The Use of Motor Mapping to Aid Resection of Eloquent Gliomas

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One of the oldest and still most important forms of treatment available for patients with glioma is surgery. Even in the contemporary milieu of multimodal regimens, including radiotherapy and chemotherapy, glioma resection remains a mainstay, given its central role in establishing a histologic diagnosis and in relieving symptoms of mass effect by mechanical cytoreduction.[1] In addition, mounting clinical data reinforce the conventional notion that a greater extent of resection can improve outcomes and prolong life expectancy.[2–6]

As is the case for all solid tumors, the advantages of surgical resection for glioma must also be balanced with the potential risks of operative morbidity, and, as such, a great deal of focus in neurosurgical oncology is placed on minimizing collateral damage to surrounding eloquent brain.

Central to performing minimally morbid surgery is a thorough understanding of neuroanatomy and physiology in the region of interest. Given that primary central nervous system (CNS) tumors are highly infiltrative, display variable gross appearance, and may incorporate functional brain, the measures and observations that are used to plan a surgical approach must be diverse and must possess great precision. To that end, functional brain mapping allows the pursuance of safer operations with more aggressive surgical resections; these techniques include "gold standard" procedures such as direct electrical stimulation as well as newer, less invasive imaging technologies that can be integrated into preoperative planning processes as well as intraoperative decision making.

The first region of the brain to be mapped was the motor cortex. Many strategies to refine surgical approaches have been developed to minimize damage to motor cortex and motor fibers. Although similar principles have since been applied to the preservation of sensory, language, and memory functions, the mapping of motor pathways in the context of intracranial malignancy is a unique entity and thus poses a distinct set of risks and challenges. As reviewed herein, the history and background of motor mapping techniques are discussed, along with the current state of functional motor mapping in neurosurgical oncology and the potential implications of complementary technologies on the surgical management of patients with glioma.

EARLY WORK ON THE MOTOR CORTEX

Cerebral localization of function is one of the most fascinating and controversial topics in neurologic history. The first observation that control over motor function could be lateralized in the brain dates back to the fifth century BC, when the ancient Greek physician Hippocrates noted that unilateral cerebral injury results in contralateral paralysis.[7] Over the next 2 millennia, there was little written

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to explain this phenomenon. Interest in cerebral physiology instead seemed to be fixated on a philosophic discussion of the brain as "the seat of the soul." It was not until the early nineteenth century that this focus began to shift toward a more localized or segmental view of brain functions, largely due to theories of phrenology set forth by Franz Joseph Gall (1758–1828). Although Gall was heavily criticized by those who believed his work to be pseudoscience and damaging to religion, he was nevertheless instrumental in altering thinking in the field.

The latter part of the nineteenth century fostered a series of seminal clinical discoveries related to specific localization of function in the cortex, beginning with John Hughlings Jackson's assertion in 1864 that "the convolutions of the brain must contain nervous arrangements representing movements."[8] In 1870, the German neurologist Gustav Fritsch and an anatomist Eduard Hitzig[9] performed the first experiment demonstrating that topographically restricted electrical stimuli could be applied to the mammalian cerebral cortex to elicit corresponding contralateral movements. Although perhaps less well recognized, these findings were shortly followed by the first recorded experience with direct electrical stimulation of the human brain by Robert Bartholow in 1874,[10] who, inspired by localized testing on animal brains by contemporary David Ferrier, attempted to elicit sensory and motor responses by applying wires to the exposed dura of a patient who had a hole in her skull caused by a cancerous ulcer.

The earliest maps that depicted specific localization of motor control in the human cortex were based on findings from Ferrier's work with monkeys, in which recordings of movements in response to cortical stimulation were grossly transferred to an outline of the human brain. These maps, along with a map developed by the surgeon Horsley,[11] which was also based on experiments on monkeys and limited observations in humans, were the first of their kind to be included in *Gray's Anatomy* in 1887.

