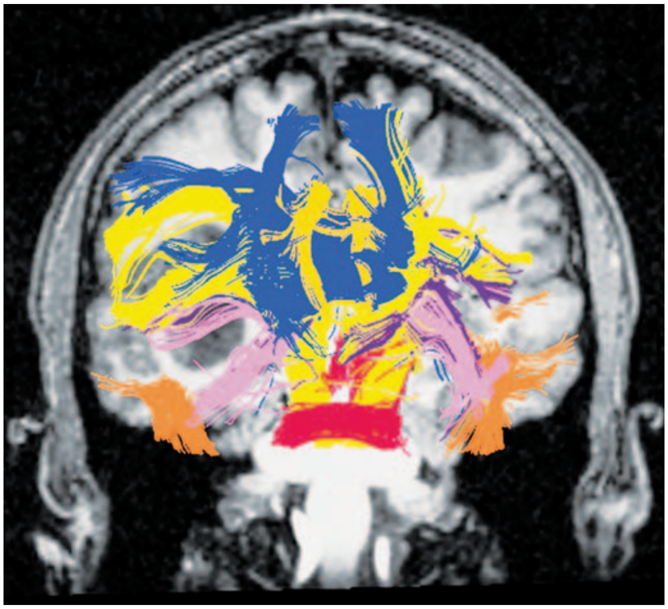

FIGURE 2. *A coronal brain slice with super-imposed diffusion tensor tractography. The tractography demonstrates alteration in the arrangement of the tracts around the tumor in the temporal lobe. Tracts have been grouped and color-coded into clusters of similarly shaped tracts, which facilitate interpretation of the findings.*

Magnetoencephalography

Magnetoencephalography (MEG) is a non-invasive method of measuring brain activity by measuring the magnetic fields that accompany neuronal activity. MEG is similar to EEG but is based on magnetic field changes rather than voltage changes.

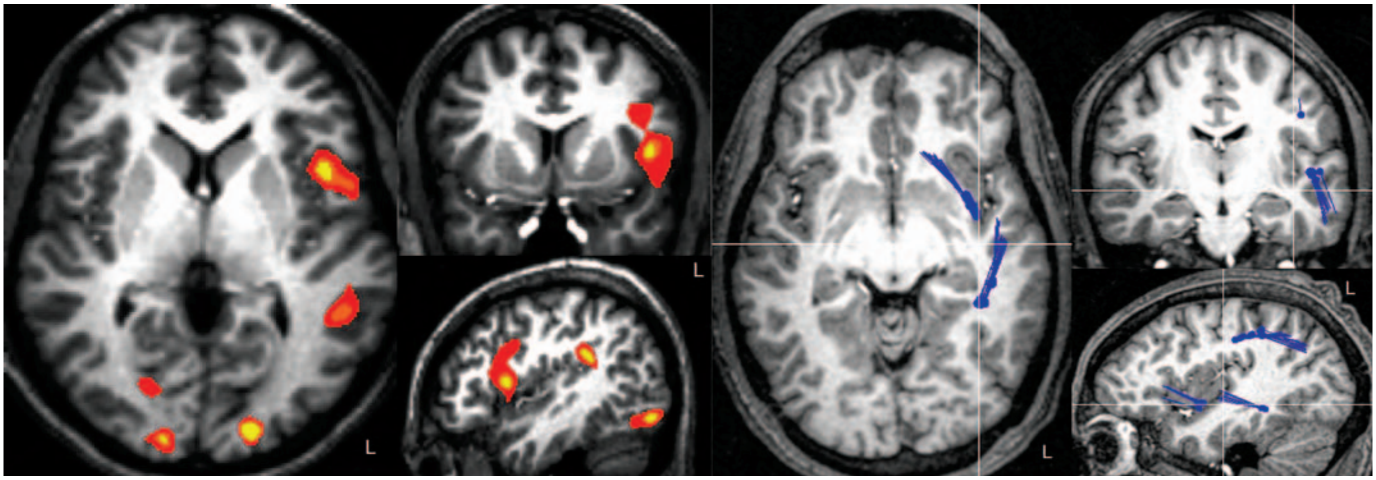

FIGURE 3. *Language mapping using both MEG and fMRI in the same subject using identical behavioral paradigms. Note that MEG generates equivalent current dipole models that tend to be located deep to the actual cortical surface, whereas fMRI generates statistically color-coded maps located more superficially. Language lateralization is clearly to the left using both methodologies. Whereas MEG results favor temporal lobe activations, fMRI results favor frontal lobe activations.*

Neural activity can be described as the generation and propagation of ion currents. The longitudinal current flow generated by several thousands of neurons firing synchronously can be detected at the scalp surface using a biomagnetometer. MEG data are gathered using a biomagnetometer made up of wire induction coils arranged in an array covering the entire head. The magnetic fields produced by neural activity induce electric currents in these coils and can be used to reconstruct an image of the distribution of evoked neural electrical activity of brain function in real-time. Because the electrical current generated by the magnetic field is very small, superconductors must be used to overcome the impedance of the recording wire. Superconducting quantum interference devices are used to record the conductance change caused by the small magnetic fields associated with neuronal activity. MEG source localization is generally modeled as the equivalent current dipole. When MEG is used for mapping the functional cortex, a stimulus task is presented multiple times. The resulting evoked neuromagnetic signals are then averaged over 80 or more trials to separate the signal produced by a focal population of active neurons from background activity.

MEG has several advantages and disadvantages. Like EEG, MEG has excellent temporal resolution on the order of 1 millisecond. Unlike surface EEG, however, the MEG signal is not attenuated by the cranium and scalp and has better spatial resolution of approximately 2 mm and better signal-to-noise ratio (136). MEG is also a reimbursable procedure, both for epileptic focus localization and for functional mapping. Because MEG source localization is modeled as the equivalent current dipole, several simultaneous sources may be inaccurately represented in MEG datasets by a spatially intermediate single location. MEG also tends to localize function deep to the cortical surface. MEG scanners require dedicated personnel as well as magnetic- and radio frequency-shielded rooms similar to MRI. The technique is extremely vulnerable to environmental magnetic noise, including the earth's magnetic field and the magnetically noisy environment in hospitals. Currently, MEG scanners are very expensive (> $2 million capital equipment costs) and have limited availability. At this time, their use is mainly restricted to centers pursuing research programs.

