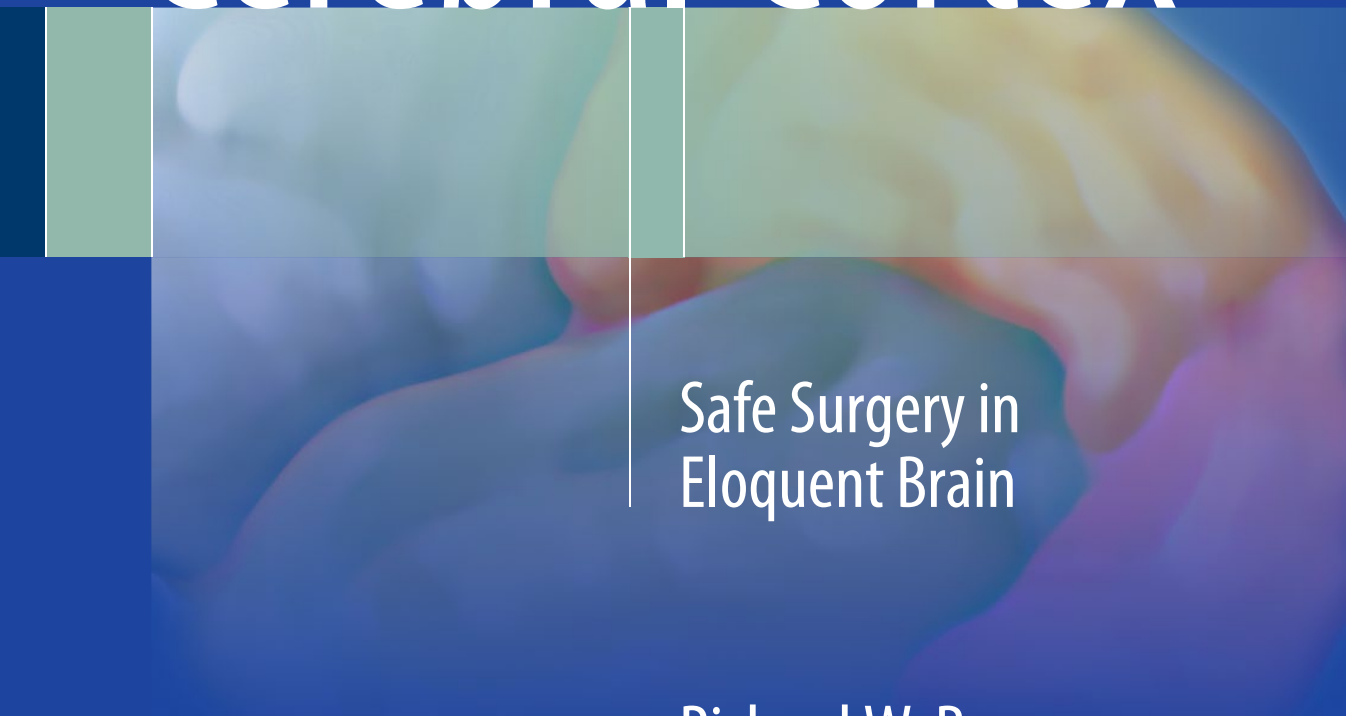
# Functional Mapping of the Cerebral Cortex



## Safe Surgery in Eloquent Brain

Richard W. Byrne
*Editor*

Springer

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*I would like to thank the contributors to this volume who saw the need for a comprehensive, practical publication on this important topic. I would like to thank Michelle Grand and TJ Enno from the Department of Neurosurgery at Rush for their editorial assistance as well as the production and editorial team at Springer including Samantha Lonuzzi, Lesley Poliner, and Rekha Udaiyar. I would like to also thank my mentors in cortical mapping over the years including Walter Whisler, Andre Olivier, George Ojemann, and Mitch Berger. All have been very generous in sharing their time and experience with me. Finally I would like to thank my family, my parents, my wife Armita, and my children Nika and Kayla for their patience with me while I took time to write and edit this book.*

Richard W. Byrne, M.D.

# Foreword

It is an honor and pleasure to be asked to write a foreword to this splendid volume on *Functional Mapping of the Cerebral Cortex*.

After having spent 35 years performing resections of epileptic foci, and trying in each case to determine with precision where we are over and within the brain, it is refreshing, instructive, and useful to see such an updated gathering of practical information on this important topic.

Techniques of cerebral mapping were developed mostly for resection of epileptic foci and brain tumors. While the early history of the brain motor responses upon stimulation reflects the collective and cumulative efforts of many neurosurgeons, the confirmation of the sensory strip resulted from the work of a single man, Harvey Cushing, in 1909.

If one had to pick a single work on cerebral mapping characterized by its thoroughness and usefulness, it should be that of Penfield and Boldrey of 1939. It illustrates the early and systematic work of Penfield and collaborators at the Montreal Neurological Institute. Over the years, the so-called Montreal procedure was used for all types of resections but mostly for temporal lobe epilepsy. Stimulation studies were systematically carried out under local anesthesia to identify the sensory strip, mainly the tongue area, to determine the position of the central sulcus and the extent of the resection along the Sylvian fissure. Identification of speech centers was more complicated, giving rise often to negative responses and anxiety. The parameters used became of paramount importance.

There came a point in time where enough physiological data gathered could be transposed to morphology. To what extent the surgeon can nowadays rely on morphological landmarks and preoperative data only is of crucial importance. With the advent of three-dimensional reconstruction and the integration of physiological findings, the process of cerebral mapping starts before the actual surgical procedure. Using navigation, the preliminary identification of the motor, sensory, and speech centers can be used for centering the craniotomy and zooming on the areas to be visually recognized and stimulated. This approach has led to smaller craniotomies often to the detriment of electrocorticography. However, in spite of their usefulness and precision, these techniques have not replaced the need for peri-operative confirmation. They rather serve to optimize the whole process of localization.

A significant advantage of peri-operative stimulation is the need to have the patient awake and cooperating, which allows not only for the acquisition of physiological data but also for the detection of an eventual early and reversible deficit. Close collaboration with anesthesia is essential and the expertise in conducting awake procedures cannot be overemphasized.

A safe removal does not relate strictly to the extent, compactness, and cruciality of the tissue resected but also to the consequence of vessels occlusion deliberate or not, venous or arterial, in the actual process of resection.

The various techniques described in this book will help the young neurosurgeon interested in the resection of epileptic foci and brain tumors to develop his own way of finding out precisely where he is over and within the brain, recognize eventual pitfalls, and avoid complications.

Montreal, QC, Canada
June 2015

André Olivier, M.D., Ph.D.

# Preface

The purpose of this book is to give practical guidance to clinicians and scientists (neurosurgeons, neurologists, neuroradiologists, neurophysiologists, neuropsychologists, and those in training in these disciplines) in their encounters with the difficult and commonly encountered problem of treating patients with lesions in eloquent cortex. These cases represent some of our greatest challenges in clinical medicine, but they also represent our opportunity to potentially make the greatest positive impact for our patients. Through careful consideration of the indications for an intervention, proper choice of brain mapping technology, and proper execution of brain mapping techniques, we are now able to offer some of our most challenging patients a safer and more effective intervention. This is made possible through a combination of advantages that brain mapping offers. First, brain mapping techniques may identify the cases in which we should not offer an invasive procedure, saving patients from operative morbidity. Second, brain mapping can show us when we can offer a more radical procedure than indicated by our imaging technology and by presumed functional localization. Finally, brain mapping can show us when we need to stop in order to avoid permanent morbidity by giving preoperative localization clues and intraoperative immediate feedback on the impact of our intervention.

The art and science of brain mapping once was the purview primarily of epilepsy surgeons. In fact, it is in this aspect of my practice that I learned and became comfortable with the various techniques of brain mapping. As both brain mapping and operative technology have advanced over the past 25 years since I first participated in a brain mapping operation, it has become more clear that this discipline could be adopted more widely by practitioners who rarely encounter operative epilepsy conditions, but rather commonly encounter intra-axial lesions such as glioma, metastasis, and congenital and vascular lesions. In fact, intra-axial lesions have become a common indication for brain mapping. Widespread acceptance and adoption of brain mapping techniques has occurred over the past 10 years. However, many practitioners have not had extensive training in brain mapping techniques and lack an understanding of the advantages and limitations of the various brain mapping techniques available. As such, many clinicians seek training in brain mapping in order to bring the advantages of brain mapping to their patients. While teaching and training residents and practicing clinicians in brain mapping, it became apparent to me that there was a need for a practical guide to brain mapping, bringing together the extra- and intraoperative techniques and technologies. This textbook is our

effort to provide this guide. In doing so, I have partnered with many of the most respected leaders in this field who have generously given their clear and careful practical guidance in their particular expertise. I am grateful for their generosity in sharing their time and experience.

The structure of the textbook emphasizes the progression of the various ways that eloquent cortex can be identified. First and foremost is anatomy. In this chapter the classic anatomic-functional correlations essential for any neurosurgeon, neurologist, or neuroscientist to achieve an understanding of brain mapping are described. As neuroanatomy is highly conserved in evolution, knowing the sometimes subtle but reliable nuances of neuroanatomy is all that is necessary to proceed with safe treatment in many cases of nonlesional or lesional neurosurgery remote from eloquent cortex. This may also be the case in a limited number of well-circumscribed lesional cases located at the surface in and around eloquent cortex. There are, however, limits to this anatomical localization. Certainty of anatomic localization is often limited in identifying areas necessary for speech function. Variable localization and in some cases even lateralization of speech function introduces uncertainty in an area that requires near certainty. Furthermore, the nature of lesional neurosurgery necessarily causes distortions in normal anatomy, and in some cases neural plasticity may cause relocation of function. Because of this, preoperative and intraoperative adjuncts in functional localization are often necessary.

The various forms of image-based functional localization have evolved over time to become more reliable and more available to practitioners. This has paralleled rapid advances in imaging technology. The history of the development of functional localization highlights the necessary reliance of brain mapping on the progress of applied technology. Early mapping efforts focused on direct recording of evoked potentials and direct cortical stimulation. Indirect noninvasive forms of mapping based on functional metabolic, electrical, and magnetic signals have continued to expand our understanding of brain function. Their ability to display all brain regions involved in a cerebral function has been their strength, but also their weakness. From a research perspective, this high level of sensitivity is ideal. From an operative decision-making standpoint, this is a weakness.

The ideal mapping technique from the standpoint of a clinician balances sensitivity and specificity for localization of truly essential cortex, as opposed to all merely involved cortical areas. Because of this, a major focus of this textbook is intraoperative and extraoperative cortical stimulation mapping techniques and practical decision-making. The described technique of "negative mapping" is described extensively in one chapter and emphasizes the advantages of this technique in brain tumor cases. Cortical stimulation mapping, with or without the awake technique, remains our gold standard in cases of lesional and nonlesional pathology involving eloquent cortex. This mapping may be done intra- or extraoperatively and can be combined with extraoperative imaging and metabolic mapping technologies. Because cortical stimulation mapping identifies essential cortex, and imaging technologies display the wider areas of diffusely involved functional cortex, the techniques are complementary. We have gathered several chapters with slightly different points of view on indications, protocol, and technique to highlight the variety

of ways cortical mapping can be used in both lesional and nonlesional epilepsy and brain tumor surgery. These chapters along with chapters highlighting indications, extraoperative mapping, intraoperative evoked potential monitoring, and anesthetic techniques offer the clinician and scientist a guide to the various options available for modern brain mapping. We have highlighted key points and have provided illustrative cases demonstrating practical applications of brain mapping.

We have also included chapters hinting at what may become a growing part of the future of brain mapping. Intra- and extraoperative techniques of gamma frequency EEG mapping and extraoperative transcranial magnetic stimulation are quickly advancing through the research phase and may soon become a routine part of clinically applied brain mapping. Although today's practitioners are becoming well versed in the accepted techniques and technology available now, we will all welcome the day when these and other technologies will mature and help us make caring for patients with pathology in eloquent cortex safer and more effective.

Finally, I would like to end with a word about clinical judgment. No matter what technology is available to clinicians treating patients with pathology in eloquent cortex and eloquent white matter connections in the brain, it must be emphasized that it takes experienced clinicians working in multidisciplinary teams with a well-informed patient to weigh decisions to operate, or not operate in these cases. The same applies to the choice of which technique or technology to employ. No technique that we describe here completely guards against operative morbidity. In fact, operating in eloquent cortex commonly leads to temporary morbidity that must often be accepted and anticipated by the practitioner and patient alike. A judicious balancing of the risks of an intervention versus the risks of the natural history of a pathological process, whether it is epilepsy, tumor or other, is the proper starting point. The final decision to intervene will in turn be made based on the wide variety of clinical factors that treating clinicians routinely encounter in treating these patients, upon their comfort level with the techniques, the resources available at their institution, and upon the wishes of the patient.

Chicago, IL, USA Richard W. Byrne, M.D.

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# Historical Perspective on the Development of Cerebral Localization, Cerebral Cortical Motor Stimulation, and Sensory Evoked Potentials

James L. Stone, Ashley N. Selner, and Vimal A. Patel

*John Hughlings Jackson* (Fig. 1), often called the "The Father of Neurology" was a keen-eyed observer with a passion for detail and brooding intelligence, which enabled him to see general laws emerging from details [1]. This remarkable British theorist by 1861 deduced motor activity to be the basic function of all nervous systems, proposed the anterior and posterior cerebrum being predominately motor and sensory respectively, and that motor and sensory brain centers represent sensorimotor movements not muscles. His thoughtful analysis based on the study of seizure patterns and neurological abnormalities demonstrated the somatotopic distribution of human motor and sensory functions across the human cerebral cortex [1, 2]. He further believed that higher levels of integration evolved to exert more extensive and progressively finer control … the cerebrum and cerebellum invariably work together … coordination being a function of the entire nervous system [1, 2].

Also in 1861, *Paul Pierre Broca* of France demonstrated clinicopathologically that the third left frontal convolution was necessary for motor/articulate speech and based on such localization 10 years later trephined and drained a traumatic abscess [3]. However, the concept of cerebral localization of function remained controversial for the next 10–15 years although evidence accumulated in animals including lower primates and man.

In 1869 or early 1870 *Eduard Hitzig* a budding neurologist and electrotherapist in Berlin, Germany found that delivering galvanic currents between the ear lobe and mastoid process of patients induced involuntary ocular movements and vertigo [4]. Believing he had electrically stimulated a brain center (later work disclosed this was probably peripheral vestibular in origin) he sought the help of *Gustav Fritsch*, a young physician with research experience [4]. During the year 1870 Fritsch and Hitzig in Berlin working with dogs, and following their lead in 1873—*David Ferrier* in England working with monkeys—proved electrical stimulation applied directly to the pre-central frontal cortical surface produced contralateral motor movements. Conversely ablation of this area resulted in contralateral paralysis [5–8]. Fritsch and Hitzig evidently used galvanic current (they talk of a chain of batteries, anode, and cath-

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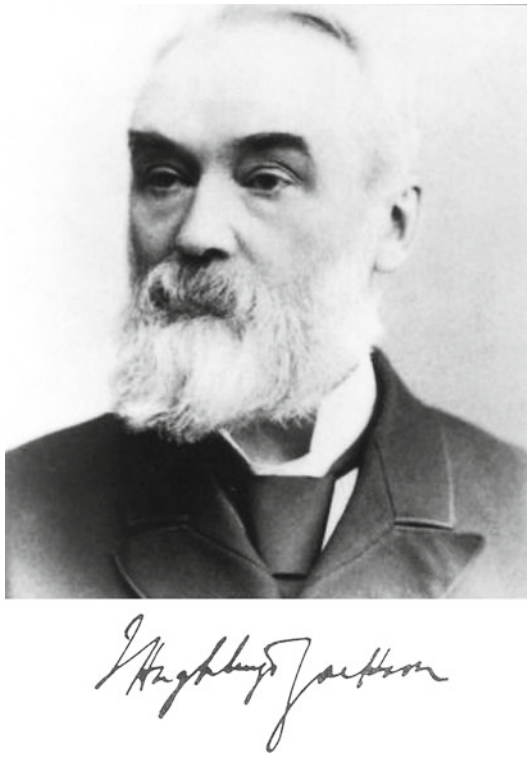

**Fig. 1** John Hughlings Jackson (1835–1911). From David W. Loring, History of Neuropsychology Through Epilepsy Eyes, Archives of Clinical Neuropsychology, 2010, by permission of Oxford University Press

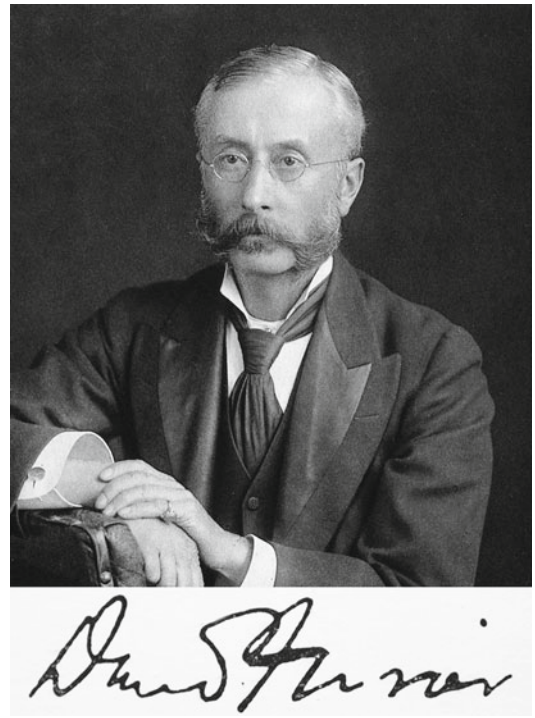

**Fig. 2** David Ferrier (1843–1928)

ode, but also used a secondary induction "spiral") and only the frontal (anterior) cortex produced motor responses which they mapped out with precision [9]. Ferrier's choice of faradic over galvanic stimuli was considered an important advance over the earlier work in elicitation of sustained and deliberate, instead of twitch-like or tetanizing movements [10].

In 1874 *Roberts Bartholow* of Cincinatti, Ohio, a neurologist familiar with electrotherapeutic methods and the above research, delivered faradic currents through insulated needles placed in the postcentral/parietal lobes of a consented volunteer with carcinoma of the scalpand erosion of the skull. He obtained contralateral sensory phenomena, motor movements, and seizures [11–14].

*David Ferrier* (Fig. 2) went on to extend his convincing cerebral localization work to studies on apes [5, 6, 10, 15], and tremendous research activity ensued world-wide to elucidate the physiology and anatomy of the nervous system. Ferrier, additionally a highly respected London neurologist predicted "the unfailing safety of experiments upon animals made it clear that similar results would soon be achieved on man himself" [16]. Charles Sherrington (see below) a noted British neurophysiologist working several decades later remarked "(Ferrier's) work was the actual pioneer-step leading to modern cerebral surgery … (and thus) to Ferrier rather than to the surgeons is primarily due the origin of modern cerebral surgery" [17].

In the 1880s *Victor Horsley* (Fig. 3a), an academic London surgeon, began extensive cerebral cortical motor mapping and pyramidal tract studies in the monkey and higher apes using direct cortical stimulation. Horsley like Jackson came to believe the pre- and postcentral gyri were functionally sensorimotor and obtained similar motor responses from each region [18–20]. In early 1886, Horsley was given a surgical appointment to London's National Hospital for the Paralyzed and Epileptic at Queen Square.

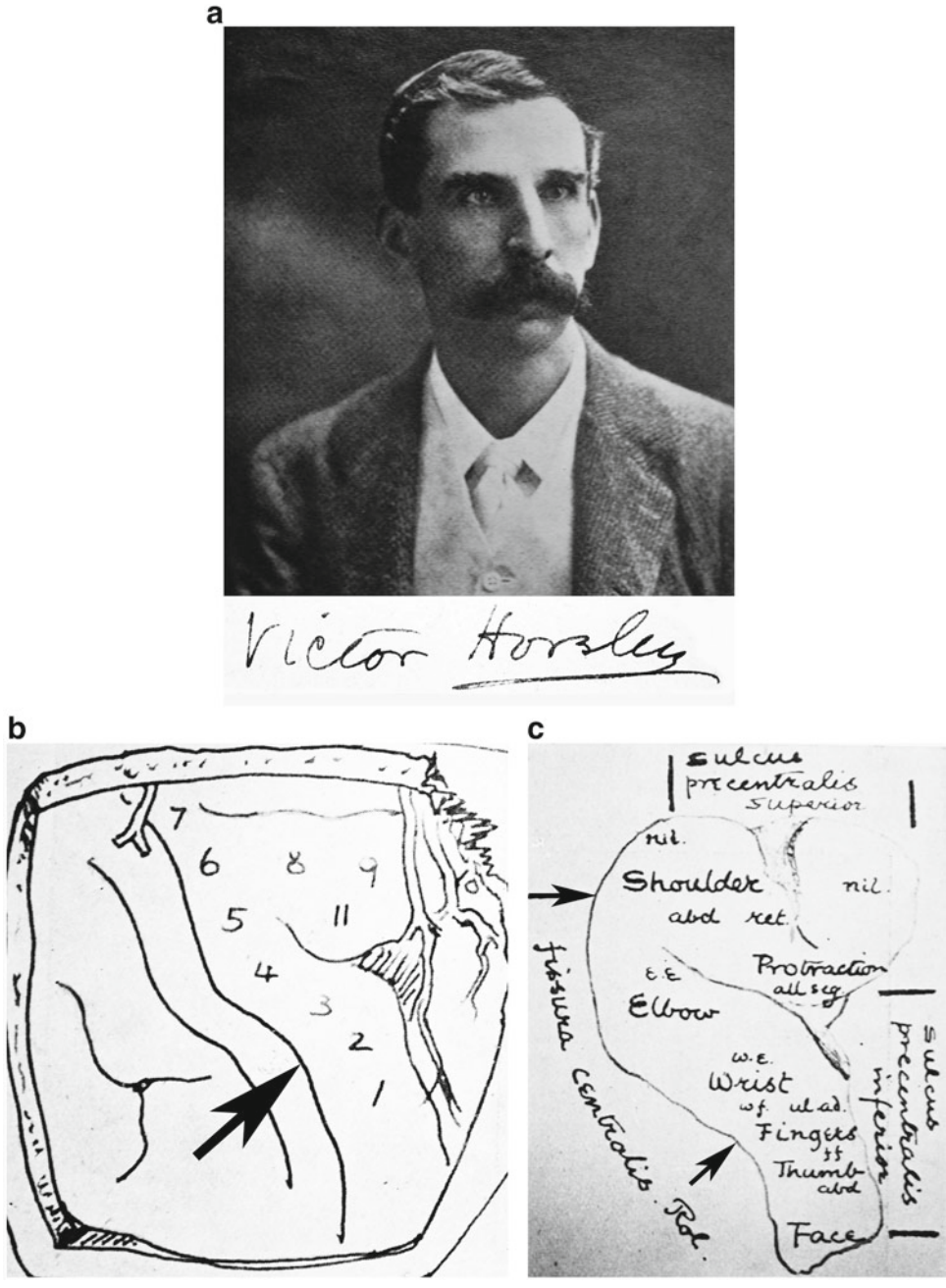


**Fig. 3** (**a**) Victor Horsley (1857–1916). (**b**) Sketch of a right-sided craniotomy in 1908 showing areas of faradic motor stimulation of the pre-central gyrus. *Arrow* shows central sulcus. (**c**) Sketch of the gross, excised central gyrus. Focal seizures of the left arm ceased, and 1 year later partial recovery of left arm voluntary function, astereognosis, and slight tactile anesthesia of the left hand [18]. Reproduced from (The British Medical Journal, The Linacre Lecture on the function of the so-called motor area of the brain, Victor Horsley, volume 2, 1909) with permission from BMJ Publishing Group Ltd

Hughlings Jackson, a senior Queen Square neurologist visited Horsley's laboratory and was "greatly impressed by the certainty and precision with which Horsley by gently faradizing a small part of the cortex could bring a monkey's thumb and forefinger into opposition. At once Jackson recalled a patient … who developed epilepsy, each attack commencing with such a movement as he now saw evoked in the monkey by electrical stimulation." [21].

Beginning in 1886 electrical stimulation of the cortex during operations on patients was extensively performed by Victor Horsley in London (Fig. 3b), and the following year by *W.W. Keen* in Philadelphia who was the first to obtain a response in the leg [22–27]. Horsley's first three craniotomy patients at Queen Square had intractable seizures. Each had a lesion within or near the motor cortex—a cortical scar, small tumor, or cyst—and responded favorably to localized excision [21]. Excision of cortical "motor points," was then believed to be a promising treatment for focal motor seizures. Additionally, Horsley considered the identification of cerebral motor points a definitive aid to localizing subcortical lesions in patients with motor findings [28]. Consequently cortical motor stimulation was highly instrumental in initiating and building confidence in the new special field of neurological surgery [29]. From this work Horsley, as well as Jackson who reached his conclusions from close clinical observations, were convinced the pre- and postcentral gyri were functionally sensorimotor and similar motor responses could be obtained from each region [18, 19].

Beginning in the mid 1880s the neurophysiologist *Charles S. Sherrington* (Fig. 4) and associates began extensive experimental study of brain and spinal cord reflexes in regard to the pyramidal tract, motor control, and feedback, and about 1900 began cerebral cortical stimulation studies utilizing about 20 great apes (anthropoids—gorilla, orangatang, chimpanzee) [30, 31]. Using unipolar faradization by induction coil stimulation they obtained clear motor responses in the higher apes they believed were more distinctive and easier to elicit from the pre-central cortex

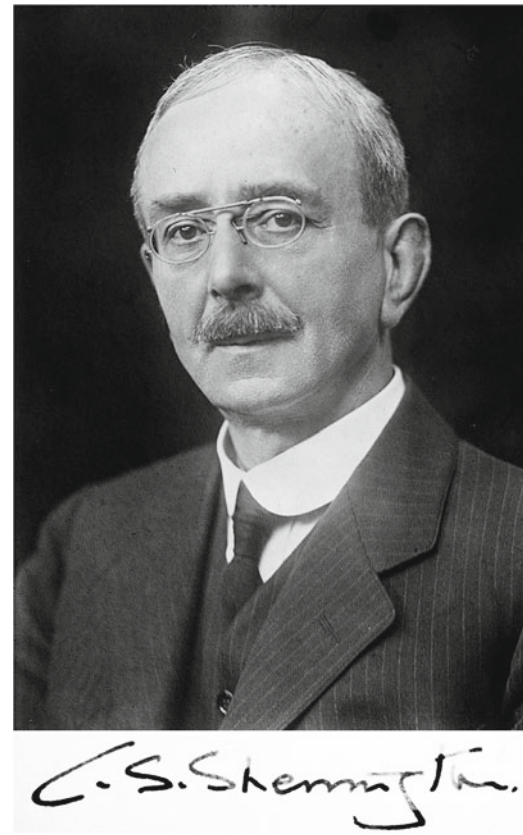

**Fig. 4** Charles S. Sherrington (1857–1952)

composing the anterior wall of the central sulcus of fissure of Rolando and adjoining surface of the pre-central gyrus [31, 32]. The young, recently trained American surgeon *Harvey Cushing* (Fig. 5a) visited Sherrington for the month of July 1901 and assisted with the surgical exposure and cerebral cortical stimulation studies on these anesthetized but arousable great apes [7]. Sherrington explained to Cushing "the disparity of his and the old observations is that Ferrier, who did the earliest work on the monkey expecting wide areas [of representation], used strong currents and succeeded in calling out responses which, [Sherrington says], however, were not as distinctive as the ascending frontal (pre-central) convolution responses" [7]. In regard to Cushing's question as to the primary cortical area for cutaneous sensation, Sherrington suggested it was the postcentral gyrus and Cushing in a letter to his father went on to say "the chimpanzee yesterday

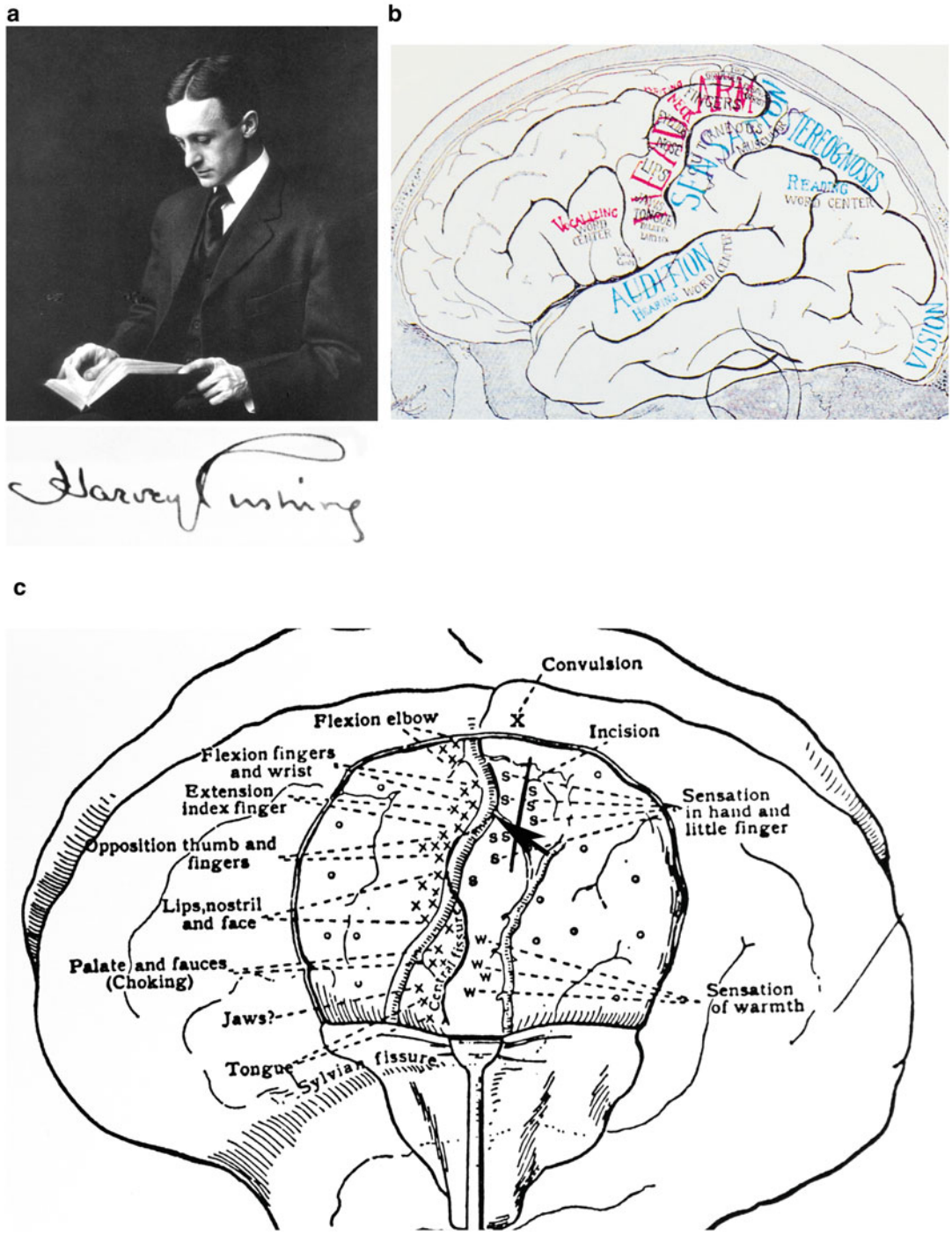


**Fig. 5** (**a**) Harvey Cushing (1869–1939). (**b**) Drawing of primary motor and sensory cortex, 1908 [33]. (**c**) Drawing of pre- and postcentral gyrus, showing central sulcus of Rolando (*arrow*) and genu [34]

responded like a sensory response when this area was stimulated. The motor responses are slow and different from the motor cortex ones, but each time when the animal was stimulated there it opened its eyes … evidently the recipient of some great stimulus." [7].

Cushing returned to Johns Hopkins, gained further experience in neurological surgery and human cortical stimulation (Fig. 5b) [34]. At that point in his career he had performed cortical stimulation for motor point mapping and central sulcus localization in more than 50 anesthetized patients in the removal of tumors or other lesions [34]. A few years earlier an unanesthetized awake patient, during preliminary palpation of the exposed postcentral region, surprised Cushing by reporting a "focal sensory attack" or sensory paresthesia [35]. This prompted Cushing to report two epileptic patients with focal sensory auras who underwent unipolar faradic stimulation of the postcentral gyrus, in the hope of improving the operative localization of the central fissure of Rolando, as well as improve localization and removal of "subcortical irritative lesions of the immediate postcentral field" (Fig. 5c) [34]. Both were operated awake in a second stage under local anesthesia. Very brief faradic stimulation was applied, and with the same current strength—motor and somatosensory impressions (numbness, tactile feeling) were obtained only from the pre- or postcentral gyri respectively. Although focal and generalized seizures occurred during stimulation, and in one patient stimulation of the postcentral gyrus produced transient focal/partial sensory phenomena identical to their typical sensory seizure aura—Cushing was unable to clearly delineate or remove a lesion in either patient [34].

Several of Cushing's above observations are of particular note despite being among the earliest human cases of clear somatosensory responses from postcentral gyrus stimulation. In his first case, Cushing comments upon "the characteristic configuration of the central fissure," and stimulation of the precentral gyrus gave "an opposing movement of thumb and fingers from points opposite to the unmistakable genu," and "below the evident middle genu" stimulation produced contraction of the contralateral face [34]. If not obscured by sulcal veins, this "omega-shaped landmark or genu" is consistently seen between the superior and middle frontal gyri bulging into the central sulcus (convex posteriorly). The gyral banks of this sulcal region were noted by Broca and represent the pre- (primary motor) and post- (primary sensory) central cortical hand areas [36, 37].

In these two cases the evoked sensations were limited entirely to the hand and arm, and Cushing questioned whether this means there is an "especially wide cortical representation for afferent impulses from this region" or whether their hand and arm were unduly excitable owing to their seizure tendency in these particular patients [34]. At that time motor and sensory cortical homunculi had not yet been constructed. In the second case, the central sulcus was less typical and obscured by a prominent vein but Cushing obtained motor responses from the gyrus anterior to the vein. This additional recording of sensory responses on the posterior gyrus stimulation for Cushing confirmed the correct location of the central sulcus [34].

*Fedor Krause* (Fig. 6) was a well-known late nineteenth and early twentieth century general and neurological surgeon from Berlin, Germany who was strongly influenced by the classical cortical stimulation work of Fritsch and Hitzig, Ferrier, and Sherrington [38–40]. Krause as early as 1893 began human cortical stimulation under partial anesthesia and used monopolar faradic stimulation, at the lowest possible current for motor stimulation to avoid unwanted stimulation of adjacent cortical regions [38–40]. Krause had extensive experience with human motor stimulation and produced a quite detailed motor map. Being highly supportive of Sherrington's work in the higher apes, it is likely any human motor responses from stimulation posterior to the central sulcus would have been considered by Krause secondary to current spread. With neurologist Hermann Oppenheim they very carefully documented the clinical results of many cortical excisions including complex sensory and perceptual findings, agraphias, and noted lesion variability in producing aphasia [39, 40]. Krause elevated an old frontal depressed skull fracture in a patient with frequent seizures beginning with head turning to the opposite side. Cortical stimulation of

**Fig. 6** Fedor Krause (1857–1937)

the second frontal gyrus anterior to the precentral region reproduced the aversive head motion heralding the attack, and the patient was greatly improved after decompression. Krause corroborated the fact that the central region contains separate motor and sensory centers "the relation of the anterior central convolution to the posterior is that of one twin to its fellow" [40]. Krause mapped cortical motor function to aid with the safe removal of cerebral tumors, and in cases of refractory epilepsy to reproduce the focus of Jacksonian seizure onset [40]. By 1910 he reported 29 patients in whom he had identified and excised a cortical focus or "primary spasmic center," thereby "diminishing the seizure tendency" [38].

Like Cushing, Krause was concerned over uncertainty in locating the central sulcus of Rolando related to venous variability or obscuration of the sulcus. Krause more definitively concluded "at the operating table we possess in faradic simulation of the cerebral cortex an indispensable method of great diagnostic value. It offers the only possibility for exact localizations in the anterior central convolutions [40].

An extraordinarily talented German neurologist and neurological surgeon *Otfrid Foerster* (Fig. 7a) of Breslau, Germany, gained experience in electrical stimulation of the human cortex beginning in 1905. He was a highly trained neurologist and self-taught neurosurgeon who began by operating on peripheral nerves during World War I. Many of his earlier patients were war veterans with intractable posttraumatic epilepsy. By 1931 he had gathered information on more than 150 cases of cerebral cortical stimulation and his experience exceeded that of any other neurosurgeon [42–46]. Foerster operated predominately under local anesthesia to facilitate cortical mapping using unipolar galvanic stimulation to reproduce the subject's clinical seizure, and excised a clear cortical focus or scar. Foerster and Krause both emphasized the importance of keeping the cortical surface dry and draining or sponging away any pooling of cerebrospinal fluid or blood [40, 43].

In regard to pre-central gyrus stimulation, Foerster noted that the motor threshold current to elicit a response in area 4 (0.3–6.0 mA, average about 0.5–1.5 mA) was lower than that of motor area 6a, but there was much individual variation. He determined the effects of stimulating either area 4 and area 6a both depend on the integrity of the pyramidal tract, but he came to believe area 6a was dependant on a relay utilizing area 4 [43, 44].

Postcentral gyrus, area 3,1,2 stimulation usually produced paresthesias and seldom pain. Here Foerster found a detailed somatotopic distribution similar to the pre-central gyrus. In addition, areas 3,1,2 reacted to stimulation not only with sensory effects, but motor effects as well. These motor effects additionally resembled those of pre-central convolution stimulation as each focus responded with an isolated movement of a single segment of the extremities or single part of the body. However, the electrical current threshold to evoke motor responses from the postcentral convolution was markedly (2.0–4.0 mA) higher than that of the pre-central gyrus (average motor threshold: postcentral—3.0–4.0 mA; pre-central—0.5–1.5 mA). The higher the threshold of area 4, the correspondingly higher the motor threshold of areas 3,1,2 [43, 44].

Foerster reminds us that destruction of the postcentral area is followed not only by defects in sensibility but also a disturbance in motility. Coordination of movements depends on the

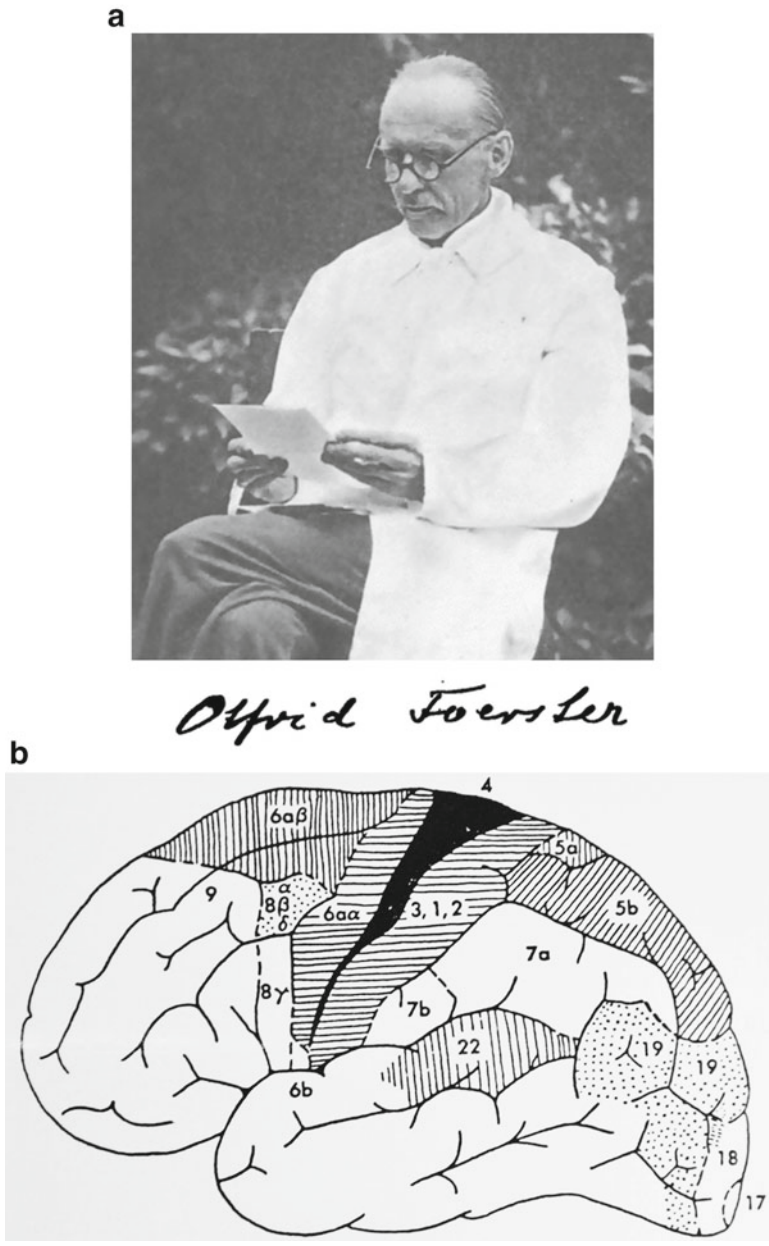


**Fig. 7** (**a**) Otfrid Foerster (1873–1941). With kind permission from Springer Science + Business Media: Archiv für Psychiatrie und Nervenkrankheiten, 1942, Otfrid Foerster. (**b**) Foerster's 1934 stimulation map of the pre- and postcentral gyrus. Together they are designated area 4 (*solid black*), 6, 3, 1, and 2 (*horizontal lined areas*) as motor cortex [41, 42]

integrity of afferent pathways and "the ataxia observed in cortical lesions may resemble that observed in lesions of the posterior columns of the cord … or cerebellar system … characterized by rhythmic oscillations … commonly called intention tremor." [43].

Foerster came to the conclusion that the isolated motor effects obtained by stimulation of the postcentral gyrus depend on the integrity of area 4 and the pyramidal tract. He determined that the postcentral gyrus has no individual direct motor pathway for isolated movements of single muscle groups, similar to the dependency of area 6a upon area 4 and the pyramidal tract. Motoric transfer from 3,1,2 to area 4 depends on the integrity of "U" fibers which originate from the deeper corti-

cal layers of area 3,1,2. Abrasion of the superficial cortical layers of area 3,1,2 does not prevent the effect of electrical stimulation, but after excision of the deeper layers the isolated movements can no longer be produced from the postcentral area. If area 4 or the pyramidal tract is destroyed—extrapyramidal pathways for mass, synergestic movements involving many muscle groups descending to the spinal cord and muscles, could be used by area 3,1,2 as well as the dependant area 6a. [43]. Foerster suggested as soon as the precentral cortex ipsilateral to the affected limb begins to play a role in compensation, some individualized movements recover [47]. Foerster saw these alternative pathways as a means for recovery of motor function after cortical injuries, realizing such motor recovery is often more proximal, synergistic, and less fine distally [43, 44]. Not surprisingly, a number of Foerster's views on motor recovery after cortical damage have been substantiated in recent years [47].

Foerster constructed a more extensive map (Fig. 7b) depicting cortical representation of motor and sensory functions, including additional or supplementary motor and sensory sites beyond the pre- and postcentral gyri and discussed his experiences stimulating all major cortical regions [38, 41–44, 47, 48]. He was among the first to diagnostically utilize electrocorticograhy (ECoG), to clearly correlate electrographic and clinical seizures, and described slow waves overlying brain tumors [13, 14, 44, 47–50]. In the 1920s and 1930s many European and American neurosurgeons were welcomed at Foerster's Neurological Institute at Breslau, and stimulated by his brilliance, depth of knowledge, and neurophysiological approaches. In 1930, Foerster completed an extended visit to Cushing in Boston, as a "Surgeon in-Chief pro tempore."

Foerster's electrical stimulation studies on the human cortex resulted in a dramatic shift away from a narrower pre-central strip motor localization emphasized by both Sherrington, and his student Cushing—to a much broader and complex motor representation as put forth decades earlier by Jackson and Horsley [41, 44, 48]. Sherrington's cortical studies were based solely on animal experiments but he clearly appreciated the higher current levels to evoke motor responses from the postcentral gyrus [7, 10, 42, 46].

From the mid-1930s onward, neurosurgeon Wilder Penfield (Fig. 8a) of Montreal, who had

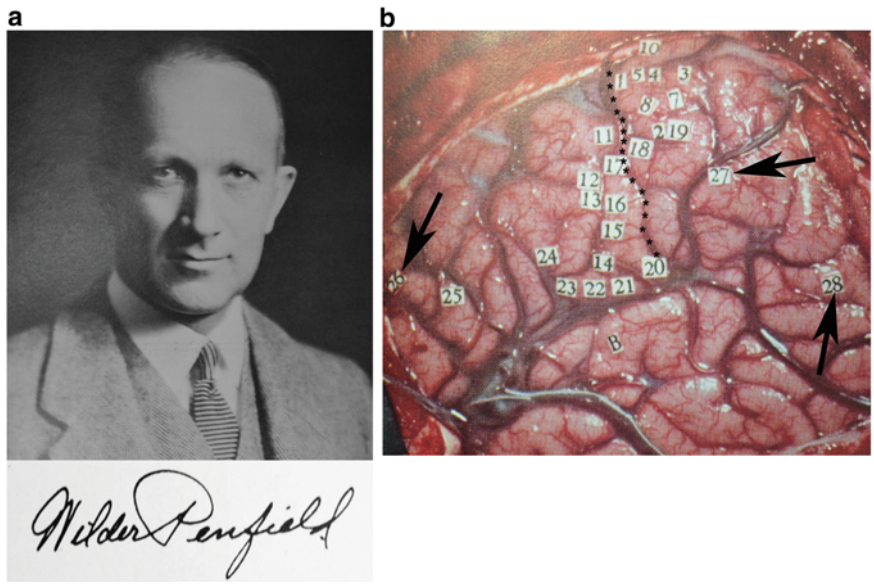


**Fig. 8** (**a**) Wilder Penfield (1891–1976). (**b**) Surgical photograph, tags at motor and sensory stimulation points. *Asterisk* delineates central sulcus. Speech arrest at *arrowed* tags 26 (frontal), 27 (parietal), 28 (temporal) [51]

studied with Cushing, Sherrington, and Foerster, was joined by neurophysiologist Herbert Jasper and began operations in conscious patients under local anesthesia studying the effects of both pre- and postcentral faradic cortical stimulation to treat refractory epilepsy [52, 53]. Later they extended their earlier work to include cortical stimulation of premotor, frontal eye fields, posterior parietal, occipital, and junctional cortical regions revealing complex behavioral and experiential responses. Penfield and Jasper in 1954 were the first to construct motor and sensory cortical maps depicting figurines or "homunculi" whose size represents a relative increase or decrease in the size of cortical representation [51]. However the homunculi are deficient and deceptive in failing to show the individual variability in location they earlier found within the human motor-sensory cortex [52]. In the 1950s they also began to use a square wave generator producing rectangular unidirectional pulses and Penfield's group was first to report the "interference effects of high frequency (30 Hz and higher) stimulation upon associational cortex such as language resulting in speech arrest (Fig. 8b) [12, 51].