In 1901, Harvey Cushing, at an early stage in his career, began to map the primate motor cortex with Charles Sherrington and by 1909 had published numerous reports on his experience with intraoperative faradic stimulation in patients being operated under local anesthesia, thus confirming somatotopy of the human cortex along the precentral and postcentral gyri.[12–14] Advances in functional cortical localization were also enhanced significantly by Otfrid Foerster,[8] who, through close collaboration with Oskar and Cécile Vogt, developed a broader, more complex human cortical map from the observations he made during surgeries for patients with epilepsy. In 1928, Wilder Penfield[15] traveled to Germany, which marked the beginning of his collaborative work with Foerster. Over the next decade, Penfield performed extensive intraoperative investigations that would ultimately shape the modern understanding of cortical organization; synthesizing data from more than 163 craniotomies, Penfield eventually simplified his findings in a proverbial homunculus cartoon to convey the relative cortical representation of various anatomic parts.

With a special emphasis on mapping, the pioneers in cortical localization tended to perceive the brain as a collection of discrete functional areas. The original observations of Sherrington and Cushing suggested that the motor cortex is delimited within a narrow precentral strip, a legacy that can still be appreciated in modern anatomy textbooks; however, this degree of localization has perhaps been overemphasized in spite of abundant scientific evidence to support the finding that sensorimotor function is in fact broader and has overlapping cortical representations. Regardless, over the past 150 years, the advancements made by forefathers in neurosurgery initiated an exponential increase in the understanding of cortical representations; the original mapping techniques used by Penfield and others, which involved continuous stimulation for 1 to 6 seconds with a 60-Hz line frequency,[16] set a standard for performing intraoperative neurophysiologic examinations based on the electrical excitability of the human brain, and many original principles of electrocortical stimulation (ECS) remain largely unchanged in current practice.

PRINCIPLES OF DIRECT CORTICAL STIMULATION

The application of ECS as a tool for functional manipulation is based on the resting membrane potential of a neuron, which varies between −60 and −100 mV because of the asymmetrical distribution of charges across the lipid layers of the cell membrane. When the membrane is depolarized (in this case, via local application of an electrode), an action potential is generated. Membrane depolarization is a binary event that, once triggered, exhibits consistent characteristics regardless of the stimulation parameters.

The first and primary concern for ECS is safety, given that electrical stimulation to the cerebral parenchyma can lead to neural damage through multiple possible mechanisms. In addition to the direct effects of power dissipation (ie, heat) on surrounding tissues, prolonged application of electrical current may also result in the toxic accumulation of negative charge at the cathode and electrode dissolution products at the anode.[17]

To address this risk, biphasic impulses are recommended, which compensate for relative depolarization and hyperpolarization of pericathodic and perianodic tissues.[18] In addition, rectangular impulses are used to offset the phenomenon of accommodation, which otherwise occurs when membrane potentials depolarize gradually.

Perhaps the greatest risk of ECS is the induction of seizure. After stimulation, neurons are transiently refractory for 0.6 to 2.0 minutes, after which they enter a short phase of hyperexcitability and are thus at greater risk for unintentional depolarization; in one study, prolonged 60-Hz stimulation produced clinical or subclinical seizures in more than 20% of patients.[19] Most such events are minor or self-limiting, and some have found that the seizures can be terminated more quickly by application of cold Ringer lactate to the cortex.[20] Furthermore, owing to its overall safety, it has been demonstrated that in the absence of epileptiform activity, repeated stimulation with impulses of the magnitude used for motor mapping do not induce permanent histologic changes in the human cortex,[21] and functionality returns to normal levels almost immediately after removal of the stimulus.

Aside from safety, the most valuable characteristics for any method of ECS are reproducibility and precision. Electrical stimuli are characterized in detail by plotting their ability to elicit a tissue response (in this case, neuron excitability). The ideal stimulus, with regard to intensity and duration, at which an action potential is triggered with minimal energy input is termed chronaxis. Chronaxis, by definition, is the shortest duration of an effective electrical stimulus that is equal to twice the minimum strength required for neuronal excitation (rheobasis).[22] These parameters are inherently dependent on the impedance of the tissue being stimulated, which in turn can vary significantly as a function of anesthesia and local pathologic condition, such as tumor.