In neurosurgical practice, MEG is used primarily in the presurgical evaluation of epilepsy patients to localize epileptogenic foci (83). The use of MEG has more recently expanded to stereotactic and image-guided surgery to aid in the safe resection of lesions adjacent to eloquent cortex (128, 145). Magnetic source imaging is the coregistration of MEG data to a structural image to facilitate the anatomofunctional correlations and to incorporate this information into stereotactic neuronavigation systems (37). Several studies report good correlation between preoperative MEG functional data and intraoperative maps of sensory and motor evoked potentials and electrocortical mapping (42, 43, 77, 144, 168). Several groups have merged functional MEG data with anatomic data to locate key functional cortex near and within cortical lesions, including arteriovenous malformations, gliomas, and brain metastases. Rezai et al. have reported a technique of integrating MEG functional mapping data for both motor and sensory tasks into a stereotactic database for use intraoperatively, as well as for preoperative planning (145). Their system combined MEG data with CT scans, MRI scans, and digital angiography in an interactive stereotactic system and was used in 10 patients undergoing surgical resection of lesions involving the sensorimotor cortex. Similarly, McDonald et al. (106) report the successful combination of both fMRI and MEG data into a frameless stereotactic system that also incorporates digital registration of cortical stimulation sites. These techniques allow the simultaneous viewing of both structural and functional brain anatomy and their spatial relationship to brain lesions, which may allow the surgeon to resect more aggressively without violating functional cortical areas.

Optical Imaging

Brain tissue exhibits optical properties such as scattering and absorption, which can be measured directly at the brain surface. It has been shown that these intrinsic optical signals (IOSs) vary as a function of neuronal activity. At least three types of IOSs are generated by neuronal activity: light scattering signals, some of which may be intrinsic to the neurons themselves; changes in absorption spectra of molecules like Hb, cytochrome and reduced nicotinamide adenine dinucleotide; and IOSs related to changes in blood volume as measured by overall changes in Hb absorption (40). So, like PET and BOLD-fMRI, imaging of intrinsic optical signals (IIOS) depends primarily on changes in local cerebral blood volume and oxygenation. Unlike BOLD-fMRI, changes in blood volume and Hb oxygenation may be measured separately by selecting the appropriate wavelengths (54). IIOS can be used to map functional areas and has been validated against ECS (52). IIOS may be used as a basis for imaging both normal and seizure activity in patients undergoing craniotomy (54). Advantages of optical imaging include low cost and high spatial and temporal resolution. Its limitations are similar to those described above for ECS, including that it is not available preoperatively, that it requires a craniotomy, and that it yields information about only the cortical surface. Optical imaging has not yet been widely adopted for neurosurgical purposes. Finally, a few groups have reported the use of infrared or near-infrared imaging of neuronal activity through the intact cranium (66, 161), although such work remains very preliminary.

Inhibition and Activation

Intracarotid Amytal or Wada Test

The intracarotid amytal (IAT), or Wada, test is an inhibition method in which the territory perfused by the internal carotid artery (ICA) on one side of the brain is temporarily anesthetized by injection of sodium amytal into the ICA. After the observed onset of contralateral hemiparesis and EEG changes, a battery of behavioral tests is applied. Wada testing was initially developed to lateralize language dominance in patients undergoing electroconvulsive therapy but has long been used for language lateralization in preoperative patients with medically intractable epilepsy (181, 182). It was subsequently modified to test lateralization of memory and to assess the risk of postoperative amnesia in patients undergoing temporal lobectomy for medial temporal lobe epilepsy (111). The spatial resolution of the Wada test is usually hemispheric. However, Wada testing has been used in a more highly localized manner with selective catheterization, e.g., to investigate function of the mesial temporal structures in epilepsy patients (17). Temporal resolution is not applicable to this technique. Because it is an inhibition method, the Wada test mimics the effect of surgical resection.

Wada testing is limited in that the examiner has only a few minutes to test each hemisphere. The test is invasive, carrying a 0.6 to 1% risk of stroke (58). The transient hemiparesis and cognitive deficits elicited during the test may be upsetting to patients. Agitation and even obtundation can preclude language testing in some individuals. Because of its invasive nature, Wada testing is not readily repeatable. Technically, the test is potentially confounded by cross flow between hemispheres when it exists, resulting in anesthesia of both hemispheres from a unilateral injection. In terms of lateralization of MTL function, in most people, the majority of the MTL is not perfused by the ICA, so inhibition during Wada testing is thought to be indirect and may not be complete.

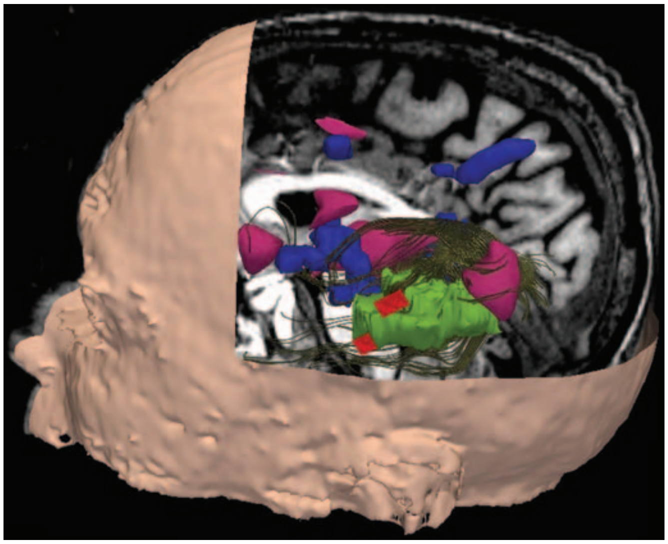

FIGURE 4. *A cut-away 3-dimensional model incorporates multi-modality brain mapping data. The segmented tumour is shown in green, fMRI activations in purple, MEG activations in blue, and cortical stimulation sites in red. White matter tracts around the lesion are demonstrated in yellow. This type of image demonstrates the complexity of displaying multiple data types as well as the potential utility. In this case, the non-invasive data accurately predicted that the patient experienced language difficulties during resection at the posterior margin of the tumour, even though there were no positive stimulation sites there.*

Electrocortical Stimulation

Since the 1930s, direct electrocortical stimulation (ECS) testing has been the gold standard method for mapping brain function in preparation for surgical resection (126, 132). The motor cortex is mapped intraoperatively by stimulating the pre- and postcentral gyri, as well as the premotor area (PMA) and supplementary motor area (SMA). ECS for motor mapping (12, 126) may be performed under general anesthesia without muscle relaxants. Low frequency stimulation delivered to the motor cortex causes contralateral muscular contractions. Kombos et al. (85) have reported the use of monopolar ECS in which muscle action potentials are recorded as a surrogate for movement, which seems to be accompanied by a decreased risk of intraoperative seizure (85). In motor mapping, ECS is used as an activation technique.