By the middle of the twentieth century, the importance of both the depth of anesthesia and the duration of the applied electrical cortical stimulus became better recognized by the work of Liddell, a student of Sherrington, and others [10, 54]. Using a square-wave faradic stimulus, and pulses of 0.5 millisecond duration they showed that movements of the opposite face, thumb-index finger of the hand, and great toe over a much wider areas of the motor cortex than those that excited larger body parts [54]. These same expanded regions would appear to more often be engaged in Jacksonian seizures [10]. Liddell's group also determined that sufficiently intense cortical stimulation can spread downwards to directly activate pyramidal axons in the white matter, thus "short-circuiting the complex of excitatory and inhibitory (graded post-synaptic potentials) effects that ordinarily activate discrete cortical threshold stimulation movements" [10]. It became clear that many discrepancies in the older work on direct electrical cortical stimulation likely related to a variations in stimulus parameters and less reliable and versatile stimulation equipment.

Electrophysiological techniques that evoke cortical potentials in special and general sensory cortex—visual, auditory, and body surface (see EPs below) have clearly demonstrated that the pre-Rolandic motor cortex has some sensory input in addition to obvious motor output. The general sensory cortex (post-Rolandic) also has a well-organized, "although subordinate" motor outflow as Foerster had earlier demonstrated [10].

Cortical stimulation studies in treating patients with refractory epilepsy were greatly expanded over the past 30–40 years by George A. Ojemann (Fig. 9) and his group in Seattle, Washington [8, 55–59]. This work has been notably extended by an associate of Ojemann—Mitchell Berger, and others to facilitate cerebral brain tumor removal in eloquent cortical regions as well as their underlying subcortical axonal pathways [60–63].

Today, direct electrical stimulation (DES) by an applied constant current or constant voltage source, modulated by pulse width and frequency is used to perform intraoperative brain mapping

**Fig. 9** George Ojemann

during epilepsy or brain tumor surgery. We routinely utilize standard Ojemann Stimulation (OS)—60 Hz 1 ms biphasic constant-current bipolar stimulation [64]. Simultaneous local EEG recording is performed during electrical cortical stimulation of the awake or general anesthetized patient to check for a build-up or accentuation of post-stimulation after-discharges, which may culminate in a focal or generalized electrographic and/or clinical seizure (see below).

An interesting historical note connects the present day neurological surgeon with nearly 150 years of cerebral cortical electrical stimulation from Fritsch and Hitzig, to Sherrington, to Penfield, and the postcentral gyrus homunculus for the tongue. One modern version of "the tongue and brain" principle in preparation for cerebral cortical stimulation is as follows [9, 65]—To fully insure that an adequate stimulus would be delivered to the patient's cortex, the surgeon was routinely required to test the current level setting on the (Ojemann) square wave generator as sufficient by feeling a "definitive tingling sensation delivered to his/her own tongue!" (JL Stone, personal communication).

**Fig. 10** Richard Caton (1842–1926)

## The Recording of Brain Electrical Activity: Electroencephalography and Sensory Evoked Potentials

The recording of cerebral cortical electrical potentials closely paralleled that of direct cortical stimulation and was influenced by advances in cerebral cortical localization resulting from the stimulation and ablation studies [13, 14, 66]. Both spontaneous electroencephalography (EEG) awake or asleep, and evoked sensory (visual, somatosensory, auditory) potentials (EPs, also referred to as evoked responses, ERs) are commonly performed measures of electrical cerebral activity.

The British physician and physiologist Richard Caton (Fig. 10) was a classmate of David Ferrier and familiar with his work on cortical stimulation in the monkey [67]. Caton believed that since he and others before him had been able to detect a recordable change in electrical potential from stimulated nerve and muscle [68], a similar phenomenon may occur in the brain. In 1875 he "quite beyond question" detected electrical current variations from the exposed cortical surface of rabbits and monkeys of both spontaneous electrical current variations (EEG), and a relationship between intervals of light and darkness and the brain's electrical current variations (Visual EPs). Two years later weaker current variations were recorded from the scalp as well [67, 69–72]. Caton was also the first to detect electric currents in the cerebral cortex opposite to the side of an electrically stimulated hind limb peripheral nerve of rabbits and a monkey—representing the first recording of a somatosensory response [71–73]. By 1913 the first photographic picture of the cortical EEG in the dog was published by Pravdich-Neminsky a Ukrainian [69, 74], who the following year photographed a sharp deflection on the dog's

cortical EEG in response to electrical stimulation of the sciatic nerve thus depicting a somatosensory EP [75].

Caton used a mirror galvanometer which reflected a much enlarged image on the wall of the fine vibrations representing current variations or fluctuations being led from the cortical surface or scalp, and a few years later others used string galvanometers combined with magnification of the minute movements to demonstrate the current fluctuations [66, 75–77]. Over the decades as amplification and recording techniques were improved, these findings were confirmed by others.

In the first several decades of the twentieth century, about a dozen American, World War I-era physician-physiologists interested in the study of muscle and peripheral nerve physiology ("axonologists") designed and built their own stimulating and recording equipment [66]. These investigators visited and were strongly influenced by the British "schools of neurophysiology"—that of Sherrington at Liverpool and later Oxford, and Edgar D. Adrian at Cambridge—who together were awarded the 1932 Nobel Prize in Medicine or Physiology [25, 78, 79]. These "axonologists" often met at meetings of the American Physiological Society from the 1920s to 1940s and significantly contributed to the many American developments that followed in basic and clinical neurophysiology as European progress was seriously devastated from two world wars [66, 79, 80].

The most notable American neurophysiologist of this period who spent several years in Britain was Alexander Forbes from Harvard Medical School [66]. Forbes, working with the radio compass in World War I, came to understand that a vacuum tube could be used to amplify nerve impulses and not just radio signals, establishing a new "electronic era" in electrophysiology [66, 81]. However, the string galvanometer was still required as the recorder of amplified electrical signals from peripheral nerve. This was problematic as the delicate silver- or gold-coated quartz conducting strings often broke from the force of the signal it received. In addition these strings had mass which significantly damped down the galvanometer's ability to capture very minute and brief changes in electrical potential, as well as the faster oscillations or frequencies. Thus the accurate study of recorded electrical potentials remained seriously limited [10, 76, 77]. In 1921 this problem was solved by the ingenious use of the cathode ray oscilloscope (CRO) at Washington University in St. Louis by "axonologists" Joseph Erlanger and Herbert Gasser, assisted by George Bishop. The moving part in this vacuum tube is the inertia-less electron beam which is deflected by the action of the amplified electrical potential, such as that derived from nerves, and would appear on the fluorescent screen as an illuminated spot of light which could be photographed. The signal output could also be fed into a loud speaker. The CRO gave the first accurate measurements of nerve action potential duration and refractory periods, and also showed that nerve trunks are made up of mixed fibers with varying conduction velocities [66, 82]. Erlanger and Gasser were awarded the Noble Prize in Medicine or Physiology in 1944 for their accomplishment [25, 78–80]. CROs replaced the string galvanometers but were not commercially available until the early to mid-1930s [66].

Hans Berger, a German neuropsychiatrist recorded the EEG from animals in the early 1900s as others had done, and by 1924 had inconsistent results from humans with skull defects and bald males [83, 84]. He continued his research in relative solitude using patients, family members, a dedicated attendant, and a few residents. Fortunate to obtain technical assistance and improved amplification, in 1929 Berger issued the first report of the human EEG [85]. Published in a neuropsychiatric and not a physiology journal it received little attention other than disbelief by the nearby Berlin neurophysiologists [66, 83, 84]. In early 1934 the EEG in was independently confirmed in human subjects by neurophysiologists Edgar Adrian in Cambridge, England and Hallowell Davis, an American trainee of Adrian and Forbes working at Harvard in Boston [66]. By the later 1930s Berger was internationally acclaimed, but became despondent in Nazi Germany and chose suicide in 1941 [66, 83].

Forbes, after frequent trips to England over a period of many years, and close professional


**Fig. 11** Hallowell Davis (1896–1992)


**Fig. 12** Ralph Gerard (1900–1974)

relationships with both the Sherrington and Adrian, had a unique neurophysiological insight and clarity. Over the following decades the eclectic Forbes went on to carefully describe the effects of anesthetic agents on spontaneous and evoked brain electrical activity [81]. With his student Birdsey Renshaw, Forbes studied spinal cord neurophysiology and single cell microelectrode cortical recordings that later helped establish the synaptic origin of the EEG [66].

Hallowell Davis (Fig. 11) with Forbes' assistance by 1929 or 1930 had assembled a neurophysiological laboratory at Harvard with the finest available differential amplifiers and a recently constructed CRO. Davis' team invasively recorded auditory evoked potentials (AEPs) from the cochlea, brainstem, and cerebrum of cats [76, 86, 87]. Visual (VEPs) and somatosensory (SEPs) evoked potentials were also recorded from the cerebral cortex of cats, in addition to spontaneous subcortical unit recordings [88]. With the cooperation of Boston neurosurgeons Harvey Cushing and Tracy Putnam, in 1932 Davis' team also recorded cortical AEPs, VEPs, and SEPs in human beings undergoing local operative procedures [88].

At the University of Chicago, neurophysiologists Ralph Gerard (Fig. 12) and Wade Marshall constructed similar recording equipment, and in 1930–1931 began unicellular or unit brain recording studies in animals using concentric needle electrodes manipulated by a Horsley-Clark stereotactic frame. Signals were fed to the CRO and a loud speaker. They explored the entire cat brain distinguishing spontaneous cortical and subcortical electrical activity from EPs (visual, auditory, and tactile/somatosensory), terms they introduced to neuroscience [66, 80, 89, 90]. Gerard's group, including neurophysiologist/neurosurgeon Oscar Sugar, described evoked responses in unexpected places such as the cerebellum and hippocampus, and used the technique to identify the anoxic susceptibility of certain brain areas such as the hippocampus [66, 91]. Also at Chicago as early as 1933, the Cushing trained neurosurgeon Percival Bailey worked with Gerard and neurologist Theodore Case to record cortical EPs in patients operated under local anesthesia [90, 92, 93]. However, as was typical for that period, inconsistent results were encountered as electrical interference in the operating room often prevented adequate study [66]. The earliest electrically shielded operating rooms to improve upon intra-

operative EEG and EP recordings were opened in the early 1940s at the Montreal Neurological Institute under Penfield and Jasper, and at the Illinois NeuroPsychiatric Institute in Chicago. There Bailey and fellow neurosurgeon Eric Oldberg worked with neurophysiologists Warren McCulloch, Oscar Sugar, Jerome Lettvin, John Garvin and Frederic Gibbs [66, 94].

In the 1940s experiments on monkeys by Clinton Woolsey, Marshall, and others showed that evoked potentials were best observed from the postcentral cortex when the spontaneous activity had been slightly suppressed with barbiturate anesthesia [95, 96]. Tactile EPs had been recorded from the postcentral gyrus of animals and man, but when detected in man were scarcely discerned from the background spontaneous electrical activity [97]. Woolsey, and Penfield trained neurosurgeon Theodore Erickson, by 1950 showed that under local anesthesia during cortical resection surgery in patients with intractable seizures, SEP localization of the postcentral gyrus was feasible and the pattern resembled the body surface representation of the precentral motor cortex [98, 99]. In 1960, Jasper compared postcentral cortical sensory stimulation and SEP recording in 11 patients, and concluded SEP recording "would seem to be of practical importance for use in neurosurgery, especially when subjective responses to stimulation are uncertain or impossible to obtain" [100]. An additional group in France also gained experience with intraoperative SEP at this time [101].

By stimulating the ulnar or peroneal nerve through the skin Dawson utilized a novel technique to detect somatosensory evoked potentials from electrodes applied to the scalp over the postcentral gyrus [102]. This was only possible by a special oscilloscope technique which superimposed 50 successive responses on one photograph to minimize interference by spontaneous cortical activity. Dawson, by 1954 had refined his "averaging technique" to apply to all the common sensory evoked responses, in its ability to separate evoked from spontaneous activity, could be used with slowly repeated or rhythmic stimuli, and preservation of the temporal dimension of the EPs [103]. Beginning in the mid 1960s, both scalp and direct cortical recordings (or both) in response to median nerve stimulation at the wrist, were recorded, electronically amplified, and fed into the analog-to-digital converter (ADC) of a computer. Responses (i.e. 50) were added, and the "average" displayed on a cathode ray oscilloscope (CRO) for photography or printed out on an X–Y paper plotter [101, 104–107]. Computer averaging greatly facilitated the recording of these small amplitude electrical potentials allowing clinical feasibility and practicality of EPs. The commercial availability of digital computers for biomedical research began in the early to mid 1970s and revolutionized their more widespread usage in clinical medicine.

A leader in the early development, as well as operative and perioperative application of SEP to the surgery of eloquent cortex was the neurosurgeon and neurophysiologist Sidney Goldring (Fig. 13). Early in his career he was influenced by the stimulating neurophysiology tradition at

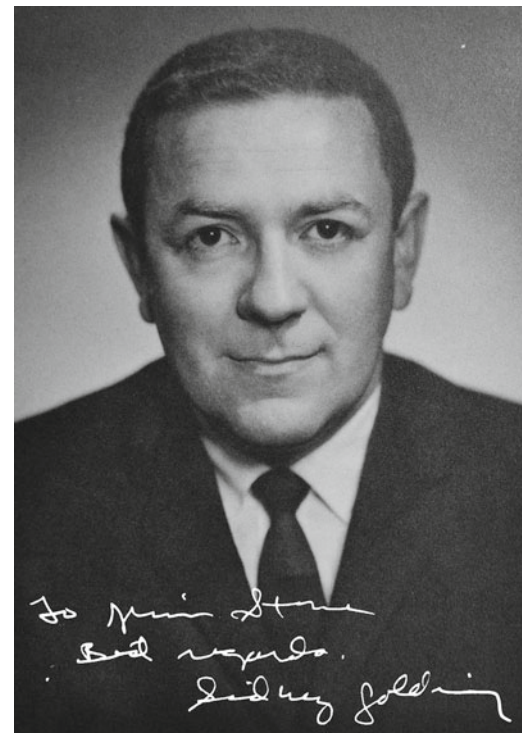

**Fig. 13** Sidney Goldring (1927–2004)

Washington University in St. Louis, Missouri. He obtained experience in experimental neurophysiology from George Bishop, and clinical neurophysiology and EEG from James O'Leary, both "axonologist" pioneers in EEG and EPs. O'Leary was additionally a neurologist and instructed Goldring in clinical and experimental epilepsy.

Goldring's active work with EPs and in particular the SEP, direct current (DC) recordings in epilepsy, and finally the direct cortical response (DCR) as a physiological signature of functionally discrete cortical areas—spanned a period of approximately 45 years [10, 28, 101, 107–117]. SEP recordings from the primary motor (precentral) and sensory (post-central, S1) cortex of animals in response to median nerve stimulation began in the early 1950s, progressed to monkeys and man by the later 1950s and early 1960s with a detailed characterization of the SEP responses in both awake and anesthetized patients. Goldring was among the first to perform such studies in man as he worked with O'Leary and maintained strong interest in epilepsy and epilepsy surgery.

By the late 1960s Goldring began to characterize cerebral cortical SEP responses to median nerve stimulation from recordings from the forepaw or hand regions of both the pre- and postcentral gyri in cats, monkeys, and man [110]. In this study of sensory input to the motor cortex, 15 human subjects (undergoing non pre- or postcentral cortical surgery for seizure resection or tumors) showed responses in the primary motor and sensory cortical hand areas evoked by electrical stimulation of the contralateral median nerve (MN). In humans the motor cortical hand region responses to median nerve stimulation had a latency identical or several milliseconds longer than the primary sensory cortical response. All animals and patients (awake or lightly anesthetized) had the pre-central cortex identified by bipolar electrical stimulation of the brain surface, and in awake patients the sensory hand area was also identified by cortical electrical stimulation producing paresthesias [110]. Stimulation of the ipsilateral MN and auditory click stimulation which elicited responses in the ipsilateral motor cortex of the cats and monkeys were ineffective in man. Goldring interpreted these findings to suggest that the human primary (pre-central) motor cortex plays a less important role in integration of disparate sensory inputs from the periphery than does the homologous primary (pre-central) motor cortex of lower animals [110]. He felt man has relegated most sensory integration functions to uniquely developed cortical association areas, permitting the motor cortex to evolve as a more highly specialized region, and less concerned with the processing of sensory information than in the lower animals. Thus, the corticofugal neurons of the human motor cortex are less concerned with the processing of sensory information that is transmitted directly from the periphery and more concerned with integrating movement-related inputs from subcortical and other cortical regions [110].

Goldring next followed with a study published in Science (1972) where he introduced single unit cortical neuron recordings to further characterize the sensory input to the human pre-central motor cortex [112]. Recordings were made from single neurons in the hand area of the human motor cortex while peripheral physiologic stimuli were applied. Some cells responded only to active and passive hand movements. Over one-half of all motor cortical hand area cells (16 out of 30) showed a motor cortex response to contralateral median nerve stimulation and none showed a response to ipsilateral median nerve stimulation. Of the cells responding to active movement, some showed an increased discharge before onset of voluntary action. These cells were excited by the same movement executed passively, indicating sensory feedback from receptors activated by that movement. The fact that 4 of the 16 responsive cells showed bilateral input indicates that there is a significant ipsilateral projection to the motor hand area in the human similar to that found in other animals. The sensory projection to the motor hand area of the human in that study seemed to be exclusively a kinesthetic one. Thus the view is that the human motor cortex is a highly specialized region that functions more like a "final common path determiner of movement," and in man the function of processing diverse sensory inputs from the periphery, a

function characterizing motor cortex of the cat and to a lesser extent that of the monkey, has been relegated elsewhere.

Although a few others had reported cortical surface SEPs from median nerve stimulation in man several years earlier, it was Goldring's team in the mid to late 1960s that first provided: (1) The observation that an SEP response appearing in the sensorimotor region under light anesthesia forms a definitive basis for sensorimotor localization [109]; (2) Explicit surgical localization guidelines for both tumor and epilepsy cases; (3) A novel "multiplexer" enabling eight simultaneous channels of SEP recordings from a large exposed cortical field to identify SEP response areas across the Rolandic cortical region; (4) Simultaneous scalp and cortical responses including earlier waves; (5) Effects upon the SEP of cortical ablation in man; (6) Lower extremity SEPs; and (7) Recommended local and general anesthetic techniques for electrocorticography and SEP (limiting halogenated inhalation agents) that remain relevant [28, 101, 107, 110, 113, 114, 116].

In 1984 the senior author (J.L.S.) was privileged to visit Dr Goldring, observe his methods, and discuss the related neurophysiology and practical issues. Treating a large number of refractory epileptic children with foci in the sensorimotor and language areas who could not cooperate under local anesthesia, Goldring had developed techniques for direct cortical stimulation in addition to SEP under general anesthesia and in the intensive care unit [28]. Large 48 channel brain surface cortical arrays were used under general anesthesia for intraoperative electrocorticography (ECoG) to detect epileptiform discharges, motor stimulation and afterdischarge analysis, and SEP recording. Goldring believed that large intradural electrode arrays kept in place under the closed dura may result in cerebral swelling, cortical damage, and electrode contacts may be short-circuited or bridged by subdural fluid [28, 118]. In the first operative stage after electrical studies were performed with the large cortical surface array, the array would be very carefully photographed including surrounding landmarks, then meticulously fixed in the corresponding extradural space and photographed for landmark verification, before wound closure [28, 113, 114]. The extradural array would be used in the intensive care unit for—capture or electrical provocation of seizure onset, awake motor stimulation (easier to perform in children than under general anesthesia), SEP site verification, and speech arrest testing—before resection, again under general anesthesia about 1 week later guided visually and with superimposed earlier photographs in a second stage [28, 113, 114, 116].

In a number of children he found "electrical inexcitability of the motor cortex with SEP preservation, regardless of the site of the epileptogenic lesions. He felt the SEP response was less sensitive to the epileptiform disease process (akin to Todd's motor paralysis) than cortically induced motor responses—similar to a comparable problem of motor stimulation under general anesthesia, versus awake surgery. An alternate explanation "…may relate to a disparity in ontogenic development between these two responses (immaturity)." [113]. Many of Goldring's views on SEP and cortical stimulation have been verified by others including his suggested anesthetic techniques.

## A Contemporary, Overall View of the Sensorimotor System in Man

### "The Central Nervous System Forms Internal Models of Sensorimotor Transformations" [119]

*Primary or "basic" somatic sensory information* from the peripheral receptors, ascends through the spinal cord in the classically known primate pathways for somatic sensation—the spinothalamic tract (pain, temperature) and the dorsal columns (proprioception, vibration). The later forms the contralateral brainstem medial lemniscus and both synapse in the ventral posterolateral thalamus and transmit thalamocortical projections principally to the primary cortical area for specific somatic sensory impulses—the somatotopic postcentral gyrus. The thalamocortical axons to

the circumscribed sensory cortical areas (somatosensory/tactile, visual, auditory) terminate in the middle cortical cell layers [10].

An additional, less well understood, upward-projecting *reticular ascending arousal system* exercises diffuse control over the electrical activity of the cortex such as facilitation and inhibition. Collateral branches from the ascending spinal and cranial nerves which carry basic somatic sensory information enter the multicellular brainstem reticular formation, some with a synapse in the nonspecific nuclei of the thalamus, to disperse to literally all cortical regions and arborize widely across all cortical cell layers. Reticular neurons are also driven by efferent impulses from the cerebral cortex, subcortical gray matter, and cerebellum [25]. Each reticular neuron is "itself a minute integrative center capable of moment-to-moment compromises in its response to several inputs," analogy having been made to the concerted, simultaneous goal directed activity of thousands of individual ants or bees [10].

Over a century ago, Cajal noted that thetraditional somatosensory system splits off separate branches within the dorsal horn of the spinal cord [120]. Some of these fibers have been traced to thalamocortical motor related networks perhaps alerting or priming all the major cortical motor centers of this peripheral information [121]. This recently suggested "sensorimotor system" may allow motor centers to template, anticipate, follow, and coordinate ongoing motor tasks and plan future motor actions [121].

The function of the cerebellum must be re-evaluated in relation to recent functional MRI studies implicating this structure in various tasks not involving motor thoughts, intention, or movements. Of particular interest is the interconnected "cerebrocerebellum' (CC) consisting of the lateral cerebellar lobes which are greatly enlarged in man compared to the subhuman primates—analogous to the greatly expanded prefrontal lobes in man. The CC receives input exclusively from the cerebral cortex and engages the contralateral dentate nucleus and lateral cerebellar hemisphere important in motor coordination and motor planning with feedback to the cerebral cortical motor centers [119]. Lesions of the CC have recently been found to result in non-motor control deficits such as cognitive learning that depends on repeated practice, working memory tasks requiring complex spatial and temporal judgements, and problems with word association tasks [119]. In man, the cerebellum may well have evolved from a predominately motor coordinating and sensory integration organ to one which now additionally modulates or coordinates tasks involving emotion, behavior, and cognition. Such an interpretation would be compatible with the global thoughts of J. Hughlings Jackson a century ago.

Further cerebral "sensory processing generatesan internal representation in the brain of the outside world or the state of the body. Motor processing begins with an internal representation: the desired purpose of the movement (prefrontal cortex) … however this internal representation needs to be continuously updated by internal and external sensory information (posterior parietal) to maintain accuracy as the movement unfolds … the next level, which is concerned with the formation of a motor plan, involves interactions between the posterior parietal and premotor areas of the cerebral cortex … The premotor cortex specifies the spatial characteristics of a movement based on sensory information from the posterior parietal cortex about the environment and position of the body in space" [119].

The lowest level of this hierarchy coordinates the spatiotemporal detail of the muscle contractions needed to execute the planned movement. This coordination of a voluntary or involuntary motor act appears to executed by the somatotopic precentral gyrus of the posterior frontal lobe being the primary motor cortex (neuronal origin of the corticospinal or pyramidal tract) whose fibers descend through the brain stem and spinal cord. "This serial view has heuristic value, but evidence suggests that many of these processes can occur in parallel." [119]. Contemporary neuroscientists believe the highly integrative motor system was likely a template upon which complex behaviors such as language, perception, emotion, mentation, and cognition were built [121].

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# Anatomy of Important Functioning Cortex

Warren Boling and André Olivier

**Core Messages**

- Important functioning cortex includes the language areas (Anterior, Posterior, and Superior), primary sensorimotor, and primary visual cortex.
- Specific white matter pathways (e.g. arcuate fasciculus, corticospinal tract, geniculocalcarine tract) are of equal importance to preserve in order to avoid compromise of critical neurological function.
- Neuronavigation greatly facilitates the recognition of gyral and sulcal patterns that can reliably identify many important functional zones as well as defining landmarks that demarcate the boundaries of regions of eloquent cortex.
- The cortex is composed of gyral folds that are connected through pli de passage. These folds connect adjacent gyri and adjacent lobes forming continuous ribbons of cortex containing a white matter core.
- The technique of subpial/endopial resection must be applied whenever preservation of bypassing vessels is critical to avoid ischemic injury to critical functioning cortex.

## Introduction

Important functioning cortex describes all the cortical brain regions that subserve discreet and critical function. Although presumably all cortical areas are capable of being engaged in useful function, some brain regions are clearly more critical to human function than others. This chapter deals with such highly critical areas of the brain that are discreet and can be defined anatomically. The classical language areas, sensorimotor cortex, and vision cortex are discussed in addition to correlative sulcal and gyral anatomy.

In general, cortical regions outside important functioning cortex are considered "safe" to resect. But there are important safety considerations of surgery outside areas of critical functional. First, beneath the cortex are white matter pathways that may be as critical to important function as the cortex itself because of the synaptic

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impulses the fibers are conveying. Second, as already alluded to, areas of cortex that do not accommodate important functioning cortex, may still engage in useful cognitive activities that would result in some degree of functional decline if resected or disconnected, an example is a frontal lobe resection that preserves Broca's area and its connections. Practically, however, the disease conditions we treat that may require a lobar resection, such as epilepsy or brain tumor, would be expected to enhance function and not detract from function if the intractable frontal lobe epilepsy focus is removed resulting in seizure freedom, or the large frontal brain tumor causing mass effect that is impairing cognitive function is resected and decompressed. Third, the vascular territory, both arteries and veins, are of critical concern when operating in or near to important functioning cortex. The arteries passing through or around a safe resection site may be irrigating critical areas distant from the resection and veins may be draining similar critical cerebral regions. In both situations, the vessels must be preserved to prevent ischemia or stroke and interference with function. The surgical strategy to protect bypassing vessels including the sulci in which vessels are coursing is called subpial gyral emptying, which will be discussed in this chapter.

The term eloquent is often used to describe all critical brain regions. However, this word is troublesome when describing sensorimotor function, for example, because the meaning of eloquent is to be fluent or persuasive in speaking, such as an eloquent speech. Eloquent takes its origin from Old French and Latin and has the same roots as loquacious (tending to talk a great deal; talkative). Therefore, this chapter will avoid the word eloquent unless referring strictly to language function.

## Topographic Brain Mapping

Neuronavigation has remarkably facilitated the process of cerebral localization [1]. Structures that are known for their specific functions such as the precentral gyrus can be readily identified and localized on the cortical surface based on the gyral and sulcal morphology. Such critical information nowadays rapidly and reliably available can make awake craniotomy and brain stimulation mapping unnecessary when a resectable lesion is located at a safe distance from such a functional area. For surgery performed within and very near to important functioning cortex, local anesthesia with cortical stimulation remains an important technique to confirm the safety of a resection. The value of neuronavigation in this case is as a guide to make the stimulation procedure more efficient by showing the surgeon where to begin the stimulation process based on anatomical localization of function. In both cases of awake surgery and under general anesthesia, neuronavigation has become an essential tool to define the location and extent of a lesion as well as to confirm normal anatomy.

It is possible with 3D reconstruction imaging to obtain a vivid representation of the gyral and sulcal pattern of the cortex (Figs. 3, 5, 6, 10, 12). The three dimensional aspects of the surgical anatomy are best appreciated by creating a volumetric reconstruction in the neuronavigation environment. For example, the central sulcus and the pre and postcentral gyri can be readily identified with imaging. Even specific function such as hand sensory and motor, tongue, lips, and face areas can be reliably identified by unique gyral patterns, which facilitates the process of cortical stimulation when needed. Many of the cerebral gyri have a typical configuration and pattern with folds and passages called pli de passage that continue into adjacent gyri that can be identified with neuronavigation. Nowadays there are a myriad of platforms and software available that can construct brain maps incorporating important structures or a lesion by segmentation of the 3D volume. In addition, these reconstructed images are invaluable learning and teaching tools, for the medical staff, patients, and their families.

## Gyral Continuum

The arrival of MRI 3D reconstruction has revived the old textbooks of anatomy that had been waiting for a new opportunity to reveal the enormous, precise, and practical information on cortical topography usually illustrated with high artistic value. Textbooks of the old French school of

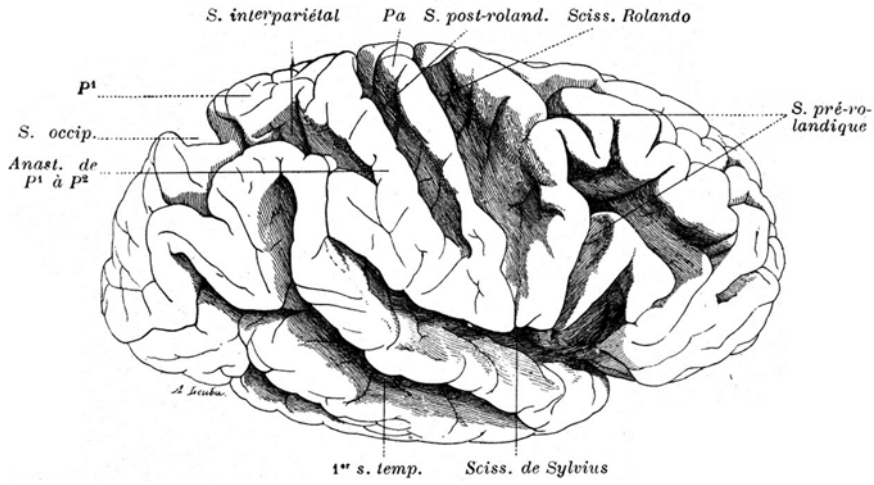


**Fig. 1** Display of gyral–sulcal anatomy. The width of sulci is exaggerated to better display the concept of gyral continuum. Reprinted from: Poirier et Charpy. *Anatomie humaine*, Paris, Masson, 1921

anatomy are excellent examples and particularly one from Poirier and Charpy published in 1921 [2] (Fig. 1). The crisp MRI 3D reconstructions display with astonishing clarity the early tedious observations made on the cadaver brain with special emphasis on the gyral and sulcal anatomy. The concept of gyral continuum is not new having been described in detail by Paul Broca [3], which he called "plis de passage," a reference to anatomical bridges joining one gyrus to another or the transition of one gyrus into another. What is new is its application to microsurgical techniques and in particular to the endopial resection technique [1]. A "pli de passage" refers to an anatomical bridge or continuum between two gyral structures bearing different names (Figs. 1, 2, 3, 4, 5, and 6). The anastomotic bridges of the plis de passage reveal the cortical continuum over the more superficial aspect of the brain. However, it is important to keep in mind the continuum around the sulci that could be described as the sulcal continuum, which is formed by the cortex applied against the pia on one side of a sulcus continuous at the bottom of the sulcus with the cortex on the opposite side that is part of a different gyrus or lobe. It is with this gyral cortical continuum in mind that a practical gyral terminology concept was developed by the old French anatomists that uses numbers

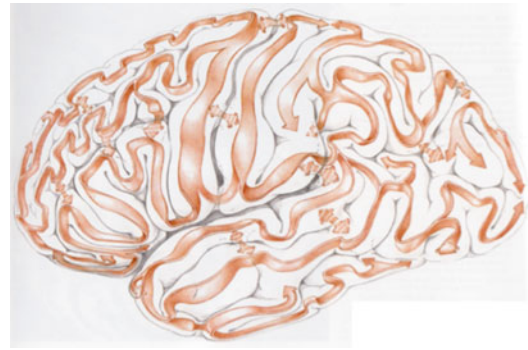

**Fig. 2** Gyral continuum. F1, F2, and F3 are continuous with the precentral gyrus via gyral continuum. The postcentral gyrus is continuous superiorly with the superior parietal lobule (P1) and inferiorly with supramarginal gyrus (P2 or inferior parietal lobule). Yasargil et al. described the concept as gyral ribbons. MG Yasargil. Thieme Medical Publishers, 1994, New York, p.24, courtesy of Georg Thieme Verlag KG.

and letters. Thus within the frontal lobe the continuum gives rise to F1, F2, and F3 gyri (superior, middle, and inferior frontal gyri, respectively, along with contributions to the mesial and orbital surfaces.) (Figs. 1, 2, 3, 4, 10, 15). Within the temporal lobe we find in a superolateral to inferomesial sequence a similar circular pattern around the lobe of T1, T2, T3, T4, T5, T6, and T7 (Figs. 3, 4, 5, and 6). In the occipital lobe the gyral sequence is O1, O2, O3, O4, O5, and O6

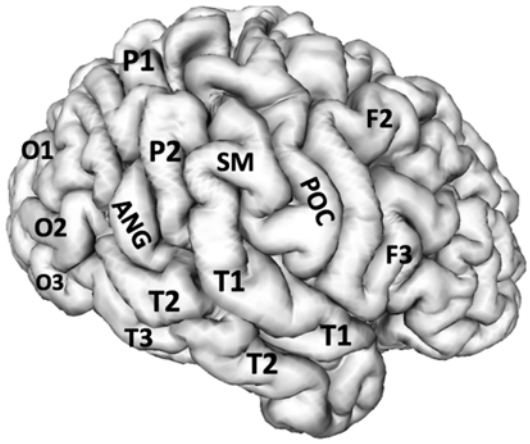


**Fig. 3** 3D MRI reconstruction. F2 and F3 are seen to take root from and are continuous with the precentral gyrus. The postcentral gyrus is continuous superiorly with the superior parietal lobule (P1) and inferiorly with the supramarginal gyrus (P2 or inferior parietal lobule). In this individual, the superior pli of the postcentral gyrus with P1 is more inferiorly located than is typical. P1 becomes O1. T1 can be identified merging with the supramarginal gyrus. T2 contributes both to the angular gyrus and O2. T3 continues posteriorly to become O3. *ANG* angular gyrus, *SM* supramarginal gyrus, *POC* postcentral gyrus

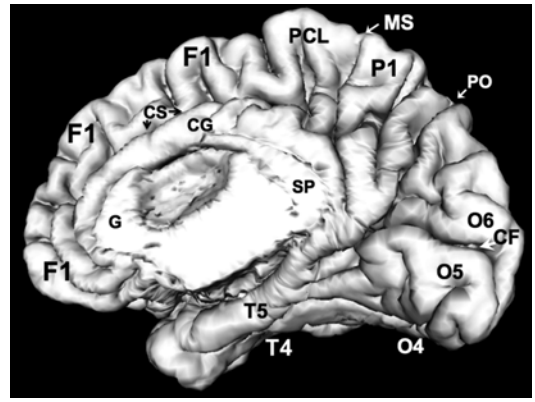


**Fig. 5** Mesial cortical surface. T5 (parahippocampal gyrus) is split posteriorly by the anterior limb of the calcarine fissure to become superiorly the isthmus of the cingulate gyrus (CG) and inferiorly the lingual gyrus (O5). The cuneus (O6) and lingual gyrus (O5) are separated by the posterior limb of the calcarine fissure (CF). The cingulate sulcus (CS) separates F1 (first frontal gyrus) from the cingulate gyrus (CG). *PO* parieto-occipital fissure, *O4* lateral occipital gyrus anteriorly is named T4 (fusiform gyrus), *MS* marginal sulcus

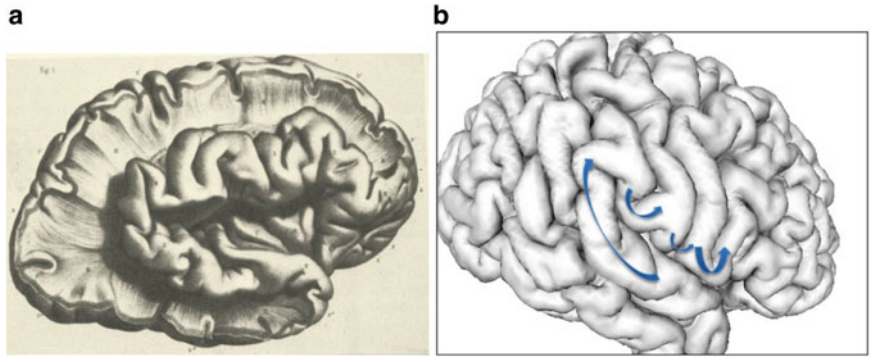


**Fig. 4** (**a**) The encircling gyrus of Foville. *circonvolution d'enceinte* (Foville 1844). (**b**) To illustrate the gyral continuum concept, one cortical ribbon winds around the sylvian fissure but with different named parts. The first temporal gyrus extends into the posterior limb of the supramarginal gyrus. The anterior limb is continuous with the postcentral gyrus. The precentral and postcentral gyri connect via the subcentral gyrus and F3 originates as a continuum from the inferior precentral gyrus

(Figs. 3, 4, 5, and 6). The parietal lobe is divided into P1 and P2 (Figs. 3, 17, 18). Knowledge of the gyral and sulcal continuum is of practical importance during cortical resections. For example, when resecting a lesion posteriorly in F2, there is no pial boundary to prevent the surgeon from entering the precentral gyrus. These two gyri of different names are in fact a continuous cortical and white matter ribbon (Fig. 2). Although the overall patterns of gyral continuum are constant, they nevertheless vary with each patient and must be recognized as such.

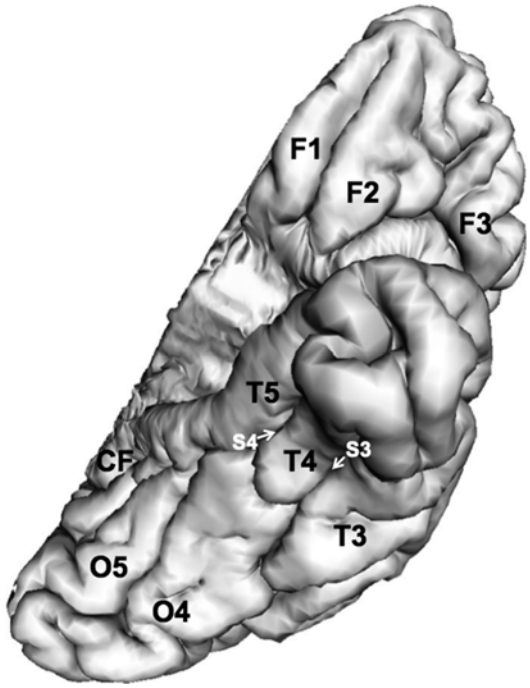


**Fig. 6** Inferior surface of the hemisphere. See text for label identification

## The Gyral Continuum over the Lateral Convexity

The three frontal transverse gyri (F1, F2, and F3) are continuous with the precentral gyrus through three plis de passage that of F1 and F2 being conspicuous and that of F3 often hidden within the sylvian fissure (Figs. 2, 3, 10, 15). The gyral continuum that forms the perisylvian area is impressive (Fig. 4). It is in fact a single gyrus surrounding the three sides of the sylvian fissure but named for its constituent parts. The first temporal gyrus (T1) continues into the posterior limb of the supramarginal gyrus then through its anterior limb the supramarginal gyrus caps the posterior ascending limb of the sylvian fissure. This feature is useful to recognize the position of the central sulcus and surrounding structures. From the supramarginal gyrus, the continuum extends forward through anatomical bridges into the lower postcentral gyrus, then precentral gyrus, and finally into the third frontal gyrus (F3).

The superior parietal lobule (P1) blends with the upper part of the postcentral gyrus through an anastomic bridge, and the supramarginal gyrus part of P2 is continuous inferiorly with the postcentral gyrus. There is variation in the structure of P2, but the typical gyral pattern consists of a posterior limb of the supramarginal gyrus merging with the anterior limb of the angular gyrus whose posterior limb is a continuation of the posterior superior extension of T2 (Figs. 3, 4, 17). The superior parietal lobule (P1) will merge with the first occipital gyrus (O1), the inferior parietal lobule (P2) along with T2 merges with the second occipital gyrus (O2), and T3 continues posteriorly to become O3 (Figs. 3, 5, 6).

## The Gyral Continuum over the Mesial Surface (Fig. 5)

T4 (fusiform gyrus) extends from the temporal pole and blends with O4 that reaches the occipital pole. T5 (parahippocampal gyrus) does not reach the temporal pole but rather bends on itself to form the hippocampal lobule (piriform lobe). The reflected inner component of the lobule is the uncus. The limbic (rhinal) sulcus separates the hippocampal lobule from the temporal pole. The parahippocampus (T5) is separated posteriorly by the proximal calcarine fissure (CF) and is continuous with the lingual gyrus (O5) inferiorly and via the isthmus with the cingulate gyrus superiorly. The mesial part of the superior parietal lobule (P1) corresponds to the precuneus. It is separated from the cingulate gyrus by a remnant of the cingulate sulcus, the subparietal sulcus. The mesial central area forms the paracentral lobule that is a fusion of the precentral and postcentral gyri. Figure 5 shows a strong pli de passage between the precentral gyrus and the posterior mesial portion of F1. The paracentral lobule is limited inferiorly by the cingulate sulcus.

Most of the mesial frontal area is occupied by the interhemispheric part of F1. The cingulate gyrus forms the remainder of the mesial cerebral cortex in the frontal area. It surrounds the corpus callosum from which it is well separated by the deep callosal sulcus. The upper border of the cin-

gulate gyrus is the cingulate sulcus that extends posteriorly behind the paracentral lobule as the marginal sulcus. Note also how the subcallosal portion of the cingulate gyrus blends with F1. Broca called this junctional zone the "carefour de l'hémisphère."

## The Gyral Continuum over the Inferior Surface (Fig. 6)

On the ventral brain surface, the most conspicuous structure is the fourth temporal gyrus (T4), which posteriorly becomes the fourth occipital gyrus (O4). It is well demarcated medially by the deep collateral sulcus (S4) and laterally by the S3 sulcus that is shallow and filled by many anastomotic bridges between T3 and T4. The parahippocampal gyrus (T5) is divided by the anterior calcarine fissure (CF). Upwards it becomes the isthmus that blends with the cingulate gyrus and inferiorly through the temporo-occipital isthmus becomes the lingual gyrus (O5).

The gyrus rectus (F1) is the inferior continuation of the F1 frontal gyrus. Its lateral border is the mesial orbital sulcus. Between the mesial and lateral orbital gyri is the H gyrus that is the inferior extension of F2. Lateral to the lateral orbital sulcus is the anterior-inferior extension of F3 gyrus, called the pars orbitalis.

**Summary for the Clinician**

- The gyral continuum are folds of cortex and white matter connecting adjacent gyri and lobes of the brain.
- There are no arachnoid-pial or sulcal boundaries separating gyri that are connected through pli de passage.
- The naming system for gyri using numbers and letters is useful because it describes the actual cortical anatomy which is gyral ribbons that flow through continuum or pli de passage between lobes and adjacent gyri.

## Endopial Resection (Intervascular Endopial Gyral Emptying)

The endopial resection describes a surgical technique defined by the selective removal of tissue while leaving in situ the pia-arachnoid sulci that envelopes the vasculature (Fig. 7). In the case of epilepsy, for example, the supportive sulci and vascular elements do not require resection since they do not participate directly in the seizure process. Frequently at surgery a scenario is encountered in which interference of bypassing blood vessels found in close proximity to important functioning areas will risk postoperative deficits. In these cases, the goal is to maintain the vascular supply to critical tissues or areas and thus preserve the integrity of the regional vascular territory. In surgery for intrinsic brain tumor, there is in most cases preservation of the pial boundaries with filling and expansion of the involved gyri by the tumor thus facilitating preservation of the vasculature. In fact, neurological complications

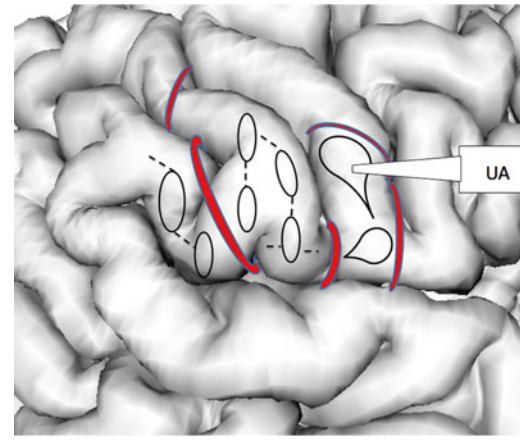


**Fig. 7** Lower central area and anterior limb of supramarginal gyrus resection, an example of endopial intervascular emptying. The ultrasonic aspirator (UA) is the ideal tool used at low settings of aspiration and amplitude. Small openings are made in the pia over the gyral surface in order to introduce the suction tip to start the subpial and endopial removal of tissue. The pial openings are enlarged by coagulating and dividing the pia with microscissors (*dashed lines*) while preserving bypassing vessels and adjacent sulci. The pial layers of the sulci, overlying cisterns and Sylvian fissure, in this case, are all kept intact. Ultimately, the desired gyrus or gyri are emptied in a subpial fashion in order to treat the condition as well as preserve function

of surgery are either due to the actual resection of functional tissue or to the secondary damage to functional areas resulting from the occlusion or injury to critical blood vessels.

The alternative resection technique is en bloc, which entails coagulating and dividing blood vessels that terminate within or traverse the resected area. A lobe or a region of the brain is then removed leaving behind a large cavity. The classical examples of en bloc technique are temporal lobectomy and frontal polar resection where the actual removal entails the division of opercular arteries and, at times, of veins running over the cortex. There are usually no side effects or complications since the resection is restricted to a rather silent area and because potential swelling from coagulating and dividing vessels is compensated by a relatively large removal cavity. However, there are many instances where an en bloc resection cannot be carried out due to risk of causing infarction in a more distal vascular territory.

The locations most appropriate for the intervascular endopial emptying technique are within or nearby important functioning cortical areas, and where an appraisal of the vascular anatomy demonstrates a risk of infarct from vessel occlusion. The technique of subpial dissection is not new. It was originally described by Horsley [4], and is well known to neurosurgeons particularly in the field of epilepsy surgery where it has been used routinely. However, the systematic use of endopial emptying, skeletonization, and preservation of blood vessels for removal of epileptogenic and brain tumor tissue is a newer and original concept [1].