Factors that affect the precision of depolarizing impulses and thus the spatial resolution of ECS include electrode size and spacing, the type of electrodes that are used, and the current level. Although 2 electrodes are always necessary for producing a current, stimulation is considered to be monopolar when a single electrode is localized to the target tissue and the second grounding electrode is placed at some distance from the site of stimulation.[23,24] Although some assert that the placement of a monopolar electrode is physically unambiguous and thus more precise, pathway of the current from a monopolar source may be less predictable than that from the bipolar approach, in which both the cathode and anode are located close to the target tissue and evoked changes are confined to an elliptical area based on the electrodes.[25–28] However, most recent evidence suggests that this perception of bipolar stimulation may not be completely accurate because the threshold of activation in the region of the cortex between electrodes has been demonstrated to be significantly greater than the areas directly beneath the anode and cathode.[29] There is a relative dearth of literature directly comparing bipolar with monopolar stimulation; however, findings suggest that bipolar mapping is more sensitive in localizing functionality for certain areas such as the premotor frontal cortex.[30] Despite evolving interest in the use of monopolar cortical stimulation for mapping,[24,31,32] bipolar electrodes nonetheless remain standard and tend to be generally preferred in practice.

Current Density Distribution Generated by ECS

Despite the extensive use of ECS both clinically and experimentally, there are relatively few data available concerning what specific cells or parts of cells in the CNS are being activated.[33,34] Although surgeons may generally have a greater interest in the behavioral consequences of stimulation, studies should be communicated in such a way to allow interpretation of findings on a cellular level. Because of uncertainties in tissue properties and geometry, the various numerical models that have been developed to describe the relationship between current density and distance from an electrode are expected to represent only crude predictions. Generally, it is thought that the amount of current applied to a given neuron is directly proportional to the square of the distance between the neuron and the electrode tip.[35] Models that predict distribution of local potential are based on the solution of the Laplace equation:

$$\nabla(\sigma\nabla V) = 0$$

where V is the scalar potential, σ is the conductivity, and ∇ is the gradient vector. Assuming uniform conductivity,

$$\sigma\left(\frac{\partial^2 V}{\partial x^2}+\frac{\partial^2 V}{\partial y^2}+\frac{\partial^2 V}{\partial z^2}\right) = 0$$

with boundary conditions (1) $V = V_o$ and (2) the derivative of the scalar potential is zero at all other points. In this way, the electric fields and current density can be derived as

$$E = -\nabla V$$

$$J = \sigma E$$

where E is the electric field and J is the current density.[27]

The lowest current threshold sites for evoking motor responses from the cortex have been demonstrated to be between layers II and V of the cortex, and, as such, most unit activity is likely encountered when current is applied to layers II, III, and V (ie, the laminae that contain pyramidal cells).[34] On applying an electrical stimulus to the gray matter, recent studies have suggested that axons, but not cell bodies, are primarily activated; however, this area continues to be an active area of research.[36]

ECS MAPPING AND IDENTIFICATION OF ROLANDIC CORTEX

Few modifications have been made to Penfield's original method for mapping the functional motor cortex by ECS.[37–42] Mapping of the motor cortex can occur in the presence or absence of general anesthesia without muscle relaxants; however, in the case in which the patient is awake, both muscle activation and inhibition can be investigated, as negative motor phenomena may assist in the identification of associative areas.[43] In typical present day practice, bipolar electrodes are applied to the cortex, delivering a biphasic square wave pulse between contacts spaced approximately 5 mm apart. During stimulation, cortical areas that correspond to movements are notated and spared during resection; to supplement gross observation, electromyographic (EMG) recordings can also be monitored to increase sensitivity for detecting even low-amplitude muscle responses or when mapping under general anesthesia.[19,44] Motor evoked potentials as measured by EMG may be especially useful when using high-frequency monopolar stimulation or when performing continuous monitoring as with the train of 5 techniques.[45]

Because gliomas may invade cortical as well as subcortical structures, functional boundaries along pathways running in the white matter must also be determined.[46–48] Direct electrical stimulation can also be used in these areas to successfully identify and spare descending white motor tracts.[49–51] Although relatively fewer studies specifically address the subject of identifying deep fibers during tumor resection, recent literature suggests that when both cortical and subcortical sites are delineated with direct stimulation, the boundaries of resection can be safely identified with an acceptable risk of postoperative morbidity. The caveat is that electrical stimulation does not predict deficits secondary to stroke from injury of perforating blood vessels. Stroke occurs more commonly in the white than in the gray matter.