To test language functions, it is necessary that the patient remain awake and able to perform certain tasks such as counting or naming (110). Awake craniotomy for language mapping is typically performed using a combination of local anesthetic field block and short acting general agents to induce a rapidly reversible hypnotic state. Once the scalp, cranium, and dura are opened, the sedation is allowed to wear off so that the patient may cooperate with behavioral testing. During the cortical stimulation testing, the patient is awake and asked to perform language tests such as counting or naming while the surgeon stimulates the cortical surface. Areas in which cortical stimulation induces speech arrest or paraphasic errors are considered essential for language function. In this case, ECS is used as an inhibition technique causing disruption in normal neuronal firing. Because the bipolar stimulating electrodes have a 5-mm tip separation, a 1-cm margin is generally respected during the subsequent resection. In their study of 40 patients undergoing removal of gliomas in the dominant temporal lobe, Haglund et al. (53) reported that among patients without preoperative language deficits, 87% had no deficits postoperatively using the above methods.

ECS can also be performed extraoperatively. This option is used primarily for epilepsy surgery for the mapping of the seizure focus through the chronic (~1 wk) implantation of intracranial electrodes. In addition to electrocorticography, cortical stimulation for the determination of eloquent cortex may also be performed during this time period. When indicated, this technique has the advantage of allowing significant time and a sufficiently relaxed and cooperative patient to allow detailed cognitive testing. However, like intraoperative ECS, this technique can only sample from limited regions and is, therefore, not suitable for certain investigations.

In spite of the excellent spatial resolution and predictive value of this technique for cortical mapping, the most obvious drawback is that it requires a craniotomy. In fact, it requires a wide craniotomy that exposes not only the lesion but also adjacent eloquent cortical regions suspected of being jeopardized by the resection. This technique, therefore, does not allow for preoperative planning. ECS language mapping requires that the patient be able to cooperate in performing these tasks during an awake craniotomy. Most children and some adults are unable to tolerate being awake for such a procedure. Even cooperative patients may have trouble maintaining task performance over the course of the investigation. Awake craniotomy generally requires dedicated neuroanesthesia support and a sufficient caseload to provide training and expertise and, hence, may not be available in many centers.

Cortical stimulation testing is also limited by the difficulty of examining the sulcal depths that comprise as much as two-thirds of the cortical surface (25), the deep structures of the mesial temporal lobe, or the underlying white matter. For example, it is not uncommon for patients who have undergone cortical mapping and resection respecting the boundaries of the eloquent cortex to nevertheless be left with neurological deficits secondary to damage to associated white matter tracts. To minimize such occurrences, a few groups have reported success using white matter stimulation intraoperatively to define critical tracts (80). Berman et al. (13) have reported the combined use of cortical ECS with DTI to image motor cortex and its descending tracts in patients with gliomas.

TMS

TMS involves the stimulation or inhibition of neuronal electrical activity via a magnetic field delivered at the scalp. The technique emerged from the discovery of the related technique of transcranial electrical stimulation (TES), in which electric currents applied to the scalp were used to activate cortical neurons (109). Unfortunately in TES a minority of the applied current flowed in the desired direction through the skin and scalp to the cortex, with the remaining majority of the applied current traveling between the stimulating electrodes, activating pain receptors and causing unwanted contraction of scalp muscles. Thus, TES through an intact cranium has not proved a useful technique. Barker et al. (7) subsequently discovered that a magnetic field could be used to set up an electrical stimulus across the scalp and cranium. In TMS, a current is discharged into an electromagnetic coil held over the cranium; this discharge creates a magnetic field that induces a perpendicular electric field. The field is conducted through the living tissues of the skin and cranium and produces an electric current in the cortex, without causing pain in the patient (155). TMS may be used as an activation technique, as is the case when single pulse TMS is used to map the motor cortex (86, 102). It may also be used as an inhibition technique, as in the use of repetitive TMS to disrupt language processing (82, 131) and may be used for the determination of language lateralization (74). Single pulse TMS has temporal resolution on the order of milliseconds; the effects of repetitive TMS can last on the order of seconds. A great advantage of TMS is that it is the only noninvasive inhibition technique. Disadvantages include poor spatial resolution and the risk of repetitive TMS causing seizures (155). Although there has been relatively little reported use of TMS in surgical planning, Krings et al. (86) have described the correlation of TMS with ECS in motor mapping in two patients with tumors near the central sulcus. Neggers et al. (116) have recently developed a frameless stereotactic navigation system for delivering TMS and validated their results showing correlation with fMRI and ECS to within 5mm in motor cortex. Recent reports also describe the coregistration of TMS and fMRI data to investigate visual processing and lateralization of different aspects of memory processing (155). Despite one study reporting that TMS does not replicate Wada testing (36), the above-mentioned reports suggest tremendous promise for the technique in operative planning in the future.

APPLICATIONS TO SPECIFIC FUNCTIONS

1. Motor Mapping

A variety of functional imaging techniques are routinely used in motor mapping in patients with tumors in the vicinity of the motor strip (84, 85) or with suspected seizure foci near primary motor cortex (70). Voluntary movement is associated with activation of primary motor cortex (M1), premotor area (PMA), supplementary motor area (SMA) and superior parietal lobule (SPL).

Pre-operatively, fMRI is used in many centers to delineate brain regions activated with motor tasks. Many groups have validated fMRI against ECS in localizing motor areas (101, 149, 151, 193). In a recent study of 33 patients with tumors near the central sulcus, Majos et al. found 84% agreement between preoperative fMRI and intraoperative ECS in identification of motor areas and 83% agreement in the identification of sensory centers between the two techniques. When sensory and motor data are combined, the agreement between fMRI and ECS increased to 98% (101). Roessler et al. recently used 3-Tesla fMRI and ECS to guide resection of gliomas in motor cortex (148). In those patients for whom the two modalities could be correlated (17 of 22), there was 100% agreement between fMRI and ECS data within 1cm.