Many of the standard resective procedures, such as the anterior temporal resection for epilepsy, consist of a combination of en bloc resection and endopial emptying. At times, however, the entire procedure is carried out through multiple openings through the arachnoid and the pia to empty one or more gyri subpially. Surgery in the inferior central area is always performed using the intervascular endopial gyral emptying technique if the goal is to preserve function in the primary sensorimotor area (Figs. 7 and 8). The technique entails coagulation of the pia that is perforated with the tip of a sharp bipolar working between the blood vessels that are to be preserved. The ultrasonic aspirator has in our hands been the ideal tool to use set at lowest parameters of aspiration and amplitude. In comparison, a regular suction tip tends to create more trauma and bleeding. The ultrasonic aspirator is introduced into the pial openings, to aspirate gyral contents creating small cavities that are extended along by subpial aspiration. The pia covering the gyral core of the resec-

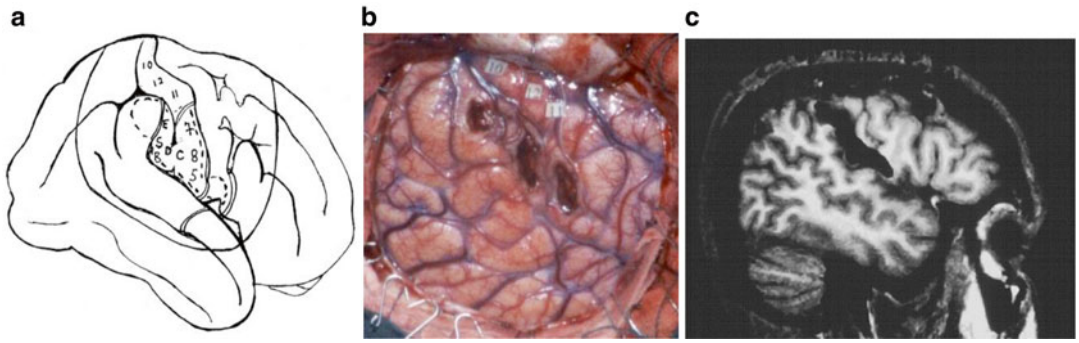


**Fig. 8** Case of intractable epilepsy with a focus in the inferior central area and supramarginal gyrus. The resection approach illustrates the intervascular endopial gyral emptying technique. (**a**) Operative diagram showing responses to stimulation and *dotted line* encompassing the resection performed in a subpial endopial fashion. (**b**) Endopial intervascular emptying has been started in the anterior limb of the right supramarginal gyrus. The pia below tag #11 has been coagulated and will be opened to allow the lower postcentral gyrus to be emptied preserving the bypassing arteries. (**c**) Postoperative sagittal MRI showing the extent of resection. The parietocentral resection included the anterior limb of supramarginal gyrus, inferior postcentral gyrus, and a small opercular portion of the precentral gyrus. The pia-arachnoid of the sulci and Sylvian fissure were kept intact as were bypassing arteries and veins

tion line is opened with micro scissors up to the neighboring blood vessels that are preserved. These cavities are joined together by dissecting between, under, and around the by-passing blood vessels (Figs. 7 and 8). The adjacent sulci that are the pial boundaries with their intrinsic vessels are recognized and left intact after the white matter and adherent cortex or brain tumor is removed in a subpial fashion. A dry surgical field is maintained by suction on a micro sponge, irrigation, and gelfoam if needed. Coagulation is used for the initial pial opening, and is not necessary for the endopial emptying of the gyrus.

For a resection in the lower central area, intervascular endopial gyral emptying is the appropriate resection technique. The inferior central anastomotic bridge (pli de passage) that connects the pre and postcentral gyrus is identified and entered (Figs. 7 and 8). The middle cerebral artery vessels (pre-central, central, and postcentral arteries) as well as draining veins are preserved. The sulci and pia arachnoid covering the Sylvian fissure is preserved. The resection is carried out through several pial openings and cavities that are progressively enlarged and joined together. The contents of the peri-Sylvian gyri can be emptied in a subpial fashion down to the insula leaving undisturbed, the M2, M3, and M4 segments of the middle cerebral artery. Multiple cavities of subpial aspirated tissue is accomplished between traversing vessels and intervening sulci; postoperative imaging makes apparent the full extent of the resection (Fig. 8).

In parasagittal frontal and parietal resections, the intervascular endopial gyral emptying approach is useful when large draining veins that are desirable to be preserved cross the area to be resected. For example the vein of Trolard draining the central area. In the dominant hemisphere it is essential to prevent interruption of vessels that supply or drain eloquent cortex. In a resection limited to the first frontal gyrus, the looping marginal branches of the anterior cerebral artery are left intact as well as significant ascending veins to prevent infarction of large areas of unresected cortex. The F1 subpial dissection can be carried out along the mesial surface pia down to the cingulate sulcus, and if the cingulate gyrus is to be removed, subpial resection is carried out around the depth of the sulcus in order to empty the cingulate gyrus proper. In this example, all intrasulcal arteries are left intact along with their enveloping pia.

**Summary for the Clinician**

- Important vessels that irrigate or drain distant cortical regions must be preserved to avoid ischemic injury.
- For surgery within or very near to important functioning cortex, the subpial endopial technique is required to preserve vasculature supplying areas of critical function.

## The Central Area (Primary Sensorimotor Area)

Neuronavigation has nowadays made routine the identification of the central sulcus during surgery. It becomes relatively easy to visually recognize the lower extent of the central sulcus including its vascular anatomy on the navigation MRI. Likewise, the vascular anatomy of the inferior central area is unique with a central artery that takes a characteristic path as it exits from the sylvian fissure, loops over the rolandic operculum then dives early and deep into the lowermost part of the central sulcus (Fig. 7). Pre- and postcentral arteries enter a sulcus at a more superior level as well as often sending a branch or directly entering the central sulcus. Not only has neuronavigation proven useful in identifying the central sulcus anatomically, certain clear anatomical landmarks can be readily identified that are useful guides specific to sensory and motor functions [5–9].

Identification of the sensorimotor area (pre- and postcentral gyrus) is frequently required in order to perform resections for brain tumor and epilepsy. Identification of the tongue is the best starting point to map the sensorimotor area, and by extension the whole central area. Figure 9 represents the somatotopic sensory organization

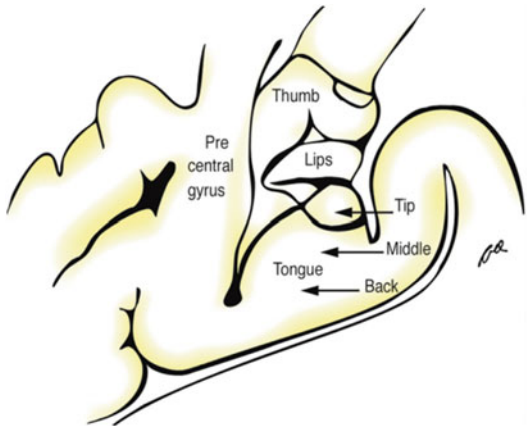


**Fig. 9** Somatotopic organization of the lower postcentral gyrus showing sensory representation of tongue, lips, and thumb

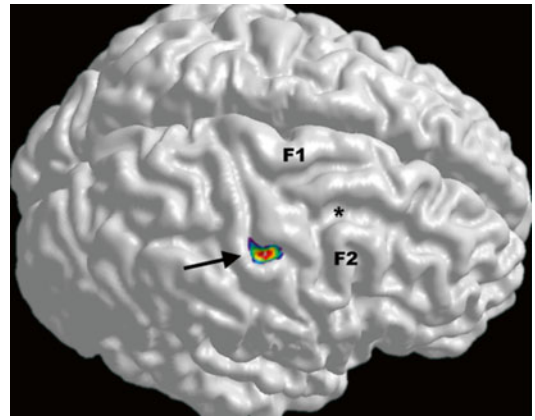


**Fig. 10** 3D reconstruction of the cortical surface with hand area activation (*arrow*) within the central sulcus. The hand activation is within a posterior pointing curve of the central sulcus that Broca described as the middle bend. The hand sensory and motor areas have a constant relationship with the posterior extent of the superior frontal sulcus (*asterisk*), between the gyral continuum of F1 and F2 with the precentral gyrus

of the lower postcentral area. The base or back of the tongue is represented along the sylvian fissure, and the tip of the tongue about 2.5 cm above the sylvian fissure, adjacent to the lips area [1, 9]. The sensory and motor areas are roughly mirror images of the functional zones representing the same body parts divided by the central sulcus.

Stimulation of the postcentral gyrus typically yields sensory phenomena that are described by patients as a feeling of numbness, tingling, or electricity. The removal of a part of the postcentral gyrus results in decreased two-point discrimination and a loss of proprioception in the body part represented. In the inferior postcentral gyrus, removal of tongue, and face areas has little clinical consequence due to the fact that there is considerable bilateral representation. However, disturbance of the more superior thumb, finger, and hand areas in the postcentral gyrus can result in significant impairment of proprioception. Removal of foot area will make ambulation difficult due to loss of foot propioception.

Stimulation of the precentral gyrus results in contraction of muscle groups in elementary flexion or extension movements of a contralateral limb or part of a limb, or simple movement of the tongue or face. Removal of the precentral gyrus causes paresis but not paralysis. The motor deficit is most profound in the distal extremity, so that the arm may have antigravity strength at the shoulder, but the hand will not have useful function. No significant deficits are expected from removal of the inferior precentral gyrus subserving face and tongue functions due to bilateral cortical representation, although, an asymmetry in the nasolabial fold is often detected after face area resection.

Identification of the lower central area has been a crucial landmark for some time. Penfield described the central and precentral sulci as guides to the posterior extent of temporal lobe resection along T1, identified with cortical stimulation. Neuronavigation nowadays is able to confirm the unique gyral pattern of the ascending pre- and postcentral gyri recognized on the MRI.

The central sulcus is the most constant sulcal landmark on the surface of the human brain. Its inferior point originates just above the sylvian fissure and reliably at the level of a plane drawn at the midpoint of the corpus callosum [10]. The central sulcus takes a sinusoidal shape with three dominant curves. The early French anatomists such as Broca and Dejerine, described a genou superieur and a genou inferieur of the central sulcus, both convex anteriorly, and a genou moyen (middle bend) convex posteriorly. The middle bend has constant anatomical relationships, lying between the gyral continuum insertion of F2 and F1 (Fig. 10). This bend is the surface landmark

identifying the pli de passage moyen or hand motor and sensory area in the pre- and postcentral gyri [5, 6, 8]. The central sulcus curves superiorly and posteriorly to end at the interhemispheric fissure in the paracentral lobule, which is found just anterior to the ascending limb of the cingulate sulcus (marginal sulcus) and posterior to the mid callosal plane (Fig. 13). Somatotopic organization maps of motor and sensory localization using cortical stimulation, evoked potentials, and functional imaging are in agreement that a somatotopic relationship exists for the representation of motor and sensory functions extending from the cingulate sulcus, on the mesial surface of the brain, to the sylvian fissure (Figs. 9, 10, 12). The sensory and motor areas are roughly mirror images of the functional zones representing the same body parts divided by the central sulcus.

High-quality MRI and neuronavigation permit routine localization of cortical function in the central area by unique gyral and sulcal anatomic patterns. The presence of a pli de passage (or knob on axial slice imaging) in the middle bend of the precentral gyrus is highly correlated with hand motor and sensory function [5, 6, 8] (Figs. 10 and 11). Additionally, the tongue sensory region is identified with cortical stimulation in a unique triangle-shaped gyral structure at the base of the postcentral gyrus (Figs. 9 and 12) [9]. Back of the tongue sensation occupies the wide, inferior base of the postcentral gyrus, which narrows superiorly to tip of the tongue, then superiorly lower face followed by thumb sensory areas [7].

Seemingly incongruous with hand motor and sensory function located in a relatively small distinct cortical fold, the pli de passage moyen, is the extensive documentation of a somatotopic representation of individual fingers and thumb along the pre- and postcentral gyri that extends along a much longer expanse of the cortex of the central area, over half or more of the precentral gyrus on the lateral convexity according to many stimula-

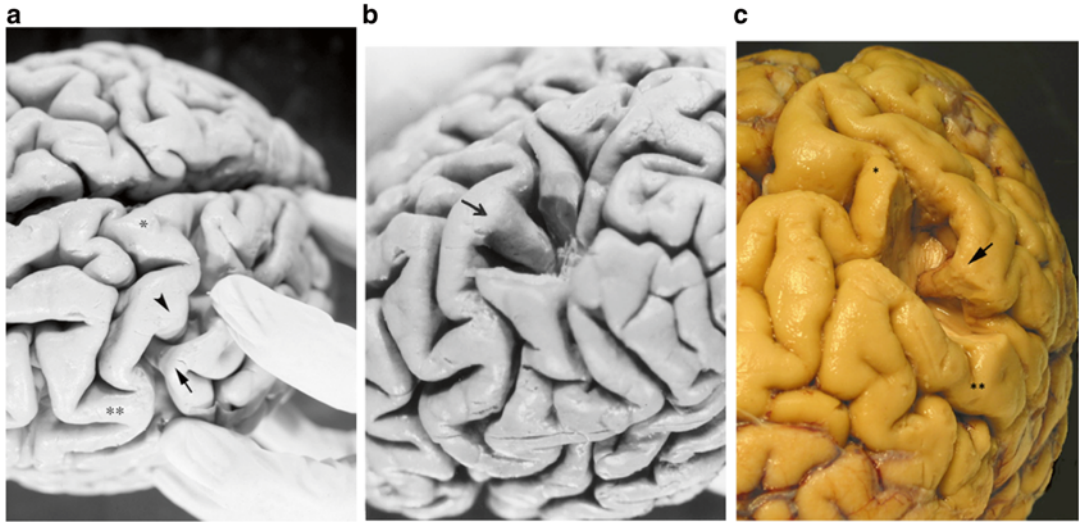


**Fig. 11** Three gyral continuum (pli de passage) connect the pre- and postcentral gyri. At the interhemispheric fissure is the pli de passage superior. Just above the sylvian fissure and at times operculated is the pli de passage inferior (subcentral gyrus). At the level of the middle bend of the central sulcus the middle pli is found mostly hidden within the central sulcus. This pli de passage moyen is the cortical representation of whole hand motor and sensory function. (**a**) Broca described this cortical fold as connecting the pre- and postcentral gyri and elevating the floor of the central sulcus. It is constantly located at the posterior termination of the superior frontal sulcus. *Arrowhead* points to the precentral hand motor area, which is the dominant of the two pli. *Arrow* points to the postcentral pli de passage moyen that is the hand sensory area. (**b**) Postcentral gyrus hand area has been cut away to illustrate the precentral hand motor area bulging into the central sulcus (*arrow*). (**c**) Precentral gyrus cut away between the F1 gyral continuum (*asterisk*) and the F2 gyral continuum (*double asterisk*). *Arrow* is pointing to the postcentral gyrus pli de passage moyen that is the sensory hand area

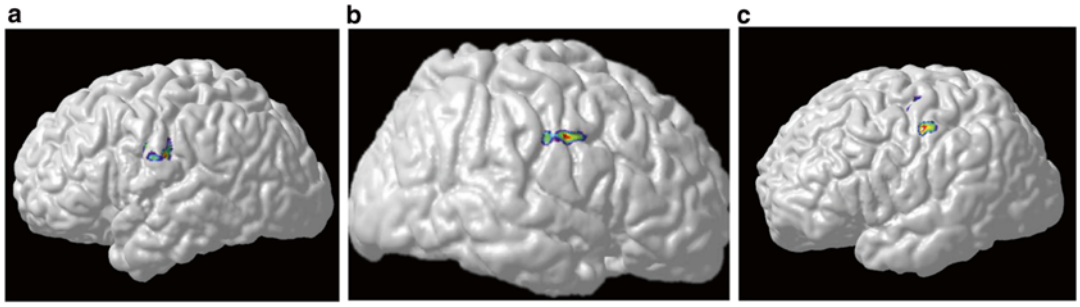


**Fig. 12** Sensory $H_2O^{15}$ PET activation studies demonstrate characteristic functional localization based on gyral morphology. (**a**) Anterior tongue sensory activation is found in the triangle-shaped tongue sensory area of the postcentral gyrus. (**b**) Lower face and lips sensory activation is within a narrowed part of the postcentral gyrus just above the tongue area. (**c**) Thumb sensory activation is the most inferior somatotopically represented digit sitting just above the lips and face area. Compare with Fig. 9

tion studies [11]. Therefore, a whole-hand motor and sensory region in the central area would imply function redundant to individual finger somatotopy. Moreover, central area function identified with cortical stimulation does not typically yield complex or coordinated movements. For these reasons, the actual functional role of the pli de passage moyen until recently has not been clearly understood. In fact, hand motor and sensory activation within the pli de passage moyen mat be an artifact of functional imaging that is not able to resolve activation of individual finger somatotopy. However, a whole hand motor and sensory functional area at the anatomical pli de passage moyen has been confirmed with cortical stimulation [5] in addition to individual finger and thumb function found more inferiorly along the precentral and postcentral gyri. The whole hand motor responses are flexion or extension movements obtained with stimulation over the precentral gyrus contribution to the pli de passage moyen. Sensory responses from stimulating the postcentral part of the pli de passage moyen are described by patients as a sensation involving the entire hand. Inferior to the whole hand sensory and motor areas resides individual finger and thumb somatopic sensory and motor functional representation.

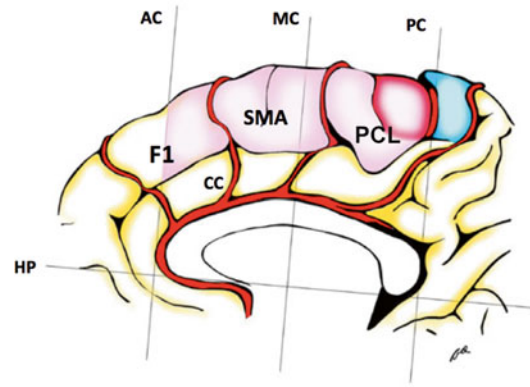


**Fig. 13** In *pink*, the location and extent of the anatomical supplementary motor area (SMA) defined as the interhemispheric portion of F1 that lies above the cingulate sulcus between the anterior callosal (AC) line and the precentral sulcus. The paracentral lobule of the central area is situated between the mid-calossal line (MC) and the posterior callosal line (PC). MC is a useful landmark at surgery. Note that a resection along the interhemispheric part of F1 can be taken safely back to the mid-callosal line, which is anterior to the paracentral lobule. Resection of the SMA region may result in a temporary SMA syndrome, especially in the dominant hemisphere, a possibility that must be discussed thoroughly with the patient and family prior to surgery. *HP* horizontal callosal plane. Reprinted with the permission of Cambridge University Press [1].

## Supplementary Motor Area

SMA stimulation generally results in movements involving multiple muscle groups or fragments of complex actions that contrast with simple flexion or extension responses resulting from MI stimulation. Foerster and Penfield described SMA stimulation responses as either: assumption of posture, maneuvers such as stepping, or rapid incoordinate movements [12, 13] (Figs. 13 and 14). Specific motor responses also observed with SMA stimulation have included turning of the

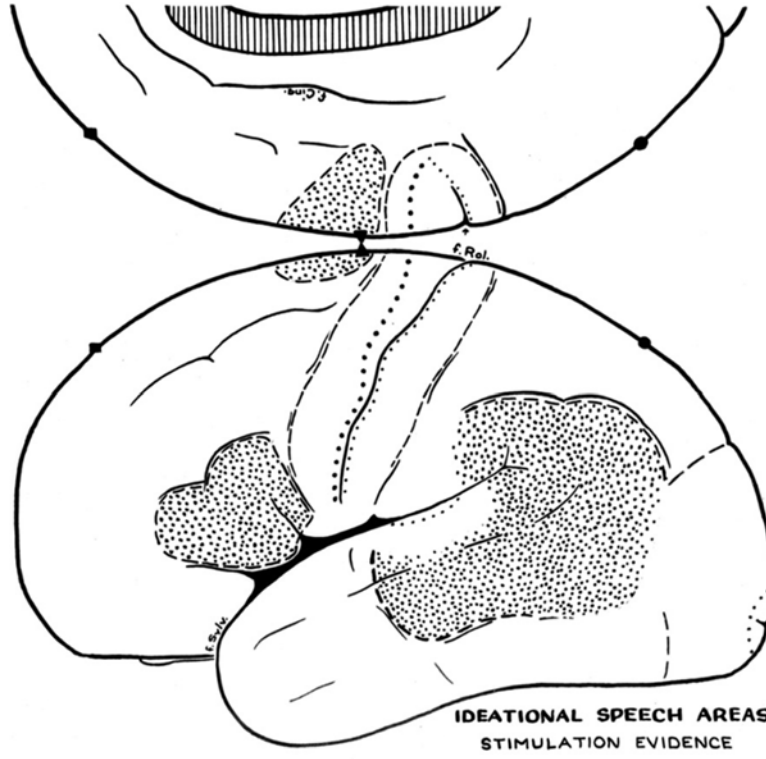


**Fig. 14** The three main areas of speech function as inferred from electrical stimulation. Anterior, superior, and posterior speech zones (Corresponding to Broca's, SMA, and Wernicke's areas, respectively). Republished with permission of Princeton University Press, from Speech and Brain Mechanisms, Penfield W and Roberts L, 1959; permission conveyed through Copyright Clearance Center, Inc.

eyes and head, stepping movements, waving, and other complex hand movements. Motor responses now recognized as specific to the SMA has been described as a "fencing posture," which consists of contralateral abduction of the arm with external rotation of the shoulder and flexion at elbow.

Removal or disconnection of the SMA may result in transient postoperative deficits in motor strength and initiation of movements. In the dominant hemisphere a language disturbance of word finding difficulty is likely that can range from mild to severe (Fig. 14). A permanent deficit is not expected provided the primary motor area or its white matter fiber tract is not disrupted and the vasculature of the central area is preserved.

The possibility of a transient SMA syndrome must be discussed fully with the patient and family prior to surgery. Typically after an SMA syndrome develops, the family is more concerned than the patient with the language or motor disturbance. Since the language and motor dysfunction is transient and the patient and family are fully aware of the possibility prior to surgery, such an occurrence is considered a side effect and not a complication of surgery.

## Surgical Anatomy of the Frontal Lobe (Figs. 2, 3, 4, 9, 10)

The frontal lobe is that large part of the hemisphere located anterior to the central sulcus. Laterally, the sylvian fissure separates it from the temporal lobe. Its mesial limit is the interhemispheric fissure. On the mesial surface the frontal lobe is separated from the cingulate gyrus by the cingulate (or callosomarginal) sulcus (Fig. 5). For practical purposes the anterior cingulate gyrus can be considered part of the frontal lobe although not strictly a part of the classical anatomical description of the frontal lobe.

The anatomy of the central sulcus was considered in detail above. The precentral sulcus is a deep sulcus divided by a large anastomotic root or pli de

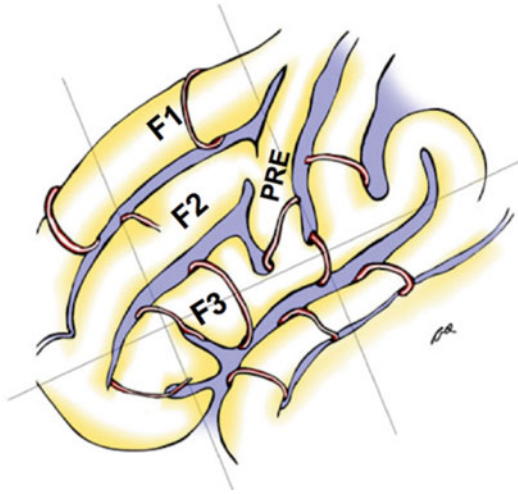


**Fig. 15** Anatomy of the frontal lobe over the lateral convexity: *PRE* precentral gyrus, *F1* first frontal gyrus, *F2* second frontal gyrus, *F3* third frontal gyrus. The three plis de passage (or gyral continuum) are robust gyral connections of the precentral gyrus with F1, F2, and F3. Reprinted with the permission of Cambridge University Press [1].

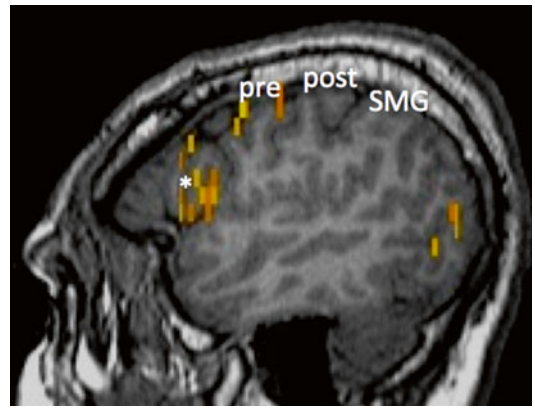


**Fig. 16** FMRI activation in Broca's area (*asterisk*), which is the anatomical pars opercularis of F3 [14]. Activation in Broca's area is best seen with word seeking functional imaging tasks such as word generation and confrontation naming [15]. *pre* precentral gyrus, *post* postcentral gyrus, *SMG* supramarginal gyrus

passage that joins the precentral gyrus with the second frontal gyrus (F2) (Fig. 15). The superior frontal sulcus separates F1 from F2 on the convexity surface of the hemisphere. It is usually shallow and may be interrupted by anastomotic bridges. The inferior frontal sulcus separates F2 from F3. Opercular frontal arteries arch over F3 then disappear into the sulcus helping to outline and identify the gyrus (Fig. 15). The inferior frontal sulcus is an important landmark separating F2 from the language cortex of Broca's area of F3 in the dominant hemisphere, which then continues onto the orbital frontal surface to form the internal orbital sulcus.

Three frontal gyri take origin from the precentral gyrus as a continuous cortical and white matter pli de passage (Fig. 15). The superior frontal gyrus is best named the first frontal gyrus (F1) since it does not occupy only a superior position but extends to the orbital and mesial surfaces. It is the only gyrus found on the three surfaces of the frontal lobe, hence its subdivision into three distinct parts: external, internal, and orbital (Figs. 5, 6, 15). The posterior aspect of internal F1 behind the anterior callosal plane corresponds to the anatomical SMA (Fig. 13).

The second frontal gyrus (F2) is located on the lateral and orbital surfaces between the first and third frontal gyri (Figs. 3 and 15). F2 is the largest of the three transverse frontal gyri. It is divided into two anatomical parts, external and orbital, that occupy a large portion of the convexity and orbital surfaces. Like F1, its external portion arises from the precentral gyrus by a large plis de passage.

The third frontal gyrus (F3) between the inferior frontal sulcus and the sylvian fissure is further divided into three parts or pars, which from posterior to anterior are: pars opercularis covering the anterior insula, pars triangularis, and pars orbitalis. At surgery, the frontal opercular arteries are seen to course over F3 then dive into the inferior frontal sulcus (Fig. 15). The pars opercularis in the dominant hemisphere is the anatomic Broca's area (Figs. 3, 14, 16). The pars opercularis is connected with the precentral gyrus through a strong plis de passage gyral continuum, and the opercular pars is a continuous gyral ribbon with the pars triangularis, which flows into the pars orbitalis.

## Surgical Anatomy of the Parietal Lobe

Although the central area is functionally distinct from both the frontal and parietal lobes, the postcentral gyrus is anatomically included in the parietal lobe. Posteriorly the boundary on the mesial surface is an obvious parieto-occipital sulcus.

More ill defined is the lateral convexity limit of the parietal lobe; typically the anatomical separation between parietal and occipital lobes as well as temporal and occipital lobes is a line drawn from the parieto-occipital sulcus supero-medially to the preoccipital notch inferiorly (Figs. 3, 5, 17, 18). The anterior inferior boundary of the parietal lobe corresponds to the sylvian fissure, but more posteriorly an arbitrary line must be drawn from the sylvian fissure to the occipital lobe. The inferior boundary of the parietal lobe on the mesial surface is the subparietal sulcus, a discontinuous sulcus that separates the precuneus from the cingulate gyrus (Fig. 5).

The key to defining the gyral anatomy on the convexity of the parietal lobe is the intraparietal sulcus (named interparietal sulcus by the French school). Although presenting numerous minor variations, the intraparietal parietal sulcus forms a "T" lying on its side. The vertical part is the postcentral sulcus with frequent small gyral bridges or accessory sulci crossing the sulcus, and the horizontal arm is deep and constant dividing the parietal lobe into superior and inferior lobules (Figs. 17 and 18). The horizontal limb of the intraparietal sulcus continues into the occipital lobe as the superior occipital sulcus. The superior parietal lobule (P1) includes all the area found on the convexity above the intraparietal sulcus.

P1 is continuous anteriorly with the postcentral gyrus through a plis de passage as well as continuing posteriorly to become the first occipital gyrus (Figs. 17 and 18). The convolution of the superior parietal lobule is named the precuneus on the mesial surface of the brain. The precuneus is bounded inferiorly by the subparietal sulcus, and posteriorly by the parieto-occipital sulcus (Fig. 5).

The inferior parietal lobule (P2) contains both the supramarginal and angular gyri. The supramarginal gyrus caps the posterior termination of the sylvian fissure just posterior to the lower

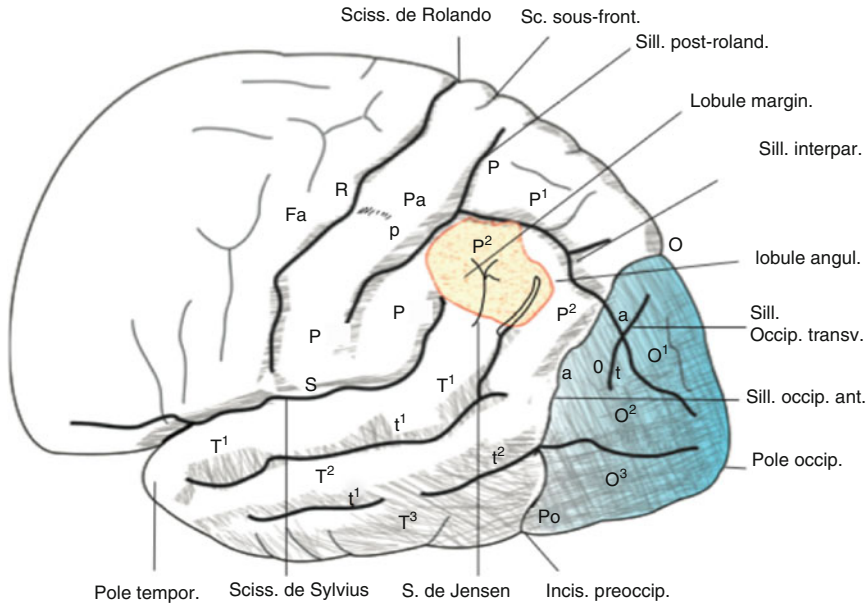


**Fig. 17** The parieto-occipital area after Poirier and Charpy, 1898. The parietal lobe comprises the postcentral gyrus (Pa), the superior parietal lobule (P1), and the inferior parietal lobule (P2). The superior temporal gyrus (T1) bifurcates to form the posterior limb of the supramarginal gyrus and the anterior limb of the angular gyrus. P1 is continuous with O1, the superior occipital gyrus. The middle temporal gyrus (T2) and the angular gyrus come together to form the middle occipital gyrus (O2). The inferior temporal gyrus (T3) continues into the inferior occipital gyrus (O3). Taken together the supramarginal and angular gyri form the inferior parietal lobule (P2), which is separated from P1 by the intraparietal sulcus (sill interpar), which the French call the interparietal sulcus. P2 is eloquent in the dominant hemisphere

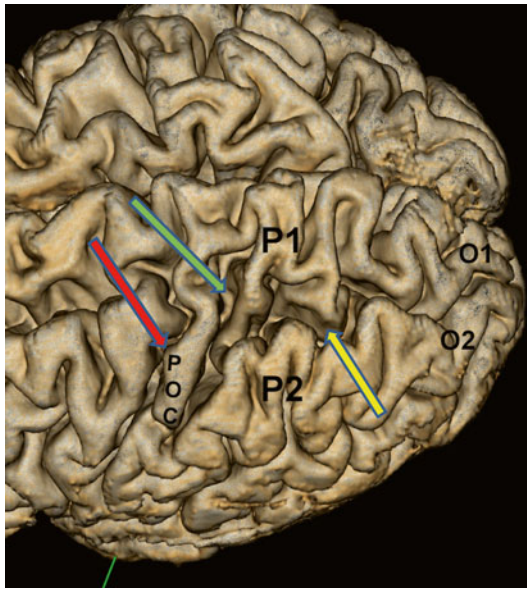


**Fig. 18** Topography of the left parietal lobe. Lateral surface showing the horizontal limb of the intraparietal sulcus (*yellow arrow*) separating the superior (P1) and inferior (P2) parietal lobules. Its vertical limb corresponds to the postcentral sulcus (*green arrow*). The intraparietal sulcus is critical to identify as the sulcus separates eloquent (P2) from noneloquent (P1) cortex in the dominant parietal lobe. The sulcus continues into the occipital lobe to become the superior occipital sulcus. *POC* postcentral gyrus. Reprinted with the permission of Cambridge University Press [1].

postcentral gyrus with which it is continuous through a plis de passage. The angular gyrus is posterior to and continuous with the supramarginal gyrus and caps the posterior termination of the superior temporal sulcus (Fig. 17). There often is considerable variation in the gyral pattern of the inferior parietal lobule, such as the presence of accessory supramarginal or angular gyri interposed within the classical pattern described. However, P2 is eloquent cortex in the dominant hemisphere. Stimulation in dominate P2 frequently is able to pinpoint a cortical region that produces speech arrest. Despite appearance of a discreet language area, the posterior language area of Wernicke is not as compact as the anterior Broca's area, and resections of P2 are likely to result in some degree of language disturbance. Therefore, considerable caution must be taken in resection of potentially functioning cortex in P2 even if no speech arrest is gotten with cortical stimulation, such as in the case of epilepsy or low grade glioma. An additional challenge to surgery in P2 is that language functional imaging has proven to be less useful to pinpointing Wernicke's speech area than for Broca's area or SMA (Figs. 14, 16, 19).

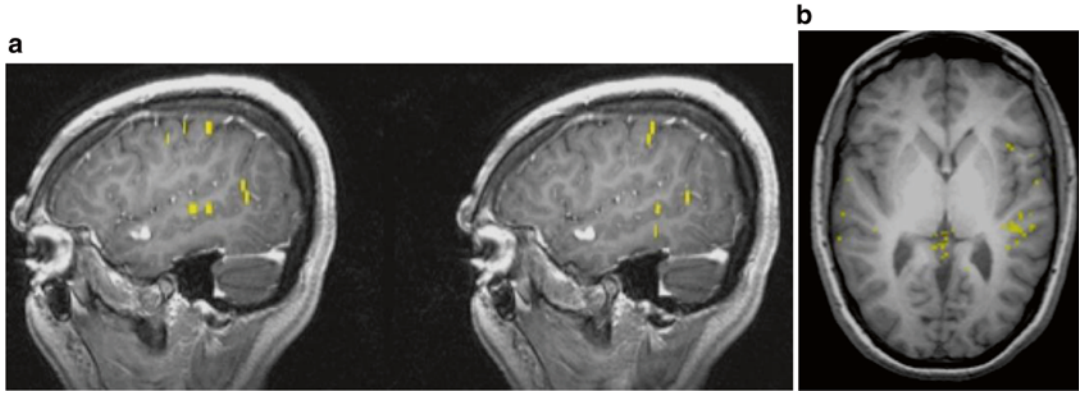


**Fig. 19** Sagittal (a) and axial (b) reconstruction of language task FMRI. Wernicke's area encompasses a large cortical region that includes posterior temporal (T1 and T2) as well as inferior parietal lobule (P2). Passive tasks with functional imaging bring out posterior language activation [15]. In this case, the task was story listening. As is typical, in this FMRI study posterior temporal regions demonstrated more activation with posterior language tasks. However, P2 cannot be ruled out as eloquent and important functioning cortex

## Surgical Anatomy of the Temporal Lobe (Figs. 4, 6, 7, 18)

The temporal gyri are oriented longitudinally around the temporal lobe. In a coronal oriented MRI, each gyrus is identified in cross section. They are named as the first or superior (T1), second (T2), third (T3), fourth or fusiform (T4), the fifth or parahippocampal (T5), the sixth or hippocampus proper (T6), and the seventh or dentate gyrus (T7). The first three gyri are found on the external surface of the lobe. Posteriorly, T1 merges into the supramarginal and angular gyri within the inferior parietal lobule. T2 is widest and the most prominent temporal gyrus on the external surface. Its superior and posterior extent merges into the angular gyrus within P2 and O2 of the occipital lobe, respectively. The third temporal gyrus (T3) occupies the inferolateral corner of the lobe. T3 continues along the floor of the middle fossa to become O3.

Posterior T1 and T2 in the dominant hemisphere are critical for language (Fig. 14). In dominant hemisphere temporal resections, the precentral sulcus is the anatomic landmark for the posterior extent of corticetomy along T1. More posterior surgery along T1 and T2 generally requires awake craniotomy to confirm presence of potentially normal functioning cortex and white matter prior to removal and disconnection.

## Surgical Anatomy of the Occipital Lobe

The occipital lobe is the cerebral region posterior to the parieto-occipital sulcus, a medial brain surface landmark. A virtual line drawn from the most superior aspect of the parieto-occipital sulcus to the preoccipital notch anatomically demarcates the occipital lobe on the lateral convexity. The most characteristic surface feature of the occipital lobe is the calcarine fissure that contains the primary visual cortex. It is confined to the mesial surface and continuous with the parieto-occipital sulcus (Fig. 5). The calcarine fissure posteriorly separates the occipital lobe into the cuneus (O6) above and the lingual gyrus (O5) below. The calcarine fissure bulges into the occipital horn of the ventricle to form the calcar avis. O5 merges with T5 (parahippocampal gyrus) anteriorly. O4 corresponds to the occipital continuation of T4 (fusiform gyrus) (Fig. 6). The gyral pattern over the convexity of the occipital lobe can generally be divided into three separate convolutions, the superior, middle, and inferior occipital gyri (O1, O2, and O3) (Figs. 3, 17, 18), which posteriorly come together to form the occipital pole.

The primary visual cortex along with the geniculocalacarine fiber tract must both be considered when evaluating the risk of visual field deficit from surgery. The fiber tract takes origin from the lateral geniculate ganglion then runs within the sub and postlenticular segment of the internal capsule in close proximity to the temporal horn and atrium of the lateral ventricle as a distinct bundle called the external part of the stratum that is separated from the ependyma by commissural fibers that form the tapetum. Fibers from the superior retinal fields pass almost directly posterior to the superior lip of the calcarine fissure. Fibers from the inferior retinal fields loop into the temporal lobe with the most peripheral visual fibers more anterior while the macular fibers mostly bypass the temporal lobe.

Surgery of the inferior parietal and posterior temporal regions must consider the prospect of a visual field deficit resulting from disruption of the geniculocalcarine fiber tract. Of course in occipital lobe surgery, a visual field deficit including hemianopsia of the contralateral visual field is an expected side effect of surgery if no visual field deficit existed prior to surgery. In surgery for epilepsy of the occipital lobe, patients generally compensate very well if the occipital lobectomy has a reasonable opportunity to stop the seizures and the patient is thoroughly counseled on the expected hemianopsia.

**Summary for the Clinician**

- Sulcal and gyral patterns can reliably identify function in the sensorimotor cortex, in particular the inferior sensory cortex (tongue, lips, and thumb), whole hand area or pli de passage moyen, and foot area or paracentral lobule.
- A whole hand area exists at the pli de passage moyen in addition to individual finger somatotopic representation more inferiorly located.
- The anterior language area of Broca is confined to the posterior part of F3, pars opercularis, in the dominant hemisphere.
- All of P2 including the posterior T1 and T2 is eloquent in the dominant hemisphere.
- The SMA can be defined by anatomical landmarks. Although considered the third language or superior language area, removal of the dominant SMA is expected to result in temporary language disruption that can range from mild word finding difficulty to mutism. The deficit can last for a variable length of time, but is typically days to weeks. Since this possibility of language disruption is discussed with the patient and family prior to surgery and it is a temporary deficit, such an occurrence is a side effect of surgery and not a complication.
- Visual fiber pathway anatomy must be considered in surgery of the inferior parietal and posterior temporal regions. The possibility of a visual field deficit should be discussed with the patient prior to surgery in these areas.

## Conclusion

Neuronavigation has greatly improved the ability to identify the gyral and sulcal anatomy of the brain. Even important functioning cortex such as the primary sensorimotor area and the pars opercularis of F3 containing Broca's language area can be reliably localized with neuronavigation at surgery. Cortical stimulation is required much less frequently nowadays due to availability of quality imaging and navigation capabilities. However, when surgery is performed within or very nearby important functioning cortex awake craniotomy and cortical stimulation should be performed to improve the safety of surgery and preserve critical function.

This chapter has emphasized that a thorough knowledge of the regional cortical anatomy is crucial to avoid complications of a neurological deficit from a resection. Although, it must be stated that preservation of critical function requires an equal emphasis on knowledge of the anatomy of the white matter pathways. The most important in the context of this chapter's discussion are the corticospinal tract and arcuate fasciculus in the dominant hemisphere as well as the geniculocalcarine pathway. The corticospinal tract is a robust fiber tract that can be traced with diffusion tensor imaging (DTI) and with most modern navigation platforms brought into the neuronavigation environment to navigate during surgery. The arcuate fasciculus has many crossing fibers that make DTI tract tracing more difficult. For this critical white matter pathway, cortical landmarks are most useful for identifying and avoiding disruption of language. Fiber tract stimulation is also an option during surgery, which has been used mostly for corticospinal tract localization. The geniculocalcarine pathway has a close relationship with the outer wall of the ventricle of the posterior temporal and parietal lobes. A visual field disturbance resulting from surgery should always be considered in surgery of the posterior temporal, inferior parietal, and occipital regions. A highly recommended authoritative neuroanatomy textbook is Human Central Nervous System by Nieuwenhuys et al. [16]. The book is an excellent resource for anatomical details and with precise illustrations that complement this chapter's practical discussion.

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# Mapping Eloquent Brain with Functional MRI and DTI

Mohammad Fakhri, Lauren J. O'Donnell, Laura Rigolo, and Alexandra J. Golby

## Introduction

The goal of surgery for brain tumors and epilepsy is maximal resection while respecting surrounding eloquent structures to avoid postoperative deficits. In order to preserve sensorimotor, language, and cognitive functions, delineating the patient-specific locations of structures supporting these networks is essential [1]. Studies have shown that the identification of eloquent cortex in close proximity to the region of tumor or a resectable lesion is a strong predictor of worsened neurological outcome postoperatively or a limited extent of resection [2, 3]. Therefore, successful preoperative functional mapping of these regions, and their connections, can assist the neurosurgeon in preserving these fundamental abilities while maximizing extent of resection.

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Invasive techniques are the reference standard in brain mapping, but there is a growing trend to use noninvasive alternatives. Direct electrical stimulation mapping of cortical and subcortical regions of the brain for functional mapping and the intracarotid amytal (IAT) or Wada test for lateralization of memory and language function [4] are supported by a large body of literature. However, both techniques have technical challenges, are resource-intensive, and are invasive adding to overall risk. Well-established drawbacks of these techniques include the risk of producing after-discharge activity and seizures (for direct electrical stimulation) or stroke (in Wada) [5], the long time necessary for mapping, and their specificity for few functional abilities [6]. Moreover, many centers do not have access to these techniques due to technical and expertise requirements. For these reasons, there is increased use of noninvasive alternatives instead of the invasive techniques. Of the proposed noninvasive methods, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) are convenient methods with variety of potential applications, due to widespread availability of MRI scanners, noninvasiveness of the techniques, and their ability to map multiple cortical and subcortical regions.

FMRI and DTI are complementary noninvasive brain mapping techniques. Blood oxygen level-dependent (BOLD) fMRI is a functional neuroimaging technique that maps the brain by detecting perfusion-related changes that are coupled with neuronal activity [7]. FMRI can be

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used to map both cognitive and motor functions of the brain, providing the flexibility to implement multiple tasks in one imaging session for the purposes of pre-operative planning. DTI is able to demonstrate white matter tracts by measuring the principal diffusion direction of water molecules as a marker for the axis of these tracts. DTI is used to visualize major white matter tracts, including tracts in the motor system (e.g. corticospinal tract) and those involved in major cognitive functions of the brain (e.g. arcuate fasciculus in the language network) [8]. DTI has also been used to image the effect of neoplasms on the integrity and trajectory of white mater tracts [9].

This chapter reviews current evidence for using fMRI and DTI as noninvasive methods for mapping both eloquent cortex and critical white matter tracts in neurosurgical planning. Technical details and limitations of each method are discussed. Finally, a clinical case presentation is provided to show how fMRI and DTI can help the neurosurgeon to perform a more complete and safer resection.

## Functional MRI

### Uses and Current Evidence

During the last two decades, with the widespread availability of high field MRI systems (1.5–3 T), much translational research has explored potential clinical applications of fMRI. Because this type of imaging requires no exogenous contrast and uses local changes in blood oxygenation with brain activity (BOLD contrast), it can conventionally be used for producing informative images for functional assessment of the brain [10]. BOLD fMRI is still in the initial stages of translation from research to demonstrate its potential for a better diagnosis or treatment of neurological and neurosurgical diseases. In general, clinical usage of fMRI can be summarized in two different categories: those related to neurosurgical planning and those used in diagnosis of neuropsychiatric diseases. Here we focus on the first category in more detail.

Most clinical applications of fMRI in neurosurgery are related to brain tumor surgery and epilepsy surgery. By demonstrating the relationship of the tumor to eloquent cortex in patients with resectable brain tumors, fMRI can help in minimizing postoperative cognitive and motor deficits [11]. As in brain tumor patients, motor, somatosensory, language, and memory functions can also be mapped in patients with intractable seizures. Here, clinical roles for fMRI can include lateralization and localization of language functions as well as site-specific mapping in neocortical epilepsy. An emerging application is in prediction of potential memory decline, especially after anterior temporal lobectomy involving the mesial structures. In some cases, a combination of fMRI-EEG may help localize lesions when other data are not sufficient alone to localize the epileptogenic region. While interictal epileptiform discharges are well-suited to EEG-fMRI studies, they may not correspond to the epileptogenic zone [12], and this has limited usage of EEG-fMRI.

Currently available data regarding using fMRI for presurgical planning in both tumor and epilepsy patients can be broadly categorized into motor and language studies. Multiple case series showed successful mapping of motor cortex in patients with lesions adjacent to the primary motor cortex, supplementary motor area, and other motor-related areas [13, 14]. Similarly, there is an increasing number of studies that established the ability of fMRI in both lateralization and localization of receptive and expressive language regions in the vicinity of brain lesions [15, 16]. However, there is a paucity of data regarding clinical usage of presurgical fMRI for other cognitive functions such as calculation, memory, and attention tasks [17].