Identification of the Central Sulcus Using Phase Reversal of Somatosensory Evoked Potentials

Through an indirect approach, the central sulcus can be identified by phase reversal of somatosensory evoked potentials (SEP-PR), a method that was first described in surgeries for patients with epilepsy by Goldring and colleagues[52,53] in the 1970s. Since then, several studies have demonstrated the utility of SEP-PR in cortical mapping during tumor resection.[23,54–64] The concept of phase reversal is based on the perceived direction of an afferent neural volley's dipole as detected from the postcentral or precentral sulcus; that is to say, a somatosensory potential recorded from the sensory cortex is the mirror image of the potential detected from the motor cortex. This phenomenon is related to the orientation of pyramidal cells located in the postcentral sulcus, such that somatosensory evoked potentials are negative posteriorly and positive anteriorly.

The physical coordinates that correspond to the point of phase reversal are determined intraoperatively by a strip electrode placed perpendicularly to the approximated central sulcus. After peripheral nerve stimulation, somatosensory evoked potentials are assessed, and the strip grid is adjusted until clear phase reversal of the N20/P20 peak is observed between a pair of electrodes, indicating that the primary motor and sensory cortical areas are located anteriorly and posteriorly, respectively. Using these techniques, SEP-PR localizes the central sulcus, with a success rate greater than 90%, with only occasional failures attributed to the influence of edema or lesions on mass effect and inaccurate placement of the strip grid.[23,62,65] Electrodes may also be placed directly on the surface of the brain for more general purposes. Although traditionally used for defining epileptogenic foci, electrocorticography has recently been suggested as a possible method for motor mapping, based on perceptible changes in power across higher spectral frequencies, also termed the χ-index.[66] Noninvasive electroencephalography has also been shown to provide high-quality signals for high gamma power changes during motor activity.[67]

When combined with ECS, the application of SEP-PR for intraoperative localization has demonstrated a clear impact on preserving function in the resection of low-grade glioma.[50,68,69] Direct cortical stimulation yields excellent spatial resolution, and the predictive value of these techniques for mapping functional motor cortex is well characterized. Several limitations persist, however, and perhaps the most obvious drawback of these

approaches is their inherent invasiveness and requirement for a craniotomy, factors that preclude their use in preoperative evaluation and planning.

Transcranial Stimulation

Transcranial magnetic stimulation (TMS) refers to the use of a magnetic field applied across the scalp and cranium to create a corresponding perpendicular electric field, which can then be used to stimulate or inhibit neuronal activity. This technique is closely related to earlier attempts at transcranial electrical stimulation; however, TMS is generally favored because of the untoward effects that direct current has when passing through superficial tissues and associated pain receptors.[70] Broadly, transcranial approaches possess the significant advantage of generating anatomofunctional information without the need for invasive technique.[71] A growing body of literature suggests that TMS before tumor resection correlates with intraoperative ECS mapping and may be a reliable tool for preoperative mapping of motor function.[72–74]

Like ECS, TMS stimulates specific regions of the brain and thus carries the risk of causing seizures on repetitive pulsing.[75] Furthermore, as with all methods that attempt to map functionality solely based on the causal relationship between stimulation and motor response, TMS and ECS may not comprehensively identify other supportive areas involved in performance, areas which may only be elicited when a patient is subject to a behavioral paradigm.

OBSERVATIONAL MAPPING TECHNIQUES

The development of newer, less invasive approaches to functional mapping has provided neurosurgeons with an unprecedented array of options to use both as alternatives and adjuncts to traditional methods of direct cortical stimulation. When combined with data from intraoperative ECS, perioperative functional neuroimaging has the potential to greatly enhance the general understanding of both neuroanatomical and physiologic associations that a specific lesion might have with surrounding eloquent brain. Moreover, such imaging modalities possess the additional capacity to define regions of the brain that may only be recruited during a motor task, areas which might otherwise be difficult to determine solely based on direct activation through stimulation.

Functional imaging for motor mapping is rapidly gaining traction in the clinical setting, and several forms of technology are currently available, each of which relies on detection of specific types of alterations and the various physiologic properties thereof. The multitude of neuroimaging modalities being developed toward this end include functional magnetic resonance imaging (fMRI), positron emission tomography (PET), magnetoencephalography (MEG), and diffusion tensor imaging (DTI); a description of each is presented in the later discussion and also briefly summarized in **Table 1**.

fMRI

Concomitant with neuronal activity is an increase of blood flow through local cerebral vessels. These changes in cerebral blood flow can be visualized by a method of fMRI that measures blood oxygen level–dependent (BOLD) variations in the area of interest. Because the ratio of oxyhemoglobin to deoxyhemoglobin increases as blood perfusion meets neuronal demand and because this change leads to perceptible elevation in T2 signal, data from BOLD analyses can be used to identify an area of the brain that is active during a particular task as a ratio over control levels observed at rest.[76,77] A map of BOLD activity is then superimposed on a conventional MRI scan to reveal detailed location of the signal relative to the adjacent neuroanatomy.