Intraoperatively, motor cortex may be mapped using bipolar ECS as described above (12, 126). Motor areas may also be mapped either intra-or extra-operatively by recording Bereitschaftspotentials (BPs) (70). These are slow electrical potentials recorded in the awake patient from motor cortex prior to the initiation of voluntary movements and represent excitatory post-synaptic potentials (EPSPs) of cortical pyramidal neurons. Often recorded via chronic subdural electrodes, BPs have the advantages of recording activity associated with planning and execution of voluntary movement, no induction of seizure activity, and yielding information for any type of movement of any part of the body (70). The disadvantage of recording BPs is that they require a very cooperative patient as movements need to be repeated at least 50 times to obtain averaged waveforms (70).

A few groups have recently reported cases in which fMRI was combined with DTI to image motor cortex and its descending (pyramidal) tracts in a patients with lesions residing within or next to primary motor cortex (76, 113, 130). Berman et al. have combined motor ECS with DTI of motor fiber tracts to visualize motor areas as well as their descending axons in patients with gliomas (13).

Several studies have shown altered motor maps in patients with lesions near motor areas. Yousry et al. have found alterations in the cortical representation of the motor hand area in intact patients with space-occupying lesions near the central sulcus (193). Using fMRI to study patients with tumors located in the vicinity of the motor strip, Krings et al. found decreasing activation in primary motor cortex in proportion to the degree of pre-operative hemiparesis (89). They also noted increasing activation in secondary motor areas with increasing pre-operative weakness. Decreased activation in M1 was thought to reflect either loss of cortical neurons or changes in cerebral blood flow secondary to the lesion; increased activation in secondary areas may represent redundant circuitry and form the basis for functional recovery following resection (89). Motor cortex may also be frequently (and unpredictably) shifted by mass lesions. These accounts of the alterations of motor maps illustrate the potential plasticity of the adult brain.

2. Language Lateralization

fMRI and Wada are used for language lateralization in patients with MTL epilepsy and in those with tumors of the frontal and temporal lobes. Wada testing with comprehensive language assessment (98) reliably lateralizes language function. Benbadis et al. have demonstrated poor correlation between language lateralization based solely on speech arrest when compared to lateralization by Wada testing based on comprehensive language assessment and lateralization by fMRI in 12 patients with intractable epilepsy, suggesting that speech arrest alone is an unreliable method of preoperative language lateralization (10). Woerman et al. compared language lateralization by fMRI and Wada in 100 patients with temporal lobe epilepsy (TLE) or extra-temporal epilepsy and found 91% concordance in the results of the two tests (188). In their study, fMRI falsely categorized language lateralization in only 3% of left-sided TLE patients but in 25% of left-sided extratemporal epilepsy patients. This large study using a simple word-generation task and a rapid (15 min) acquisition time suggests that fMRI may reduce the need for Wada testing in TLE but is less useful in the determination of language lateralization in extratemporal epilepsy. Other studies have reported 100% concordance in language lateralization between fMRI and Wada testing in patients with temporal lobe epilepsy (21, 41). Furthermore, Aldenkamp et al. have obtained the expected language dominance distribution in right-handed healthy volunteers using fMRI and a silent word generation task (4). Lehericy et al. have demonstrated that frontal, not temporal, asymmetry of language dominance correlated with Wada testing (93). Further validation of fMRI for preoperative language lateralization comes from studies demonstrating atypical (bilateral or right-dominant) language dominance in 22 to 24% of non-right-handed subjects (140, 169), in agreement with earlier findings using Wada testing of left-handed epileptic patients (141). Furthermore, Fernandez et al. have recently demonstrated high within-test and test-retest intrasubject reproducibility for language lateralization fMRI in patients with epilepsy (38). In addition to carrying fewer risks, fMRI has the advantage of taking less time and costing less than Wada testing. Medina et al. performed cost analysis demonstrating that Wada testing costs 3.7 times more than fMRI (107).

One frequently identified shortcoming of fMRI in language mapping is that, for reasons of motion artifact, silent word generation tests are generally used, as opposed to spoken tests standard during Wada testing. Aldenkamp et al. addressed this issue with the development of a protocol involving alternating scan acquisition with overt naming of pictures (4). Interestingly, the authors found that overt naming lateralizes poorly in fMRI, with all subjects showing bilateral activation. Silent word generation on the other hand, lateralizes well, validating this method (4). Bilateral activation with overt language tasks probably results from non-language-specific activations in face motor, auditory and other areas. Region of interest analysis in putative language areas during overt language tasks may still effectively show lateralization (167). The finding of Aldenkamp et al. also illustrates the inherent difference between observational and inhibition techniques: although both hemispheres are activated by overt naming, only one may be necessary for language function (that side which, when inhibited during Wada testing, results in aphasia). Furthermore, an important difference between the two techniques in illustrated: in fMRI both hemispheres are tested simultaneously, whereas in Wada testing each hemisphere is tested alone. Despite the fact that Wada testing, as an inhibition technique, mimics the effects of resection, fMRI may come closer to replicating the context (both hemispheres active) of behavior in the postoperative patient. Binder et al. noted a linear relationship between the intensity of right hemispheric activation on fMRI and the severity of language deficits observed on Wada testing of right-dominant individuals (15), suggesting a role for fMRI in predicting the severity of language deficits in right hemisphere surgery in this population and underscoring the possible advantage of the fMRI with its graded output over the Wada test with binary output (166).

3. Language Localization

While the emphasis in patients undergoing anterior temporal lobectomy has been on lateralization of temporal lobe speech areas for operative planning, fMRI and PET studies have demonstrated significant involvement of other cortical regions in language. These are particularly pertinent to patients with seizure foci or mass lesions away from the MTL but within these other speech areas. Some of these areas can be preferentially activated with different protocols, such as frontal regions with word generation paradigms (93, 140). Patients with epilepsy show greater variability of language dominance (166) and increased activation of contralateral language areas (21) than healthy control subjects on fMRI. These data point to additional areas that may produce deficits with resective surgery but also to areas of cortex that may be recruited during recovery from surgery or longstanding injury to primary language areas. They also underscore that an observational technique like fMRI cannot distinguish essential from participating, but non-essential, areas.