When deciding to use fMRI for presurgical mapping, certain factors are of vital importance. Among these, selection and implementation of the appropriate task are critical for conducting successful brain mapping in patient populations. Although fMRI has been used in both motor and language paradigms, usually, there is a larger task correlated BOLD-signal change in motor tasks compared to language tasks [18]. It has been well-established that fMRI is more accurate in predicting the location of motor areas compared to language areas [19, 20]. Hence, there is an

ongoing controversy regarding similarity of fMRI findings in language tasks with those of cortical stimulation; as some studies report inconsistencies between the two methods [20] while others have shown high degree of consistency between fMRI and intraoperative mapping data [21]. It is believed that the difference between the studies can largely be attributed to the selection of language tasks [15, 20]. Therefore, one of the ongoing problems in conducting presurgical fMRI mapping studies for language is the selection and utilization of appropriate tasks. Tumor location can guide a clinician to select an appropriate task based on categorization of language tasks into those which emphasize "receptive" versus "expressive" aspect of language processing. Task duration, use of visual or auditory paradigms, complexity, and baseline cognitive abilities and alertness of the patient can influence the resulting functional maps. These parameters will be discussed elsewhere in the current chapter. Another key issue in consideration of fMRI as a measure for clinical decision making is that as an observational technique, it demonstrates cortical areas participating ("activated") during performance of a task, but does not determine "necessity" of these active areas for the task performance. This is in contrast to deactivation electrocortical mapping or the Wada test in which the necessity of an area for task performance is demonstrated [11].

It should be emphasized that most of the previous studies regarding applications of fMRI in neurosurgery are confined to comparison of this method with the gold standard techniques (direct cortical stimulation and Wada) rather than studies with a clear clinical endpoint. Hence, although validity of fMRI is proved for both brain tumor and epilepsy surgeries in multiple comparative studies, there is paucity of high-level evidence with data supporting fMRI in prognosis and functional abilities of patients after the surgery. Very few multicenter studies with large sample size [22], and subsequently lack of systematic review articles call for a serious effort to study the impact of the diversity of imaging protocols at different centers and possibly to work on the development of universal imaging protocol recommendations based on validated approaches.

## Technical Considerations

### Task Specification

Task selection is the first step in conducting a successful fMRI mapping for neurosurgical planning and is based on location of the brain lesion. Proximity of the brain lesion to sensorimotor, receptive, or expressive language or any other critical regions drives the selection of sensory, motor, or other paradigms. In functional neuroimaging studies, behavioral tasks can be categorized into two different types: block and event related designs. In block designs, which are most common in clinical fMRI, subjects alternate between active and rest periods that are not necessarily equal in duration. The number of active and rest conditions, as well as their length can affect signal to noise ratio [23]. Another consideration is increasing power in statistical analysis. Many studies suggest a total number of six activation periods in block designs for best results in statistical analysis [24]. On the other hand, in event-related paradigms, patients perform multiple short events of cognitive or motor tasks interspersed with rest periods of varying lengths. This paradigm is mainly useful in designing complex cognitive tasks where understanding the pattern of hemodynamic response and temporal events is of major importance. Compared to conventional block designs, longer acquisition time, and adequate performance by the subject are more important for event related designs. Although some studies recommend against using this type of paradigm in a patient population, others have found similar and even better results in event-related designs at least for cognitive tasks such as language [25]. A typical block paradigm usually takes 5–10 min, depending on the number of repeats and the duration of each block, while this time might take a few more minutes in event related designs.

Generally, there exists a tradeoff in using fMRI in patient populations. As a general rule, increasing scan time to acquire more alterations between activation and rest periods may increase signal to noise ratio, but patient cooperation, movement, and the time needed to study multiple functions/paradigms are limiting factors. Price and Friston as pioneers of clinical functional

imaging stated this tradeoff in one of their early works [26]. They presented an overview of the types of imaging experiments that can be performed on impaired patients. In order to accurately interpret changes in the pattern of activation in patients and controls normalizing for task performance is needed. Thus, patients should be assigned to specific fMRI tasks that they can perform [26].

### Motor Paradigms

To map motor areas, usually simple block designs are sufficient. Common tasks include hand clenching, sequential finger tapping, lip pursing, ankle plantar flexion, toe wiggling, and tongue movements. During motor tasks, especially tongue and lip movements, it is very important to minimize head motion. Head motion is detrimental to fMRI because it leads to false positive and false negative inference of activation maps [27, 28]. This problem is more prominent for motor tasks because the motion is temporally associated with the task itself [27, 29]. Object manipulation can also be used especially if the lesion involves sensory cortex as well. The surgeon should have a low threshold for ordering motor tasks. If the lesion is just close to motor homunculus, even in the absence of clinically evident paresis, motor tasks should be utilized [24]. FMRI can also help approaching seemingly inoperable lesions with mass effect causing displaced cortex by localizing the precentral gyrus.

In elderly patients and those with significant paresis, passive sensory paradigms, such as foot or hand stimulation by the examiner, can produce both post- and precentral gyrus activations, and then the location of the corresponding motor homunculus can be extrapolated [24]. However, these results should be interpreted with caution because pre and postcentral gyri usually show concurrent sensory activations.

To overcome this problem, we have developed a pneumatically driven finger movement paradigm as a novel passive functional MR imaging technique for presurgical motor and sensory mapping. This task not only activated primary motor and sensory cortices, but also activated supplementary motor area (SMA) [30]. Mapping of the SMA is also important when it is adjacent to lesions, since it has been shown that the SMA resection can result a contralateral motor deficit, regressive speech disorders, or both, similar to the SMA syndrome initially described by Laplane [31]. The topography and severity of these deficits are correlated with the extent of SMA resection and this somatotopy can be mapped via preoperative fMRI with most motor tasks [32].

### Language Paradigms

Selection of language tasks for patients is associated with additional challenges due to the complexity of the language network, numerous task designs available, the clinical status of the patient and task presentation modality (visual or auditory). Key for successful task selection is the location of the lesion and the patient's cognitive abilities. Language tasks can target either expressive or receptive areas but for many paradigms, both areas show concurrent activations. However, it has been stated that with fMRI posterior language areas are more difficult to activate compared to expressive frontal areas [33].

Expressive tasks usually elicit activation in the inferior frontal lobe in the region of frontal operculum. These tasks require patients to generate words in response to specific visual or auditory cues. These tasks can potentially be modified to illicit semantic functions as well. Generating words that fit a given category is an example of an expressive task that needs some degree of semantic processing. Among expressive language tasks, verb-generation tasks have been shown to be more successful in measuring hemispheric dominance [24].

On the other hand, receptive language tasks normally involve reading a visual cue or simply listening to presented words. Here, semantic manipulations can also be added to the task to provide a more detailed view of language network. For this category of language tasks, patient cooperation is very important and there should be a measure to determine how well the patient is performing the task during the scan session. To address this concern, some studies prefer

responses of patient to be vocalized (overt) so that the investigator is able to confirm that patients are actually performing the paradigm (however, this requires additional MRI compatible hardware to record responses and can introduce motion artifacts due to head motion or air movement in the oropharynx). For patients with brain tumors, some authors recommend silent (covert) paradigms to minimize artifact from speaking, while others use button pushes to address this issue [34]. In our own experience, a good practice session before the real scan session, performed by a skilled examiner who has experience with fMRI in patients, can evaluate patients' ability to perform tasks and predict and improve compliance during the scan. With a practice session and clear instructions to the patient, covert response by the patient has yielded good results in nearly all cases. Possible neurologic deficits, illiteracy, hearing or visual problems, and inability of patients to follow instructions while in the scanner may necessitate using simple language tasks such as visual object naming, or passive listening. Moreover, in patients whose primary language is not English, tasks could be modified to be used in their own language. Another option for this group or illiterate patients is to use visual object naming.

To monitor patient compliance and the successful completion of the tasks, the examiner should closely observe the patient during motor and overt language tasks. For silent tasks with a semantic process, real-time fMRI data analysis, as an option, which is embedded in most of the current scanners' software, can be utilized to get an indirect estimation of patient's performance and possible need for repeating the task. Obtaining consistent and valid results may require more than a single run especially in patients with cognitive deficits or those patients who have difficulty complying with task instructions. Using auditory paradigms for patients with severe visual problems is an option, but it should be noted that scanner noises, especially during EPI image acquisition, might be a source of false positive activations, especially in superior temporal gyrus [35]. This necessitates a dedicated team to dynamically monitor results and revise steps involving practice session with patients, image acquisition parameters, and possible real-time analysis and repeating in the case of questionable results.

## Data Analysis

Typically, the blood oxygenation level dependent (BOLD) signal change is approximately 2–5 % in sensorimotor tasks and lower for higher cognitive tasks such as language and memory [36]. For this reason, maximizing signal to noise ratio is of vital importance. Here, preprocessing steps play a major role to prevent signal loss during data analysis. In commercially available software with FDA approval for fMRI analysis in patients, there are often parameters that are not adjustable. The typical preprocessing steps that are usually embedded in commercial software packages are motion correction and spatial smoothing. After these preprocessing steps, statistical methods are used to show active regions associated with the patients' task performance. Here, those voxels whose BOLD signals are time correlated with the task paradigm will show a significant activation if above a minimum user defined threshold. Clusters of active voxels can be mapped at different statistical thresholds, often with different representative colors. If a resection is planned, it is often useful to view the activation maps with a variety of threshold levels (Fig. 1). This is because false positive and false negative activations can mislead the surgeon if activations are displayed at a static threshold, which does not take the dynamic effect of threshold level on the size of active clusters. Figure 1 shows an example of thresholding effects on activations maps.

For analysis purposes, two different models can be used; (1) hypothesis driven (or model-based for the BOLD response) and (2) data driven (model free). Hypothesis-driven analysis is currently the more popular method in clinical fMRI and typically utilizes the general linear model to test a hypothesis regarding the involvement of brain areas in performance of the task [37]. Recently, studies have demonstrated the applicability of independence component analysis (ICA) as a model-free approach in patients requiring surgery [38]. This method shows some promise but few studies have used this approach in patient

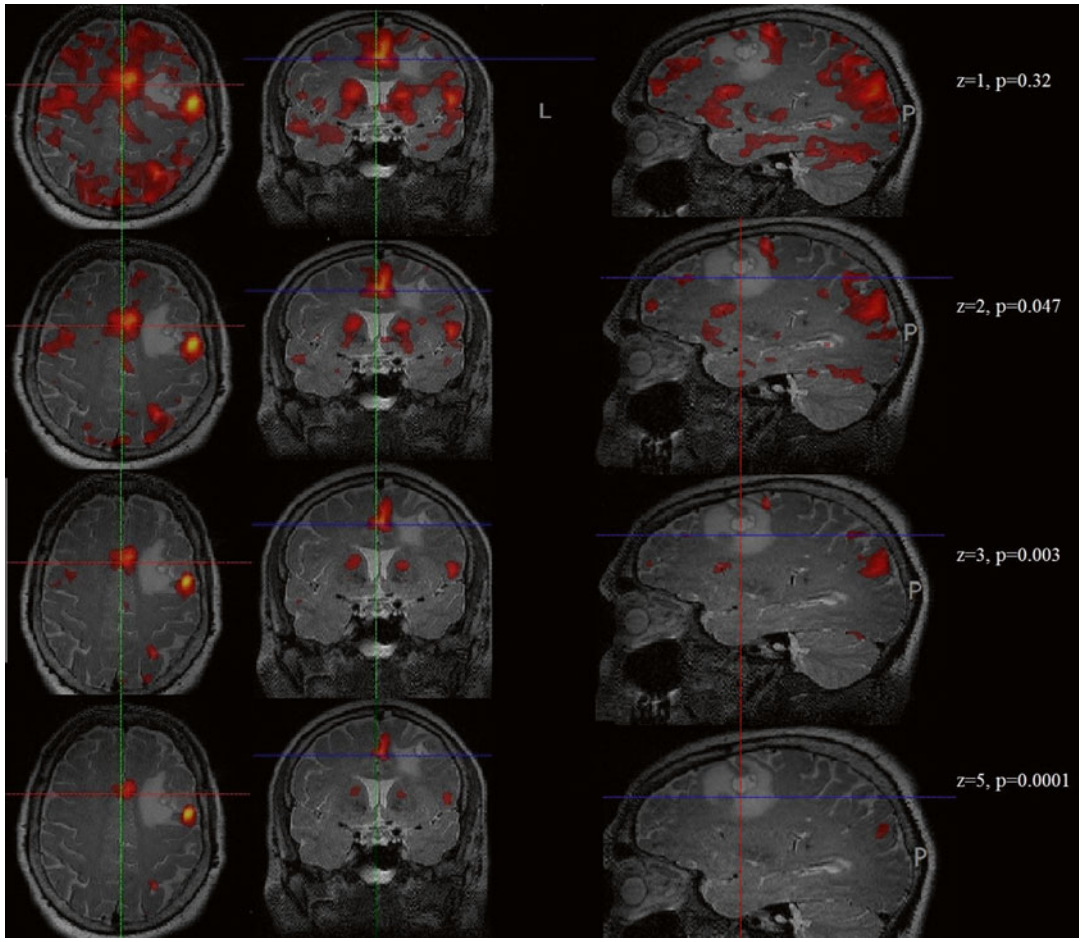


**Fig. 1** Thresholding and interpretation of results. Four different statistical thresholds applied to fMRI data from a patient with left frontal lesion performing a sentence completion language task. The apparent overlap between expressive language cortex and the lesion decreased as the threshold was increased

populations, and this method is not currently available in clinically approved software packages [39, 40].

Accurate coregistration of low-resolution fMRI maps to high-resolution structural images is necessary to view the activations' spatial relationship to brain lesions. Coregistration also enables importing functional activations maps to the neurosurgical navigational systems. Here, a valid registration is critical and not always straightforward due to the very different imaging characteristics of BOLD and structural images. Thus, it is important to review the registration results before interpreting the functional map or using during neurosurgical intervention. See Fig. 2 that shows an inaccurate coregistration of EPI to the structural image.

## Limitations of fMRI

Beside general limitations of an fMRI study such as low temporal resolution and large dependence of activation maps on thresholding, some limitations are more specific to neurosurgical patient populations. Of these, susceptibility artifacts, brain reorganization, and effects of brain lesions on neurovascular coupling are well-studied limitations.

The most common causes of clinical fMRI failure are existing neurological deficits and

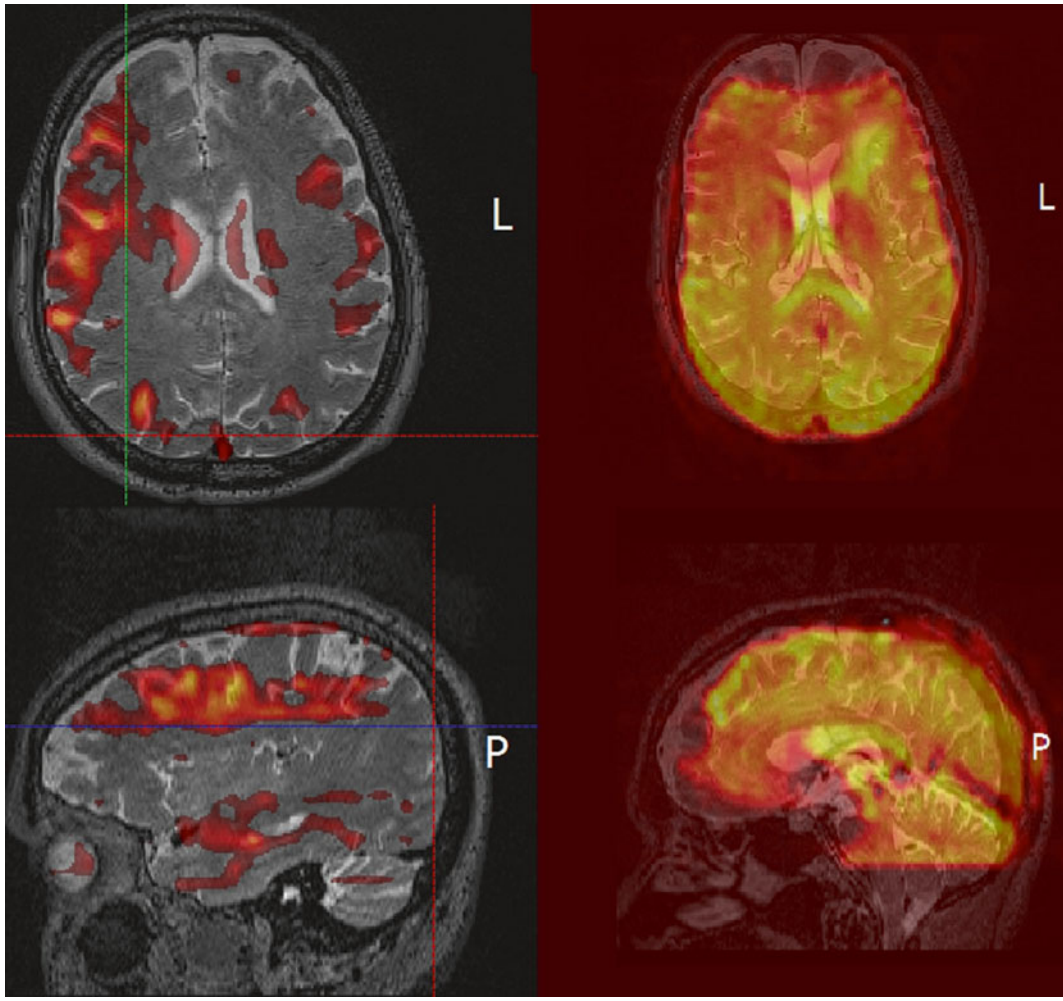


**Fig. 2** False positive activations in fMRI studies. An inaccurate coregistration of functional to structural image (*right*) and false positive activations in the lateral ventricles (*left*) in a left hand motor task. Previous studies [29] showed that an increase in signal noise would decrease the sensitivity of detecting significant activation, or could lead to false positive activation. If respiration becomes task-correlated, the signal fluctuation due to respiration could be mistaken for BOLD signal changes directly associated with the task, leading to misinterpretation of the functional data. It is very important for the surgeon to review both registration and activation maps to be sure about the validity of the results

patient movement [41]. As discussed earlier, head motion can be a source of false activation, especially in motor tasks (see Fig. 2). Moreover, any neurological deficit can result in poor patient performance during scan acquisition. Moreover, studies have shown that it is more difficult for patients to remain still during the MRI session [27]. This leads to increased motion artifacts in this population.

Another frequent problem seen in fMRI in patient populations is related to magnetic susceptibility. Magnetic susceptibility is a measure that indicates the amount of magnetization of a tissue or substance in response to an external magnetic field. Any large differences in magnetic susceptibility of nearby tissues can cause distortions in the local magnetic field and produce artifacts. This is particularly important in patients with prior surgery

since previous manipulation and implantation of plates, metallic staples, and even postsurgical gliosis, and hemosiderin staining can cause strong susceptibility artifacts. Although studies exist that show applicability of fMRI in such patients [42] there should be always a suspicion for a potential false negative results in patients with prior surgery [24]. This can be explained by T2* effect. T2* decay refers to an exponential decrease in signal strength following the initial excitation pulse as a function of time constant T2*. Changes in BOLD contrast, which is the key event in fMRI signal generation, are maximized if the echo time (TE) is equal to the susceptibility-mediated transverse relaxation time constant, T2* image. The acquisition is very sensitive to intravoxel dephasing resulting from macroscopic field gradients established near air–tissue interfaces [43]. These susceptibility-induced field gradients result in severe dropout of signal in the frontal orbital regions due to the difference in magnetic susceptibility of tissue and air [43].

Brain plasticity is another issue that can complicate interpretation of patient fMRI studies. Cortical reorganization due to a growing lesion within the brain can result in novel areas of activation. This plasticity and compensation can be found near the primary lesion, as well as in more distant regions including the contralateral hemisphere. For this reason an unusual activation should not simply be dismissed as a false positive in patient populations [44–46].

Another concern in using fMRI in patients is possibility of altered neurovascular uncoupling in presence of any pathology in the brain. Since a valid BOLD interpretation largely depends on coupling of neural activity and subsequent and predictable increase of local blood flow, any pathology that can affect this coupling can cause false positive or false negative results. Studies have also revealed that the presence of abnormal tumor neovasculature in high-grade lesions, such as glioblastoma multiforme, can lead to a decrease in the fMRI activation volume [47].

In summary, there are two different limitations in using fMRI in patient populations: (1) difficulties that are related to image acquisition (motion, poor performance due to neurologic deficits and susceptibility artifacts); and (2) those that are related to interpretation such as brain reorganization. These factors should be considered when interpreting activations maps in patients.

### Future Perspective

Functional MRI is now a commonly used tool for mapping different brain networks, but its role for routine clinical practice for presurgical planning requires additional study. More research with clinical and objective outcomes should be performed to produce high quality evidence. Studies that can help the clinician understand which activations represent critical eloquent areas as well as which tasks can best elicit activations in these regions are needed to extend clinical applicability of fMRI. Another promising area in the functional neuroimaging for neurosurgical planning is resting state-fMRI. Thus far, some potential clinical applications of this method have been investigated [38]. Its applicability especially for those patients who cannot cooperate well is intriguing and could extend fMRI to more neurosurgical candidates despite difficulties with cognition of and cooperation.

Besides the ongoing research on the technique itself and introducing new applications, it might be a proper time to revisit research aims for functional neuroimaging and shift from comparative studies (fMRI versus traditional gold standards), to delineate fMRI prognostic values. Although theoretically use of fMRI can help surgeons to perform wider and safer resections, there remains a paucity clinical data especially from large multicenter cohorts.

## Diffusion Tensor Imaging (DTI)

### Uses and Current Evidence

Clinical deficits after neurosurgical intervention may result not only from damage to cortical structures, but also from injury to critical subcortical white matter connections. For this reason, mapping cortical regions by means of fMRI itself

is not sufficient to guide a safe surgery, and the surgeon should consider the course of the subcortical white matter structures originating from eloquent cortex as well. Here, the gold standard technique is intraoperative subcortical stimulation to delineate pathways directly related to motor and language functions [48]. Yet, application of this invasive method is even more limited compared to direct cortical stimulation, because it is very difficult to discriminate tracts of interest from other white-matter tissue [49]. Another problem with the direct stimulation is determining the optimal stimulation points as well as stimulation thresholds [49]. Moreover, studies have shown that subcortical pathways might be stimulated only once the resection margin is already within these pathways or as little as to 2–3 mm away, which may increase the risk of injury [50].

## Basics in DTI Tractography

For visualization of individual patient white matter anatomy, a noninvasive MRI-based alternative is diffusion tensor imaging (DTI) [51]. The physiologic basis of DTI lies in the increased diffusion of water molecules parallel to white matter fibers compared to the hindered diffusion perpendicular to the fibers. The underlying physical process of diffusion can be modeled with a Gaussian or diffusion tensor model, which describes diffusion using ellipsoidal isoprobability surfaces. Water molecules initially located at a point would gradually diffuse to reach the surface of an ellipsoid. The ellipsoid itself has a principal (longest) axis and two perpendicular axes that describe its width and depth. The axes in this setting are called eigenvectors and the measures of their lengths are defined by the eigenvalues. Mapping the principal eigenvector in each image voxel forms the basis for DTI tractography, or tract tracing. Here, the assumption is that the principal eigenvector is aligned with the direction of the fiber bundle. The disparity in the diffusion pattern, where the eigenvalues are not equal, is known as diffusion anisotropy and is related to the presence of the cellular membranes and myelin sheaths [52]. White matter tracts can be visualized using fractional anisotropy maps, directionally color-coded maps [53], and tractography, which can demonstrate large subcortical white matter pathways and their relation to the tumor or any lesion to be resected. Unlike subcortical stimulation, DTI can demonstrate the organization of white matter bundles and their integrity prior to the surgical intervention. The spatial organization of fiber tracts shown by DTI is generally consistent with their known anatomical course and the somatotopic organization of the corresponding tracts [54]. Compared to most fMRI studies, DTI and tractography do not require active cooperation of the patient for data acquisition, which makes DTI tractography more applicable for patient populations.

## Is DTI Valid?

The validity of DTI tractography has been compared with subcortical stimulation mapping and the results have been promising except for relatively low spatial resolution. To show concordance between the DTI results and the intraoperative subcortical stimulation, some studies [55, 56] have calculated the distance between the intraoperative stimulus point and the motor tracts as demonstrated by DTI and coregistered to the surgical field by means of neuronavigation systems. The measured distance between the stimulus point and the DTI-identified tract in patients with positive subcortical motor evoked potentials after bipolar stimulation was shown to be less than or as near as 8.7 mm [57, 58]. It should be acknowledged that the use of neuronavigation systems is not the best option for validation purposes since these systems use preoperative images that do not take into account intraoperative brain shift. To address this potential drawback, some authors [57–59] have examined the relationship between subcortical stimulation and motor tracts using *postoperative* DTI tractography. These studies showed that the distance between motor evoked potential responsive sites and intraoperative tractography is correlated with the intensity of subcortical stimulation but the average distances were not different from previous findings which used preoperative data.

Studies confirming the accuracy of the DTI tractography are not limited to motor studies. Some reports [55, 60] have shown a correlation

between tractography and subcortical stimulation in patients with gliomas near the language tracts. Overall, most studies suggest that DTI-based tractography results are a reliable way to map motor, language, and visual tracts throughout the brain for clinical use. It should be noted that crossing tracts and edema are the two key challenges in using DTI tractography in clinical setting. These limitations will be discussed below. Moreover, it remains a challenge to understand which tracts highlighted by the method are critical for preserving neurologic functions of the patient.

### DTI Tractography in Neurosurgery

Current evidence for using DTI in neurosurgical interventions could be broadly categorized into preoperative and intraoperative applications. As stated earlier, brain shift is the major source of error in intraoperative usage of the method. On the other hand, DTI data are an invaluable resource for the neurosurgeon to plan a safer surgery preoperatively. Here, unlike in fMRI studies, more clinical outcomes have been reported. One of the key studies was conducted by Wu and colleagues [61] investigating the pyramidal tracts. They showed that DTI-based functional neuronavigation contributes to maximal safe resection of cerebral gliomas with pyramidal tract involvement, thereby decreasing postoperative motor deficits in patients with gliomas. Romano and colleagues also [62] evaluated the impact of the information provided by preoperative tractography on surgical planning and the procedure itself in 28 patients. Three key tracts were identified and evaluated separately: The corticospinal tract, arcuate fasciculus, and optic radiations. Preoperative assessment of the visualized trajectories close to the brain lesions resulted in a modification of the surgical approach in about one-fifth of the cases, and had an impact on the definition of the resection margins during surgery in 64 %. Similar results have been shown in other studies with tumor patients [63]. Thus, studies support that DTI is valid compared to the gold standard technique, as well as a useful clinical tool that can affect surgical decision making. However, as with fMRI studies, there are few long-term prognostic cohorts to show effects of DTI on survival and other clinical endpoints [61, 64].

## Technical Considerations

### Data Acquisition and Tractography Methods

Acquisition sequences for DTI are readily available on most commercial 1.5 and 3.0 T MR scanner platforms. DTI for tractography is usually obtained as echo-planar images [65, 66]. Detailed parameters of image acquisition for DTI are beyond the scope of this chapter but one should know that magnetic field gradients are applied in multiple orientations or directions, and increasing the number of directions [67] can significantly improve image quality for tractography. Moreover, image slices must be contiguous and be as thin as 3 mm or less to obtain good results [65]. In addition to DTI, high-resolution 3D structural images are also acquired to provide an anatomic frame of reference and for integration into neuronavigation systems.

After image acquisition, there are numerous different methods to perform the tractography; two widely used approaches are deterministic and probabilistic methods [68, 69]. Usually fiber tracts are first generated from a starting region (seeds) on the $b = 0$ s/mm$^2$ echo-planar images or the colored fractional anisotropy maps from the DTI sequence. For deterministic fiber tracking, the main direction of the diffusion tensor is tracked in a stepwise fashion, beginning from the seed voxel or the region of interest. This continues until the fractional anisotropy is lower than a predefined threshold [70]. In the probabilistic approach however, tracts will be identified by sampling a Gaussian probability density function at each voxel, whose covariance matrix is defined by the tensor at that voxel [71].

### Which Tracts to Map? Where to Seed?

For the purpose of neurosurgical planning, three pathways are of vital importance: motor tracts (corticospinal tract), language fibers (arcuate or uncinate fasciculus), and visual pathways. For the motor tract, two seeding areas are usually selected; the cerebral peduncle and primary motor cortex [57, 58, 72]. A combination of three seeds including the cerebral peduncle, posterior limb of the internal capsule, and precentral gyrus has also been used in some studies [65]. Our team

recently compared five different seeding methods for the best results in the motor tract [73]. Results indicated that whole brain seeding followed by *selection* of the tracts that pass through two anatomically relevant regions of interest could delineate more plausible hand and lip motor tracts than seeding from a single region of interest. For the foot motor tracts, all seeding methods work very well. It should be noted that increasing the size of the seeding region would increase the computational time to perform tractography.

For language tracts, different regions of interest for the initial seeding can be used. Thus far, manual seeding in the white matter bundle [74], seeding in both anatomically defined expressive and receptive language areas [75], and seeding in the functionally defined language areas [76] have been proposed. The latter method might be more accurate in patient populations because the normal anatomy might be distorted. This also opens up avenues for current efforts for integration of fMRI and DTI for presurgical planning (see below). Regardless of the initial seeding for language pathways, almost all studies reliably showed the classical C-shaped segment of the arcuate fasciculus (Fig. 3). Although, in some cases, crossing fibers might prevent the arcuate fasciculus tracing from reaching Broca's area [77] using the traditional DTI single-tensor model.

Successful tracing of the visual tract can be more challenging to delineate with DTI because it is a thin band of white matter that turns at a sharp angle through Meyer's loop [65]. Selected regions of interest for initial seeding include the lateral geniculate ganglion [62], the lateral geniculate body and paraventricular area of the lateral ventricles [78], the lateral geniculate body and the adjacent temporal lobe, and the lingual and cuneus gyri in the occipital lobe [79].

In summary, DTI can be acquired on almost all new MR machines. Motor, language, and visual pathways are the three main tracts that are usually studied for presurgical planning. Seeding and starting points are important choices for performing a good tractography. Thus far, multiple anatomic and functional seeds have been used to show tracts of interest. For the patient population, white matter that is around functional maps from fMRI studies could be employed as seeds [80]. As stated in fMRI section, a fully experienced team is of vital importance to get valid and reproducible results. For DTI tractography, a team including physicists, technologists, computer scientists, and analysis members is very important for obtaining the most useful results.

## Limitations

Although DTI is the only noninvasive tool for in vivo delineation of white matter anatomy, certain limitations may limit its use in the patient population [81, 82]. Some limitations such as the inability to model crossing fibers are present in

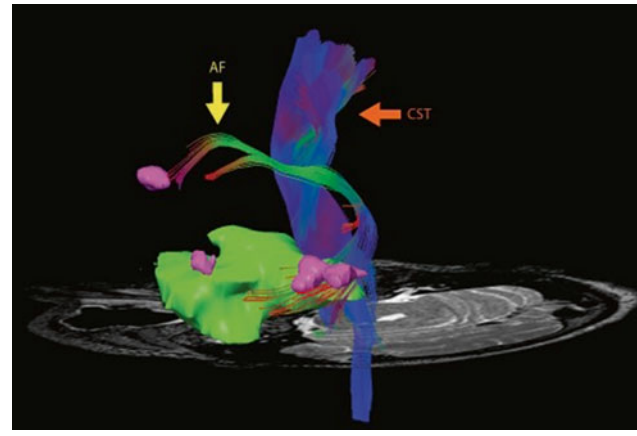


**Fig. 3** DTI tractography in a tumor patient. The corticospinal tract (CST) and arcuate fasciculus (AF) were mapped in a patient with a left temporal tumor. Tumor was segmented as *green*. AF is shown between the receptive and expressive language areas as defined by fMRI (*purple*)

all DTI studies, while artifacts due to tumors, edema [83] and inhomogeneities in the magnetic field are additional issues in patient populations.

Algorithms based on the major eigenvector cannot resolve regions of crossing white matter pathways because the anisotropy in such regions is planar rather than linear. New diffusion imaging methods, such as q ball imaging and high angular diffusion imaging may be able to resolve the intersections of crossing white matter regions more accurately but these methods require higher diffusion weighting and take much more time in acquisition [84]. Hence, many studies have tried to develop better analysis algorithms to address fiber crossing [85].

For the patient population, a false "interpretation" of the results is a potential pitfall. It has been shown that tracking may underestimate the size of a fiber tract in pathologic conditions [55]. Tumor infiltration and edema near the tumor can result in decreases in anisotropy of water diffusion. When brain tissue is affected by the tumor and its resulting edema, the distribution of fiber orientations can be more random. Hence the fractional anisotropy value can be significantly reduced, even if the functional integrity of fibers is maintained [55]. The decreased anisotropy leads to difficulty in tracking through regions of edema, which in turn leads to false negatives. Moreover, as mentioned earlier, brain shift during surgery is another potential source of error especially if DTI is used as an intraoperative guidance tool.

Finally, for clinical purposes, most clinicians tend to do a simple and conventional analysis by means of commercially available software. A recent study showed that there is a statistically significant difference in the anatomic accuracy of the commonly used DTI tracking software packages [86, 87]. This finding could potentially misinform surgical decisions if used without thoughtful interpretation and verified where necessary by intraoperative cortical stimulation. Thus, a clinician must be able to critically appraise any unexpected data from DTI results and retest it with other packages if applicable.

## Integration of FMRI and DTI

As stated in the limitations section for DTI, tracking of fibers in the vicinity of or within lesions and tumors is prone to numerous challenges. The mass effect secondary to tumor can warp the architecture of the white matter and in some cases prevent a confident selection of the seed region of interest from which tracking initiates. In patients with a large brain tumor with adjacent edema, conventional approaches for seeding based on anatomical landmarks may result in unsatisfactory results. To address this problem in the patient population, studies have proposed to select the seed points based on functional MRI activations [88]. It has been shown that fMRI-based seeding enables a more comprehensive mapping of fiber systems for both language and motor areas in patients with brain tumors [89, 90]. These results support the integration of fMRI and DTI to perform multimodality mapping in patient populations. Usually, the clinical interpretation of complex white matter tractography data is done in a collaborative fashion, in which a clinician selects tracts of interest. In order to try to guide the selection of tracts, our group has developed a semi-automatic method (landmark distance model) that can identify tracts based on a white matter statistical "atlas". The multimodality input data used to construct the model includes DTI, fMRI, and structural MRI [91]. Our results in healthy subjects were quite satisfactory and because the model is robust to displacements of the scale typically found in patients with mass lesions, it can also be used for patient populations. There is a huge potential room for future research in combining fMRI and DTI and automated models for prediction and detection of fiber tracts in patient population.

## Clinical Case Presentation

In this section, two patients will be reviewed to show how fMRI and DTI can be used to guide surgery. We go through a systematic framework to get results. This framework is summarized in

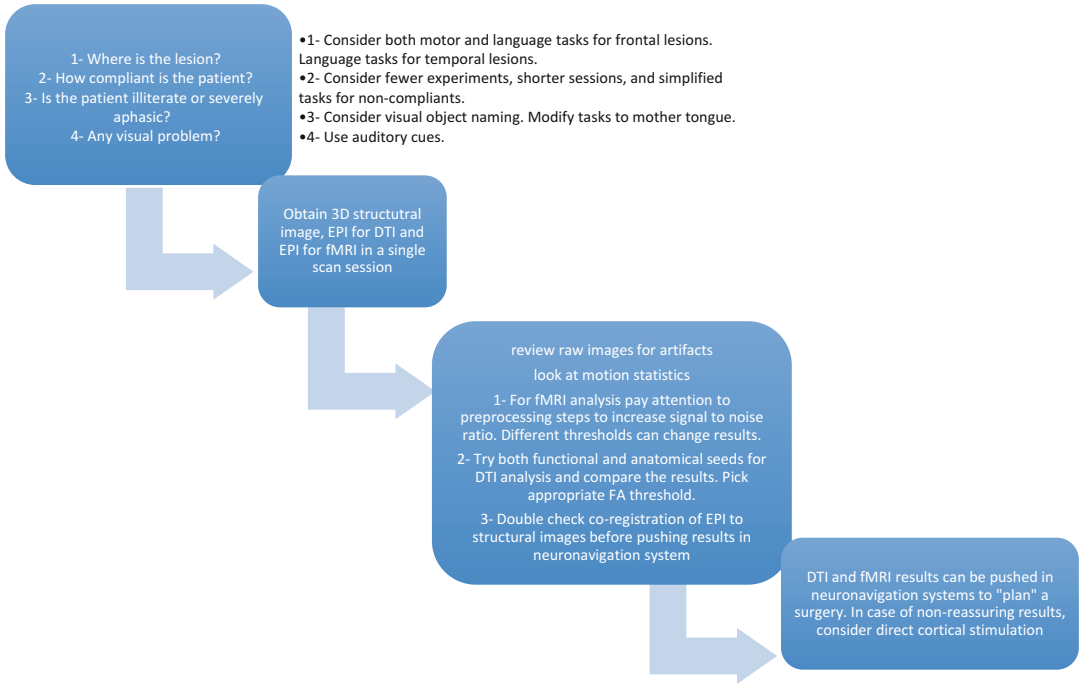


**Fig. 4** Steps involved in presurgical brain mapping with fMRI and DTI in patients

Fig. 4 and involves identification of tracts and regions of interest; task selection for fMRI; and image acquisition parameters. After acquisition, fMRI processing can be performed either on scanner proprietary software (which may require additional licenses) or at a separate workstation with fMRI analysis software installed. A separate workstation is recommended, to free up the scanner console and improve patient exam flow. This workstation must be able to reliably receive and transfer DICOM images; raw images need to be received from the MRI scanner (or PACS), and processed images need to be pushed to the hospital PACS system. The workstation must also meet hardware requirements as specified by the fMRI analysis software manufacturer. It should be noted that fMRI (and DTI) DICOM files typically require significantly more hard disk space compared to structural MRI studies. This can be incompatible with some hospital PACS servers, and additional servers may be required. Some scanner manufactures have developed DICOM file formats (i.e. Siemens "mosiac") that reduce file size and facilitate faster file transfer.

Upon completion of image acquisition and analysis for both fMRI and DTI, results could be pushed to a neuronavigation system for surgical planning.

## Case One: Language Cortex

A 27 year old male patient with a large non-enhancing left frontal lesion was referred for tumor resection. Presenting symptom of the patient was seizure and he had no focal neurological deficit or language and cognitive decline. The patient was working as PhD student and fully functional. MRI scan shows a large left frontal and insular lesion that involved the frontaloperculum where it seemed to be involving Broca's area. There was some tumor in the left anterior temporal lobe as well. The tumor was T2 and FLAIR hyperintense and did not enhance with gadolinium injection.

Since the patient had no language deficit prior tosurgery and was fully cooperative, there were no limitations in selecting language tasks during

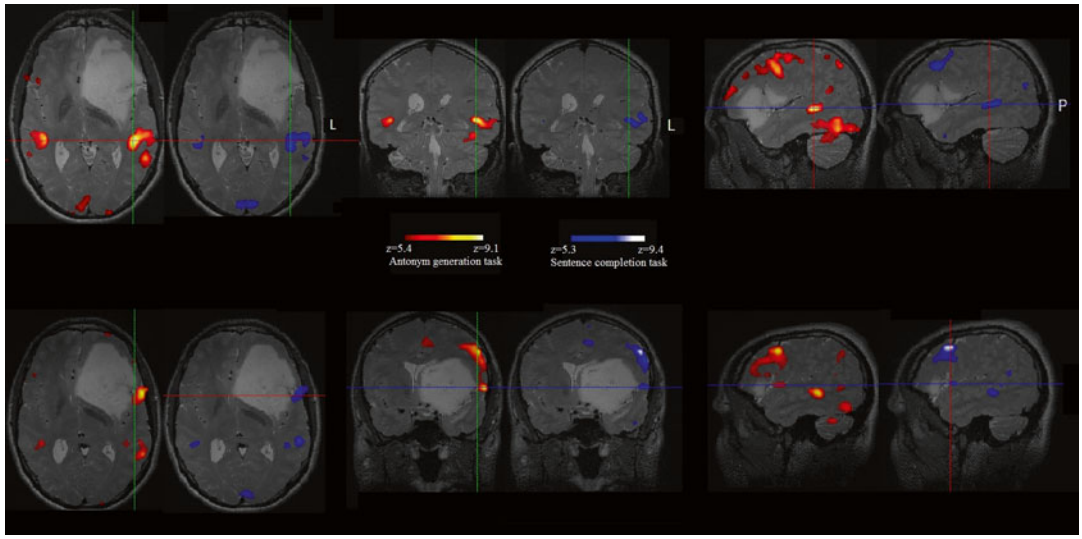


**Fig. 5** Case #1: Language mapping. *Top row* shows brain activations in receptive language area in superior temporal gyrus. Both antonym generation (*red*) and sentence completion tasks (*blue*) show this area with no displacement. *Bottom row* are slices to show expressive portion of the language system. Both tasks show evidence that this area is displaced posteriorly and superiorly by the tumor

the fMRI session. After reviewing the options, antonym generation and sentence completion tasks were chosen for evaluation of language function. More than one task was used to get a comprehensive view of the language cortex (see Fig. 5). We chose block design paradigms for the patient. Both tasks had 20-s blocks of alternating task and rest conditions. For activation periods, generation of antonyms for visually presented words and completing unfinished sentences were used. Task instructions were reviewed with the patient before the scan session and no issues with task performance were noted. EPI acquisition parameters for the fMRI were as follows: 24 axial slices with no gap, TR = 2000 ms, TE = 30 ms, flip angle = 85°, slice thickness 5 mm, 64x64 matrix, voxel size = 3.475 × 3.475 × 5 mm. After data acquisition, image registration was performed. The lower resolution echo planar images (raw fMRI data) were linearly co-registered to a high-resolution three dimensional T2 image, for purpose of visualization and surgical planning. Finally, activation maps for both tasks were mapped to patient's 3D structural image. As evident in Fig. 5, the two tasks showed consistent results. Slices in the top row focuses on expressive portion of the language and shows a displaced Broca area because of the tumor bulk and in the temporo-parietal region receptive areas seem to be intact (Fig. 5).

The next imaging analysis was DTI tractography,which was obtained in the same scanning session. For this particular patient, and because of the location of the tumor and the surgical approach, the corticospinal and arcuate fasciculus tracts were studied. For DTI, image acquisition used these parameters: EPI sequence with TR = 5000 ms, TE = 109 ms, *b* value = 1000 s/mm$^2$, 20 gradient directions, 2 baseline images, 192 × 192 matrix, Voxel size = 1.14 × 1.14 × 5.2 mm. Although these parameters are not ideal (near-isotropic voxels are preferred for DTI), they yielded a relatively satisfactory result for presurgical mapping. The results of tractography, fMRI activations, and tumor segmentation are illustrated in Fig. 6. For this analysis, tumor and fMRI results were used as regions of interest for initial seeding.

The patient underwent awake craniotomy withintraoperative stimulation of language areas based on the coregistered activation maps that were uploaded to the neuronavigation plat-

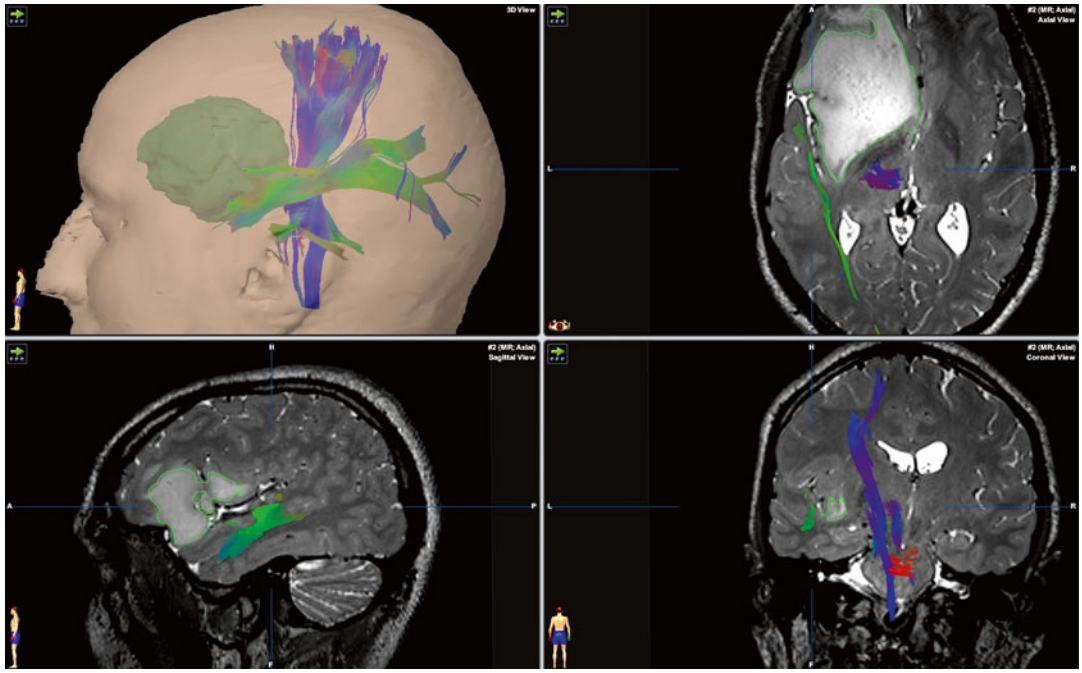

**Fig. 6** Case #1: DTI tractography and 3D reconstruction. Corticospinal tract (*blue*) and arcuate fasciculus (*green*) were mapped in a patient with a large left frontal tumor (same patient as Fig. 5). Tumor was segmented as *green*. Arcuate fasciculus is shown between the receptive and expressive language areas

form. The patient was speaking well throughout the surgery, but in several instances, especially while dissecting superiorly and close to corona radiata, he had trouble with speech. The surgeon then stopped dissection in that area and waited for his speech to return to normal. Intraoperative MRI showed a complete resection and patient had uneventful recovery with no motor and language deficits following the surgery. Pathology demonstrated diffuse astrocytoma (WHO grade II).

## Case Two: Frontal Lesion and Motor Functions

The second case is a 40-year-old female presented with left hand paresis. Brain MRI after contrast injection showed a heterogeneously enhancing, subcortical large right parietal/supramarginal gyrus mass in the subcortical white matter extending to the cortex of the posterior Sylvian fissure located in the lateral posterior frontal cortex close to the putative motor cortex (see Fig. 7). She had a previous biopsy with WHO grade III glioma (oligoastrocytoma V. astrocytoma) as diagnosis. The patient reported intermittent tingling in her left hand. Concern for preservation of hand and face movements motivated a preoperative fMRI study. We chose finger clenching and lip pursing as activation components of the motor design for fMRI study. If the lesion were medial or if the patient had paraparesis, ankle movement could also have been considered. Given her presenting symptom and tumor location, the corticospinal tract was targeted for DTI tractography.

The patient underwent both fMRI and DTI with imaging acquisition parameters as stated for the previous case. FMRI activation maps showed a close proximity of left hand activation to the tumor (Fig. 7). Then, fMRI activation maps and corticospinal tracts were rendered into neuronavigation software to reconstruct three-dimensional relations of the tracts; segmented tumor and fMRI activations (Fig. 8).