Depending on the magnitude and rate of neuronal depolarization, signal as measured by fMRI has been shown to vary proportionally[78,79] with a typical spatial resolution of 2 to 5 mm[80];

Table 1
Summary of motor mapping techniques

Modality	Type	Spatial Resolution	Temporal Resolution	Invasiveness
ECS	Stimulation	■ ■ ■	■ ■ ■	■ ■ ■
TMS	Stimulation	■	■ ■ ■	■ ■
PET	Observation	■	■	■ ■
fMRI	Observation	■ ■	■ ■	■
MEG	Observation	■ ■	■ ■ ■	■
DTI	Observation	■ ■	■ ■	■

however, these data may be confounded by technical limitations, including motion-related artifacts and predominant signal from macrovascular venous drainage.[81] Furthermore, because fMRI does not directly detect neuronal activity, instead relying on changes in cerebral blood flow as a surrogate, factors that disrupt normal hemodynamic physiology (eg, lesions, medication, general attentiveness) may ultimately reduce the specificity of analysis and lead to misinterpretation of the acquired data. Early studies suggested that fMRI, when used alone to map functional regions (ie, without support from intraoperative ECS), might be associated with higher incidences of new postoperative neurologic deficits.[82] Conversely, several centers have validated fMRI against ECS in the identification of motor areas with nearly universal agreement between the 2 modalities.[83–86]

Despite the fact that indications and parameters for the use of fMRI are still developing, the role of fMRI in neurosurgical oncology has rapidly expanded, given that it provides many advantages; these include its completely noninvasive nature, ease of acquirement, and its specific ability to localize neuronal activation in deep cortical sulci or other areas that may not be readily accessible by standard cortical stimulation. In current practice, fMRI is successfully integrated as an adjunctive mapping modality in most neuro-oncological cases[87]; for example, one recent prospective study reported that inclusion of fMRI findings in the surgical plan altered treatment approaches and increased the extent of tumor resection for more than 40% of patients.[88] One major shortcoming of fMRI is that it does not map white matter pathways.

PET

Much like fMRI, PET also has the capability to assess changes in cerebral blood flow as a surrogate for neuronal activation and can similarly be used to map motor areas before tumor resection.[89–91] Imaging with PET, however, relies on the administration of a radioactive tracer, such as ^{15}O in the form of $H_2{}^{15}O$, the relative abundance of which indicates an area of increased cerebral perfusion. Radioactive molecules can also be administered in the form of fluorodeoxyglucose F 18, a glucose analogue that, once injected, is retained by tissues with high metabolic activity (ie, tissues found in tumors or, for the purposes of functional mapping, areas of the brain that are activated during task performance).[92]

One possible advantage accompanying PET is the ability to grade a tumor and simultaneously perform motor mapping during a single session.[93] As an imaging modality, PET scanning continues to develop. However, its general clinical use is hindered by technical drawbacks, including poor signal-to-noise ratio, moderate spatiotemporal resolution, and undesirable, albeit low level, radiation exposure. Nevertheless, a broad range of emerging applications for this technology exists, and successful attempts at integration into neuronavigational guidance systems have recently been demonstrated.[94]

MEG

On performing a behavioral paradigm or motor task, synchronized neuronal currents in the cerebrum induce the production of weak orthogonal magnetic fields, which can then be recorded by a biomagnetometer as an MEG signal. Because data during MEG are measured extracranially, the actual location of electrical activity must be estimated based on models that take into account prior knowledge of functional cerebral anatomy. This requirement leads to some inherent ambiguity and thus variable resolution depending on the model used; however, several studies report a generally high degree of correlation for MEG mapping with intraoperative ECS,[44,95–98] and coregistration of these technologies has been integrated into stereotactic databases to support preoperative planning and intraoperative neuronavigation in multiple settings.[99–102]

Perhaps the most demanding aspect of MEG technology is that the magnitude of signal derived from ionic flow within brain tissue is exceedingly weak. Therefore, great efforts must be made to minimize influence of external sources, including the earth's natural geomagnetism and other magnetic fields that are produced by standard hospital equipment. The need for specialized personnel and heavily shielded rooms makes the purchase and maintenance of an MEG apparatus extremely costly, thereby restricting its current availability and hampering its implementation in common practice.