In epilepsy patients undergoing EEG monitoring via implanted electrodes and awake intraoperative patients undergoing lesion resection, ECS may be used to map specific areas involved in various aspects of language. In these as well as other patients, fMRI may be used in a complementary fashion. While fMRI protocols in current use have demonstrated excellent concordance with Wada testing for language lateralization, correlation between pre-and postoperative fMRI and intra-operative cortical mapping remains inconsistent in studies. In a study of 14 right-handed patients with left hemisphere tumors, Roux et al. (150) compared language areas activated by naming and verb generation tasks with intraoperative speech mapping using ECS. The authors identified 22 language sites with cortical stimulation, 5 of which were concordant with sites identified by fMRI, but 17 of which were not associated with fMRI signal. Based on these findings they conclude that while fMRI is a helpful adjunct its failure to identify speech areas identified by ECS in the operating room makes it insufficient to form the basis of critical pre-operative decision making prior to resection. Postoperative fMRI of a subset of their patients identified language foci that correlated with those identified intraoperatively with ECS in only 6 of 8 patients examined, with complete agreement in only 3 of 8 patients (150). The authors note that sensitivity and specificity of fMRI can be improved by combining data from both tasks, suggesting that modification of the behavioral paradigms used could improve correlation with ECS data. In patients with MTL epilepsy, on the other hand, Carpentier et al. have demonstrated concordance in intrahemispheric language maps generated by fMRI and via cortical stimulation (21). The authors did find additional areas identified by fMRI, partly owing to limited coverage of cortex by electrodes and partly owing to the fundamental differences between fMRI, an observational technique, and ECS, an inhibition technique.

APPLICATIONS TO SPECIFIC DISEASE PROCESSES

Tumor

In patients with brain tumors, the goal of maximizing resection competes with that of not causing any additional neurological symptoms. Many patients with primary tumors of the central nervous system have infiltrative lesions; thus, resections are performed for reduction of mass effect and disease burden but generally not for cure. Thus, minimizing resultant neurological deficits and associated reduction in quality of life is paramount. Similarly, patients with brain metastases usually have limited life expectancies, and palliative surgery must not worsen existing symptoms or introduce new deficits. There data suggest that the degree of resection of low-grade gliomas correlates with long-term survival (11, 24, 96, 134, 186), although the evidence remains controversial (79, 105). Because low-grade gliomas can have a slow clinical course, the need to balance aggressive resection with postoperative morbidity, particularly in the neurologically intact patient, is heightened when they are located within or near eloquent brain. Preoperative fMRI has been widely used either alone (3, 56, 87, 89, 185) or in combination with ECS (64, 88, 151) to map eloquent cortex in the vicinity of low-grade gliomas before resection; in some cases, it has been used in conjunction with intraoperative MRI scanning (56).

Owing to their infiltrative nature, low-grade gliomas may have functional tissue within the tumor (127, 163). Indeed, Russel et al. (154) have found that resection of low-grade gliomas involving the supplementary motor area (SMA) results in a higher incidence of transient weakness (SMA syndrome) than the resection of high-grade gliomas in the same region, presumably owing to the presence of more functional SMA cortex within the lower-grade lesions. Detailed and accurate functional imaging is, therefore, particularly important for planning their resection.

Tumors of higher grade present a somewhat different set of challenges. There is inconsistent evidence that the degree of resection of a glioblastoma multiforme (GBM) correlates with time to progression and median survival (78). However, with the best median survival times being 1 to 2 years (78, 91), the time for postoperative recovery and the duration of even transient deficits are particularly relevant for GBM patients. The transient hemiparesis of the SMA syndrome, for instance (154), which usually resolves within weeks to months, could represent an unacceptable morbidity when the expected survival of the patient may not significantly exceed that time.

The BOLD effect is sensitive to altered regional blood flow as is found in high-grade tumors of the central nervous system (16). Higher-grade tumors are associated with hemodynamic-neural uncoupling, and fMRI data must be interpreted accordingly with this in mind. Perhaps owing in part to this effect, Liu et al. (95) have reported that BOLD fMRI activation volume in the SMA is affected by both tumor type (intra- versus extra-axial) and distance from the motor cortex. Edema surrounding the tumor can also affect the MRI signal. Although a potential source of error in the interpretation of fMRI, this effect has been capitalized on in DTI to distinguish between primary and metastatic brain tumors. In the area of edema surrounding a metastasis, there is an increase in the diffusion of water along white matter tracts, whereas a decrease in diffusion is generally noted in primary brain tumors, presumably owing to their infiltrative nature (99, 100, 139).

DTI may also be used to image the effect of tumor on fiber tracts, as well as to measure early response to therapy in densely cellular tumors (62). FDG-PET and SPECT are commonly used to distinguish radiation necrosis from tumor recurrence in cases in which MRI data was ambiguous (18).

Functional imaging has revealed new information concerning plasticity and suppressed activity in patients with tumors and neurological deficits. Roux et al. (149) have shown recovery of function and of fMRI signal in patients with tumors in the primary motor cortex with preoperative weakness and with no pre- or intraoperative fMRI or ECS activation in the affected cortex.

There will likely be an increased role for functional imaging in the guidance of minimally invasive techniques such as focused ultrasound, laser thermal ablation, stereotactic radiosurgery, and other, emerging techniques in patients with brain tumors.

Vascular

Location within eloquent cortex is an unfavorable prognostic factor for the surgical resection of arteriovenous malformations (AVMs) (165). However, because AVMs are congenital lesions and in view of the plasticity of the developing and even adult brain, eloquent cortex may not reside in the expected position owing to reorganization of functional areas during embryonic development or as a consequence of hemorrhage or steal in the adult (178, 179). Functional imaging is, therefore, particularly helpful and has been described by several groups in planning therapies in these patients (8, 20, 102). Shimamura et al. (162) have recently reported the use of preoperative MEG to localize the central sulcus in patients with AVMs residing near the motor cortex. They describe two cases of displacement of the functional central sulcus from the expected anatomic location in patients with peri-Rolandic AVMs, presumably demonstrating plasticity related to these congenital lesions. This is important in the selection of surgical versus expectant management or radiosurgical treatment options. Cannestra et al. (20) have used fMRI and Wada testing to identify those patients with dominant hemisphere pre-Sylvian AVMs who are suitable for surgery with intraoperative ECS and optical imaging.