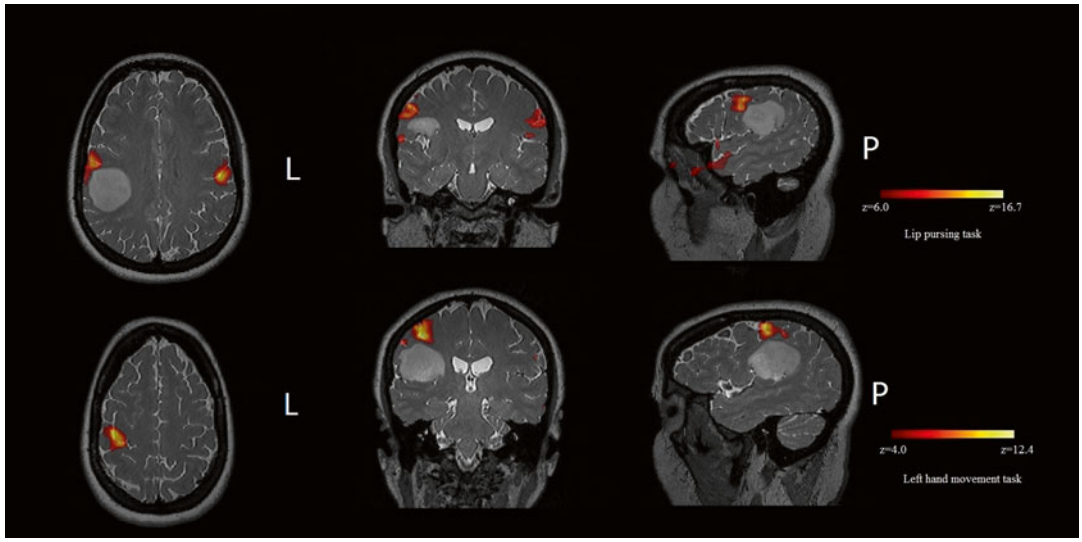


**Fig. 7** Case #2: FMRI to localize motor function. A 40-year-old female presented with left hand paresis. Given the location of her lesion and its relationship to the motor homunculus, hand clenching, and lip pursing tasks were selected for motor fMRI. Slices in *top row* were selected to focus on face activations (lip pursing task) while *bottom cuts* focus on left hand activations. See Fig. 8 for 3D visualization of fMRI activation

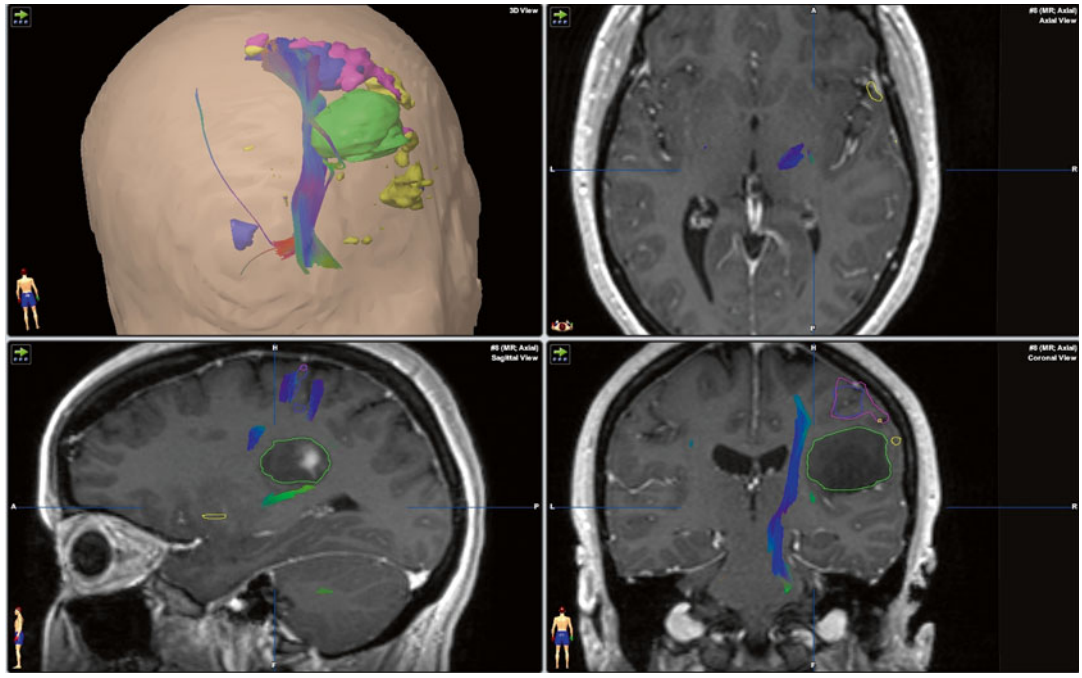

**Fig. 8** Case #2: 3D visualization for surgical planning. Multimodal preoperative imaging in a 40-year-old female with a left hemisphere lesion (same patient as Fig. 7). Corticospinal tract (*blue*), segmented tumor (*green*), and fMRI motor task activations (*purple*: hand movement, *yellow*: lip pursing) were demonstrated in three planes. Three-dimensional reconstruction of tracts and fMRI activations (*top left*) can be integrated into the neuronavigation system for operative guidance

During surgery, her head was placed in three-point pin fixation. The image guidance system was then used to co-register the patient's head position to the preoperatively acquired MRI scan and 3D reconstruction of DTI and fMRI results. An excellent co-registration was achieved and neuronavigation guidance with tract and activation maps was used to plan the approach and trajectory towards the lesion.

During the operation, no long-acting paralytics had been used to enable motor mapping. With the aid of coregistered maps of activation, hand responses were found immediately adjacent to the area of the planned resection. Continuous somatosensory evoked responses as well as intermittent motor evoked potentials were used during the resection. Based on the results from the cortical mapping and the preoperative mapping guidance, which were quite similar, an incision point and approach for resection was determined and a successful resection of the tumor was made. Data from fMRI and DTI, which was obtained before surgery, was very helpful to speed up and facilitate intraoperative mapping.

## Conclusions

Both fMRI and DTI tractography are valuable noninvasive tools for presurgical brain mapping and planning. Although their validity has been confirmed in comparative studies with their traditional invasive predecessors such as direct electrical stimulation, there is a paucity of clinical data confirming their potential benefits in patients' functional outcome and survival. There are numerous technical considerations and limitations when using these methods clinically, and this necessitates familiarity of the practicing surgeon with the underlying physiology and the methodology for both techniques. Moreover, future avenues for research are open not only for technique optimizations but also for clinical studies of effectiveness of the current knowledge.

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# Intraoperative Cortical Mapping Techniques and Limitations

Juanita M. Celix and Daniel L. Silbergeld

## Introduction

For greater than 50 years, electrical stimulation and recording of the cerebral cortex has been an important neurosurgical tool. Electrical stimulation of the cortex can be used to identify primary sensory, primary motor, and essential language cortices, as well as functional association areas and important subcortical tracts. Stimulation mapping remains the gold standard for localizing cortical function during surgery. Because of their reliability, intraoperative cortical and subcortical stimulation mapping techniques are used to guide resections in regions of brain near eloquent cortex. In the surgical management of primary brain tumors, the current trend is toward greater extent of resection, which has been shown to provide a survival benefit [1–5]. The potential benefits of greater extent of resection, though, must be balanced with the risk of loss of function, which has been shown to decrease overall survival [6]. Cortical mapping is an intraoperative tool that can enable more extensive resections while reducing operative morbidity.

Stimulation mapping is used primarily in patients undergoing resection of intrinsic brain tumors, metastatic lesions, or epileptic foci located within or adjacent to regions of essential brain function. Sensory and motor mapping is performed for lesions in/near Rolandic cortex, supplementary motor cortex, corona radiata, and internal capsule. Language mapping is performed for lesions in the dominant temporal, posterior frontal, and anterior parietal lobes. Although the classic teaching is that cortical language is located in the posterior inferior frontal gyrus (Broca's area) and posterior superior temporal gyrus (Wernicke's area), among tested individuals actual cortical language representation varies significantly [7]. A useful guide when approaching intrinsic tumors is to remember that removing a brain tumor is removing a piece of brain with tumor cells in it. Similarly, removing an epileptic focus is removing a piece of brain with epileptogenic neurons in it. With this in mind, stimulation mapping is a powerful tool to aid in safer neurosurgical resection.

**Core Messages**

- Stimulation mapping is the gold standard for intraoperative localization of cortical function.
- The benefit of surgical resection must be balanced with the risk of loss of function.
- When in doubt about proximity to eloquent cortex, cortical mapping provides a reliable method of localizing and thereby protecting function.

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## Preoperative Evaluation and Preparation

There are two primary ways of knowing preoperatively that a resection will be near important functional cortex: imaging and the patient's symptoms. The presence of a preoperative deficit indicates a tumor or abnormality in or near functional cortex. The successful use of stimulation mapping to guide surgical resection requires that certain functional criteria be met. To reliably identify loss of or alteration in function during intraoperative stimulation, the patient must have a robust and reliable baseline from which to assess change. Therefore, the preoperative neurological examination must thoroughly evaluate the function to be localized during surgery.

For successful somatosensory mapping a patient must have normal cortical sensory function (proprioception, light touch, two-point discrimination) or only a mild sensory deficit. Successful motor mapping requires at least antigravity (grade 3 or better) strength. If a severe hemiparesis (grade 1 or 2) is present, then motor mapping is not usually possible. In children, cortical electrical excitability is reduced. As a result, the motor cortex and subcortical pathways in children younger than 6 years often cannot be excited by cortical stimulation, even in the setting of a normal motor exam. In a patient with a severe motor deficit or in a young child, somatosensory-evoked potential (SSEP) mapping can be used to identify sensory cortex, and then the central sulcus and pre-central gyrus.

Successful stimulation language mapping requires a patient with only mild language deficits. A moderate to severe deficit in either language expression or language comprehension will provide unreliable mapping results, with potentially disastrous consequences. To test for language errors, a standardized object-naming task is performed during the preoperative evaluation. A series of images of common objects is presented at a rate of 3–4 s per image. For intraoperative language mapping to be considered reliable, the baseline naming rate must be at least 75 %. It may be helpful to perform the object-naming task after a course of corticosteroids in those patients with significant language deficits, as some will improve to acceptable baseline naming.

In addition to minimum functional requirements, stimulation mapping of either somatosensory or language cortex requires an awake cooperative patient. In general, stimulation language mapping is not performed in children younger than 10 years, nor in patients with developmental delay or significant psychiatric illness. The anesthetic concerns when performing an awake craniotomy will be discussed below. A pre-anesthesia evaluation should be performed to identify patients with medical comorbidities that may preclude awake anesthesia. The most common relative contraindications for awake neurosurgical procedures include pulmonary disease, airway abnormalities, obstructive sleep apnea, and obesity. Both SSEP mapping of somatosensory cortex and stimulation mapping of motor cortex do not require patient cooperation and can be performed in a patient under either general or local anesthesia.

Magnetic resonance imaging (MRI) is the preoperative imaging modality of choice when evaluating a patient for intraparenchymal tumors or epileptogenic foci. The MRI provides information valuable for diagnosis, management, and surgical planning. Functional MRI (fMRI) can aid in the preoperative localization of sensory, motor and language cortex. Rolandic cortex can be accurately identified using fMRI, but fMRI localization of language cortex is less reliable [8]. Atypical language sites or multiple essential language sites are often missed. For language lateralization, overall concordance of fMRI data with the Wada procedure (discussed below) is as high as 91 % [9]. While 91 % is relatively high, 9 % of patients will be placed at risk. Furthermore, those with bilateral language and those with more than the two classic language sites are unreliably identified with fMRI. Diffusion tensor imaging fiber tractography (DTI-FT) is used to identify the ascending and descending fiber tracts that subserve sensory and motor function, respectively. The corticospinal tract, and other white matter connections, can be reliably identified using DTI-FT [10]. The MRI, fMRI, and DTI-FT can be integrated in the

intraoperative neuronavigation system to guide resections in eloquent brain.

The gold standard for preoperative speech and language lateralization is the Wada procedure (Intracarotid Amytal Test) [11]. Sodium amobarbital is injected into the internal carotid artery, causing ipsilateral cerebral dysfunction. Functional testing performed after injection will reveal deficits in speech production. Preoperative lateralization of speech function is only necessary in certain patient groups. Patients with preoperative language deficits do not require a Wada test, as language cortex is clearly affected by the lesion or abnormality. Completely or predominantly left-handed patients with normal language and a lesion or abnormality in either the left or right temporal or inferior frontal region usually require a preoperative Wada test. Both right- and left-handed patients with a lesion or abnormality in the left temporal or inferior frontal region and normal language may also require a preoperative Wada test. These guidelines are based on the incidence of atypical speech lateralization from greater than 800 uncomplicated Wada tests performed at the same institution [12]. In general, if there is any doubt about preoperative language lateralization a Wada test should be performed.

**Core Messages**

- Preoperative imaging and patient examination are the key factors that determine whether or not mapping is necessary.
- Near normal function is necessary for successful mapping.
- Functional MRI, while useful, is not a substitute for intraoperative mapping.
- The Wada procedure remains the gold standard for preoperative lateralization of language, and is required during the preoperative work-up in specific patient populations.

## Anesthesia Considerations and OR Setup

Successful intraoperative cortical stimulation mapping requires a multidisciplinary approach. If an intraoperative awake period is planned for the patient the anesthesiology team should have experience with awake anesthesia techniques. A neuroelectrophysiology team is essential for evaluating functional testing and physiologic monitoring during stimulation mapping. Clear and constant communication is important throughout the neurosurgical procedure.

There are several anesthetic requirements when performing intraoperative cortical mapping. SSEP mapping, MEP mapping, and motor stimulation mapping can be performed under general anesthesia. The primary anesthetic concern with patients undergoing general anesthesia is the avoidance of halogenated inhaled anesthetic agents, which can increase the latency and decrease the amplitude of evoked potentials (EPs). Total intravenous anesthesia (TIVA) using a combination of amnestic/hypnotic and analgesic agents is the common method of inducing and maintaining general anesthesia without the use of inhalational agents. Low to moderate dose propofol or dexmedetomidine, used separately or in combination, is typically used. Additionally, chemical muscle relaxation must be avoided when motor stimulation mapping is performed. When airway difficulties are anticipated, a laryngeal mask airway should be electively placed.

When sensory or language stimulation mapping is performed, the patient must be awake and cooperative. There are several anesthetic techniques that are used for awake neurosurgical cases, including monitored anesthesia care, asleep–awake–asleep protocol, asleep–awake protocol, and continuous awake craniotomy protocol. We use the asleep–awake–asleep technique for awake mapping procedures, and prefer propofol TIVA without the addition of narcotics, which can cause respiratory depression. The usual dose (1 g/kg body weight) of preoperative mannitol that is given to reduce brain swelling during tumor surgery is known to cause nausea and

vomiting. To prevent this undesirable side effect in the awake patient undergoing a craniotomy, an IV dose of 0.5 g/kg body weight 20 % mannitol is used instead.

With cortical stimulation mapping there is a risk of evoking intraoperative seizures. All stimulation mapping patients should receive a preoperative dose of an anticonvulsant. We typically use 15–20 mg/kg body weight phenytoin or 1000 mg levetiracetam. In addition, the anesthesiologist must be prepared to quickly abort an intraoperative seizure. A short-acting IV benzodiazepine, such as midazolam, should be prepared and immediately available.

The placement of drapes and equipment must allow for easy access to the patient for anesthesia care and functional testing and assessment. An L-shaped bar is attached to the operating table and the surgical drapes are attached to the L-bar and not allowed to cover the patient's face (Fig. 1a, b). This provides the patient a clear line of site to view the object-naming slides during language testing. This also provides for direct visual contact between the patient and the anesthesiologist. To prevent the placement of cords and surgical instruments on the patient, we prefer the use of an overhead surgical table (Phalen Table; Fig. 1a). This improves patient comfort and allows for patient movement without disrupting surgical equipment.

**Core Messages**

- Intraoperative mapping requires a team approach. The anesthesia, neurophysiology, and nursing teams need to work together to achieve success.
- Special anesthesia considerations include the use of TIVA, asleep–awake transitions, airway control, and seizure prevention and treatment.

## Patient Positioning and Opening

In general, standard patient positioning based on surgical approach and exposure is used. For most mapping procedures, the head will be in a nearly lateral position, with adjustments made to ensure easy airway access, good venous return, and a clear visual line to the object-naming slides. Extra care is taken when padding the extremities and securing the patient to the operating table. Any patient discomfort during the awake portion of the case can lead to anxiety that prevents reliable cortical stimulation mapping.

A soft head holder or rigid pin fixation can be used to hold the head during awake stimulation mapping procedures. We prefer to use rigid fixation as it provides more stable head control. When pin fixation is used, local anesthesia at the pin sites is

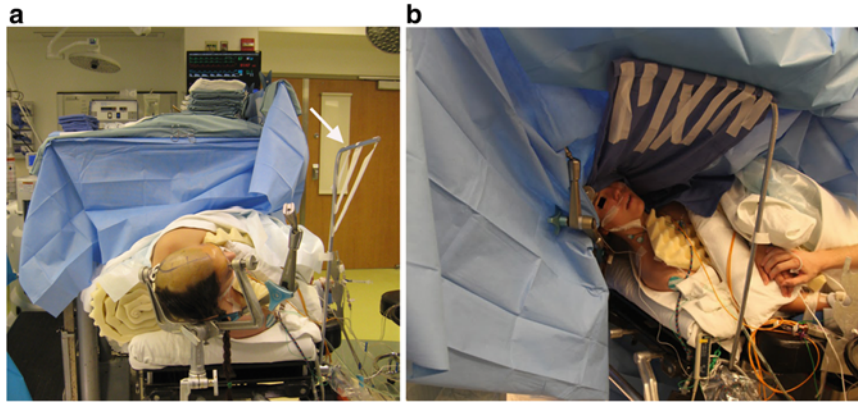


**Fig. 1** Patient positioning and draping. (**a**) The Phalen overhead surgical table is positioned above the patient. An L-bar (*arrow*) is attached to the head of the operating table. (**b**) The sterile surgical drapes are attached to the L-bar, allowing easy access to the patient's airway and creating an unobstructed viewing corridor for the object-naming task

necessary to prevent pain once the patient is awake. We use a local anesthesia mixture of 0.25 % bupivacaine and 1 % lidocaine with 1:200,000 epinephrine prior to placement of the pin fixation head holder. A generous (greater than 100 mL) regional field block around the proposed incision is used to prevent incisional pain (Fig. 2). For most stimulation mapping cases, a scalp block that includes anesthesia of the supraorbital, preauricular and postauricular nerves will provide sufficient relief of incisional pain. Care is taken not to place the field block below the zygomatic arch. Local anesthesia of the facial nerve located there will cause dysarthria and interfere with language mapping. If an intraoperative analgesic is needed for pain control, we prefer the ultrashort acting opioid remifentanil.

Successful cortical stimulation mapping requires a generous craniotomy. The goal is to expose not only the area for surgical resection, but also the surrounding cortex in a manner that allows access to all probable cortical stimulation sites. If the craniotomy is too small and functional cortex is atypically located, essential functional cortex may not be identified. Standard neurosurgical technique is used for the scalp opening and craniotomy. Once the dura is exposed the anesthetized patient can be returned to consciousness. To protect the brain from any misadventures that may occur during emergence, we typically do not open the dura until the patient is fully awake and cooperative. In many patients, manipulation of the dura can cause significant pain that is referred to the ipsilateral eye or ear. To prevent this pain, the dura around the middle meningeal artery can be infiltrated with local anesthesia prior to dural opening.

**Core Messages**

- Patient comfort is a crucial aspect of awake surgery.
- A regional scalp block and local anesthesia of the dura will help to prevent patient discomfort.

## Somatosensory-Evoked Potential Mapping and Monitoring

SSEP mapping provides a quick and reliable way of identifying primary somatosensory cortex, and the central sulcus and motor cortex, in a patient under either general or local anesthesia. A standard 8-contact strip electrode, with 1 cm center-to-center spacing, is positioned transversely (axially) on the cortical surface spanning presumed sensory and

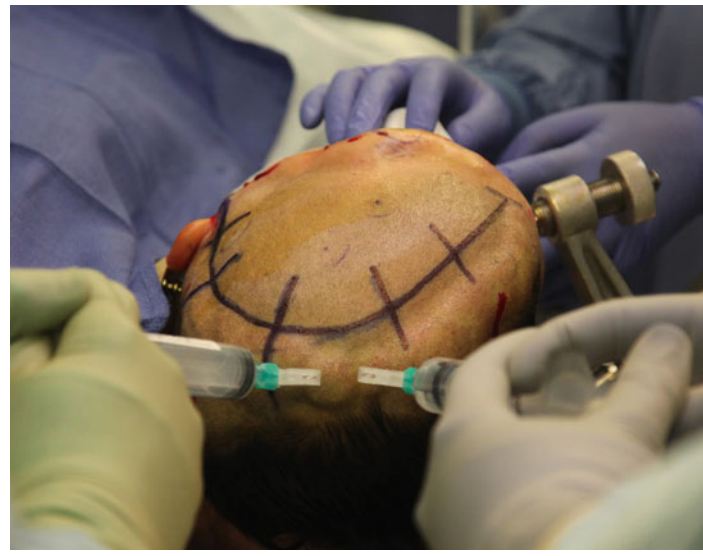

**Fig. 2** A regional field block is used to anesthetize the scalp circumferentially around the marked incision

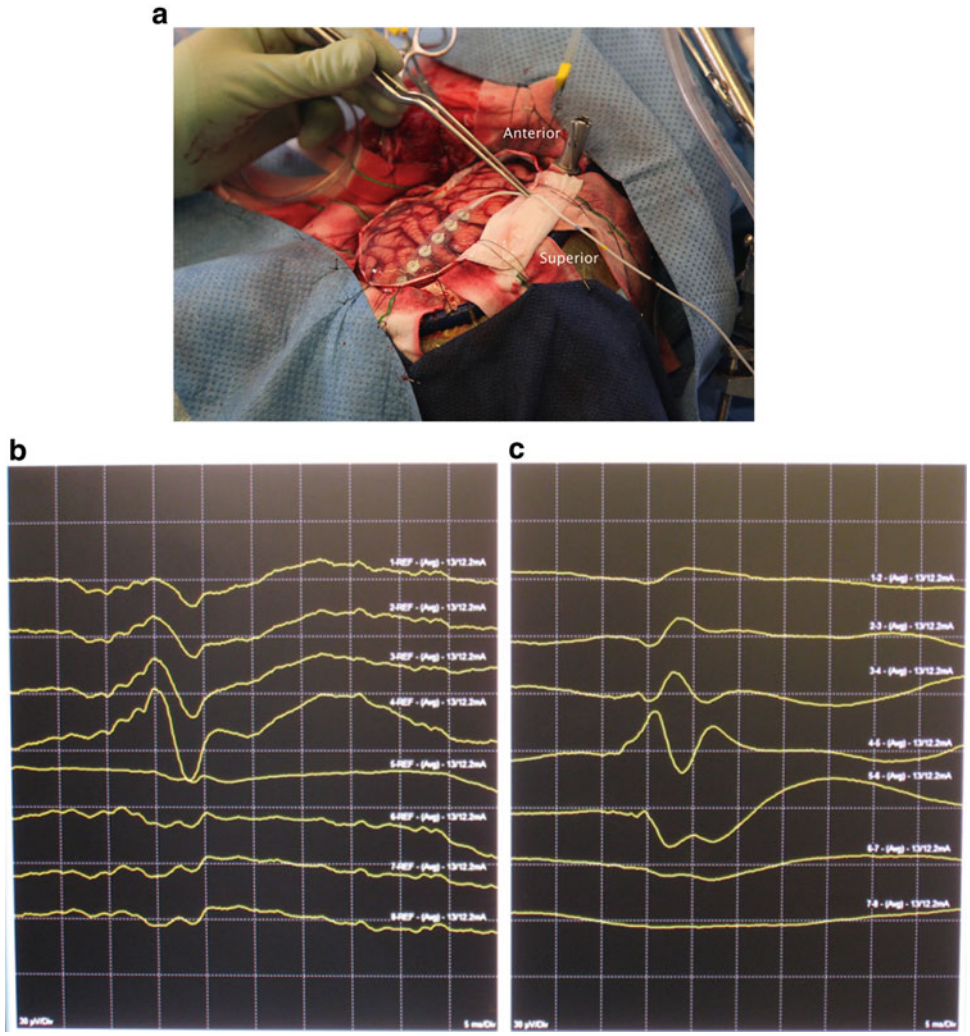


**Fig. 3** Somatosensory-evoked potential mapping of sensory cortex. (**a**) A strip electrode is positioned transversely across the estimated location of arm Rolandic cortex (*anterior* and *superior* noted for orientation). (**b**) The referential montage (*left*) shows the highest amplitude N20 waveform at electrode 4, indicating the position of underlying sensory cortex. The bipolar montage (*right*) shows the phase reversal of adjacent waveforms, with somatosensory cortex located beneath the shared electrode 4, identifying the position of underlying sensory cortex

motor cortex (Fig. 3a). The contralateral median nerve or contralateral posterior tibial nerve is stimulated and recordings are made from the strip electrode positioned to approximate arm sensory cortex or leg sensory cortex, respectively. The electrode is positioned in several cortical areas and multiple recordings are made to verify localization of sensory cortex. Table 1 shows the acquisition parameters necessary to clearly define sensory cortex using SSEP mapping.

**Table 1** Acquisition parameters for intraoperative somatosensory-evoked potential mapping of sensory cortex

| Parameter | Value |
|---|---|
| Stimulus current | 5–15 mA |
| Stimulus rate | 2–5/s |
| Stimulus duration | 100–300 μs |
| Stimulus intensity | Visible motor twitch (saturation) |
| Filter | 1–3000 Hz |
| Analysis time | 100 ms |
| Stimulations | 100–200/trial |

The cortical responses consist of positive (P) and negative (N) waves, based on polarity relative to a reference electrode, and waveform peak latency, in milliseconds. For example, stimulation of the contralateral median nerve will produce a somatosensory cortical response consisting of an initial negative wave with a peak occurring 20 ms after stimulation, the N20 sensory component, and a subsequent positive wave with a peak occurring 22 ms after stimulation, the P22 motor component. Although median nerve stimulation provides the most robust cortical response, other large peripheral nerves can also be stimulated. For example, the posterior tibial nerve is used to identify lower extremity sensory cortex.

Two different recording montages are available (Fig. 3b). A *referential montage* utilizes a reference electrode that is positioned outside the field of interest. We use a "balanced neck" reference to cancel ECG signal. The position of the electrode recording the highest amplitude N20 waveform identifies the underlying sensory cortex. A *bipolar montage* utilizes an adjacent electrode on the strip as the reference electrode. Where phase reversal of waveforms occurs along the strip electrode identifies the underlying sensory cortex. Sensory cortex localization using SSEP can be performed through the dura prior to dural opening. If a craniotomy does not expose sensory cortex, the strip electrode can be positioned in the subdural space under the edge of the craniotomy.

After identification of Rolandic cortex, the strip electrode can be positioned medial to lateral along the somatosensory gyrus and continuous SSEP monitoring can be performed during the resection [13]. This provides continuous real-time assessment of sensory function during resections that risk intrusion into sensory cortex or undercutting subcortical ascending fibers. Continuous SSEP monitoring can also be used to monitor the posterior limb of the internal capsule during resection of deep-seated lesions.

**Core Messages**

- SSEP mapping can be performed in children and adults under general anesthesia.
- The technique does not use direct cortical stimulation, therefore there is no risk of seizure related to SSEP mapping.
- SSEP mapping can identify both somatosensory cortex and motor cortex.
- SSEP monitoring can be used continually to prevent encroachment on ascending sensory tracts.

## Cortical Stimulation Mapping of the Somatosensory Cortex

Cortical stimulation mapping of somatosensory cortex can only be performed in an awake, cooperative patient. Stimulation mapping requires repetitive electrical stimulations of the cortex at or near the same site, with successively higher currents, which can cause a focal or generalized seizure. Prior to any stimulation of the cortex the patient must have adequate serum anticonvulsant levels. Iced irrigation solution should be immediately available to the neurosurgeon throughout stimulation mapping. In the event of a focal seizure, quickly irrigating the cortex with cold irrigation can often terminate the seizure activity. If iced irrigation fails to abort a focal seizure or if a generalized seizure occurs, a short-acting IV anticonvulsant should be administered.

The SSEP mapping technique previously described is used to quickly identify Rolandic cortex and the central sulcus. A bipolar stimulator is then used to stimulate discrete locations along the sensory cortex. The Ojemann Cortical Stimulator (Integra Radionics, Inc.), with 5 mm spacing between electrodes, utilizes a 60 Hz constant-current, biphasic square wave (Fig. 4). Stimulation begins at a low current setting of 2 mA in an awake patient. A current duration of 1–2 s per stimulation is used. If no response is elicited during systematic stimulations of the cortex, then the current is

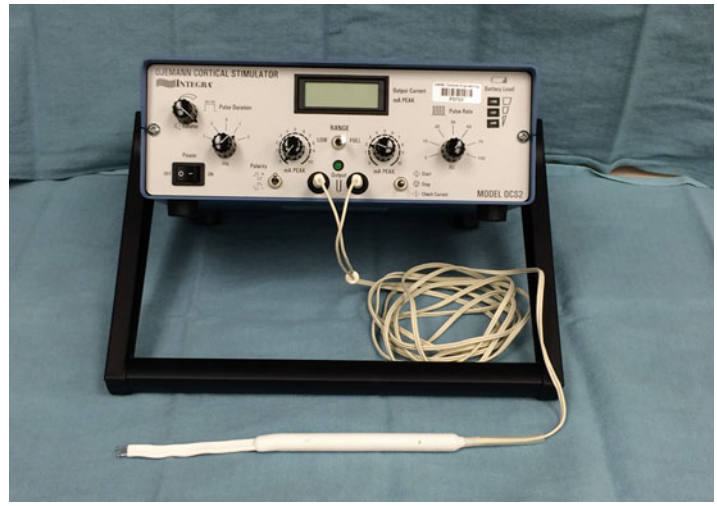


**Fig. 4** Bipolar Ojemann cortical stimulator

increased in 1- to 2-mA increments until paresthesia is elicited. Typically, a stimulation current greater than 12 mA is not necessary to generate a paresthesia response. To reduce the risk of seizures, high stimulation currents should be avoided and the same cortical site should not be stimulated in succession without a pause. Electrical stimulation mapping can be performed through the dura (transdural mapping), but higher current settings will be necessary.

**Core Messages**

Cortical stimulation mapping of somatosensory cortex requires an awake patient.

Escalating current levels are used to perform cortical stimulation mapping. Evoked seizure risk is managed with preoperative anticonvulsants, iced saline lavage, and short-acting benzodiazepines.

## Cortical Stimulation Motor Mapping and Motor-Evoked Potentials

Cortical stimulation mapping of motor cortex can be performed in both children and adults, under either local or general anesthesia. Motor responses in children younger than 6 years and in both children and adults under general anesthesia are more difficult to elicit. Under these conditions, motor stimulation may require a longer stimulus duration or higher current settings. The technique for motor stimulation mapping follows that described above for sensory stimulation mapping. Stimulation begins at a current setting of 2 mA in the awake patient or 4 mA in the patient under general anesthesia. If systematic stimulation of the motor cortex fails to generate a motor response, then the current is increased in 1- to 2-mA increments to a maximum of 20 mA until motor movement is elicited.

The bipolar stimulator is used to map arm, hand and face sensory and motor cortex on the lateral brain surface. When mapping of leg sensory or motor cortex is necessary, a strip electrode positioned on the medial brain surface along the falx is used. The stimulation current using a strip electrode is the same as bipolar stimulation current. If a craniotomy does not expose the motor cortex, a strip electrode can be positioned in the subdural space under the edge of the craniotomy.

Subcortical sensory and motor fibers can also be localized using the stimulation mapping technique. Subcortical stimulation mapping utilizes the bipolar stimulator and the stimulation parameters described above. Identifying subcortical pathways can define the subcortical limit of resection. This can be useful during resection of infiltrative tumors that may contain functional

tissue within the tumor or tumor walls, or that may extend outside obvious tumor margins. Subcortical mapping may also be useful during resection of lesions in association areas, such as the supplemental motor area, or in deep locations, such as the insula.

Motor-evoked potential (MEP) monitoring provides a method for mapping and for continuous real-time assessment of motor function during resections that abut motor cortex or descending corticospinal tract fibers. One advantage of MEPs over stimulation is that evoked seizures are exceedingly rare. A second advantage is that the surgeon does not need to stop resection to repeat stimulation. While MEP monitoring is widely used to monitor the spinal cord during spinal surgery, the use of MEPs during supratentorial surgery is a more recent application. The technique of motor cortex stimulation was modified to make MEP monitoring under general anesthesia possible [14]. A strip electrode is positioned along the precentral gyrus, with a contact at the point corresponding to the cortical area with the greatest amplitude P22-N30 response on median nerve SSEPs. A subdermal needle electrode positioned at the frontal pole ($F_{pz}$ by the international 10–20 EEG system) serves as the cathode. Monopolar, monophasic, anodal, rectangular wave stimulation is used to stimulate the motor cortex, and compound muscle action potentials are recorded from the face, hand, arm, and/or leg. Table 2 shows the acquisition parameters necessary to monitor the corticospinal tract using MEP mapping.

There are a few literature reports of MEP monitoring during resection of cortical or subcortical lesions located in or near motor cortex or descending motor pathways. Successful MEP monitoring after cortical stimulation mapping can be performed in the setting of partial neuromuscular blockade and preoperative paresis, and reliably predicts postoperative motor function [15, 16].

**Table 2** Acquisition parameters for intraoperative motor-evoked potential monitoring of motor cortex

| Parameter | Value |
|---|---|
| Stimulus current | 5–30 mA |
| Stimulus rate | 250–500/s |
| Stimulus duration | 200–500 μs |
| Stimulus intensity | Stable motor twitch |
| Filter | 30–3000 Hz |
| Stimulations | 4–7/trial |

**Core Messages**

- Cortical stimulation mapping of the motor cortex can be performed in children and adults under general or local anesthesia, although higher stimulation currents may be required for young children and general anesthesia.
- Cortical stimulation can be used to identify motor cortex and descending motor fibers.
- MEPs can be used for continuous monitoring, with a decreased risk of seizures compared with stimulation mapping.

## Localization of Language Cortex Using Cortical Stimulation Mapping

The classic localization of essential language function is pars opercularis, in the posterior inferior frontal gyrus (Broca's area), and the posterior superior temporal gyrus (Wernicke's area), but stimulation mapping has demonstrated that essential cortical language sites are variably located in the frontal, parietal and temporal lobes [7]. Resection of the cortical areas that are essential for language will result in aphasia. Therefore, prior to any surgical resection, identification of the cortical areas critical for language is imperative. In surgical candidates with lesions in the dominant temporal, posterior frontal or anterior parietal lobes, resection should be guided by cortical stimulation mapping to identify essential language sites and minimize postoperative language deficits.

Successful cortical stimulation language mapping requires an awake, cooperative patient. Language mapping can be performed in children and adults who meet the criteria for language mapping described above. Any sensory and/or

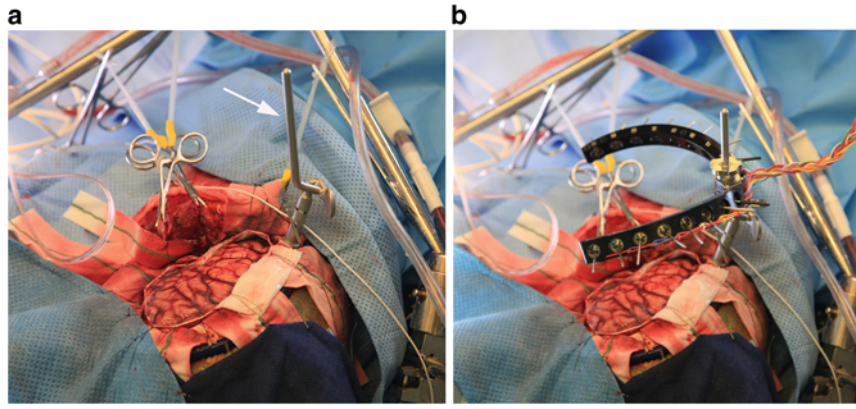


**Fig. 5** Grass CE-1 cortical electrode holder. (**a**) The electrode holder post (*arrow*) is positioned in a separate twist drill hole at the margin of the craniotomy. (**b**) The U-shaped electrode holder is placed on the post and positioned over the area to be mapped

motor mapping is performed prior to language mapping, and, similar to sensory and motor stimulation mapping, language stimulation mapping can be performed transdurally.

The first step in language stimulation mapping is to determine the after-discharge threshold. This is necessary to prevent the spread of depolarization to adjacent cortex, which can cause local seizure activity, or produce false-positive or false-negative results. Electrocorticography (ECoG) is performed throughout the language mapping procedure to monitor the after-discharge threshold. We use the U-shaped CE-1 Cortical Electrode Holder (Grass Technologies; Fig. 5b). It can be attached to the skull at the superior edge of the craniotomy using either an electrode holder post screwed into the skull in a separate twist drill hole or using an epidural skull clamp (Fig. 5a). An alternative to the Grass electrode holder is the use of strip or grid electrodes. Five to ten carbon-tipped electrodes are positioned in a montage on the exposed cortical surface. Electrodes are spaced 2–3 cm apart and cover the entire area to be mapped (Fig. 6a). The electrode positions are marked on a brain diagram for use by the neurophysiologist reading the electrocorticogram (Fig. 6b). The bipolar stimulator is used to stimulate the cortex, starting at a current of 2 mA and using a current duration of 1–2 s per stimulation (Fig. 6c). )After several cortical areas are stimulated without evidence of after-discharges, the stimulus is increased in 1- to 2-mA increments for successive stimulations until the after-discharge threshold is reached (Fig. 6d). Once the after-discharge current threshold is established, the stimulation current used for language mapping is set to 1–2 mA below the after-discharge threshold. A single cortical area is never stimulated twice in succession, as this can lead to temporal summation and evoke after-discharges or a seizure.

Language stimulation mapping proceeds with the selection of cortical sites for stimulation. Ten to 20 sites are selected to represent all exposed cortex, including areas where essential language function is estimated to be located and areas at the proposed surgical resection. The selected sites are marked with 5 mm by 5 mm numbered tags (Fig. 7). The positions of the numbered tags on the cortex are marked on a brain diagram and used to record the outcome of the naming task for each stimulation. With continuous ECoG monitoring for after-discharges, and cortical stimulation ready to commence, the patient begins the object-naming task. The patient is shown a series of 50–100 object-naming slides containing simple, well-recognized objects. The object-naming slides can be presented using a computer, flip chart, or other available method (Fig. 8). The series of object slides used during intraoperative stimulation mapping should be the same one used for the preoperative language assessment.

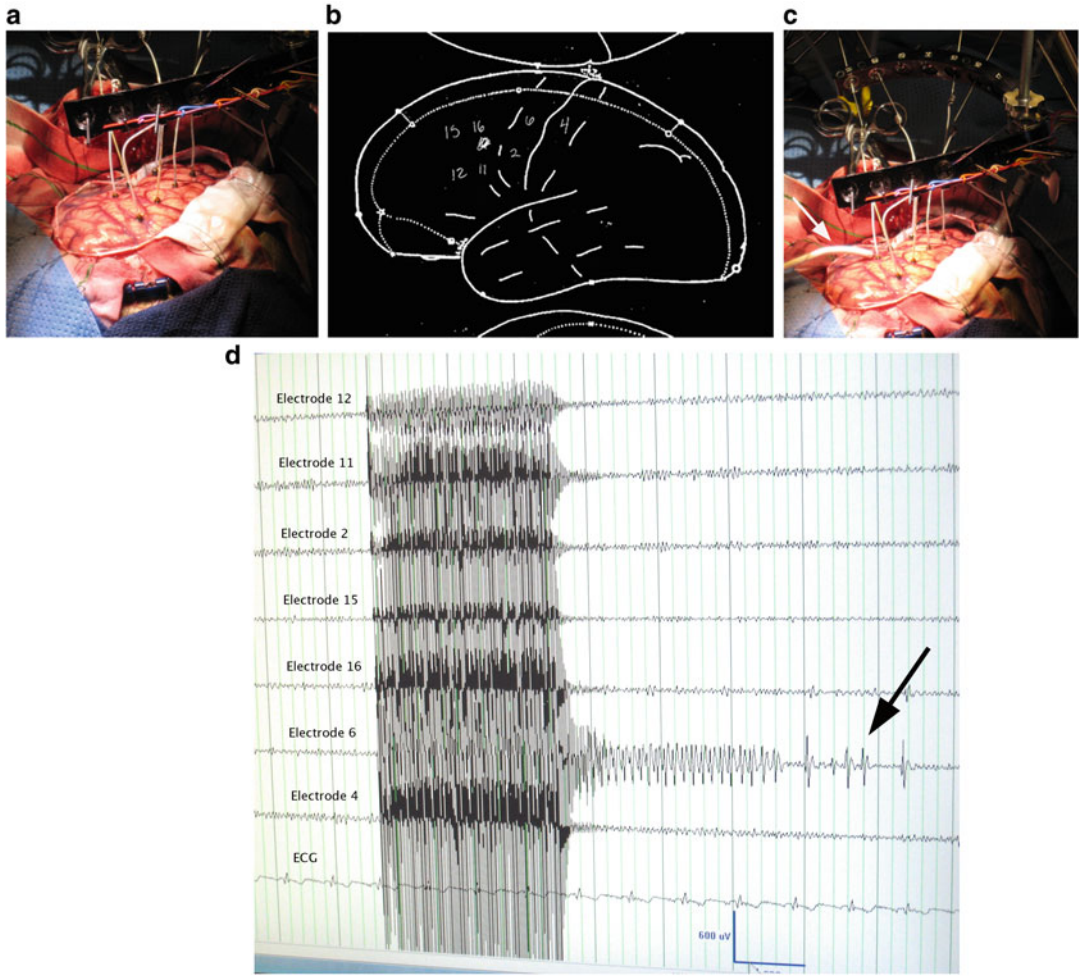


**Fig. 6** Electrocorticography for determination of the after-discharge threshold. (**a**) Carbon-tipped electrodes are positioned on the cortex covering the entire area to be mapped. (**b**) The positions of the cortical electrodes are noted on a brain diagram. This is used by the neurophysiologist who is monitoring the electrocorticogram for after-discharges during stimulation. (**c**) The bipolar stimulator (*arrow*) is used to systematically stimulate the cortex until the after-discharge threshold is identified. (**d**) After-discharges (*arrow*) are identified on the electrocorticogram during bipolar stimulation

Based on the patient's baseline verbal ability, a new image is presented every 3–4 s.

As the patient performs the naming task, cortical stimulation is applied at a numbered site immediately before the presentation of an image. The stimulation is applied either for the duration of the image presentation or until the object is correctly named, whichever occurs first. At each stimulation, the neurosurgeon calls out the number identifying the cortical site, and the patient is assessed for correct naming and speech slowing, speech arrest, or paraphasias, and the outcome recorded. Each marked cortical area is stimulated a minimum of three times to evoke stimulation-induced error, though a single cortical site should never be stimulated in immediate succession. When cortical sites critical for speech production are stimulated reliable alteration of function, expressed as anomia, dysnomia, paraphasia, or speech arrest, will result. The electrocorticogram is monitored throughout the stimulation mapping procedure, looking for after-discharge spikes that may indicate a risk for focal seizures or false naming errors.

If a craniotomy does not expose all sites for language stimulation mapping, a strip electrode can be positioned subdurally under the edge of

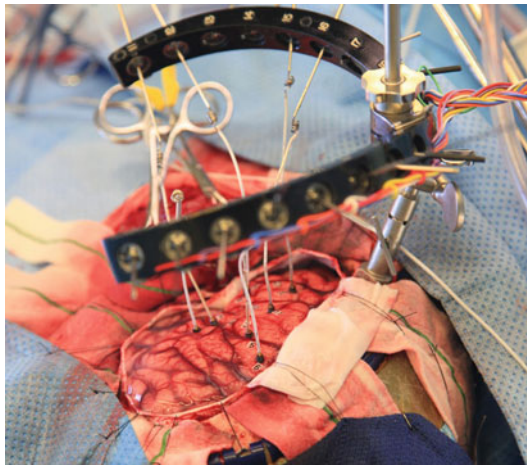

**Fig. 7** Numbered tags are positioned on the cortex covering the entire area to be mapped. During stimulation language mapping, the number closest to the site of bipolar stimulation is called out and the patient's performance of the object-naming task during the stimulation is recorded. The electrocorticogram is recorded throughout stimulation mapping

the craniotomy and used with direct bipolar stimulation. It is best to plan for a generous craniotomy, though, and extend the craniotomy if needed. Confident language mapping tests all regions at risk and identifies the sites where language is and is not located. While many patients have only two essential language sites, one quarter of patients will have three or more essential language sites [7]. Language mapping should not stop once two language sites are identified; the entire cortical region at risk should be interrogated. If language cortex cannot be identified, the patient should continue the object-naming task during the resection to ensure safety. It is crucial to bear in mind that normal conversation is not a reliable test during resection or mapping. Instead, object naming should be used.

When language mapping is completed, the numbered markers that identify essential language sites can remain in position during the

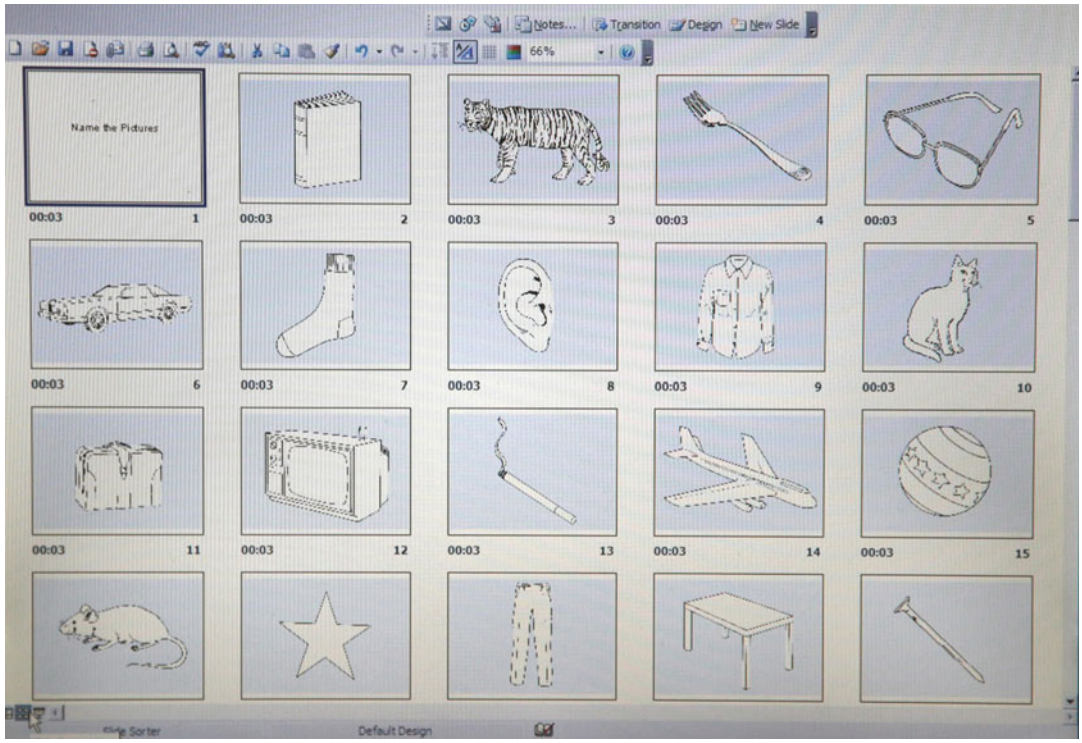


**Fig. 8** During cortical stimulation language mapping, a computer is used to present the object slides during the object-naming task

resection. For resections that are far removed from an identified language site(s), the patient can be returned to TIVA. If the resection site is adjacent to an identified language site(s), then the patient should remain awake. When a resection is planned within 20 mm of an essential language site, the patient should continue the object-naming task. Resection within 10–20 mm of an essential language site along a continuous gyrus does not commonly result in permanent postoperative language deficits [7, 17]. Resection within 10 mm of an essential temporal lobe language site will often result in postoperative language deficits, transient greater than permanent [17].