Anisotropic DTI

Recent developments in DTI have made it possible to visualize the trajectory of subcortical white matter bundles, as well as to obtain data regarding the potential effects of proximal neoplasms on the integrity of these tracts. The diffusion of water molecules throughout the cerebrum is anisotropic (ie, flow is directionally dependent) and is greatest along vectors tangential rather than perpendicular to axon fibers.[103] As a molecule of water moves along a neural fiber, MRI is used to derive the direction of maximum diffusivity, which in turn is

used to determine the orientation of the major principle axis of white matter tracts traversing each voxel.

Disruption of normal anisotropic patterns can be detected in the presence of a tumor because of the effects that neoplastic lesions have on water molecule diffusivity. Signals, as evaluated by DTI, can be altered either in intensity or position, and variations in these parameters may suggest different pathologies. For example, a decreased signal with normal direction and location is thought to indicate vasogenic edema, whereas displaced or complete loss of anisotropy may correspond to mass effect or obliteration of white matter anatomy by direct tumor infiltration.[104]

Because DTI does not independently provide functional data per se, its use in motor mapping is often in conjunction with ECS[105] or fMRI.[106–110] This coregistration allows the neurosurgeon to approximate fibers spatially that are associated with cortical areas and other eloquent tissues involved in motion or task execution. In current practice, structural data from diffuse tensor analyses are more commonly used in the preoperative setting; however, a few recent studies have integrated DTI with intraoperative neuronavigational systems with some success.[111,112]

Although DTI is the only available technology specifically designed to image white matter, its widespread clinical use has been hindered by certain technical limitations including poor signal-to-noise ratio and spatial resolution.[113] Furthermore, although DTI reliably visualizes major subcortical structures with relative ease, some reports suggest that it is a less consistent imaging modality for other areas, including the optic tract, fornix, and tapetum.[104]

SURGICAL CONSIDERATIONS FOR FUNCTIONAL MOTOR MAPPING

As discussed earlier, various complementary techniques are available for use in motor mapping, each of which uses a separate set of electrophysiologic principles, thus yielding distinct types of data to assist in the preparation and execution of an operative approach. The clinical use of these technologies is increasing dramatically in neuro-oncology, thus meeting the need to tailor treatment according to anatomofunctionality that can be significantly altered because of the presence of space-occupying lesions in and around the area of interest. It has been shown, for example, that motor-associated cortex may be unpredictably displaced by tumors located in perirolandic areas, either as a result of direct mass effect or from cortical plasticity associated with compensatory cerebral reorganization of function in and around the lesion.[107,114]

Although combinatorial imaging for preoperative motor mapping clearly possesses multiple applications, perhaps the greatest challenge in optimizing the information gleaned from these studies is the concept of brain shift. Because of mechanical and physiologic strain that occurs during a neurosurgical operation (eg, edema, cerebrospinal fluid and blood loss, body position), the position of the brain can change significantly, leading to anatomic discrepancies with preoperative imaging of more than 1 cm within the first hour of surgery.[115–118] Moreover, these changes have been shown to variably affect cortical anatomy and deeper subcortical structures, further hindering extrapolation of preoperative data to intraoperative relevance.[119] Given the dynamic character of peritumoral cortical organization, strategies have been developed to combine intraoperative imaging with preoperative data to account brain shift phenomena[120]; however, despite these advances, the classical method of direct intraoperative mapping with ECS still remains paramount.

SUMMARY

The landscape of technologies available to assist in the planning and execution of safe maximal tumor resection is rapidly expanding. Although the traditional approach of motor mapping by direct ECS is still the most widely applied technique, the clinical use of newer, less invasive imaging modalities such as fMRI and DTI is currently evolving and has in many cases been successfully implemented with varying degrees of validation; similar advances are also being explored in the mapping of sensory, language, and cognitive functions with promises of enhancing care and improving outcome after surgery. In the future, it will fall to neurosurgeons to gain familiarity with these widely complementary sources; the rapid synthesis and interpretation of such abundant and highly processed material will be necessary to realize its great potential and to translate benefits directly to patient care.

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