Many types of abnormal blood flow may be associated with AVMs, including altered vasoreactivity, steal, and shunting (102). For this reason, BOLD fMRI data, which depend on alterations in cerebral blood flow associated with neuronal activity, must be interpreted with caution in these patients. Indeed, Lehericy et al. (92) have demonstrated cases of incorrect language lateralization on fMRI in patients with dominant hemispheric AVMs residing near language areas. Functional imaging studies have also been reported in the preoperative planning of resections of cavernous malformations (31, 113).

Epilepsy

In patients with severe or medically intractable epilepsy, surgical resection of the epileptogenic focus may represent the best treatment option (184). Distinct from resections of tumors or vascular lesions, in epilepsy surgery, functional imaging is sometimes used for the localization of the lesion itself, in addition to lateralization and localization of critical functions.

Seizure foci may be localized during seizure activity (ictal imaging), between seizures (inter-ictal imaging), or both. These areas tend to be hyperactive and hyperperfused during a seizure and hypoactive and hypoperfused when compared with normal brain between seizures. Traditionally, subdural grids and strips in combination with depth electrodes have been used to localize seizure foci based on ictal and interictal recordings (70). Intraoperative optical imaging may be used to localize and confirm seizure foci, both ictally and interictally (54). Ictal SPECT (177) and MEG (83) may be used to localize epileptogenic foci non-invasively. Spike triggered fMRI (29, 65, 156, 157), FDG-PET (2, 34, 35, 172) and $H_{215}^{\text{O PET}}$ (171) may be used interictally to localize neocortical seizure foci as well as to lateralize MTL seizure foci.

MEG scans are more commonly used for interictal observations. Although the correlation is not universally accepted, several studies have reported good correspondence between MEG recorded interictal spikes and seizure foci. In a series of 11 children with neocortical epilepsy, Minassian et al. (112) reported a strong regional correspondence between the location of MEG identified interictal spikes and ictal activity confirmed by subdural grid electrode recordings. Wheless et al. (183) compared the accuracy of MEG for locating seizure activity with MRI scans, scalp video EEG, and interictal and ictal subdural grid electrode recording, as determined by each method's ability to predict the clinical success of surgical resection. They found that MEG was second only to ictal intracranial recordings in predicting a positive surgical outcome but made no direct comparison between the anatomic location of seizure foci determined by each method. Mamelak et al. (103) compared MEG interictal data with intracranial electrode monitoring in 23 epilepsy patients. They found that MEG accurately localized seizure foci to the correct lobe and was, thereby, useful in guiding the placement of subdural electrodes, particularly in neocortical epilepsy.

The critical function of greatest concern in patients with medial temporal lobe (MTL) epilepsy is the encoding and retrieval of memory. For these patients, preoperative functional imaging may be particularly helpful for assessing risk of memory deficit, as the structures of the medial temporal lobe, including the hippocampus, amygdala and parahippocampal cortices, are substrates for memory formation (138). This is illustrated by the dense anterograde amnesia observed in a now famous patient after bilateral medial temporal lobectomy for intractable epilepsy (160). Lateralization and localization of MTL activation varies depending on the modality (verbal versus nonverbal) and the stage (encoding versus retrieval) of memory task tested (47, 138). Wada testing is the current gold standard used to screen candidates for anterior temporal lobectomy at risk of postoperative amnesia. The limitations of Wada testing of memory include cost, invasiveness, and perfusion of part of the MTL by the posterior circulation, and are discussed above. fMRI is increasingly used to lateralize memory function in candidates for anterior temporal lobectomy. A number of studies have compared Wada testing to fMRI in these patients (138). In general, patients with MTL epilepsy show greater activation of the contralateral MTL during memory testing (48, 75, 146), and excellent agreement exists in memory lateralization between Wada and fMRI testing in the same patient (30, 48). Unfortunately, fMRI is subject to geometric distortion as well as loss of signal in this region, particularly in the anterior MTL (138). It must also be remembered that loss of fMRI signal in a sclerotic MTL may merely reflect loss of tissue, rather than complete relocalization of function (138).

Other

As functional brain mapping techniques become less invasive, they may be used to investigate increasing numbers of disease processes, as well as to suggest targets for functional neurosurgical interventions to treat these conditions. Roux et al. (152) have described a case of the use of fMRI to guide placement of a chronic motor cortex stimulator for the treatment of phantom limb pain. Casey et al. (22) have used $H_2{}^{15}O$ PET to image brain activity in an experimental model of heat allodynia, a kind of neuropathic pain. The authors show altered forebrain activity in this setting compared to perception of normal heat pain. These reports suggest that functional imaging might be used both to better understand the mechanisms, as well as identify potential targets for functional neurosurgical interventions in pathological pain conditions. Other groups have described the use of functional imaging techniques to identify alterations in activity in various brain regions in depression (5, 32, 49, 50) and obsessive compulsive disorder (174, 176). Again, research of this type may eventually identify targets for functional neurosurgical interventions for a wide variety of disorders.

Future Directions

As illustrated in *Table 1*, current functional brain mapping techniques suffer from limitations in either temporal or spatial resolution, or are highly invasive. It follows that resolution and quality of data can be improved by integrating, or coregistering, data from multiple complimentary sources (26).

Improved integration of functional data with conventional imaging data and neuronavigation systems is also needed (129, 153). Although pre- and intraoperative coregistration of data from multiple functional mapping techniques has yet to find its way into mainstream use, an increasing number of studies suggesting its utility may be found in the literature. For instance, Roessler et al. (148) recently used 3-Tesla fMRI and ECS to maximize resection of gliomas in motor cortex with no permanent morbidity. Cannestra et al. (20) have combined preoperative fMRI and Wada testing with intraoperative ECS and optical imaging in the selection of treatment and preoperative planning in patients with dominant pre-Sylvian AVMs. Krishnan et al. (90) describe the use of neuronavigation-integrated fMRI, combined with intraoperative ECS, to predict and minimize risk of new postoperative neurological deficit in resection of tumors near motor cortex. Two recent studies describe the use of neuronavigation-integrated fMRI together with intraoperative cortical mapping to improve the accuracy of placement of epidural chronic motor cortex stimulation for intractable neuropathic pain (46, 135).