**Core Messages**

- Cortical stimulation mapping of language cortex requires an awake patient.
- ECoG should be used during language mapping to determine the after-discharge threshold and to monitor for after-discharges and seizures.
- The neurosurgeon verbally identifies the site stimulated, while the patient naming responses are assessed for alterations and the neurophysiologist monitors the electrocorticogram for after-discharges.
- The object-naming task is the language test used during stimulation mapping. Normal conversation should never be used to assess language function during the mapping procedure.
- When in doubt, keep the patient awake and naming during the resection.

## Overall Considerations

Cortical mapping and monitoring are the first steps to a safe resection. However, the neurosurgeon needs to prevent injury to blood vessels subserving essential cortex and to critical subcortical fiber tracts. Good rules for safety are:

- When in doubt map.
- When mapping does not work, or resection is near eloquent areas, continue mapping or testing patient function.
- The number one goal of surgery is deficit avoidance. For glioma surgery, an operative deficit not only lowers the patient's quality of life, it shortens overall survival.

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# Anesthetic Considerations in Cortical Mapping and Awake Surgery

Lee A. Tan, Richard W. Byrne, and Mary K. Sturaitis

**Summary of Key Points**

- The awake craniotomy can be divided up into four stages: exposure, intraoperative electrophysiological testing, resection of target lesion, and closure.
- The goals for anesthesia during awake craniotomies are maintenance of oxygenation and ventilation, stabilization of intraoperative hemodynamics, optimization of cerebral perfusion, management of intracranial pressure (ICP), and to provide appropriate analgesia and/or sedation with minimal anesthetic interference with intraoperative testing.
- Particular attention should be paid during positioning to ensure patient comfort and airway patency.
- Light sedation, local anesthetic infiltration, and scalp block are effective methods to provide pain relief during head holder placement and for the exposure stage of the surgical procedure. Agents used for intraoperative sedation, anxiolysis, and additional analgesia should be titratable and readily reversible. Infusions of propofol, remifentanil, and dexmedetomidine are commonly administered.
- An optimal anesthesia regimen will depend on the experience and preference of the surgical and anesthesia teams, as well as the specific requirements for a particular patient.
- Good rapport and clear communication amongst the surgical, anesthesia, neuromonitoring teams, and the patient are essential to a successful awake craniotomy.

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**Awake Craniotomy Checklist (Asleep–Awake–Asleep)**

**Preoperative holding area**
- Airway assessment and review of pertinent medical history
- Patient counseling regarding expectation at each stage of the procedure
- First IV is established
- Famotidine 20 mg IV is given for GI prophylaxis

**Prior to induction in OR**
- Double check all drugs are ready and available (Propofol + remifentanil or dexmedetomidine, labetalol gtt, phenylephrine gtt, mannitol, etc.)
- Ensure availability of neuromonitoring equipment
- A-line setup
- IV bag for second IV
- IV pump setup

**Induction**
- Propofol (bolus 30–50 mg IV, then 25–75 mcg/kg/min) + remifentanil (0.03–0.1 mcg/kg/min) OR dexmedetomidine (bolus 1 mcg/kg infused over 10 min, then drip at 0.2–1 mcg/kg/h)
- Dexamethasone 10 mg IV and ondansetron 4 mg IV can be given to prevent emesis
- Both the anesthesia and surgical teams need to verify patient's positioning to ensure patent airway, patient comfort, and access for intraoperative neurophysiological testing
- All pressure points must be well padded

**Post-induction**
- Start second IV
- Start A-line
- Insert Foley catheter
- Give prophylactic antibiotics
- Give seizure prophylaxis
- Local anesthetic infiltration at pin sites as well as for nerve blocks
- Recheck airway after Mayfield head holder placement

**After dura opening**
- Consider turning off propofol + remifentanil or dexmedetomidine drip at the time of dura opening
- Wake up time is usually 10–15 min for intraoperative electrophysiological testing
- Iced saline should be available for surgeons to irrigate the cerebral cortex if seizure occurs after cortical stimulation

**After cortical mapping or resection of lesion**
- Anesthesia can be resumed for patient comfort either after cortical mapping or tumor resection depending on the need of the particular procedure

## Introduction

Neuroanesthesia has been an essential component of intracranial surgery since the beginning of modern neurosurgery. The goals of neuroanesthesia generally include maintaining adequate oxygenation and ventilation, optimizing intraoperative hemodynamics, and cerebral perfusion during surgical manipulation, as well as providing adequate analgesia and sedation. Even though the field of neuroanesthesia has had tremendous technologic and pharmacologic advancements since the initial use of chloroform and ether more than a century ago [1], the fundamental goals of neuroanesthesia have not changed. Furthermore, surgical resection of epileptogenic foci and brain tumors near eloquent areas often requires intraoperative electrocorticography (ECOG) recording or brain mapping; therefore, the need for the patient's wakefulness and cooperation during electrophysiological testing places additional

constraints on the anesthetic management in awake craniotomies.

The workflow of awake craniotomies can be broken into four stages: surgical exposure, intraoperative electrophysiological mapping and functional testing, resection of target lesion(s), and surgical closure. The common theme for any awake craniotomy anesthesia protocol is to have the patient awake and cooperative in the second stage during monitoring and testing. With recent literature demonstrating survival benefits with maximal tumor resections [2], awake craniotomies are becoming increasingly popular amongst tumor surgeons in an effort to maximize tumor resection in eloquent regions of the brain, while ensuring the preservation of neurological functions. Despite the recent renewed popularity, awake craniotomy is not a new concept at all. It had been an essential part of epilepsy surgery for almost 100 years [3–5]. Harvey Cushing, one the fathers of modern neurosurgery, coined the term "regional anesthesia" early in his career [6] and awake craniotomy was actually the predominant method for most intracranial procedures in the 1930s [1, 7].

In this chapter, various anesthetic management strategies for awake craniotomies are reviewed, and relevant pharmacologic considerations are discussed.

## Historical Perspective

In 1874, Roberts Bartholow reported the first description of direct electrical stimulation of the human brain [8]. He inserted electrodes through the dura of a patient whose scalp and skull were eroded away by a tumor, and found that electrical stimulation of the ipsilateral cerebral cortex caused contralateral motor contraction. In the 1920s, Otfrid Foerster, a famous German neurologist and self-taught neurosurgeon, treated WWI soldiers with posttraumatic epilepsy utilizing electrical stimulation of the cerebral cortex under local anesthesia to delineate the eloquent areas of the brain during seizure focus resections [5]. In 1928, Wilder Penfield observed the cortical mapping method after visiting Foerster in Germany. He adapted the cortical mapping technique upon his return to the Montreal Neurological Institute and subsequently made tremendous contributions to our current understanding of the functional anatomy of the human cerebral cortex [1].

Anesthesia as a medical specialty was also at its infancy during the formative years of modern neurosurgery. In the 1840s, the anesthetic properties of ether [9] and chloroform [10] were discovered in the United States and Europe, respectively. General surgeons and dentists quickly adapted these agents for use in surgical and dental procedures. By the 1880s, these agents had been successfully used in early craniotomies [11]. Ether was widely used in the United States after its initial public demonstration in the Massachusetts General Hospital in 1846 [12]. However, major drawbacks of using ether included increased cardiac output and arterial blood pressure, which equated to elevated intracranial pressure [13] and increased intraoperative bleeding, as well as ether-induced nausea and vomiting [1]. In fact, Harvey Cushing had a detailed account regarding a patient who died from intraoperative aspiration after emesis when he was administering ether anesthesia as a medical student for this patient during a strangulated hernia repair [6]. Chloroform, on the other hand, was popular in Europe due to its ability to decrease the systolic blood pressure and reducing intraoperative bleeding; however, it had a dangerous side effect of causing fatal cardiac arrhythmias [14].

The method of anesthetic drug administration was also primitive during that period. Anesthetic agents were usually administered by dripping onto a folded towel or a wire-framed mask covering the patient's face ("open-drop technique") [1]. The airway was often maintained by performing jaw-thrust by the anesthesiologist throughout the case. In the late 1920s [15], development of the endotracheal tube and mechanical ventilation ("iron lung") finally facilitated wide adaptation of general anesthesia for surgical procedures. Short-acting intravenous barbiturates such as hexobarbital and thiopental were introduced in the 1930s [16, 17], and, by providing rapid and

smooth anesthesia induction, further popularized general anesthesia for neurosurgical procedures. With better understanding of the functional anatomy of the brain, more and more epilepsy surgeons started to utilize standardized anatomical resections in temporal lobe epilepsy [18], leading to a progressive return to general anesthesia for intracranial surgeries after the 1940s.

Because of the potential dangers of general anesthesia by chloroform and ether as noted earlier, alternative methods of controlling intraoperative pain were explored. In 1884, Karl Koller, an Austrian ophthalmologist, conducted a series of experiment after reading Sigmund Freud's writings on cocaine, and discovered the local anesthesia effect of cocaine on the cornea [19]. William Halsted then experimented with using cocaine for nerve blocks at Johns Hopkins University, in which Harvey Cushing further developed the local anesthetic techniques and introduced the term "regional anesthesia" [6]. As surgical procedure became more complex with increased duration, the intermediate-acting anesthetic lidocaine was developed in the 1940s, and the long-acting drug bupivacaine was developed in the 1950s to provide longer pain relief for patients. In the 1960s, opioids in combination with neuroleptics were used to provide sedation and pain control and became the preferred method during awake craniotomies. Today, newer short-acting drugs such as propofol, remifentanil, and dexmedetomidine are easily titratable to provide smooth transition from sedation to wakefulness during awake craniotomies.

## General Considerations

The goals for anesthetic management in awake craniotomies are to optimize conditions for cortical mapping, and to keep the patient awake and cooperative during intraoperative neurological testing—while minimizing the pain and anxiety during the stages of exposure, surgical resection, and closure. Several anesthesia techniques have been developed for awake craniotomies, which most commonly include an "awake" approach utilizing local anesthesia and scalp blocks without any sedation, or, the "asleep–awake–asleep" (AAA) approach wherein varying degrees of sedation is provided during the exposure and closing stages of surgery to minimize patient discomfort and anxiety. The level of sedation for the AAA approach can vary, based on differing institutional practices or according to surgical and patient requirements, from light sedation with monitored anesthesia care (MAC) to a fully anesthetized patient under controlled ventilation. Each approach has its own advantages and drawbacks. Appropriate preoperative patient education and clear communication between the surgical and anesthesia teams are essential to ensure a successful awake craniotomy. Several important factors must be carefully considered in order to choose the optimal anesthetic strategy.

## Preoperative Evaluation and Preparation

Various surgical and patient-specific factors can affect the anesthetic approach and drug selection. The surgical and anesthesia teams should have clear preoperative understanding regarding the location of lesion, potential ICP issues, hemorrhagic risk, and surgical positioning. A detailed medical history should be obtained (Table 1). Pertinent issues should be carefully considered and discussed between the surgical and anesthesia teams (Fig. 1).

**Table 1** Pertinent past medical history for awake craniotomy

| |
|---|
| • Cardiac (e.g. coronary artery disease, conduction abnormalities, pulmonary hypertension) |
| • Pulmonary (e.g. metastases, recent respiratory infection, asthma) |
| • Airway (e.g. snoring/sleep apnea, morbid obesity, difficult airway anatomy) |
| • Epilepsy history |
| • Home medications (anti-hypertensives, anticonvulsants) |
| • Predisposition for rapid drug metabolism (due to medication or genetic predisposition) |
| • Psychological (anxiety, pain tolerance, disinhibition) |
| • Existing neurologic deficits |

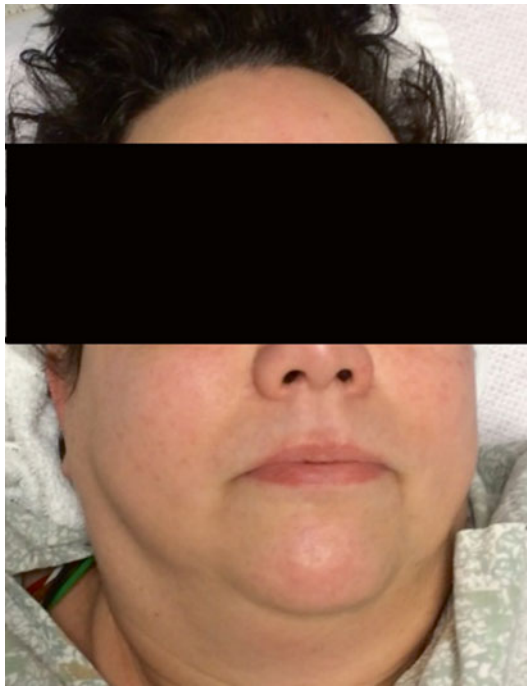

**Fig. 1** Photograph demonstrating an obese patient with a short neck and history of sleep apnea, who is at increased risk for airway obstruction during awake craniotomy

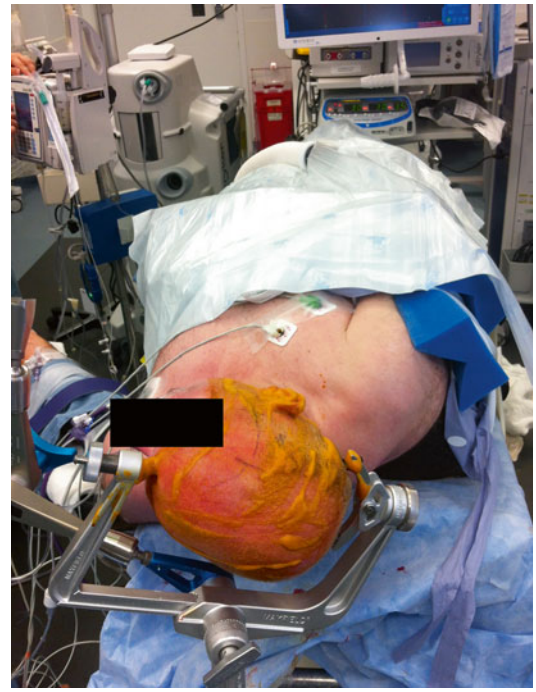

**Fig. 2** Intraoperative photograph demonstrating the head positioning with the neck neutral to minimize airway obstruction; supplemental oxygen is provided via nasal cannula

## Airway Maintenance

The maintenance of an adequate airway is essential for any successful surgical procedure. Many airway management options exist for awake craniotomies; the specific airway management strategy for a particular patient depends on the anesthesia protocol chosen as well as the specific needs of the patient and the intended procedure. It can range from simple supplemental oxygen from nasal cannula, to nasopharyngeal airway, or laryngeal mask airway (LMA), or even endotracheal intubation [1, 20–24]. Regardless what airway management strategy is chosen, the goal is to ensure adequate oxygenation and ventilation (i.e. avoidance of hypoxia or hypercarbia) during surgery. Factors affecting oxygenation include the inspired $O_2$ content ($FiO_2$), patency of the airway, adequate gas exchange in the alveoli, and ventilation and perfusion matching. Ventilation is largely controlled by the respiratory rate and tidal volume.

In patients undergoing local anesthesia or monitored anesthesia care (MAC), spontaneous breathing is maintained throughout the procedure. Usually a nasal cannula or facemask is adequate to provide $O_2$ supplementation in the face of potential respiratory depression (Fig. 2). Airway instrumentation with LMA or endotracheal tube (ETT) is generally avoided in this incidence. If the "asleep–awake–asleep" approach is used however, the LMA or endotracheal tube can be used to secure the airway in conjunction with increasing the depth of anesthesia. The big drawback with this approach can be the need for intraoperative removal of the airway during language testing and reinsertion of the LMA or ETT afterwards. This can be very challenging as the manipulation of the airway while the patient is in the Mayfield holder can be difficult and fraught with added risk for laryngospasm, emesis and aspiration, coughing, as well as contamination of the sterile field.

In addition, anesthetic agents such as propofol, can decrease both the respiratory rate and the tidal volume in a dose-dependent manner. Therefore, it is important to avoid over-sedation with hypoventilation in the non-intubated patients during awake craniotomies, given the risk for airway obstruction and aspiration. Proper positioning of the head preoperatively (the "sniffing position") can reduce the risk for airway obstruction and improve venous drainage.

A study on patients receiving electrodes placement for deep brain stimulation revealed that severe airway obstruction can occur in up to 1.6 % patients during awake craniotomies [25]. Another study revealed that oxygen desaturation ($SpO_2 < 95$ %) occurred in 4.8 % patients, hypoventilation ($EtCO_2 > 50$ mmHg) occurred in 9.5 % patients, and respiratory depression (rate < 8 per minute) occurred in 7.1 % patients undergoing awake craniotomies [26]. Therefore, it is important to assess the airways of patients preoperatively in case of need for assisted mask ventilation or emergent intubation (pic of obese pt, smaller black bar). GlideScope or fiber-optic bronchoscope should be immediately available for use in such rare, but potentially dangerous situations where laryngoscopy would be difficult.

## Management of Systemic Blood Pressure, Cerebral Perfusion, and Intracranial Pressure

The management of blood pressure, cerebral perfusion, and ICP is another challenging aspect of neuroanesthesia. Cerebral perfusion is controlled by autoregulation under normal conditions and it is maintained in a narrow range despite wide variations of systemic blood pressure. However, many anesthetic agents can alter the autoregulation afforded by the constriction and dilation of cerebral vasculature. Inhalational agents (including nitrous oxide) can increase cerebral blood flow and subsequently increase the intracranial blood volume and pressure, which can then lead to increased intraoperative bleeding and brain swelling during intracranial procedures. The anesthesiologist can avoid or minimize the concentration of agents that can have deleterious vasodilatory effects on ICP, especially in patients who may already have raised ICP from existing intracranial mass lesions.

On the other hand, since cerebral perfusion pressure (CPP) equals the difference between mean arterial pressure (MAP) and ICP, systemic hypotension in the face of impaired cerebral autoregulation can lead to reduced cerebral blood flow, and cause regional or global ischemia in the brain. Therefore, the anesthesiologist must be aware of anesthetic properties of each agent on cerebral blood flow to prevent unexpected and untoward complications. Optimization of systemic and cerebral blood flow can usually be achieved by using a combination of vasopressors (small doses of ephedrine or phenylephrine), beta-blockers (esmolol, labetalol, etc.), hydralazine (direct smooth muscle vasodilation), and calcium-channel blocker (nicardipine) and alpha-2 adrenergic agonists along with titrating the means and depth of general anesthesia or sedation. Of note, nicardipine is a known cerebrovasodilator, whereas, vasopressors and beta-blockers in general work systemically and do not cross the intact blood–brain barrier. The vasodilatory effect of hypercarbia can be mitigated by increased patient ventilation. An arterial line is especially helpful for continuous blood pressure monitoring and blood sampling.

Coughing and sneezing should be avoided if possible, and nausea and vomiting treated preemptively as Valsalvas can cause sudden surges in ICP and lead to increase in brain swelling. Several measures can be taken to reduce ICP intraoperatively. The simplest maneuver is to raise the head of the operating table or put the patient in slightly more reverse Trendelenburg position. This will facilitate venous drainage and have a relatively immediate effect in lowering ICP. Propofol can have a moderate effect in lowering ICP due to lowering of cerebral metabolism (CMR) and cerebral vasoconstriction. If further reduction is needed, intravenous mannitol can be given preemptively. Or if further ICP reduction is needed, a bolus with dosing ranging from 0.25 to 1.0 g/kg, depending on the acuity of the ICP reduction needed. However, mannitol

has a diuretic effect and urine output must be monitored closely. In addition, cerebral spinal fluid (CSF) can be removed intraoperatively either from adjacent cisterns or by placing a ventricular catheter.

## Analgesia and Sedation

Perhaps the most stressful aspect of an awake craniotomy from the patient's perspective is the anxiety and pain associated with local anesthetic infiltration and the exposure stage of the procedure. The anesthesiologist must find an optimal balance between an under-sedated, anxious patient with inadequate pain control, versus an over-sedated, somnolent, uncooperative/disinhibited patient with respiratory depression. Given that each person's anxiety level and pain tolerance are different, the sedation and pain medication requirement may also vary greatly. Nonetheless, several anesthesia techniques utilizing local anesthetic infiltration of the incision, scalp blocks, as well as short-acting intravenous agents have been developed to provide adequate analgesia and sedation for patients undergoing awake craniotomies.

### Local Anesthesia and Nerve Blocks

Local anesthetic infiltration of the skin incision and pin sites is probably the most widely used method for pain control during awake craniotomies. However, local injection alone may not provide adequate pain control. In these situations, nerve blocks are an effective method for intraoperative pain control. In fact, some studies have shown that nerve block is superior to local infiltration in term of pain control and hemodynamic stability [27, 28]. A widely used regimen for nerve blocks is a mixture of 0.5 % bupivacaine with or without epinephrine (1:200,000 dilution); usually 5 ml is adequate for a single nerve block. The use of epinephrine in scalp blocks can maximize block duration and minimize risk for systemic dissemination and toxicity. Avoidance of epinephrine may be a consideration for scalp flaps with tenuous perfusion or in patients with a significant history of cardiac abnormalities. Other long acting local anesthetics such as ropivocaine or levobupivacaine can serve as safe alternatives.

The scalp is innervated by branches of the trigeminal nerve and upper cervical spinal nerves [21, 29, 30]. There are six nerve branches mainly responsible for the cutaneous sensory innervation of the forehead and scalp, which include the supraorbital, supratrochlear, zygomaticotemporal, auriculotemporal, greater occipital, and lesser occipital nerves.

The supraorbital and supratrochlear nerves are distal branches of V1, or the ophthalmic division of the trigeminal nerve. They both pass through the supraorbital notch/foramen, and are responsible for sensory innervation of the forehead and anterior scalp. Palpating the supraorbital notch/foramen and injecting local anesthetics about 1 cm medial to it can effectively block the supraorbital nerve. The supratrochlear nerve travels just medial to the supraorbital nerve after exiting the supraorbital notch/foramen. Therefore, extending the supraorbital nerve injection about 1 cm medially can effectively block the supratrochlear nerve.

The zygomaticotemporal nerve is a branch of V2, the maxillary branch of the trigeminal nerve. It emerges through the zygomaticotemporal foramen in the center of the zygomatic bone, and is responsible for sensory innervation of side of the forehead. The zygomaticotemporal nerve can be blocked by injecting local anesthetics just above the zygoma at the posterior portion of the zygomatic arch.

The auriculotemporal nerve is a branch of V3, the mandibular branch of the trigeminal nerve. It runs just posterior and deep to the superficial temporal artery and supplies the skin in the temporal region, the auricle, the external auditory meatus, and the temporomandibular joint. It can be blocked by injection of local anesthetics at the level of the zygoma, about 1 cm anterior to the tragus. Palpating the superficial temporal artery can be helpful in both avoiding intra-arterial injection and locating the nerve located just posterior to the artery.

The greater occipital nerve arises from the *dorsal* ramus of C2. It travels just medial to the

occipital artery at the level just below the superior nuchal line and occipital protuberance, where it supplies the medial posterior part of the scalp. It can be blocked by injecting local anesthetics at the midpoint between the occipital protuberance and the mastoid process, or about 2.5 cm lateral to the occipital protuberance. Another reliable method is palpating the occipital artery and then injecting local anesthetics just medially to the artery.

The lesser occipital nerve arises from the cervical plexus and is derived from the *ventral* rami of the C2 and C3. It travels along the posterior border of the sternocleidomastoid muscle and supplies sensation for the scalp just behind the ear. The lesser occipital nerve can be blocked by infiltration along the superior nuchal line, about 2.5 cm lateral to the point of injection for the greater occipital nerve block, or roughly 5 cm lateral to the occipital protuberance.

### Intravenous Anesthetics

Propofol is a short-acting, intravenous drug that can provide sedation through its interactions with GABAa receptors and sodium channels [31, 32]. Rapid redistribution and clearance affords the sedative effect to be quickly reversed in a dose-dependant manner after stopping an infusion, thus patients can quickly return to a conscious state with minimal residual effect. This property has made propofol the drug of choice for providing temporary sedation that is easily titratable during awake craniotomies. However, several points must be kept in mind. Propofol is a potent respiratory depressant; yet propofol has no analgesic effect and therefore it is often used in combination with short-acting opioids, adding to risk of apnea. Propofol can decrease the systemic blood pressure, decrease peripheral vascular resistance, decrease cardiac filling, as well as lesser effects on heart rate and cardiac contractility. Propofol can interfere with electrophysiologic monitoring, and produces electroencephalographic (EEG) burst suppression in a dose-dependent manner. In contrast, potential benefits could be derived from the drug's anti-convulsant properties and previously discussed favorable effects on ICP and cerebral hemodynamics.

Remifentanil is an ultra-short acting intravenous opioid analgesic drug that specifically activates the mu-receptors. It is metabolized by rapid hydrolysis via tissue and plasma esterases with no redistribution or accumulation despite prolonged infusion. This unique feature makes it an ideal agent for providing titratable and quickly reversible sedation and analgesia. Like other opioid drugs, it can cause respiratory depression and reduction in sympathetic tone in a dose-dependent fashion. Therefore, a decrease in blood pressure, heart rate, as well as respiratory rate and tidal volume may be observed with remifentanil infusion. In addition, it also exerts synergy with propofol and thus they are often used together to reduce overall drug requirement, particularly in instances of patchy block, foley catheter, and position discomforts.

Dexmedetomidine, a relatively newer drug, is a highly selective alpha-2 agonist that can produce rapid sedation with minimal respiratory depression (even with opiates), and minimal interference with electrophysiological monitoring [20]. It exerts its effects through activation of central alpha-2 adrenergic receptors in locus ceruleus, which plays important roles in arousal, the sleep–wake cycle, and sympathetic response. Because of its specific mechanism of action, the patient receiving dexmedetomidine is usually cooperative and can easily transition from a "natural sleep" to awake state without compromise of cognitive functions. In addition to its ability to produce anxiolysis and dose-dependent sedation, it has also been shown to have an analgesic effect that can reduce pain medication requirement by up to 50 % [20]. The exact mechanisms of its analgesic effect is unclear but is thought to be due to activation of alpha-2 adrenergic receptors within the spinal cord that potentiates the effect of opioid pain medications. It is believed that the (often profound) hypertensive response to initial loading dose is related to calcium-channel receptor mediated vasoconstriction of peripheral vessels. Dexmedetomidine subsequently reduces circulating serum catecholamine levels (central locus ceruleus effects); therefore, it can cause decreases in blood pressure and heart rate that may require treatment. Dexmedetomidine has

been shown in human studies to decrease CBF without a matched decrease in CMR, but without detrimental changes in brain tissue oxygenation measured in areas at risk [33]. Effects of dexmedetomidine on cardiac conduction and pulmonary vasculature present a relative contraindication to its use in patients with heart block or pulmonary hypertension.

## Anesthesia Effects on EEG and Seizure Threshold

The EEG or ECOG signal contains two basic parameters including amplitude (voltage of the signal) and frequency. Anesthetic drugs affect both the amplitude and frequency of EEG/ECOG waveforms [34]. In general, both intravenous and inhaled anesthetics produce an initial increase of beta waves in the frontal lobe, with a subsequent decrease of the alpha waves in the occipital lobe. As the anesthesia deepens, the brain waves show an increase in amplitude and a decrease in frequency. Further increases in the dose of the inhalation or intravenous agent will produce further slowing of the EEG, and eventually lead to complete suppression of EEG activities. Both barbiturates and propofol can produce effects on EEG following this general pattern. However, other agents such as opioids, benzodiazepine, or dexmedetomidine do not produce isoelectric EEG or burst suppression.

In addition, intravenous and inhalational anesthetics may also increase or decrease a patient's seizure threshold. In patients with history of seizures, agents that lower the seizure threshold should be avoided. However, drugs that increase the seizure threshold may interfere with ECOG's ability to capture the epileptiform signals intraoperatively to facilitate seizure focus resection. Therefore, the ideal anesthetic drug for awake craniotomies should have minimal effect on seizure threshold, and its effect on EEG/ECOG can be quickly reversed when administration of the drug is stopped. One important point to note is that cortical stimulation itself can induce seizures during neurophysiological testing,; if this occurs, irrigation of cerebral cortex with ice-cold saline can effectively terminate stimulation-induced seizure activities.

A brief overview of the effects of anesthetic drugs on EEG and seizure threshold is provided in the following sections.

### Intravenous Anesthetics

Propofol, barbiturates, and etomidate all produce similar effects on EEG following the general dose-dependent depression as described previously with initial EEG activation, followed by dose-related depression [34]. As the patient loses consciousness, EEG shows an increase in frontal spindles initially, followed by polymorphic 1- to 3-Hz waves, then with progressive slowing, and eventually leads to burst-suppression. A propofol dose range of 40–200 mg produces burst-suppression in almost all patients except during refractory status epilepticus. Benzodiazepines also follow the general anesthesia-related EEG pattern, but they are incapable of producing burst suppression on EEG. Ketamine and opioids, on the other hand, do not follow the general anesthesia related EEG pattern. Ketamine produces a dominant rhythmic theta waves with increased amplitude in the frontal lobes; increasing doses produce intermittent polymorphic delta waves with of large amplitude interspersed with low-amplitude beta waves [35]. Opioids usually produce a dose-related decrease in frequency and increase in amplitude on EEG. Without continuous dosing, alpha and beta waves will eventually return with opioids. Remifentanil is very short-acting and has the most rapid return to normal [36]. Neither ketamine nor opioids are capable of producing burst suppression. Sedation with dexmedetomidine induces an EEG appearance visually indistinguishable from stage II sleep [37]. The ability of dexmedetomidine to produce a state of sedation that does not significantly alter EEG features makes it an attractive drug for awake craniotomies [38].

Propofol increases the seizure threshold and anticonvulsant effect; it is an effective alternative in the treatment of status epilepticus. Barbiturates generally have significant anticonvulsant activities

and are safe for induction of anesthesia in epileptic patients. However, methohexital is an exception, in that it is the only barbiturate that actually lowers the seizure threshold. Because of this property, it is often used for electroconvulsive therapy. Benzodiazepines also have anticonvulsant activity and are commonly used to treat seizures; the anti-epileptic effect is thought to be due to due to the potentiating action on the GABA-a receptors, which increases the opening frequency of chloride channels, leading to hyperpolarization of neurons. Etomidate lowers seizure threshold at a normal clinical doses but increases seizure threshold at high doses. The amplitude of somatosensory evoked potentials is increased with etomidate, and small doses can be administered to help differentiate epileptic foci during ECOG; therefore its use in neurological procedures is selective. Ketamine has significant epileptogenic potential at usual clinical doses and should be also avoided. Opioids in general have no effect on the seizure threshold; however, they may affect the hepatic metabolism of anti-epileptic medications, (and vice-versa) which needs to be kept in mind.

## Inhaled Anesthetics

Isoflurane, sevoflurane, desflurane, enflurane, and halothane all follow the general anesthesia-related EEG pattern. Isoflurane can produce periods of EEG suppression at 1.5 minimum alveolar concentration (MAC), and produce an isoelectric state at 2–2.5 MAC. Halothane follows a pattern similar to that of isoflurane, but the greater doses of halothane are needed to produce similar effect (3–4 MAC), and profound cardiovascular depression can occur at this dose. Nitrous oxide does not follow the general pattern; instead, it causes a decrease in amplitude and frequency of the dominant alpha waves with fast oscillatory waves in the frontal lobes. It may take up to an hour for EEG to return to baseline after discontinuation of nitrous oxide [39]. Older patients and those with EEG slowing at baseline are more sensitive to the EEG effects of inhalational agents.

Halothane and isoflurane increase the seizure threshold and have potent anticonvulsant effect. Sevoflurane and enflurane may lower the seizure threshold and should be avoided in high concentrations. Desflurane has minimal effect on the seizure threshold. Nitrous oxide has some excitatory effects on central nervous system, but its epileptogenic potential is low; however, due to its tendency for increasing ICP, it is often avoided in neurosurgical procedures. In general, however, while most volatile anesthetics have the capacity to provoke neuroexcitation, at low doses this occurs minimally, usually manifesting at near burst-suppression.

## Anesthesia Protocol

There is no standard protocol for anesthetic management in awake craniotomies. Many different techniques exist and they can vary greatly among institutions ranging from local anesthesia, with or without sedation, with or without airway instrumentation [1, 4, 7, 21–23, 27, 29, 40]. However, all of these techniques are designed to meet the safety goals of maintaining good oxygenation and ventilation, optimizing intraoperative hemodynamics, and cerebral perfusion, providing appropriate analgesia and reversible sedation, as well as avoiding anesthetic interference with intraoperative electrocorticography or cortical mapping. The optimal anesthesia protocol for a particular patient may depend on the experience and preference of the surgical and anesthesia teams, as well as the specific need of a particular patient or operation.

Thorough preoperative education of the patient is vital for a successfully awake craniotomy. The patient should be offered a full description of the procedure and operating room environment, including positioning, urinary catheter insertion, sensation during local anesthetic infiltration, noise during craniotomy, etc. The patient also should be informed of what is expected of them during each stage, and the potential for neurologic sensations. They should be encouraged to ask questions and express concerns to avoid surprises during the case. Baseline speech and motor functions should be clearly documented for intraoperative comparison. Prior

to starting the surgical portion of the procedure, all patients should have standard monitoring, adequate intravenous access, usually an arterial line, and urinary catheter in place. The patient should be properly positioned with padding to ensure comfort and offer continuous facial visualization throughout the case. Leather belt straps and 6-in. tape can be used to secure the patient to the table and avoid intrusions into the sterile field (Fig. 3). Strategies to avoid or immediately manage intraoperative complications should be in place. Patients may be prophylactically premedicated with anti-nausea and anticonvulsant medications as indicated. Ice-cold saline must be available for cortical irrigation in case of stimulation-induced intraoperative seizures. Usually seizures are self-limiting with rapid recovery of airway reflexes. A small dose of propofol can be given to break a prolonged or recurrent seizure, with the intent to avoid intubation or subsequent limitations of a longer acting benzodiazepine on neurologic testing. Emergent airway management strategies should be in place in case of sudden complications, including the ready availability of LMA, endotracheal tube, endoscope, GlideScope, as well as tracheostomy kit, should they be needed. Problems that can be encountered during awake craniotomies are listed in Table 2.

The commonly used anesthesia techniques for awake craniotomies include regional scalp anesthesia alone in the "awake" patient and the "asleep–awake–asleep" (AAA) approaches. The workflow and nuances of these approaches are discussed below.

## The "Awake" with Regional Scalp Anesthesia Approach

Local anesthetic infiltrations at the pin sites and incision, along with circumferential scalp blocks as described previously in this chapter, can usually provide adequate intraoperative pain control. Excessive amount of local anesthetics can cause systemic toxicity. The typical dose limits are 2–3 mg/kg for bupivacaine, 5 mg/kg for lidocaine,

**Table 2** Potential issues during awake craniotomy

| |
|---|
| • Airway obstruction, respiratory depression, nausea/vomiting, aspiration, negative pressure pulmonary edema |
| • Hemodynamic changes in HR and BP due to brain stimulation, medication, or pre-existing cardiac conditions |
| • Allergic reaction/pruritus |
| • Disinhibition due to hypoxia, medication |
| • Pain and discomfort |
| • Intraoperative seizures |
| • Air embolus (increased risk with negative thoracic pressure from spontaneous breathing) |
| • ICP variations due to bleeding, brain ischemia, or swelling |

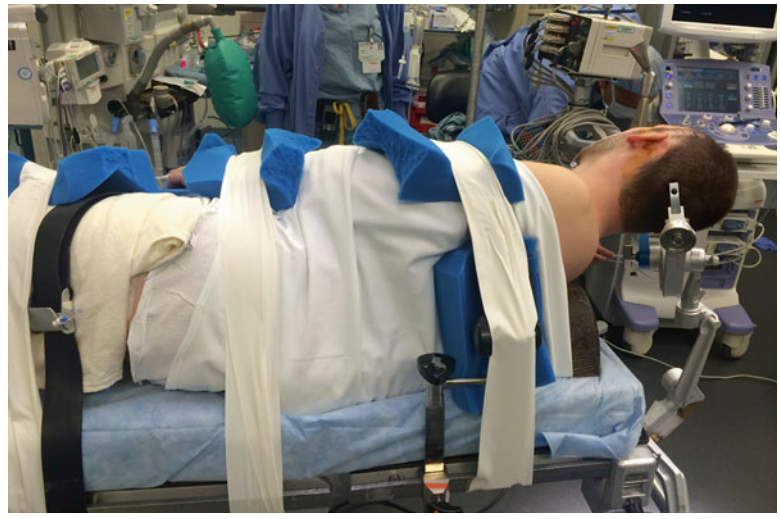

**Fig. 3** Intraoperative photograph demonstrating leather belt straps, 6-in. tape, foam padding, and gel-roll are used to secure the patient and to ensure patient comfort during the craniotomy

and 7 mg/kg for lidocaine plus epinephrine [41]. Re-dosing may be necessary over time. The advantage of using local anesthesia alone in awake craniotomies is that the consciousness of the patient is preserved throughout the procedure and there is no interference of intraoperative electrophysiological testing and the patient [3]. However, since no sedation is provided, the fear and anxiety that the patient may have, prior to and during the craniotomy, must be dealt with by preoperative assurance and continuous intraoperative communication. In addition, therapeutic communications and physical contact have been cited to be an effective method to establish sense of trust and security and relieve anxiety during the procedure [3]. Nonetheless, remifentanil and propofol should be readily available in case where the patient experiences sudden pain or agitation during the procedure.

## The "Asleep–Awake–Asleep" (AAA) Approach

This approach provides the maximal patient comfort and minimizes fear and anxiety during the opening and closing parts of the procedure. This is perhaps the most widely used anesthetic method for awake craniotomy in North America. The level of sedation for the asleep period could vary from light sedation with monitored anesthesia care (MAC) to essentially full general anesthesia. While techniques for LMA/nasotracheal general anesthesia are used by some centers under varying indications, there are increased risks (previously described), associated with transitioning from a deep anesthetic plane to adequate arousal; as well as less predictable dissipation of anesthetic agents that interfere with neuromonitoring and patient examination. MAC, with conscious sedation, has been a consistently successful approach at our institution, using light sedation with intravenous agents, and analgesia with local anesthesia and scalp nerve blocks. The goal for MAC sedation is to provide a safe level of sedation under spontaneous respiration, while adequately controlling anxiety and pain from the surgical procedure. A small limited dose of midazolam and fentanyl may be titrated at the start for comfort, but subsequently held. Typical agents used for sedation are infusions of propofol or dexmedetomidine, plus remifentanil. The patients under MAC sedation should be able to protect their airways, as well as be easily arousable to answer verbal questions and follow commands appropriately. The typical dose for propofol is a 30–50 mg bolus, followed by infusion at a rate of 25–75 mcg/kg/min. Remifentanil is usually used in concert with propofol to provide analgesia (and with perhaps the added benefit of offsetting any propofol-induced disinhibition), at an infusion rate of 0.03–0.1 mcg/kg/min. With this regimen, the patients generally retain their abilities to protect their airways and maintain spontaneous breathing. During intraoperative brain mapping (Fig. 4), the sedation is reduced or stopped approximately 15–20 min prior to testing. Every effort must be made to avoid a startled arousal. At the completion of brain mapping or surgical resection, the sedation regiment is resumed or deepened during closure. A modified "asleep–awake" approach has also been used where the patient is kept awake after brain mapping to avoid the potential risk of airway compromise with resedation [23].

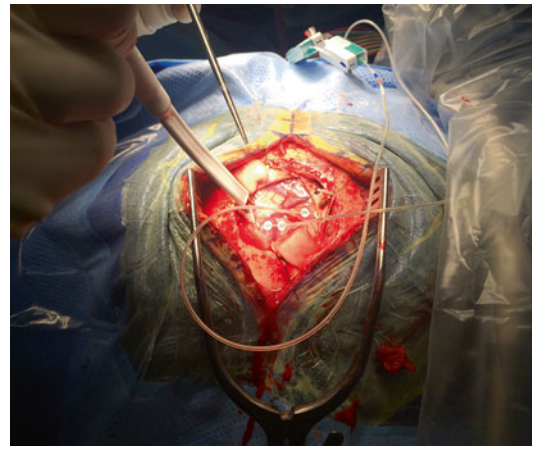

**Fig. 4** Intraoperative photograph demonstrating cortical mapping using Ojemann cortical stimulator

Dexmedetomidine can also be used to provide sedation for the "asleep–awake–asleep" approach. The typical regimen is a loading dose of 0.5–1 mcg/kg over 20 min, with a subsequent

continuous infusion at the rate of 0.2–1 mcg/kg/h. The infusion should be reduced or stopped somewhat earlier (approximately 30 min prior), depending on degree of sedation. (Also of note, the unit dosing for dexmedetomidine is different than that of propofol, which is in mg/kg/min; confusion between these units may result in overdose and prolonged sedation of the patient.) Of note, benzodiazepines can be excessively sedating when administered along with dexmedetomidine.

Given that many of these neurosurgical patients manifest rapid metabolism of anesthetic drugs, including local anesthetics, higher drug infusion rates and/or additional scalp and pin-site infiltration of local anesthetics may be required intraoperatively.

## Conclusion

Awake craniotomy is an indispensible tool in epilepsy, tumor, and functional neurosurgery. It is a safe and effective method to ensure preservation of neurological function with surgical treatment of lesions in eloquent areas. Optimal anesthesia management may depend on the experience and preference of the surgical and anesthesia teams, as well as the specific needs of a particular patient. Early anticipation of potential problems, good rapport, and clear communication amongst the surgical, anesthesia, neuromonitoring teams, and the patient are essential to a successful awake craniotomy.

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# Mapping Cortical Function with Event-Related Electrocorticography

Vernon L. Towle, Zhongtian Dai, Weili Zheng, and Naoum P. Issa

Today's neurosurgeons have a variety of ways to identify eloquent cortex. Increasing utilization of these techniques over decades has dramatically reduced the degree of postoperative morbidity related to cortical resections [1–5]. Today, as part of the preoperative workup, virtually all patients undergo structural MRI scans to determine the location, extent, and nature of their lesion. In some cases, their gyral organization, underlying white-matter pathways, and nearby vascular structures are also imaged. In the same imaging session, cooperative patients can undergo functional MRI protocols to identify primary sensory and motor cortex and language areas (chapter on "Anatomy of Important Functioning Cortex"). Such data, especially when rendered as 3-D images, can facilitate preoperative planning. If registered to the patient after surgical positioning, they can help optimize the location of the initial incision, and define the extent of the lesional resection.

The most widely used intraoperative technique for confirming preoperative functional MRI, PET, MEG, and transcranial magnetic stimulation mapping findings is Otfrid Foerster's direct cortical stimulation technique [6], as popularized by Wilder Penfield [7, 8] in the first half of the last century (chapter on "Mapping Eloquent Brain with Functional MRI and DTI"). The main disadvantages of this technique are that it may cause a seizure; it is time- and manpower-consuming; motor mapping prevents neuromuscular blockade in the sedated patient, and language and sensory mapping requires the patient to be awake during the surgery for language testing [9]. Many young or anxious patients cannot tolerate this. Another limitation is that there is no procedure for locating areas necessary for memory storage and retrieval. Postoperative memory deficits and anomia are a major source of distress for surgery patients [10]. In truth, all functional mapping techniques have serious limitations, and it is prudent to use more than one technique to have the benefit of converging lines of evidence to increase one's confidence in the functional findings.

## Early Electrocorticography

Foerster also pioneered the application of recording the electrocorticogram (ECoG) during surgery (see [11]). Before the MRI era, ECoG recordings were used to locate unseen neoplastic or heterotopic lesions by revealing adjacent localized slowing and/or spiking [1, 12]. Although structural MRI scans have largely supplanted ECoG for locating tumors, ECoG has been increasingly utilized in seizure surgery since the introduction of modern implantable subdural

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electrodes [3, 13]. Chronic recordings can reveal the onset of focal seizures (Fig. 1), as evidenced by their accompanying high-frequency spiking and DC-shifts [14].

Of increasing interest is the relationship between ECoG patterns and cognition. Hans Berger, who first described the human EEG [15], reported that the 10 Hz occipital alpha rhythm of his 14-year-old daughter, Ilse, was blocked while doing mental arithmetic ([16], Fig. 2). Other manipulations of consciousness, such as opening one's eyes or touching one's hand, had a similar effect of increasing EEG frequency. Similarly, the central 10–12 Hz Mu rhythm is blocked by motor activity, an indication that the recording electrode is over motor areas [17, 18]. More recently, as we shall see, higher frequency rhythms have been related to sensory, motor, and cognitive events, but are not as easily recognized in unprocessed raw ECoG recordings.

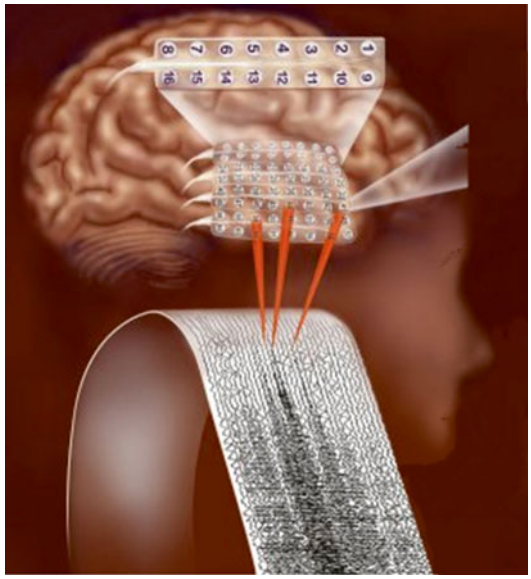

**Fig. 1** Raw electrocorticogram (ECoG) from the right temporal cortex is recorded directly from the surface of the brain through an 8×8 array of subdural electrodes during the onset of a seizure

## Processed ECoG

One of the oldest forms of EEG signal processing is to signal-average sensory responses. Averaging somatosensory evoked potentials to median nerve stimulation is a quick and reliable method to identify the primary hand sensory area [19, 20] and the primary auditory cortex [21] from ECoG recordings. Standard evoked potential systems that are used in the diagnostic clinic can also be used in the operating room. A single strip of electrodes can be moved to different locations on the cortex to identify the inversion of the initial component (N20 posterior—P20 anterior), along with the area of the maximum response (50–100 μV) (Fig. 3). Technical details are listed in Practical Box 1.

## Gamma Activity

High-frequency EEG activity was described much later than the slower EEG rhythms. Most recordings before the digital computer era were limited to frequencies below about 40 Hz, because the

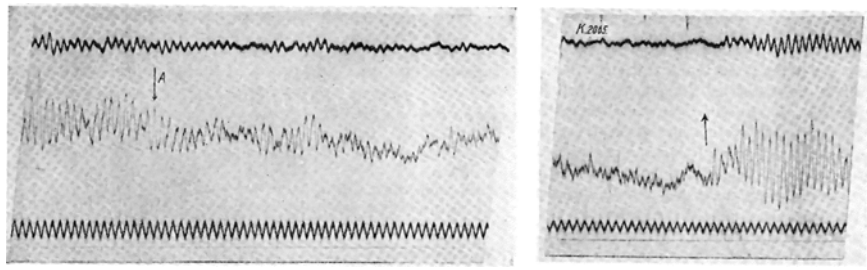

**Fig. 2** Hans Berger's recordings from his 14-year-old daughter, demonstrating the blocking (A) and recovery (*up arrow*) of alpha at the beginning and end of mental arithmetic. (© Springer-Verlag Berlin Heidelberg 1932), reprinted with permission

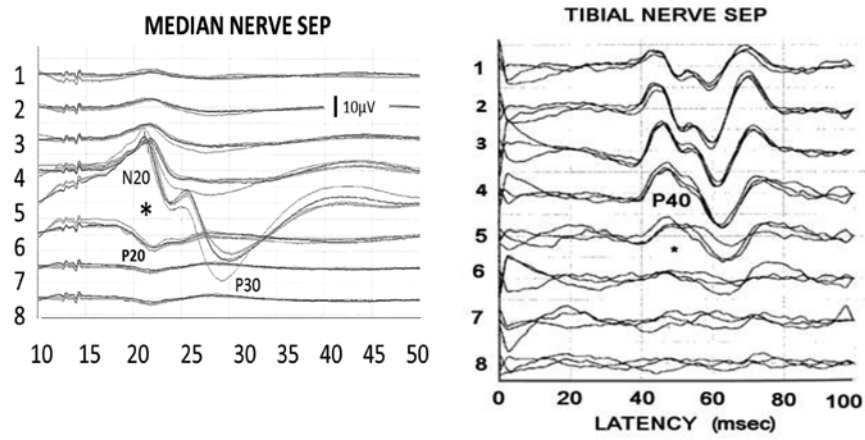


**Fig. 3** The distribution of averaged somatosensory evoked potentials from median nerve and tibial nerve stimulation. Note that the median nerve SEP inverts in polarity over the central sulcus, but the tibial nerve SEP merely attenuates (*asterisks*)

**Practical Box 1. Evoked Potential Mapping**

Stimulus parameters:
- Location medial wrist, medial ankle
- Intensity: 4–20 mA (motor threshold)
- Duration: 0.2 ms
- Rate: 5/s
- *N*: 50–200 repetitions

Recording parameters:
- Recording channels: 4–16
- Filters: 1–100 Hz
- Sweep duration: 50–100 ms
- Display sensitivity: 5–10 μV/division
- Two superimposed replications
- Negative up

Reference: contralateral mastoid

Ground: scalp

Relevant Peaks:
- Median nerve: P/N20 (anterior–posterior)
- Tibial nerve: N/P40 (contra-ipsilateral)

Suggested Anesthesia:
- Propofol: 50–100 mcg/kg/min
- Remifentanyl: 0.02-0.05 mcg/kg/min
- Desflurane: 1–3 % ET

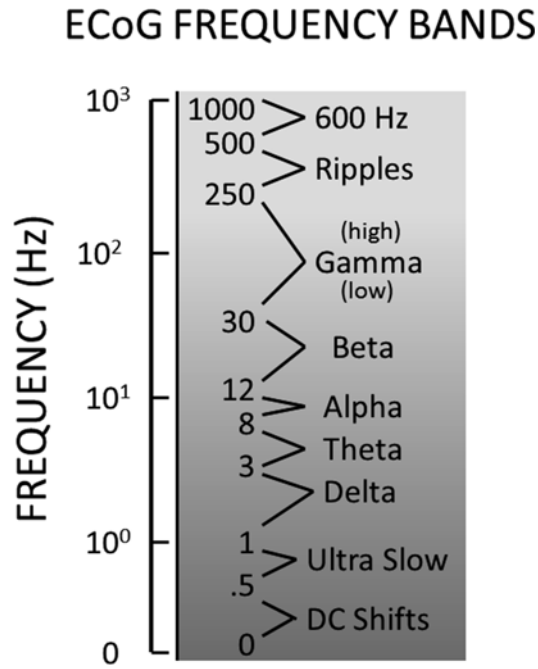


**Fig. 4** The newly emerging high-frequency EEG bands

mechanical pens through which they were recorded could not follow faster activity. Modern recordings can now digitize the ECoG at up to 2 kHz, and have allowed us to observe much higher cortical rhythms. There is not yet complete agreement about the names and borders of these bands (Fig. 4). One of the most interesting frequency bands is the gamma band (30–250 Hz), which appears to indicate that information processing is taking place [22]. Although the sensory respon-

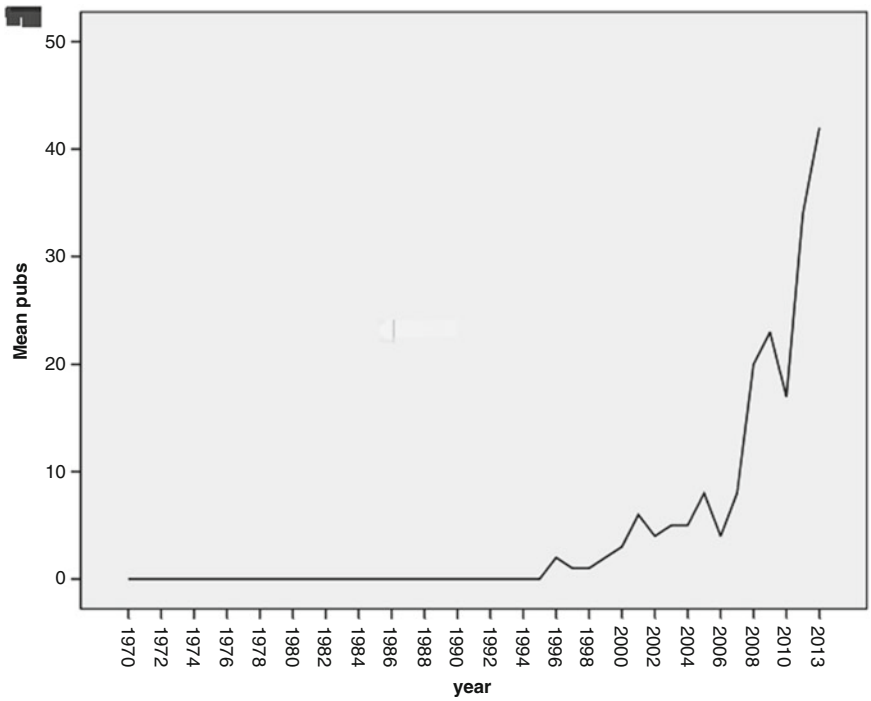


**Fig. 5** The number of publications/year involving ECoG gamma activity

siveness of the animal ECoG was described more than a century ago [23], its gamma activity has only been appreciated for the last 20 years (Fig. 5). At the time of this writing (early 2015), more than 200 reports have been published about gamma activity in the ECoG, over half of which have been published in the last 3 years. This field is clearly still in its infancy [24]. For the remaining portion of this chapter, we will describe ECoG changes in gamma activity during various language tasks, in an attempt to determine to what degree it can be used to map eloquent cortical areas.

## Three Levels of Phase-Locking to Events

EEG rhythms can be phased-locked to external stimuli to various degrees. We have already mentioned signal-averaging, which is the tightest level of linking the EEG to an external event. Averaged evoked potentials obtained from repeatedly presenting electrical pulses to a nerve, or flashes of light to the eyes, or tones or a single word repeatedly presented to the ears, ***evoke*** an averaged response as long as each individual stimulus is the same. They summate best when the amplitude and latency (phase) of each individual response to be averaged is nearly identical on each trial. This is in deep contrast to the lowest degree of phase locking, like that obtained by Hans Berger in Fig. 2, in which EEG rhythms are related to behavior or states of mind. Berger's daughter was exhibiting the lowest concordance between EEG and external and internal events when the EEG signals she ***emitted*** visibly changed with alterations in her cognitive state. Today, in the digital era, we can tease out a middle ground of concordance with events in the form of ***induced*** high-frequency ECoG rhythms that are not as highly time-locked to external events as with ***evoked*** signal-averaging, but are still more closely time-locked than spontaneously ***emitted*** potentials. For example, cortical responses to different words cannot be averaged because each stimulus will elicit a somewhat different response within the brain, which will not consistently summate with the responses from other trials. This can be overcome by the use

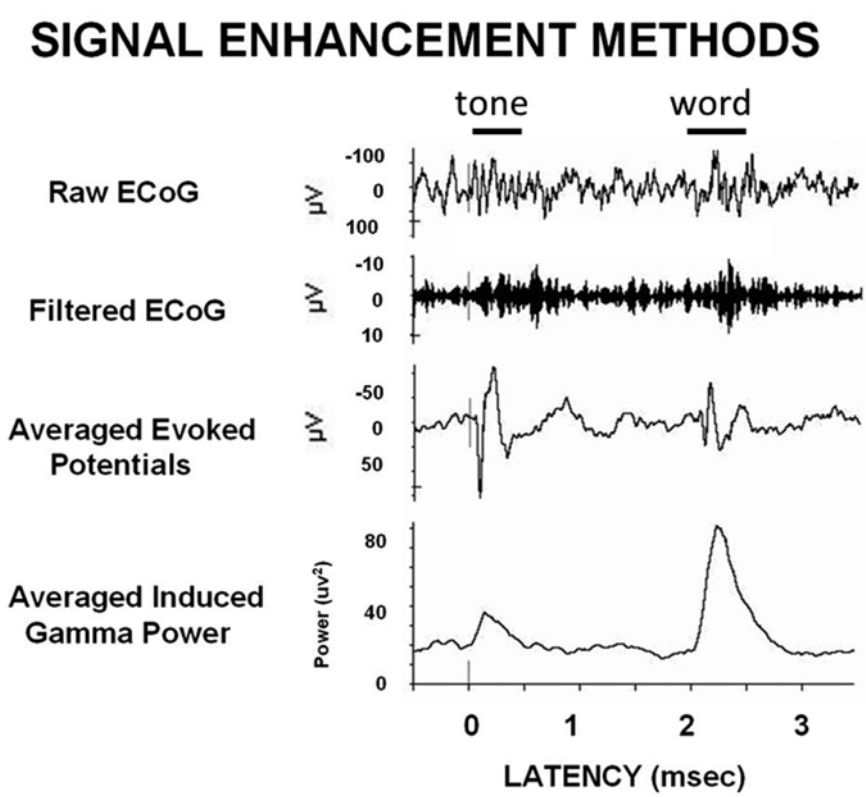


**Fig. 6** A comparison of various signal-enhancement techniques to identify a repetitive tone and the presentation of different words. Although it is very difficult to identify a response in the raw ECoG, filtering out the slower activity gives a sense of an external event. Simple averaging of the responses enhances the evoked response to the repetitive tone, but the response to the words is less clear. Averaging the non-phase locked gamma activity also detects the tone, but dramatically increases the response to the presentation of different words

of event-related band-pass averaging. This technique does not require that the responses be phase-locked to the stimulus, like signal averaging, but rather accumulates the power in the chosen band regardless of its phase. This effectively yields the average envelope of the activity that is ***induced*** (not emitted or evoked) by external events (Fig. 6). The combination of these three analytic approaches, along with several others, provides a suite of tools for mapping cortical function from ECoG. In the next sections we review how these tools are applied to gamma band activity.

## Recent Gamma Activity Findings

Interest in high-frequency ECoG recordings was inspired by a series of papers by Nathan Crone, beginning with sensorimotor mapping in 1998 [25, 26]. This was followed by an award-winning article described his group's ECoG findings detailing gamma activity as a sign of speech perception and production [27, 28]. Since then, gamma activity has largely become accepted as a sign of local information processing, from movements to language and memory to higher-order cognition. Indeed, in the last two decades, localized, task-related enhancements of gamma activity have been related to a variety of cognitive phenomena. Increased gamma activity recorded from chronically implanted subdural arrays of electrodes has been described over the primary motor cortex during hand movements [25, 26, 29–33] and expressive speech [34–36]. Similarly, gamma increases have been recorded over the lateral occipital region during reading words [36–38], and over the basal temporal region during picture naming or viewing [37, 39–43]. Task-

induced cortical mapping also has the potential to be used in a clinical setting to identify memory encoding and retrieval (Tallon-Baudry 2001; [44, 45]). In addition to neocortical activation, Sederberg et al. [46] found that gamma activity in the hippocampus during the encoding portion of memory tasks predicted successful retrieval. Axmacher [47] observed that high gamma activity (~100 Hz) found in the rhinal cortex predicted the consolidation of long-term memory.

Recent studies of gamma augmentation have allowed better segmentation and localization of language processing. Models of language processing and production can be tested with even finer spatial resolution [48]. The model of speech as proposed in the late nineteenth century, when Paul Broca localized speech production to the inferior frontal gyrus, and Carl Wernicke localized speech reception to the posterior superior temporal gyrus has been supplanted by newer models [49, 50]. The studies cited above indicate that speech is processed in a widely distributed and parallel manner early on. Enhanced gamma activity has been described over the superior temporal gyrus in response to sounds [51] and spoken words [27, 28, 37, 38, 52]. The more nuanced models feature dorsal and ventral streams of activity leaving primary auditory cortex (BA 22) in opposite directions along the STG [53, 54]. The anterio-ventral stream projects to the inferior frontal lobe via the uncinate fasciculus. As the anterio-ventral stream traverses the STG (the auditory analogue to the inferior visual "what" pathway), it processes phonemes, words, and even short phrases, [54]. In support of this, note that there is no posterior activation of silently processed words in Fig. 7. The posterio-dorsal stream, exiting the auditory cortex in the opposite direction towards the temporal parietal junction, supports phonological memory, and awareness [49]. As such, the dorsal stream engages in cortical monitoring of self-produced speech, correcting for overt errors in speech output. This is in contrast to the classical model, in which speech production was thought to be localized to the left frontal lobe. The posterio-dorsal stream ascends via the parietal lobe to the frontal lobe Broca's area via the arcuate fasciculus and modulates the pre-motor cortex during speech production.

A summary of areas associated with cognitive specialization and localized with gamma activity can be found in Practical Box 2. It is important to realize that in addition to the classical areas mentioned here, focal activations have also been noted to be widely distributed in different areas of cortex in these reports. No one has yet described a comprehensive information processing model to incorporate all of these empirical findings. Their relationship with direct cortical stimulation in the same patients is complex, and needs to be understood before gamma augmentation can supplant direct brain stimulation in clinical practice [55]. We are reminded of Hughlings Jackson's [56] warning from over a century ago, that "To locate the damage which destroys speech and to locate speech are two different things." It remains a challenge to determine which areas of gamma augmentation are critical for the performance of these tasks, or are merely contributory, and might be considered as "boutique" areas that enhance the behavior studied. A noteworthy report by Kojima et al. [57], found that in a group of 57 patients in which surgical resections were guided by direct cortical stimulation, those patients in which areas of gamma augmentation were resected had a statistically significantly more postoperative language deficits. More broadly, comparing electrical stimulation sites, areas of gamma augmentation, functional MRI, PET, MEG, and transcranial magnetic stimulation interruptions of processing to postoperative deficits will be an area of fertile research.

## Inter-electrode Coherence and Causality

The ability to identify areas that are active during various tasks, such as is seen with functional MRI is important, but only partially satisfying. Identifying functionally active locations within brain states ("spotology") is not enough. It is desirable to understand the dynamics of the flow of information and functional interactions between these active areas, which some consider

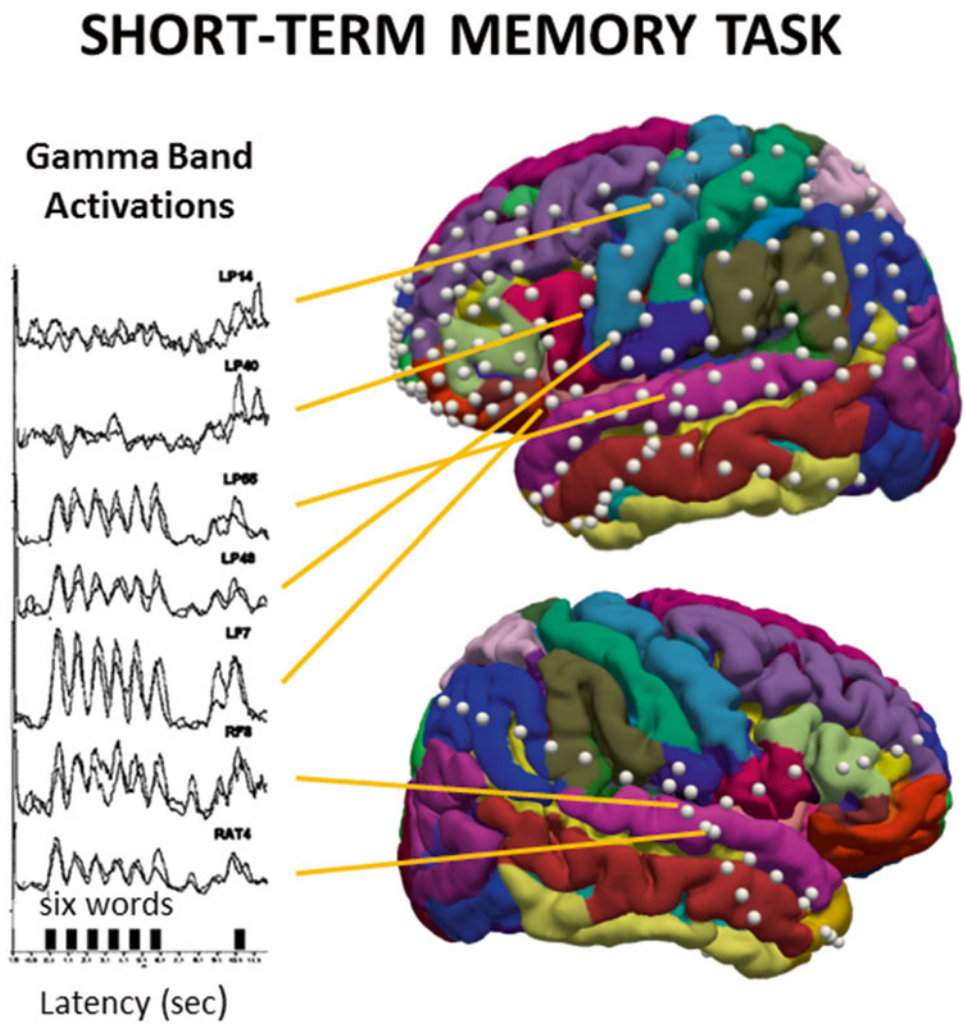


**Fig. 7** ECoG gamma activity recorded while a patient listens to six words aurally presented at 1/s, and tries to remember them. The subdural electrodes are registered to the MNI average normal brain as rendered with FreeSurfer

**Practical Box 2. Functions That Can Be Identified with High Frequency Gamma Mapping**

| Function | Disorder | Cortical locations | Task |
|---|---|---|---|
| Limb movement | Paresis | Primary motor cortex (BA 4) | Wiggle fingers |
| Limb sensation | Numbness | Primary sensory cortex (BA 3) | Hand, foot SEP |
| Audition | Deafness | Primary auditory cortex (BA41/42) | Hearing tones |
| Expressive speech | Aphasia | Opercularis, triangularis (BA 6, 4/45) | Repeating words |
| Receptive speech | Auditory agnosia | Posterior superior temporal (BA 22) | Hearing words |
| Formed vision | Visual agnosia | Primary visual cortex (BA 17/18) | Viewing pictures |
| Reading text | Alexia | Fusiform gyrus (BA 37) | Reading words |
| Face recognition | Prosopagnosia | Fusiform face area (BA 37) | Viewing faces |

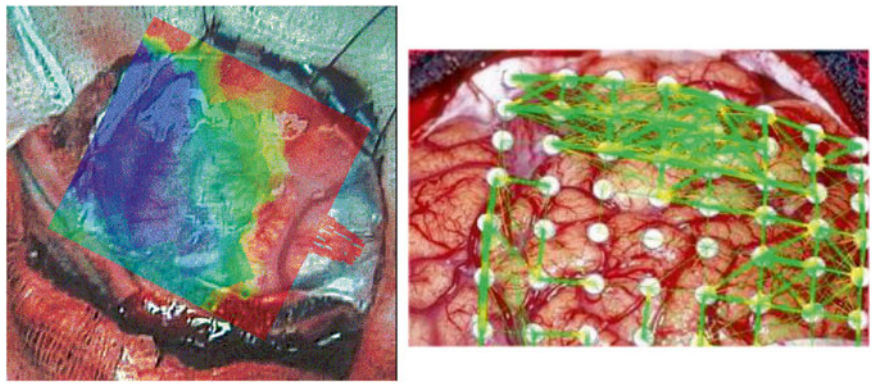

**Fig. 8** *Left*: Registering ECoG to the surgeon's view: (*left*) the inversion polarity of the median nerve somatosensory evoked potential superimposed over the craniotomy (*blue* = negative, *red* = positive). The central sulcus can be appreciated at the point of inversion. *Right*: Increased inter-electrode coherence over the lateral temporal lobe (*green* at *top*) in a *right* TLE epilepsy patient

nodes in the cortical network. This can be gleaned, in part, by observing the succession of activations in different areas of cortex, but also by looking at the similarity of the signals measured between electrodes. We have calculated the inter-electrode coherence between all possible pairs of electrodes [58, 59], and found that the distribution of similarities is clearly not random, but instead was related to gyral structure and the borders of neoplastic intrusions (Fig. 8). At this point in time, the functional significance of these patterns eludes us [60]. Others, using different types of measures of similarity or causation [29, 47, 61, 62] have interpreted these similar patterns in terms of information flow along white matter pathways. One would expect that such functional connectivity can be consistent with white-matter tractography [63–65].

## Combining Neurophysiology with Neuroanatomy

Recording gamma activations for functional mapping and clinical decision-making is relatively straightforward. Although many researchers have developed their own signal-analysis applications in house through MATLAB or other programming environments, this is not necessary for clinical applications. Several user-friendly systems are currently under development, and at least two commercial systems currently on the market: Neuroscan (Compumedics, Victoria, Australia) and BCI2000 [66, 67]. The results from these systems can be used in a manner similar to how direct brain stimulation findings are utilized (Figs. 1, 3, 6, and waveforms in Fig. 7).

However, registering the findings to the MRI scans (Fig. 7 right, Fig. 9), or to the patient in real time is more technically challenging. Some knowledge of computer programming is required to download and set-up the free, but sophisticated, public domain imaging software packages such as FreeSurfer, SPM, Slicer, and EEGview. More expensive intraoperative patient registration systems such as Stealth (Medtronic, Inc., Minneapolis, MN) can provide information helpful to superimpose ECoG findings directly on the brain in real time (Fig. 8).

## Passive Mapping

Because the experimental activations described in the above studies are so robust, and extend so far above baseline values, one wonders whether they might be detected during spontaneous behaviors, natural conversations with family and friends, eating, reading, watching television, and

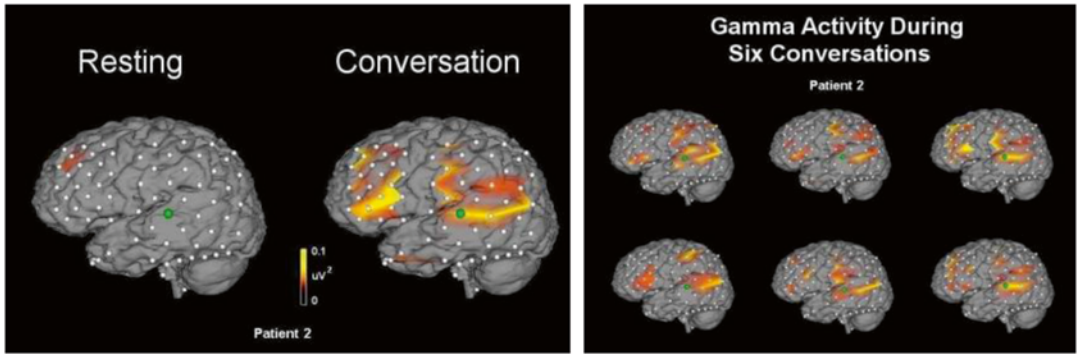


**Fig. 9** Induced gamma activity (*gold*) during resting with eyes open, compared to participating in a spontaneous conversation. Note that the activation is strongest over what is considered Broca's and Wernicke's areas, as well as over the sensory mouth area and dorsal-lateral prefrontal cortex

playing video games, as well as thinking, resting, or sleeping. Perhaps it is not necessary to perform artificial tasks to identify eloquent cortical areas. If such spontaneous behaviors can be identified through examination of the video monitoring and their ECoG maps compared to each other, it might be possible to passively obtain clinically useful maps of brain function in the background, while the patient is being monitored in the epilepsy unit. This would be using the loosest form of connectivity between behavior and the ECoG, as Berger did in Fig. 1, but with the advantage of much longer time segments and modern EEG processing.

Several reports have indicated that it is possible to review the video records to identify periods when the patient is performing some of the above behaviors. They have used increases in gamma activity to map spontaneous speech and upper and lower limb movements [32, 38, 66, 68–72], compared to when they are relaxing with their eyes open (*cf* Fig. 9). We have observed consistent parietal activations during eating and when a patient played video games. (Perhaps we need to compare video game scores before and after surgery?) Killingsworth and Gilbert [73] have identified 22 active cognitive and behavioral states and have determined how their subjects liked or disliked being in them (Fig. 10). Eleven of these states (red) could easily be identified during the surgical monitoring work-up [74]. If so, the challenge ahead will be to devise decision algorithms to objectively identify such states in video records [75, 76]. (Well, okay, maybe not making love or praying.)

To date, the functional significance of these activations is not well understood, inasmuch as, they have only been partially confirmed with direct electrical stimulation. However, as has been reviewed by Hamburger [77], direct brain stimulation mapping is not a pure gold standard, but is to some degree alloyed with lesser metals. Rather than testing a technique to an imperfect standard, it might be more reasonable to compare how direct brain stimulation, ECoG mapping, and functional mapping predict postoperative deficits that are objectively assessed with clinical examination and comprehensive neuropsychological testing change scores.

A passive mapping approach would have several advantages: There is no risk of causing a seizure from brain stimulation. ECoG would be recorded in the patient's natural states. If it is a frequently performed behavior, it is likely that it would be based on longer ECoG segments, and perhaps be more stable. If such states can be identified with an automated algorithm, there would be less manpower required than for formal testing. We have reviewed the ECoG records from one patient over several days, and marked the times when the patient was watching television, reading, eating listening to someone talking, rest-

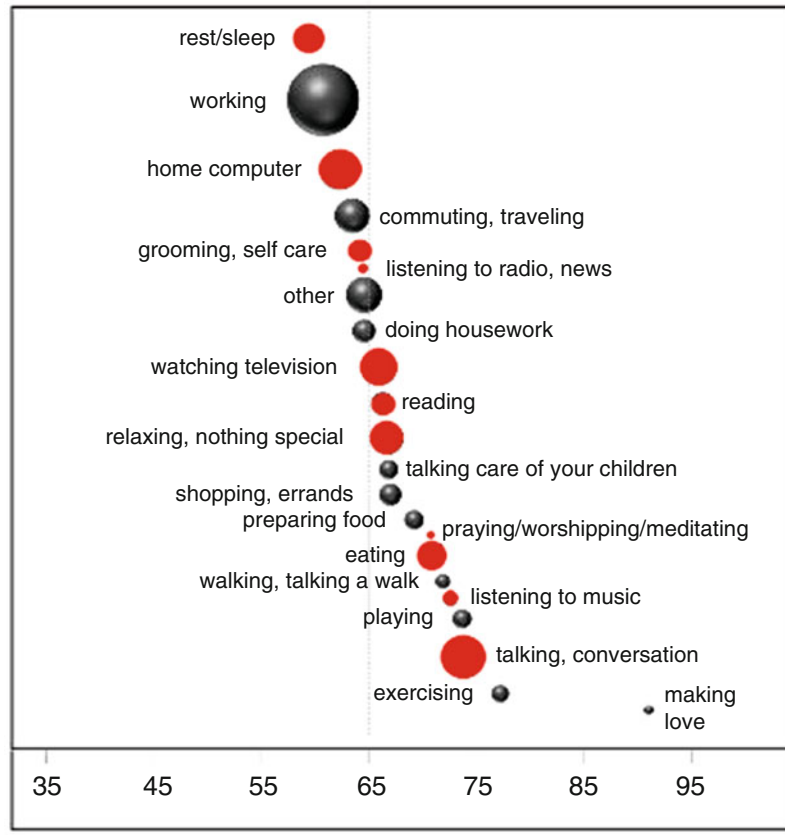


**Fig. 10** Twenty different cognitive states described by Killingsworth and Gilbert [73]. Dot size indicates the amount of time spent in each state, and the lateral position indicates the pleasant/unpleasant rating of the state. *Red*: could be done during recordings

ing with eyes closed and sleeping. We then used multidimensional scaling of the power spectra to arrange the ECoGs in terms of similarity. As can be seen in Fig. 11, the ECoG segments appeared to self-organize into separate groups. Interestingly, when the patient appeared to be resting with eyes closed, those ECoG segments clustered into two groups, with some more close to awake behaviors (television and reading) and others closer to sleeping segments. These preliminary findings encourage us to imagine that the ECoG can be used to discriminate various mental and behavioral states, and that these differences might be used to identify which parts of the brain are active in each state. It seems like functional maps specific to each patient might be able to be generated completely passively toward the end of an epilepsy workup, and could be used to aid in planning the optimal resection for that patient.

## Functional Mapping in the Near Future

Now that EEG has moved from the analogue era to the digital age, innovations in signal processing and communication promise dramatically improved functional mapping in the near future. Several groups are currently testing fully-implantable subdural grids, *sans* cables, which can be powered and communicated with through a completely closed craniotomy via telemetry. These chronic implants will be capable of both recording from and stimulating the brain. Allowing untethered ambulation, these implants can be implanted for months, not days, and could transmit the recordings to the clinic via a mobile cellular device. Devices that discreetly and unobtrusively encode behavior and the surroundings of the patient are also readily available commercially.

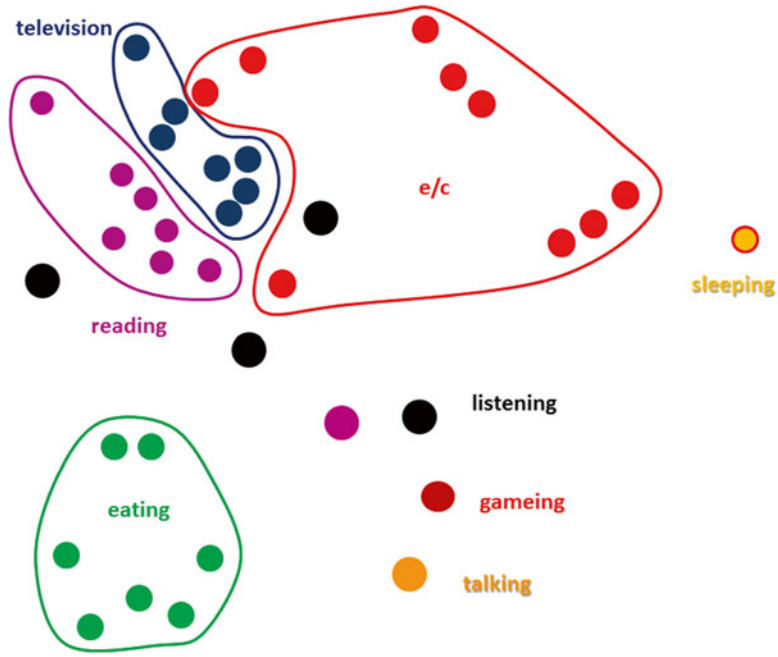


**Fig. 11** Power spectrums from ECoG recordings obtained during different behavioral states were analyzed with multidimensional scaling. This procedure groups the recordings based on their similarity. Recordings that are similar to each other are plotted close to each other. The groupings based on electrical similarity largely match the behavioral states of the patient. They are projected here into a two-dimensional similarity map, which does not represent physical space on the brain

These chronic implants will largely eliminate the need for expensive 24/7 coverage by large, heavily-staffed epilepsy monitoring units. The cost of epilepsy monitoring will be substantially reduced by eliminating the need for continuous medical care, sitters, and hospitalization.

Except through the magic of optical imaging, the electrical activity of the brain is invisible to the eye. New and effective ways need to be developed to display and communicate the electrophysiological findings to the surgeon in a timely and intuitively natural way. Similarly, the findings from imaging and physiologic studies need to be combined into dynamic, multimodal 3-D images that can easily be manipulated by staff without advanced expertise with computers. These need to be available in the operating room, and should ideally be registered to the patient, so that the neurosurgeon can see the electrophysiologic data superimposed on the craniotomy through the operating microscope or surgical glasses (Fig. 8).

We expect to see a gradual shift away from Foerster's direct stimulation mapping for a myriad of reasons. The sequential stimulation of pairs of electrodes is a tarnished standard, which carries the risk of seizures, and is time, and labor intensive. Instead, we anticipate an increased use of active and passive processed ECoG techniques, such as the augmentation of gamma activity described in this chapter. Qian et al. [33] found that ECoG mapping achieved nearly identical specificity and sensitivity as compared to direct stimulation. Their mapping based on gamma activity took mere minutes, compared to the hours used in direct cortical stimulation, and was accompanied with minimal additional risk. It may prove to be even more expedient to identify putative eloquent cortical areas with passive ECoG mapping algorithms. A formidable challenge will be to discriminate between necessary and ancillary areas of cortical function, which are probably not discrete entities, but rather points along a continuum. Finally, to overcome the limitations of spatial coverage with subdural grids and depth electrodes, it will be fruitful to combine ECoG results not just with direct cortical stimulation, but also with noninvasive fMRI, PET, MEG, transcranial magnetic stimulation findings and outcomes. The ultimate goal will be to view all of these functional findings in a single, multimodal, dynamic image merged with 3-D anatomy of the cortex, white matter and underlying vasculature that is registered to the patient. This is easily achieved in the not-too-distant future.

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# Mapping of Eloquent Cortex in Focal Epilepsy with Intracranial Electrodes

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## Introduction

Epilepsy surgery has revolutionized the management of treatment-resistant focal epilepsy. Its success is based on the total resection of the epileptogenic zone (EZ) in the absence of any neurologic (e.g., motor, sensory, and cognitive) deficits. Clearly, the ideal candidate is a patient with focal epilepsy with an EZ that does not involve eloquent cortex and is easily accessible to surgical resection and in whom the noninvasive studies of the presurgical evaluation can yield concordant data of the neurophysiologic (interictal and ictal electrographic recordings), structural (e.g., high-resolution brain MRI) and functional (e.g., positron emission tomography [PET]) neuroimaging studies and neuropsychological evaluation. Unfortunately such is not the case in a significant percentage of patients, for one of the following reasons: (1) the presurgical evaluation fails to yield concordant localizing data among the various diagnostic studies; (2) the epileptogenic zone cannot be localized or even lateralized in a reliable manner; (3) the epileptogenic zone appears to be close to or involve eloquent cortex. Under those circumstances, there is a need to recur to invasive EEG monitoring with intracranial electrodes. Specifically, these are the circumstances when intracranial recordings should be considered:

(a) In case of discordant data from scalp interictal and ictal recordings.
(b) In case of discordant data from neuroimaging (structural and/or functional), and scalp EEG interictal/ictal recordings.
(c) In lesional focal epilepsy with an ictal onset that is not lateralized to the side of the lesion.
(d) In bilateral mesial temporal sclerosis with bilateral independent epileptiform activity.
(e) In non-lesional focal epilepsy.
(f) In focal epilepsy in which the epileptogenic zone is suspected to encroach upon or to be in the vicinity of eloquent cortex [1].
(g) In focal epilepsy with dual pathology.

The ultimate goal of a video-EEG monitoring study is to identify the following zones:

1. The irritative zone (IZ), defined as the cortical area with interictal epileptiform discharges. In approximately 10 % of patients with documented focal epilepsy, no irritative zone may be identified in the course of prolonged scalp video-EEG recordings, as the generator of the interic-

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tal activity may fail to activate in a synchronous manner an area of at least 6–10 $cm^2$ and/or the angle subtended by scalp electrodes may not be able to detect the discharges' vectors.
2. The ictal onset zone (IOZ), defined as the cortical area at the onset of clinically detectable seizures; this term has been applied this term to the ictal pattern recorded with intracranial electrodes, which precedes or occurs at the moment of the first clinical sign or symptom and presents as a fast synchronizing low-voltage activity the pattern of which varies depending of the cortical structures responsible for its occurrence.
3. The EZ defined as the cortical area that needs to be resected to abolish the generation of seizures.
4. The symptomatogenic zone (SZ) represents the first eloquent zone activated by the Ictal activity.
5. The functional deficit zone (FDZ), defined as the cortical area that is functionally abnormal interictally.

While these five zones are often superimposed, in general the IZ may be larger than the IOZ and EZ, while the IOZ is smaller than the EZ. Furthermore the IZ is at times at a significant distance from the EZ. For example, focal epilepsy of mesial temporal origin may have a well-identified IOZ in one of the mesial temporal regions and yet, interictal recordings may reveal bilateral independent epileptiform discharges. When these are rare in the contralateral side (<20 %), the prognosis for postsurgical seizure remission is very good. On the other hand, when the relative frequency of epileptiform discharges is 50 % in each side, the postsurgical seizure outcome is worse as the relative high frequency of epileptiform discharges in the contralateral side heralds a potential for ictal activity.

The SZ may be at a )distance of the IOZ, which is often the case of focal epilepsy in which the EZ is in non-eloquent cortex. For example, in seizures of basal-temporal occipital origin, the initial ictal semiology is often suggestive of involvement of mesial temporal structures (e.g., epigastric discomfort, sensation of deja-vu, fear, or excessive salivation).

## Type of Intracranial Recordings

Intracranial recordings can be achieved with a variety of electrodes, often used in combination. The choice of electrodes is typically individualized depending on the problem at hand, the experience of the epilepsy center team with a given type of electrode and financial considerations [1–3]. The types of electrodes include: (1) Epidural electrodes, which are available as pegs or strips; these are typically used as "sentinel" electrodes to lateralize and narrow down the potential EZ. (2) Foramen ovale electrodes, which consist of electrode strips inserted through the foramen ovale to lay under basal temporal cortex mesially and are used to lateralize the ictal onset in patients with suspected TLE of mesial temporal origin. (3) Subdural strips and/or grids and (4) Depth electrodes.

Subdural grids and strips are the most frequently used intracranial electrodes for demarcation of the EZ and mapping of eloquent cortex in a majority of epilepsy centers in the USA and Latin America. Conversely, invasive video-EEG monitoring studies are conducted with depth electrodes in some of the major epilepsy centers of France [3]. In recent years, an increasing number of epilepsy centers around the world have recognized the advantage of each type of electrodes and started to use both types of electrodes in the same case. Figure 1 illustrates such a case in which subdural grid and strips and one depth electrode were implanted in a patient with suspected left occipital and temporal epilepsy.

The specific process involved in the demarcation of the EZ, IZ, and IOZ is beyond the scope of this chapter and will not be discussed any further. The reader is referred to comprehensive review articles on this topic. In the next sections, we review the basic principles that need to be considered in the mapping of eloquent cortex with intracranial electrodes and in particular with subdural electrodes.

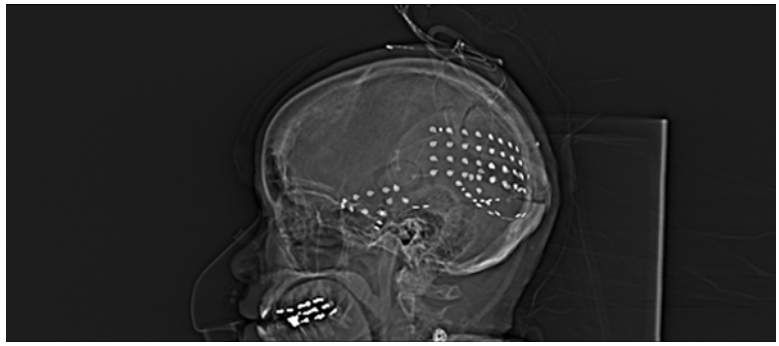

**Fig. 1** Patient with suspected epileptogenic zones in occipital and mesial temporal structures. She was implanted with an 8×5 grid placed over the lateral occipital-temporal neocortex, basal and mesial occipital strips, one depth electrode in mesial occipital cortex, and basal and antero-temporal strips

## Mapping of Eloquent Cortex

(a) Basic concepts

Eloquent cortex is defined as the cortical area with an identifiable function, which can result in a permanent deficit when it undergoes a resection and/or disconnection. Clearly, one of the essential steps of any presurgical evaluation is the determination of whether eloquent cortex is encroaching upon and/or is completely superimposed with the targeted area of resection. Cortical electrical stimulation is one of the methods used to map eloquent cortex via subdural and/or depth electrodes [1, 2].

Ideally, intracranial electrodes should cover in its entirety the presumed eloquent cortex area, so that at the conclusion of the mapping process, a circle of "silent electrodes" surrounds it. For the purpose of mapping eloquent cortex, placement of electrodes is based on data derived from non-invasive neurophysiologic studies such as magneto-encephalography studies (MEG), structural and functional neuroimaging studies including functional MRI and Diffusion Tensor Imaging (DTI), which can provide important information on the connection between functional areas. After all, permanent deficits can result not only from the resection of eloquent cortex but also from its disconnection.

In most cases, mapping of eloquent cortex is aimed at identifying language (expressive and receptive), sensory, motor, auditory, and visual functions [4–6]. While memory processing can be investigated with electrical stimulation of hippocampal structures with depth electrodes, it is usually achieved with noninvasive methods (neuropsychological testing, functional brain MRI with or without the Intracarotid Sodium Amytal test [Wada test]). Limbic structures mediating fear and panic can be identified with stimulation of amygdala and cingulate gyrus with depth electrodes as well. Identification of eloquent cortex mediating complex cognitive tasks (e.g., executive functions) in frontal lobe structures remains an unresolved challenge, which has resulted in cognitive deficits following resections of prefrontal and mesial frontal structures.

Resection and/or disconnection of some eloquent cortical areas can result in significant and potentially permanent functional deficits [7–11]. These areas are referred to as "*indispensable*" cortex and include: (1) primary motor cortex mediating function of distal segments of the upper and lower extremities; (2) primary sensory cortex; (3) primary visual area and (4) Language cortex, involving Broca's (anterior) and Wernicke's (posterior) language cortices and adjacent language cortex in temporal lateral and frontal regions (see below) [12–17].

In contrast, dispensable cortex refers to cortical areas in which resection and/or disconnection may result in none, transient, or subtle functional deficits. These include: (1) Primary auditory cortex (Heschl's gyrus); (2) supplementary sensory motor area, including the eye-fields premotor area; (3) The face area of Brodman's area 4; (4)

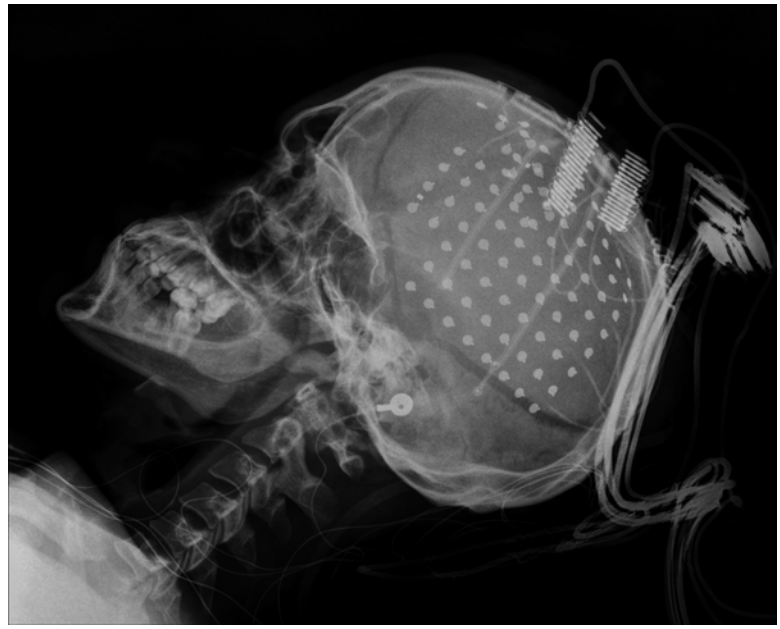

**Fig. 2** 8×8 Subdural grid positioned over the lateral convexity of the left hemisphere with additional 2×4 grid placed anterior to the large grid

secondary sensory cortex and (III) basal temporal language area [14, 16].

The following responses can result from electrical stimulation: (1) no clinical phenomena; (2) a positive motor, sensory, auditory, visual, and psychological effects (e.g., clonic movements with stimulation of primary motor cortex); negative motor, language and visual effects.

Electrical stimulation can elicit positive phenomena when testing the patient in a resting state. Conversely, to identify negative phenomena, patients must perform one of the functions mediated by the area that is being stimulated (see below).

Of note, the absence of any response does not automatically exclude the possibility of eloquent cortex in the stimulated area. Indeed, the false negative finding may have resulted from a failure to reach an adequate current intensity, either because of after-discharges at low-intensity stimulation (see below) or because the current necessary to elicit a response is higher than the maximal current delivered by the stimulator [18]. Any findings of eloquent cortex have to be reproducible during repeated stimulations to be considered reliable.

Mapping of eloquent cortex must be conducted following the completion of the identification of the EZ, once the patient has been restarted on his antiepileptic drug regimen, in order to minimize the risk of stimulation-induced afterdischarges and seizures.

Cortical stimulation for mapping of eloquent cortex per-se is safe. The only risks include provocation of epileptic seizures [4] and pain, associated with stimulation of electrodes in the vicinity of highly innervated meninges (e.g., basal temporal region).