A problem common to the intraoperative use of preoperative mapping techniques is the failure to take into account brain shift after the opening of the craniotomy flap and dura. Shifts of up to 24 mm at the cortical surface have been described (60). Causes of brain shift include patient positioning and gravity, edema, administration of osmotic diuretics, drainage of CSF, retraction, and resection (23, 59, 60, 117, 137). Furthermore, investigations of brain shift have revealed that displacement of the cortical surface and of deeper structures are uncorrelated (60, 143). Because of this, and because of the heterogeneity among lesions encountered in the operating room, intraoperative MRI is necessary to address this problem by providing images of the brain during surgery (55). Recently, multiple groups have put forward algorithms to update neuronavigation systems with intraoperative MRI images after brain shift (23, 60). Imaging or modeling intraoperative brain shift and applying these transformations to preoperative functional datasets will allow more accurate intraoperative information to be available to the surgeon.

In addition to adjusting preoperatively acquired images to compensate for brain shift, future prospects will include the intraoperative acquisition of functional data, such as intraoperative DTI and fMRI. Nimsky et al. (120) have demonstrated the feasibility of intraoperative DTI to assess shift of white matter tracts. By comparing DTI data acquired pre- and intraoperatively, the authors describe variable and sometimes marked shifting (8 mm inward–15 mm outward) of white matter tracts during the resection of adjacent mass lesions (120, 121). Schulder et al. (159) have described the use of low-field intra-

TABLE 1. Functional brain mapping techniques[a]

Technique	Basis	Spatial resolution	Temporal resolution	Invasiveness	Applications
PET	Perfusion, metabolism	≥4 mm	Several seconds	++	Identification of seizure foci
fMRI	Perfusion	2–5 mm	Several seconds	+	Localization of language and memory; localization of motor, sensory areas; identification of seizure foci
DTI	Restricted water diffusion	<1 mm3	N/A	+	Localization of WM tracts; assessment of integrity of WM tracts
Scalp EEG	Electrical potentials	Poor	Milliseconds	+	Lateralization of seizure foci
Intracranial EEG	Electrical potentials	Poor	Milliseconds	++++	Localization of seizure foci for resection
MEG	Magnetic potentials	Poor	Milliseconds	+	Localization of seizure foci, localization of motor, language cortex, emerging applications
IIOS	Intrinsic optical signals	Excellent	Milliseconds	++++	Intraoperative motor and sensory mapping
IAT	Reversible anesthesia	Usually hemispheric	N/A	+++	Lateralization of language and memory
ECS	Direct electrical stimulation	Excellent	Instantaneous	++++	Intraoperative motor, sensory and language mapping
TMS	Applied magnetic stimulation	Medium	Milliseconds to seconds	+ to ++	Localization of motor areas, emerging applications

[a] PET, positron emission tomography; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; N/A, not applicable; WM, white matter; EEG, electroencephalography; MEG, magnetoencephalography; IIOS, imaging of intrinsic optical signals; IAT, intracarotid amytal test; ECS, electrocortical stimulation testing; TMS, transcranial magnetic stimulation.

operative fMRI of the motor cortex. Intraoperative fMRI would be facilitated by the use of high field strength systems (>1.5 T) (118). Gasser et al. (44) have demonstrated the feasibility of high field intraoperative fMRI. The authors used peripheral sensory stimulation and measured fMRI activation of sensory cortex, which was verified with phase reversal of SSEPs.

New minimally invasive functional imaging techniques such as functional transcranial Doppler ultrasound imaging (fTCDs) are finding increasing use in preoperative planning. Rihs et al. (147) have recently validated fTCDs for determination of language lateralization against Wada testing and have demonstrated the utility of fTCDs when patients may be unable to undergo Wada testing. fTCDs have also been used to map areas involved in visual (1) and auditory (104) perception. Studies comparing the reliability of less invasive methods with that of the more invasive gold standard techniques will pave the way for increasingly noninvasive testing. As fMRI has revealed, non-invasive studies carry the advantage of applicability to more patient populations, including children, repeatability during a session, repeatability over the patient's clinical course, and whole-brain coverage. In addition, the ability to prepare preoperative, non-invasive functional brain maps will be particularly important as more minimally invasive treatments are developed.

Functional imaging may also find use in monitoring the response of tumors to treatment. Henson et al. (62) have suggested that the use of BOLD fMRI to measure oxygen levels within tumors (68) could be used in monitoring the efficacy of agents that increase deoxyribonucleic acid damage from chemotherapy or radiation, and are currently investigating this in animal models (67).

CONCLUSIONS

Functional imaging is playing an increasing role in neurosurgical planning. The use of newer, less invasive techniques has enabled the assessment of more brain areas in individual patients, as well as the imaging of many functions in healthy subjects. One theme emerging from these more recent studies is that of plasticity, both of the developing brain, best illustrated by the relocalization of functions in patients with AVMs, and the adult brain, best seen in patients with slowly progressive lesions or during recovery. The combination of functional imaging with conventional imaging, image-guidance, and intraoperative imaging systems will lead to our ability to perform more complete and precise resections of lesions while preserving neurological functions. Functional brain mapping stands to eventually change the way intracranial processes are treated by creating a road map of brain function that not only defines eloquent "no-go" areas but also illuminates potential functional targets. Such a non-invasively obtained road map will be critical to the development of minimally invasive therapies.

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COMMENTS

Today, the complexity of imaging and neurophysiological techniques are increasingly similar in their application. This review provides a comprehensive and systematic overview of current and available functional brain mapping techniques and their application to neurosurgery. The diverse presentation of not only functional imaging techniques such as functional magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography, but also of neurophysiological mapping techniques such as electroencephalography, magnetoencephalography, and transcranial magnetic stimulation is very useful because it stresses the strengths and limitations of each of the techniques. The elaborate discussion of these preoperative mapping techniques and their comparison with intraoperative electrical stimulation applied directly to the cortex is beneficial for judging the value of each technique value and is essential for understanding their complementary application. In specific neurosurgical context, this article is a helpful guide for the application of functional brain mapping techniques.

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Functional brain mapping is an important tool in modern neurosurgery. The sophisticated use of these techniques allows for extended resections without causing additional morbidity. Tharin and Golby provide an excellent overview on the currently available mapping techniques. They distinguish observational techniques, such as positron-emission tomography, functional magnetic resonance imaging, diffusion tensor imaging, electrocorticography, electroencephalography, magnetoencephalography, and optical imaging, as well as inhibition and activation techniques such as intracarotid amobarbital/Wada testing, electrocortical stimulation, and transcranial magnetic stimulation. The application of these techniques, grouped by various functional systems (i.e., motor, language lateralization, language localization), are presented by their use in tumor, vascular, and epilepsy surgery. Registration of the various functional modalities to high resolution, anatomical magnetic resonance datasets opens the possibility to integrate all of these data in a navigational setup, leading to so-called functional neuronavigation.

This functional navigation allows the direct visualization of the mapping results in the surgical field, allowing pre- and intraoperative modalities to be compared easily. This concept of registering data to the standard anatomical image setup is open for further data beyond the standard anatomical and functional imaging. Adding data from magnetic resonance spectroscopy and other molecular imaging modalities enables the correlation of histology to the results of advanced imaging modalities, which proves or disproves their clinical value. This results in the so-called multimodal navigation setup. Besides the challenge of registering these data with a low error, a big challenge is finding the most suitable presentation of all of these data in the surgical field. The goal must be to avoid disturbing the surgeon during his work by an information overflow and present only the data necessary to achieve the maximum benefit for the patient. Furthermore, the overall application accuracy of modern navigation systems has always been of concern to surgeons, especially intraoperative events such as brain shift outdating the preoperative data, which must be compensated for. The combination of intraoperative imaging with a multimodal navigational setup offers the best possibility to solve these challenges.

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Until neurorestoration is realized in practical terms, neurosurgeons will continue to be faced with the need to meticulously preserve neurological function while surgically treating pathologies of the nervous system with eloquence of tissue defining not only surgical risk but also operable versus inoperable lesions. Over the past several decades, the ability to preoperatively define the anatomic substrate in neurosurgery has increased dramatically, and sophisticated imaging is available in all but the most modest of venues. In addition, the fusion of imaging and surgery has been brought into the operating room with the routine use of image-guided, frame-based stereotaxy and frameless neuronavigation technology. The availability of intraoperative magnetic resonance imaging is also increasing. Although the ability to define the preoperative anatomy has dramatically evolved and gained widespread utility, the routine use of methods of localization of cerebral function within the anatomic structures, both cortical and subcortical, has perhaps lagged behind. In this topic review, the authors provide a timely overview of the principal modalities for functional brain mapping. These topics cover tools that, although familiar to most neurosurgeons, are used less widely than anatomic imaging. Ultimately, the developments described in this review will lead to the fusion of anatomy datasets and functional imaging to guide surgery and increase safety in manipulating the least forgiving of surgical substrates.

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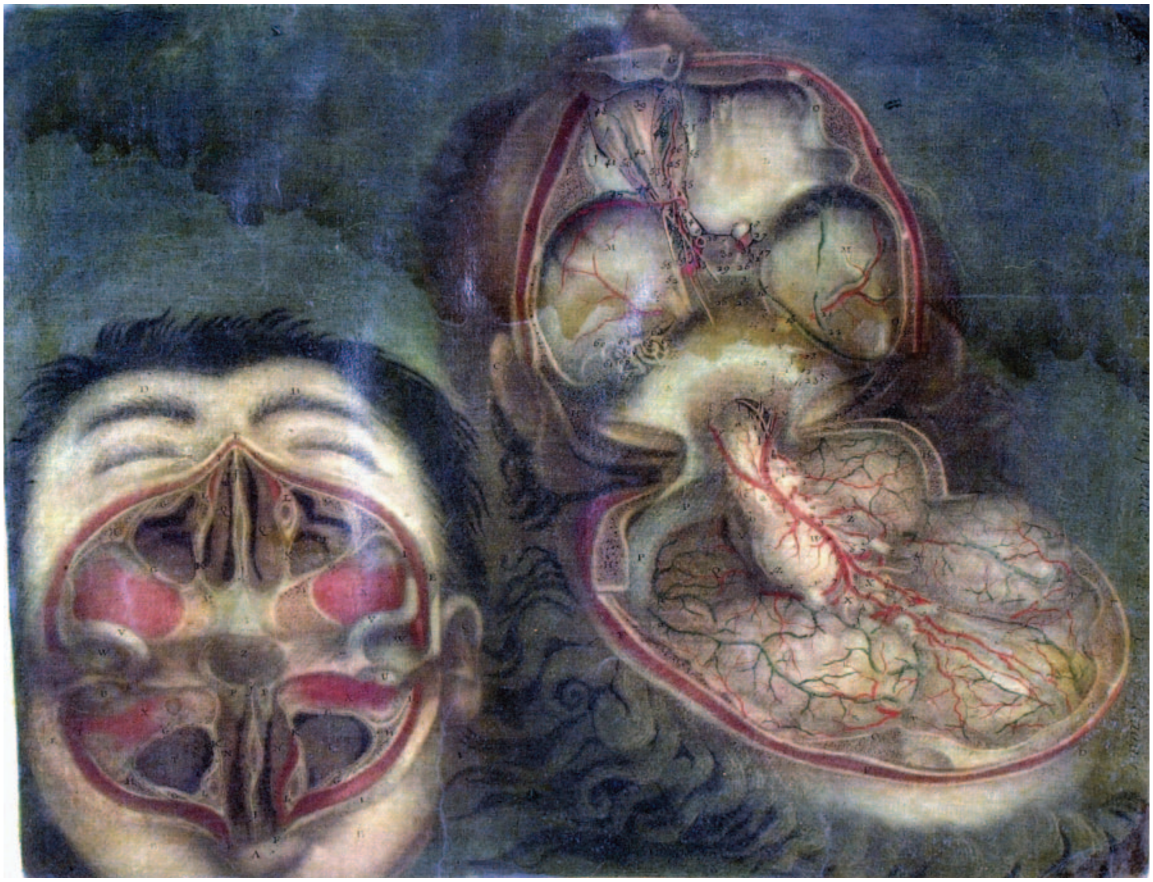

*Jacques Fabian Gautier d'Agoty, 1717–1785, **Myologie complette en couleur et grandeur naturelle**. Paris: Gautier & Quillau, 1746. (courtesy of Killam Library, Special Collections, Dalhousie University, Halifax, Nova Scotia and the U.S. National Library of Medicine, National Institutes of Health, Bethesda, Maryland).*