(b) Methodological aspects

*Electrodes*: As indicated above, mapping of eloquent cortex has been performed with subdural grids and strips and to a lesser degree with depth electrodes. Today, grids and strips are available in various shapes and dimensions and consist of platinum electrodes embedded within a silastic sheet, and placed 5–10 mm apart from each other. Thus, mapping of the basal temporal region can be achieved with a 4×5 cm grid, while an 8×5 cm grid can be used to map the temporal lateral convexity and 8×8 cm grids are available when more extensive areas need to be explored. Furthermore, additional smaller double (2×6 cm) or single-row strips (1×8 cm or 1×4 cm) can be placed if necessary (see Fig. 2). In addition, these single and double-row strips are used to map

mesial temporal, mesial frontal, parietal, and occipital regions. Mapping inter-hemispheric structures with subdural electrodes (frontal, parietal, and occipital) can be limited by bridging veins. Furthermore, these strips often may move from the intended target area.

Depth electrodes are also made of platinum contacts with inter-electrode distances ranging from 1.5 to 10 mm [5]. The length and number of contacts of these electrodes varies with as few as four and as many as 15 contacts. The smaller number of electrodes at the cortex limits mapping of eloquent cortex with depth electrodes. Accordingly, their greater yield is in the mapping of eloquent cortex in deep structures such as mesial temporal regions, insula, and opercular regions.

*Stimulation parameters* include: (1) a biphasic polarity; (2) stimulus duration of 0.3 ms; (3) frequency of 50 Hz; (4) duration of train of 3–5 s; (5) the stimulus intensity depends on the type of stimulator used: 1–15 mA with a Grass S88; 1–17.5 mA with a Grass S12 and 1–20 mA with an Ojemann stimulator; (6) Stimulation of electrodes can be bipolar and/or monopolar [19]. Initially, a screening of "eloquent electrodes" can be achieved with bipolar stimulation of a grid and/or strips followed by monopolar stimulation of electrodes in which a response was obtained. The selected referential electrode is identified among the "silent" pairs of electrodes during bipolar stimulation.

Electrical stimulation is started with the lowest current (0.5–1 mA), which is increased in a step-wise manner by 0.5–1 mA until a response is obtained, the maximal current is reached or afterdischarges are triggered [18, 19]. Afterdischarges are defined as a train of epileptiform discharges of at least 1-s duration in the electrode stimulated, but which can propagate to adjacent electrodes. Clinical responses associated with these discharges are not considered to be reliable indicators of eloquent cortex. Furthermore, afterdischarges can lead to an electrographic and/or clinical seizure. Thus, in case of the current intensity must be lowered and increased at a slower pace (e.g., by 0.5 mA increments) to minimize their recurrence. Yet, electrical stimulation can cause a clinical seizure by activation of the EZ either because the stimulated electrodes are in proximity and/or over EZ and/or by propagation of the stimulus to the EZ.

In contrast to stimulation parameters used for subdural electrodes, the following apply to depth electrodes: (1) the stimulus intensity ranges from 0.6 to 3.6 mA; (2) the duration of the stimulus ranges from 1 to 3 ms; (3) the duration of the stimulation train can be as long as 5 s with stimuli at 50 Hz; stimuli at 1 Hz are typically used to elicit ictal activity; (4) all stimulations are bipolar.

## Eliciting Clinical Phenomena in Eloquent Cortex

As indicated above, electrical stimulation can elicit positive and negative motor, sensory, visual, auditory, and language responses. These will be reviewed briefly in this section.

(a) Motor cortex

Stimulation of motor cortex can elicit positive and negative responses [14–16, 20–22]. Motor functions are mediated primarily by activation of three areas: (1) primary motor area (indispensable cortex) located in the precentral gyrus (Brodman's area 4) and two dispensable areas: (2) the supplementary sensory motor area (SSMA) (dispensable cortex), located in the mesial frontal region anterior to primary motor cortex and (3) the premotor area, located on the lateral cortical convexity anterior to the primary motor cortex. Both primary and SSMA have a somatotopic representation, which is more easy to identify with stimulation of primary motor than the SSMA [23]. Negative motor responses have been elicited by stimulation of an area anterior to the SSMA and over the lateral convexity anterior to the precentral gyrus (see below).

*Positive motor response*: A positive motor response can be elicited with stimulation of the precentral gyrus and SSMA, while the patient is at awake at rest. While clonic activity of distal muscles is a typical expression of primary motor area activation, tonic contraction of proximal muscles result from activation of the SSMA;

however, both types of responses can potentially be elicited in the stimulation of both areas, with the stimulation intensity playing a significant role in the type of response [14–16].

Stimulation of the primary motor area causes a contralateral motor response, while stimulation of the )SSMA can elicit an ipsilateral and/or contralateral unilateral and/or bilateral tonic contraction in abduction of the upper extremities as well as tonic contraction in extension of the lower extremities. In addition, motor phenomena can be associated with sensory symptoms such as paresthesias and speech arrest. SSMA-induced motor responses are not limited to stimulation of the mesial frontal region but encompass as well stimulation of the superior frontal gyrus.

Stimulation of precentral gyrus can yield a positive response at low intensities and follow a somatotopic distribution illustrated in the homunculus with toes, foot, and leg in mesial frontal cortex, and trunk, arm, digits, thumb, face, lips, and tongue over the lateral convexity. In the SSMA, the face has an anterior location followed by the arms and legs, posteriorly. Sensory symptoms can also be reported with stimulation of primary motor and SSMA and are described as tingling sensations, which at times can be painful. In such cases, small increments of the current intensity are necessary to minimize their occurrence.

Stimulation of premotor area (lateral segment of Brodman's area 6) leads to a contralateral gaze deviation, with or without head version following the eye movements [23]. It is the expression of SSMA's eye field activation and can also result from stimulation of the superior frontal gyrus.

*Negative motor response*: To identify negative motor phenomena, patients must engage in an active motor task for periods of 10 s, including maintaining the upper extremities elevated, wiggling of the fingers, repeated flexion of the wrists and fingers or of the ankles and toes, and thrusting the tongue. The stimulation is done at the fourth or fifth second of motor activity.

Two negative motor areas have been identified: (1) a primary negative motor area, located in the inferior frontal gyrus anterior to the face region in the precentral gyrus; (2) a mesial area (pre-SSMA area), which is located anteriorly to the SSMA in the mesial aspect of the superior frontal gyrus, anterior to its face representation [20, 22] In a study by Luders et al., stimulation of both areas elicited contralateral inhibition of movement of all four extremities involving distal segments as well as movements of the tongue and gaze of variable duration [22]. Stimulation of the lateral negative motor area of dominant hemisphere can be associated with speech arrest.

Resection and/or disconnection of primary motor cortex can result in permanent contralateral deficit, with exception of resection of the face area. Resection of the SSMA can lead to transient deficits (lasting from several weeks-long to up to 24 months long) including bilateral or contralateral motor neglect, apraxia, and poor manual coordination, which may or may not be associated with speech arrest (the latter of several weeks duration). Finally, resection of negative motor areas has not resulted in a permanent deficit [10, 11].

(b) Sensory cortex

There are two eloquent sensory cortical areas: (1) a primary sensory cortex (indispensable), located in the postcentral gyrus in Brodman's areas 1, 2 3a and 3b [14, 15, 21, 23]. A second sensory (dispensable) area known as secondary sensory cortex is located on the superior bank of the Sylvian fissure in the planum infraparietale of the operculum [24]. Stimulation of the primary sensory cortex elicits a variety of sensations (e.g., tingling, numbness, painful and pulling sensations) in the contralateral side and its resection results in permanent sensory deficits. On the other hand, stimulation of the secondary sensory area can lead to ipsilateral, contralateral, or bilateral sensory phenomena. Its resection does not result in permanent sensory deficits.

(c) Language cortex

Traditionally, language cortex has been divided into an anterior and posterior areas located in the dominant hemisphere. The anterior area or Broca's area (named after Paul Broca who described it in 1861) [12] is located in the inferior frontal gyrus anterior to the face area of the primary

motor area; it mediates expressive language. The posterior area, also known as Wernicke's area (named after Carl Wernicke who discovered it in 1871) is located in the posterior segment of the superior temporal gyrus and processes receptive language functions [13]. Both areas are connected through the arcuate fasciculus.

A review of the available literature devoted to mapping of language cortex has confirmed the existence of these two areas, and identified a secondary language cortex in basal temporal region (a dispensable area) [25–27]. Its exact extension has yet to be established and its resection in antero-temporal lobectomies has resulted in disturbance in confrontation naming [25]. In addition, using a naming task during intraoperative mapping of language cortex, Ojemann identified eloquent cortex extending to temporal lateral neocortex anterior to Wernicke's area (and extending up to 3–4 cm from the temporal pole) and involving as well the middle temporal gyrus [26–29]. In addition, he identified naming errors in regions superior and anterior to Broca's area. Ojemann has suggested that language processing involves "parallel activation of multiple, function-specific modules," as language is the expression of complex multimodal functions that include perception (through visual and/or auditory means), comprehension, and expression [30, 31]. Thus, from a pragmatic standpoint, resection of temporal lateral structures in the dominant hemisphere require the mapping of language cortex including anterior and posterior temporal lateral neocortex and peri-sylvian regions, while mapping of language cortex in frontal lobe resections must extend to areas anterior and superior to Broca's area.

Typically, identification of eloquent cortex can be achieved with the patient performing one of the following tasks: reading sentences and/or paragraphs, naming objects from drawings (e.g., from the Boston naming test), counting, reciting the days of the week, the months of the year, or nursery rhymes [32]. Receptive language areas can be tested having the patient follow one and two-step commands and/or through auditory naming driven by a phrase or sentence (e.g., what is a pen used for: "writing").

Of note, mapping of eloquent cortex can yield false negative findings, which can result from one of the following reasons: (1) the position of the intracranial electrodes is not covering language cortex. (2) The stimulated area only involves the crown of the gyri. (3) The development of afterdischarges and/or seizures, which limits the use of the necessary current to identify eloquent cortex. In fact, in a 1989 series, Ojemann failed to identify Broca's and Wernicke's areas in 21 % and 36 %, respectively [27]. Likewise, false positive findings have been reported which can result from activation of areas at a distance from the stimulated electrodes.

(d) Auditory cortex

The primary auditory cortex occupies the superior temporal gyrus in its middle part, known as Heschl area (Brodman's areas 41) [23]. Electrical stimulation elicits elementary auditory hallucinations heard on the contralateral or in both ears and described as simple sounds. Stimulation of the secondary auditory cortex was reported to cause distortions of perceived sounds or voices. Mapping of auditory cortex must be complemented with brainstem auditory evoked potentials. The resection of auditory cortex does not result in deafness but can be associated with difficulties with music processing and disturbances in spatial localization.

(e) Visual cortex

Primary visual cortex is located in the mesial aspect of the occipital lobe calcarine fissure. Its electrical stimulation elicits different visual responses, depending on the stimulated area: (1) elementary visual hallucinations in the form of flashes of light, shapes in colors or black and white with stimulation of the superior and inferior banks of the calcarine fissure; (2) geometric shapes and complex hallucinations with stimulation of the fusiform gyrus and temporal-occipital region and temporal lateral neocortex [17]. Of note, Penfield observed that complex visual hallucinations described as scenes of people or a recognizable object can be elicited with stimulation of the posterior segment of temporal lobe in the nondominant hemisphere, involving the

inferior and middle temporal gyri, in adjacent areas to the occipital lobe [23].

## Concluding Remarks

In this chapter we reviewed the basic principles of mapping of eloquent cortex with electrical stimulation of subdural electrodes carried out in the course of a video-EEG monitoring study. The data derived from such stimulation must be coupled with those of other diagnostic modalities to ensure their validity. Often, intraoperative mapping may be necessary to clarify and/or complete the mapping process which could not be achieved during the course of the monitoring study.

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# Somatosensory- and Motor-Evoked Potentials in Surgery of Eloquent Cortex Under General Anesthesia: Advantages and Limitations

Ashley N. Selner and James L. Stone

In this chapter we will discuss two neurophysiological tools: somatosensory-evoked potentials (scalp and cortically recorded) and motor-evoked potentials (transcranial stimulation, direct cortical stimulation, and direct subcortical white matter stimulation), which assist the neurological surgeon operating under general anesthesia upon a patient with a cerebral lesion in proximity to eloquent cortex. We define eloquent cortex as a region whose damage may likely result in a neurological deficit within the realm of motor (paralysis, weakness, coordination), or sensory discrimination (perceptual, visual, spatial orientation, agnosia, apraxia).

Due to the inter-connectivity of the precentral and postcentral gyri, combined motor/sensory deficits can appear. Stable SSEP and MEP monitoring often correlate with a lack of clinical deficit, though false negatives can occur. Accessory pre-motor cortical regions and the frontal motor eye fields are not tested by present techniques under general anesthesia, but postoperative deficits in these areas often improve if SEPs and MEPs have been stable.

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## Short-Latency Somatosensory-Evoked Potentials (SSEPs)

Somatosensory-evoked potentials have been utilized intraoperatively to assess real-time function of somatosensory pathways since the early 1970s [1]. Currently, surgical procedures in which SSEPs are routinely used include any which may affect structures in the SSEP pathway: peripheral nerve or plexus, spinal cord, brainstem, or brain [2–4]. This may directly or indirectly affect the central nervous system-generated SSEP waveforms by jeopardizing the vascular territory relating to these structures.

The following professional societies have guidelines, policies, or position statements regarding the use of SSEPs: American Society of Neurophysiological Monitoring [5], American Clinical Neurophysiology Society (ACNS) [6], International Federation of Clinical Neurophysiology (IFCN) [7], American Society of Electroneurodiagnostic Technologists (ASET) [8], and the International Organization of Societies for Electrophysiological Technology

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(OSET) [9]. These guidelines, positions, or policies represent the recommended best practices of utility, methodology, and interpretive criteria for intraoperative SSEPs.

## Anatomy and Physiology

The large fiber sensory system, which is responsible for proprioception and perception of vibration, is assessed during SSEP testing. Stimulation of peripheral nerves conducts signal to the spinal cord via dorsal roots, and ascends through multiple pathways, though the general consensus is that SSEPs are primarily mediated by the ipsilateral dorsal column. Nerve fibers originating from thoracic and cervical innervation terminate in the cuneate nucleus, and nerve fibers originating from the lower body terminate in the gracillis nucleus. Fibers cross to the contralateral side of the medulla upon exiting the dorsal column to form the ascending medial lemniscus, which terminates in the somatosensory nuclei located in the ventral posterior lateral nucleus of the thalamus. The primary somatosensory cortex receives input from the thalamus in a somatotopic distribution: the lower extremity is closest to midline, followed in the lateral direction by the trunk, upper extremities, and face [2, 4, 5].

The middle cerebral artery, which is the terminal territory of the carotid artery, provides blood supply to the area of cortex mediating upper extremity SSEPs, while the cortex mediating lower extremity SSEPs is supplied by the anterior cerebral artery. The vertebral arteries supply the upper cervical cord and medulla, while the basilar arteries largely supply the pons and midbrain, and perforating arteries off the proximal portions of the above-mentioned arteries or their communicating arteries supply the deep paramedian areas of the diencephalon and cerebral hemispheres.

## Stimulation and Recording

A number of FDA-approved multimodal intraoperative neurophysiological monitoring systems are available for stimulation and recording of SSEPs simultaneously with other evoked potentials. The recommended SSEP stimulation sequence is to interleave stimulation and recording for each limb individually. Cathodic rectangular current pulses are used to stimulate peripheral nerves and generate SSEP responses. Disposable conductive solid-gel surface electrodes or disposable subdermal needle electrodes may be used to deliver constant-current stimuli.

Stimulation sites are most commonly located at the median or ulnar nerve at the wrist for upper SSEP responses, and at the posterior tibial nerve at the ankle for lower SSEP responses. Possible alternative sites for lower SSEP stimulation are the peroneal nerve at the knee, or posterior tibial nerve at the popliteal fossa. It is important to note that when proximal alternative stimulation sites are utilized, that the latency of SSEP responses will be shortened, and latencies are increased for tall or long-limbed individuals [2–5].

The ranges of recommended stimulus parameters are as follows:

- Pulse width: 200–300 μs.
- Frequency: 1.5–5 Hz.
- Amplitude intensity: Supramaximal, <60 mA for surface electrodes, <40 mA for subdermal electrodes.

Supramaximal stimulation is recommended to minimize response variation. Sufficient intensity can be selected by a number of methods. One common method is to incrementally increase the stimulus amplitude until a repeatable, visible twitch in the thumb or toe is present (assuming median and posterior tibial nerve stimulation). Though this method is only useful in the absence of muscle relaxation, it indicates adequate stimulation of the nerve. To verify if the stimulus is supramaximal, another technique that can be used is the incrementing of stimulus intensity to the point where further increments do not appreciably increase the amplitude of recorded responses. This can be done in the presence of muscle relaxants, and eliminates any induced asymmetries in recording from differing levels of stimulation in each nerve.

The frequency of stimuli is recommended to not be a factor of 60, as this is a frequently encountered source of electrical artifact. Selecting a frequency that is not a factor of 60 allows for signal averaging to effectively remove this out-of-phase noise from the averaged signal.

All SSEP responses are on the order of microvolts when recorded from an electrode with appropriate electrode impedance (ideally below 5 kΩ). Electrical artifact and interference from other equipment or electrical lines in or near the OR makes averaging necessary to obtain an appropriate signal-to-noise (SNR). Typically, several hundred to one thousand responses are averaged before analyzing a waveform. Bandpass filter settings are typically 30–500 Hz for upper and lower SSEP cortical recording.

In order to isolate any observed changes in SSEP responses, recording at various locations in the SSEP pathway is essential. This gives information regarding the level at which potential injury has occurred. It is also recommended to record individual responses from bilateral upper extremity and lower extremity nerve stimulation regardless of the location that is at risk for injury. Bilateral upper and lower recording allows for determination of global versus local signal changes. This will be further discussed in the Interpretation section.

Cephalic SSEP electrode positions are located according to the 10–20 International System of EEG electrode placements.

SSEP waveform features are identified as positive or negative deflections at their usual post-stimulus latency. Some examples are: N13, P19/N22, and P37/N45. Differing sources of literature may label these peaks at a slightly different latency: for example P19 is sometimes referred to as P20. However, these are both referring to the positive deflection in the cortical potential from median stimulation. By knowing which waveform is being referred to, it should be intuitive which waveform feature is being discussed [2–5].

SSEP signal recording utilizes high gain amplifiers, and bandpass filtering. A low-cut filter between 10–30 Hz and a high-cut filter between 300–500 Hz is recommended for the cortical responses, while the recommendations for subcortical and peripheral responses is a band-pass filter with cutoffs between 10–30 and 1000–3000 Hz.

Technical considerations that can cause false positives in recording may arise from electrodes becoming displaced or equipment malfunction in the acquisition system and software. It is crucial for neurophysiology team personnel to be properly trained with the commercial system, as well as the availability of technical experts with extensive computer troubleshooting skills to remedy issues. Utilizing checks such as verifying stimulus artifacts and measuring electrode impedance values can aid in identifying confounding technical issues.

*Brachial Plexus/Erb's Point Potential:* The ascending upper SSEP is generally first recorded at the level of Erb's point. Subdermal or solid-gel electrodes can be used for the recording of this signal. It is picked up from electrodes located approximately 2 cm superior to the midpoint of the clavicle. The Erb's point waveform is recorded referentially, with the reference electrode being placed at the contralateral Erb's point. The recorded signal reflects the activity at the brachial plexus. The waveform consists of one negative peak located approximately at 9 ms (N9) post median or ulnar nerve stimulus.

*Subcortical Potential:* The subcortical potential, or cervicomedullary potential, is generally recorded from an active electrode located on the posterior neck at the location of C5 or C2, referenced to an electrode placed at Fpz or a noncephalic reference. The peak commonly used for interpretation in this montage is the P/N13. There are multiple generators for this deflection, including the root entry zone in the dorsal horns, dorsal columns, and the cuneate nucleus. Peaks after 12 ms contribute to the waveform from Fz when it is used as a reference, but are not as routinely used for interpretation as P/N13.

*Thalamocortical (cortical) Potential:* Subdermal spiral electrodes or gold-cup electrodes are typically used for recording thalamocortical potentials. The active electrode is placed at either C3′ or C4′, which is 2 cm posterior to C3/C4 respectively, contralateral to the upper SSEP stimulus to record from the somatosensory

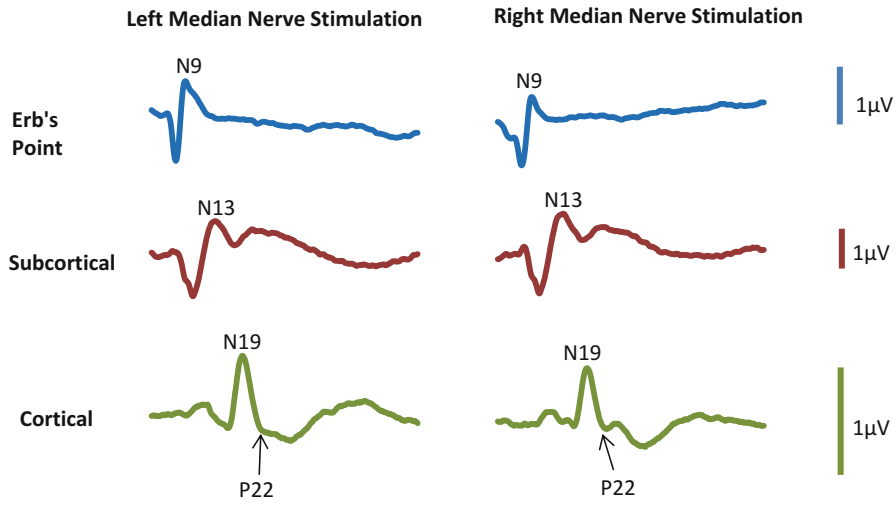


**Fig. 1** Median nerve SSEP responses recorded from a patient with no neurological deficits, 500 responses averaged. Scale bars for each set of left and right responses are indicated. Standard polarity convention shows N-peaks as an upward deflection, and P-peaks as a downward deflection

parietal cortex. Either the ipsilateral C3′/C4′ electrode, Fz, or the earlobe can be used as the referential recording electrode. N19 (or N20) and P22 are the deflections typically analyzed for interpretation of the cortical potentials, which are mostly thought to be generated by the electrical volleys in the thalamocortical fibers, which synapse in the primary somatosensory parietal cortex (Fig. 1).

## Lower Limb SSEPs

*Popliteal Fossa potential:* The first ascending potential typically measured in lower extremity SSEP recording with posterior tibial nerve stimulation is located peripherally at the popliteal fossa. This potential is analogous to the Erb's Point recording in upper SSEP recording. The active electrode is placed in the posterior crease of the knee, with the reference 3–5 cm superior to it. The recorded negative deflection at approximately 8 ms is a sensory nerve action potential (SNAP) of the posterior tibial nerve, proximal to the stimulation site.

*Subcortical Potential:* The subcortical potential for lower SSEP responses utilizes the same active and reference electrodes as the upper SSEP: C5/C2 and Fpz. The most commonly interpreted deflection in this waveform is referred to as N34, sometimes N30. It is thought to be the equivalent of P/N13 in the upper SSEP response, though there is debate whether this is the case.

*Thalamocortical (cortical) Potential:* Two montages can be used for capturing the lower SSEP thalamocortical potential: Cz′-Fz or C3′-C4′ (for the left lower response, and inverted to C4-C3 for the right). C3′, C4′ and Cz′ are approximately 2 cm posterior to C3, C4, and Cz in the EEG International 10–20 System. The deflections in the waveform observed at approximately 37 and 45 ms post-stimulus are thought to be the analog of N19/P22 in the upper SSEP recordings, corresponding to the electrical volleys in the thalamocortical pathways. For the lower SSEP waveform, the electrode ipsilateral to the site of stimulation is first more electropositive than the reference, in contrast to the upper SSEP waveform. Thus, the deflections used for interpretation for lower SSEPs are P37 and N45 (Fig. 2).

## Anesthetic Considerations

Anesthetic agents can have varying effects on recorded SSEP responses, depending on the com-

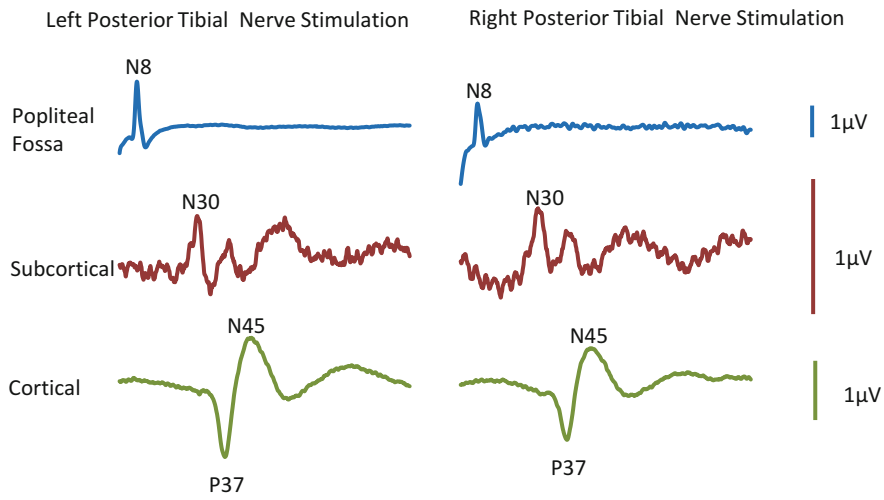


**Fig. 2** Posterior tibial nerve SSEP responses recorded from a patient with no neurological deficits, 500 responses averaged. Scale bars for each set of left and right responses are indicated. Standard polarity convention shows N-peaks as an upward deflection, and P-peaks as a downward deflection

bination of agents used. It is therefore crucial for the neurophysiology team to communicate with the anesthesia team in order to optimize the anesthetic plan for intraoperative neurophysiologic recording [5, 10–12]. For more detailed information pertaining to the mechanism of actions causing influence in the SSEP pathway, please refer to the references at end of the chapter. The following table is a summary of anesthetic agents commonly used and their impact on SSEP recordings (Table 1).

Muscle relaxants may be used in the presence of SSEP recordings, and may enhance the signal clarity. However, if motor-evoked potentials are simultaneously recorded, muscle relaxants decrease the compound muscle action potential. This will be discussed in the next section.

## Interpretation and Application during Lesion Resection in Proximity to Eloquent Cortex

It is advantageous to obtain peripheral, subcortical, and cortical SSEP responses during intracranial surgery as opposed to cortical responses alone. The same holds true for lesions located in either the right or left hemisphere: recording contralateral as well as ipsilateral responses aids in interpretation.

When identifying a change in SSEP responses, it is important to determine if localized change(s) proximal to the operative site are present, or if observed changes are a result of an anesthetic or technical issue. This can be done by analyzing the level of the signal change (peripheral, subcortical, or cortical), and whether the change occurred unilaterally or bilaterally. Systemic signal changes, limb malpositioning, or cerebral infarcts can potentially be identified when bilateral peripheral, subcortical, and cortical recording is performed.

The generally accepted criterion for significant intraoperative SSEP changes during intracranial surgery is the 50/10 rule: an amplitude reduction equal or greater than 50 % or 10 % latency increase for a waveform compared to its baseline should be reported immediately to the surgical team [2–6, 12].

Systemic factors that can lead to signal changes are: temperature, hypotension, or hypoxia. Hypotension and hypoxia are associated with amplitude decrease or loss. Decreases in temperature cause increased SSEP latencies in

**Table 1** Anesthetic agents and their effects on SSEP recording

| Anesthetic agent | Effects on SSEP recording |
|---|---|
| Benzodiazepines | Mild reduction of cortical amplitudes [92, 93] |
| Barbiturates | Reduction of cortical amplitudes, increase of cortical latencies [5, 10, 92] |
| Propofol | Progressive reduction of cortical amplitudes, increase of cortical latencies [5, 10, 11, 92] |
| Opioids | Mild increase in cortical latencies [92, 94] |
| Inhalational agents | Dose-dependent reduction of cortical amplitudes<br>Concomitant use of nitrous oxide and halogenated agents compounds amplitude reduction [5, 10, 92] |
| Etomidate | Increase of cortical amplitudes at low doses [95–97] |
| Ketamine | Increase of cortical amplitudes [98] |
| Dexmedetomidine | No significant effect [99] |

affected limbs. Cold IV fluid injection may increase the latency only in the limb of injection site. Pre-existing neurologic deficits that are detectable with SSEP responses can be amplified such that the response in the affected limb is more sensitive to minor degrees of hypotension compared to unaffected limbs [2–5].

Limb malpositioning is highly suspected, by comparing postpositioning responses to baselines and identifying signal deterioration at a peripheral site and ascending recording sites. In this regard, SSEPs are very valuable for any time which prolonged surgical positioning will put the patient at risk for a postoperative compressive or stretch-related nerve injury.

For procedures in which the patient is in sitting position, the presence of intracranial air correlates with deterioration of cortical SSEP amplitudes. SSEP recording is of particular value when neurovascular structures are at risk, since there is a near linear correlation between cortical amplitudes and cerebral blood flow (CBF) when decreased below 15 ml per 100 g of brain parenchyma per minute. Cortical amplitude loss shows correlation with middle cerebral artery and carotid artery infarcts; however, cortical SSEP responses remain relatively insensitive to subcortical ischemia [2, 13–15]. EEG also may be utilized to identify diminished CBF, as ipsilateral slowing and amplitude decreases can be sensitive indicators. However, this is less commonly used during lesion resection proximal to eloquent cortex, due to placement of recording electrodes located in the way of the surgical site.

## Practical Limitations

The most obvious limitation to intraoperative SSEPs as a monitoring tool near eloquent cortex is that they can only be obtained from scalp recordings if electrode positions are not in the surgical field. Scalp-recorded SSEPs serve a monitoring purpose as opposed to mapping or a direct localization technique. If the somatosensory cortex is exposed during surgery, SSEP postcentral gyrus localization/mapping and monitoring may be performed via direct cortical recording, while scalp recording is not possible.

Another limitation of SSEP responses intraoperatively is the variation between observed deficit and clinical correlation. As previously mentioned, mixed nerve SSEP responses are conducted via the large-fiber sensory system, responsible for vibration sensation and proprioception. A common misconception is that clinically symptomatic decreased sensation or pain will de detectable with SSEP responses. This can sometimes be the case, but only if the underlying cause of neurological symptoms also affects the specific large fiber pathway being tested.

SSEP responses are averaged signals, so there is a limit to how immediately responses can be obtained and analyzed. Depending on the frequency of stimulation and number of averages being used, signals can be obtained for interpretation between 1 and 5 min. Higher stimulation frequencies and lower number of averages can correspond to lower response amplitudes and more noise in the signal, making interpretation less clear. Optimizing stimulation and recording parameters for every patient, such that an adequate signal-to-noise ratio is achieved

with consistent responses for interpretation will achieve the best trade-off for signal acquisition time versus signal clarity. Well-trained personnel are essential.

Effective and frequent communication between the surgical and neurophysiology teams can reduce the delay between averaged signal interpretations and critical surgical steps. Changes in SSEP signals can be masked during signal averaging, which can further delay the detection of changes. The neurophysiology team must have a clear understanding of critical structures in the nearby vicinity of the surgical field or dissection and correlate particular vigilance to the pertinent monitoring modalities. If the neurophysiology team does not have a clear view of the surgical field, this delay can be avoided if the surgical team announces when a critical manipulation or resection occurs. The neurophysiology team will then immediately begin a new series of averaging responses, such that waveforms collected before that manipulation or resection will not average in the interpreted response, and potentially mask any changes.

Reports of SSEP sensitivity for neurophysiological monitoring vary depending on the type of surgical procedure being studied; however, most reported series are around 80 %. In a review concerning the predictive values of SSEPs only, SSEP sensitivity and negative predictive value for minor cerebral hemisphere deficits were 64 and 95 %. When severe deficits only were considered, the sensitivity and negative predictive values were 81 and 98 % [16]. In general, when using the 50/10 rule, false positives are more likely to occur than false negatives. However, careful attention to possible systemic and anesthetic confounds may identify potential false positive results intraoperatively.

## Localization of the Somatosensory and Motor Cortex with SSEPs

In contrast to the use of SSEP responses for monitoring functional integrity of the somatosensory pathway, the phase-reversal technique can be used for mapping the location of the central sulcus intraoperatively. The phase reversal technique, first introduced in the late 1970s, has since been described by numerous studies for its application during cranial lesion resections [17–24]. Many, if not most, will also stimulate the precentral gyrus for motor movement verification, which is discussed in Section "Direct Cortical Motor Mapping."

### Stimulation and Recording

Stimulation is typically performed at the contralateral median nerve, with settings analogous to scalp SSEP recordings. Commercially available grid or strip electrodes are placed on the cortical surface, at the anticipated location of the hand sensorimotor gyri (approximately 3–8 cm from midline) across the central sulcus with an optimal angle of 15°. If a lesion is present, the strip should be placed adjacent to the visible margins of the lesion. The placement of the grid/strip should then be adjusted to maintain peak amplitudes by rotating or displacing the grid/strip [25–27]. Communication with the neurophysiology team is again essential, and patience is required from the surgical team.

Posterior tibial SSEP phase reversal can also be performed, but the cortical representation is limited to a much smaller area, closer to midline. Furthermore, alternative peripheral nerve sites have been used for central sulcus localization, including the femoral, peroneal, and ulnar. A group in 2005 successfully localized the phase reversal utilizing stimulation of the contralateral lower lip mucosa [25–28].

Each electrode site within the strip/grid serves as an active recording site, with a common reference. The reference electrode is typically a subdermal needle or solid-gel electrode placed on the contralateral mastoid or cephalic reference, or a needle electrode placed in the exposed temporalis muscle. Impedance checks should routinely be performed to verify the electrodes are making adequate contact. Saline irrigation can improve impedance; however, excess irrigation can lead to shunting between electrode sites (Fig. 3).

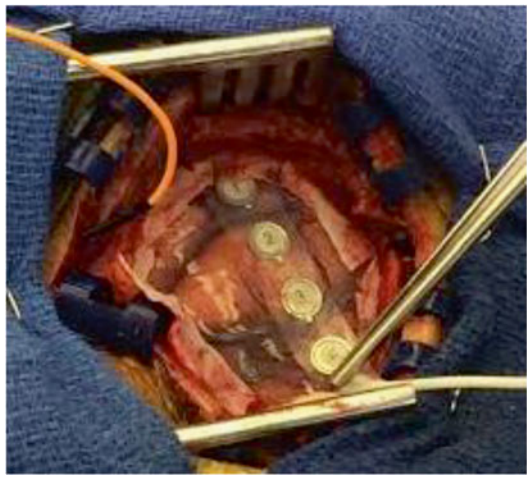

**Fig. 3** Subdural electrode strip placed on exposed sensorimotor gyri for direct cortical recording. The reference electrode is the orange subdermal needle inserted into exposed temporalis muscle. Diameter of strip electrode is 6 mm

## Interpretation and Application during Lesion Resection in Proximity to Eloquent Cortex

The recorded thalamocortical potentials in the postcentral gyrus have the characteristic N19 and P22 components, as previously discussed. Electrodes located anterior to the central sulcus exhibit an inverse polarity: at approximately 19 ms post-stimulus: they become more electropositive than the reference electrode. The reason for this phase reversal is based on the perpendicular electrical dipole generated on the postcentral gyrus relative to the central sulcus from median nerve stimulation: the polarity of the dipole changes on the adjacent precentral gyrus [29]. The phase-reversal technique is dependent on the neurophysiology team identifying the electrode locations where the reversal of phase is observed. The pre-central electrodes exhibit a peak positivity at a slightly increased latency when compared to the peak negativity (N19) of the post-central electrodes. Figures 4 and 5 are examples of cortical median nerve SSEP phase reversal waveforms. In Fig. 4 two 1×4 electrode strips were placed across the central sulcus in the hand sensorimotor region. Phase reversals are observed in between electrode positions 2 and 3 for both electrode strips. In Fig. 5 two 1×4 electrode strips were placed parallel to the central sulcus, and a phase reversal can be observed between the two electrode strips.

In situations where a clear phase reversal cannot be adequately identified, increasing the number of grid or strip electrode contacts, and utilizing a bipolar montage where adjacent electrode positions are differentially amplified can provide a clearer phase reversal.

Once the central sulcus has been identified, it is recommended to adjust the position of the electrode grid/strip such that the localized sulcus is situated between different electrode positions, to verify the cortical potentials again identify the same location.

## Practical Limitations

Though the central sulcus can often be identified using anatomical landmarks and MRI images, the SSEP phase reversal technique is regarded as one of the most reliable tools for identifying the central sulcus. Distorted anatomy resulting from displaced cortical structures in the presence of a lesion, individual variations in functional organization and anatomy, and limitations of spatial sensitivity in preoperative imaging studies all support the complementary use of SSEP phase reversal intraoperatively for increased accuracy of central sulcus identification [25–27].

Reports of success rates for identification of the central sulcus with the SSEP phase reversal technique range from 90 to 97 % [23, 30–32]. Situations in which SSEP phase reversal cannot identify the central sulcus include lesion-related displacement of the central sulcus, anesthetic, or technical confounds analogous to those relating to scalp SSEP recording, and pre-existing marked sensorimotor deficits.

The proposed causes for absent or distorted cortical potentials in tumor patients are: (1) the tumor desynchronizes propagated afferent electrical volleys along the thalamocortical pathway, (2) the mass effect of the lesion distorts the spatiotemporal projection of cortical electrical

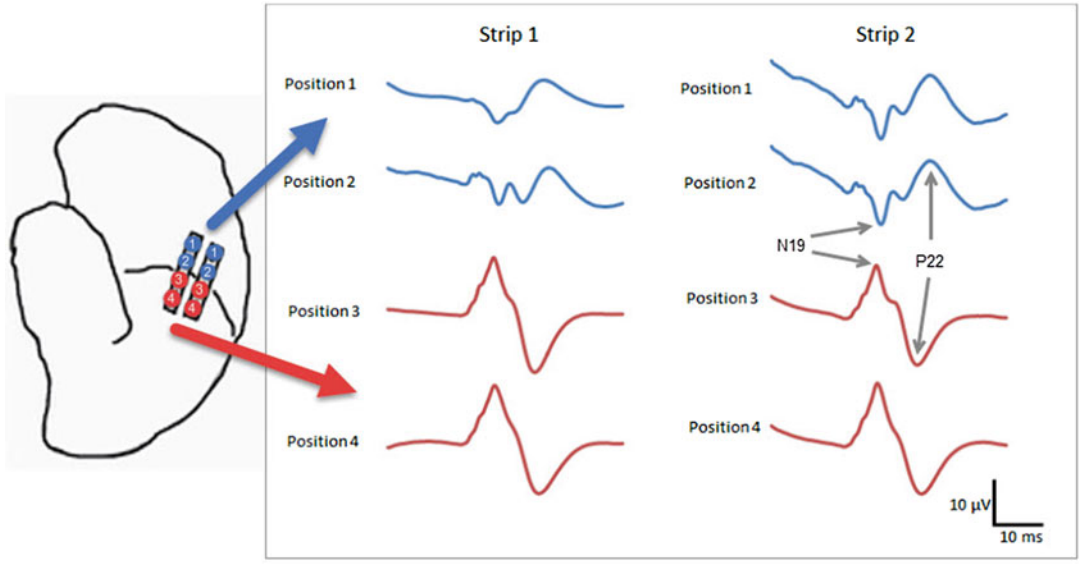


**Fig. 4** Two 1×4 electrode strips were placed across the central sulcus in the hand sensorimotor area of an adult patient with no sensory deficits as indicated, and median nerve cortical responses were recorded. Positions 1–2 for each strip show an early positivity (precentral) and positions 3–4 show an early negativity (postcentral). The central sulcus was identified to be located in between electrode positions 2 and 3. Standard polarity convention shows N-peaks as an upward deflection, and P-peaks as a downward deflection. The phase reversal of N19 and P22 is labeled between position 2 and 3 on strip 2

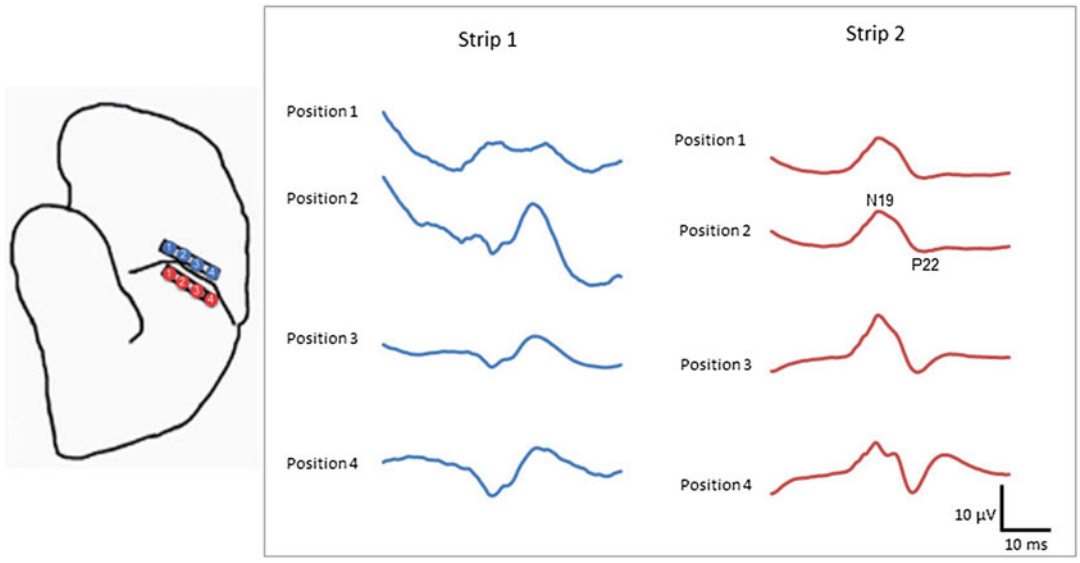


**Fig. 5** Two 1×4 electrode strips were placed parallel to the central sulcus in the hand sensorimotor area of an adult patient with no sensory deficits as indicated, and median nerve cortical responses were recorded. All positions on strip 1 show an early positivity (precentral) and all positions on strip 2 show an early negativity (postcentral). Standard polarity convention shows N-peaks as an upward deflection, and P-peaks as a downward deflection. The central sulcus was identified to be located in between strip 1 and strip 2. N19 and P22 are labeled on position 2 for strip 2

dipoles to the brain surface and (3) the recording site may not be appropriate for recording a potential generated in the hand area of the postcentral gyrus [25].

Most importantly, although SSEP phase reversal is reliable for verifying the location of the central sulcus, it does not identify motor function, and when used alone is inadequate for preventing postoperative motor deficits: motor mapping methods are also indicated.

## Transcranial Motor-Evoked Potentials (tcMEPs)

Due to multiple technical difficulties in the application of magnetic stimulation, the preferred intraoperative stimulation method for motor-evoked potentials is electrical cortical stimulation. Nevertheless, the lessons learned from magnetic tcMEP in experimental primates and man for optimization of anesthetic agents used has carried over to electrical tcMEPS [33–40]. In 1996, three groups first demonstrated the now clinically standard pulse train technique under anesthesia [41–43]. After the 2002 report by MacDonald alleviating safety concerns regarding transcranial electrical stimulation, and the first government approved commercial stimulator that same year, tcMEPs began to increase in intraoperative clinical use and research [44, 45]. Under general anesthesia, this electrical stimulation can be performed transcranially or directly on the primary motor cortex (discussed in Section "Direct Cortical Motor Mapping"), with compound muscle action potentials recorded in response.

### Anatomy and Physiology

The motor-evoked pathway monitored intraoperatively originates with stimulation at the primary motor cortex, which is located on the pre-central gyrus and responsible for voluntary movements. Not unlike the somatosensory cortex, the primary motor cortex is organized somatotopically, with the tongue and face motor neurons near the sylvian fissure, hand and arm neurons in its middle convexity, and leg and foot neurons from its crest to mesial parasaggital region. The primary motor cortex is selected for electrical stimulation due to the low electrical threshold necessary to induce muscle responses [45].

The large myelinated axons in or just below the primary motor cortex are thought to be the predominantly activated fibers during tcMEP stimulation, consisting of the corticospinal and corticobulbar pathways, which conduct action potentials to lower motor neurons without intervening synapses [45–48]. These large fibers converge in the corona radiata, and travel through the internal capsule, to form the crus cerebri. Next the fibers travel through the cerebral peduncle of the midbrain, descend the pons and medulla where the major of fibers decussate, forming the large lateral corticospinal tract (CST). The CST descends via the lateral funniculus, mainly terminating in dorsolateral lamina IX and VII. The CST branches off at spinal segments, primarily at the cervical and lumbar levels. The majority of axons synaptically transmit to interneurons, then alpha motor neurons, while some synapse directly on the alpha motor neurons, which in turn innervate upper and lower limb muscles. Compound muscle action potentials are recorded as a result of the temporal and spatial summation of lower motor neuron excitatory postsynaptic potentials [4, 45].

Corticobulbar tract fibers originating in the motor cortex travel alongside CST fibers, until they diverge into the brainstem and terminate on interneurons, and to a smaller extent directly to motor neurons to generate cranial muscle movements [45].

Indirect motor pathways, the propriospinal system and neuromodulatory pathways might influence MEPs, but are not thought to significantly contribute to them [45].

The middle cerebral artery and the anterior cerebral artery primarily supply blood to the motor cortex, lenticulostriate perforators and the anterior choroidal artery supply the internal capsule, and vertebral and basilar artery branches supply the brainstem, all of which may produce distinct changes to MEP responses in the presence of ischemia [15, 45].

## Stimulation and Recording

Studies in monkeys showed direct waves (D-waves) recorded from the corticospinal tract are produced as a result of a single pulse transcranial electrical stimulus, and have been verified in humans during intramedullary tumor surgery. However single electrical pulses are typically insufficient under general anesthesia to elicit muscle responses. Multipulse stimulation elicits a series of descending volleys (D-waves), produced by direct axonal stimulation. I-waves (Indirect waves), which are produced by intracortical circuits that incite additional cortico-motor neuron discharges, follow D-waves in conscious patients, or under anesthetized patients when a sufficiently strong pulse-train stimuli are used. Stimuli with adequate activation of D-waves along with some I-wave recruitment produces enough temporal summation of excitatory postsynaptic potentials (EPSPs) which summate to activate some lower motor neurons, ultimately resulting in CMAP potentials [4, 15, 45–47].

Anodal monophasic trains of rectangular pulses are delivered through the scalp to the motor cortex in each hemisphere for tcMEP stimulation. C1, C2, C3, and C4 may all be used as active stimulation sites. It is recommended that during baseline testing, optimal electrode sites are selected which minimize threshold current for repeatable maximized muscle responses. Hemispheric, inter-hemispheric, and midline stimulation montages optimize CMAP recording for different applications. It is recommended to use a hemispheric montage for supratentorial procedures. However, the hemispheric montage will preferentially activate facial and arm responses, therefore optimal settings would include the ability to stimulate with an additional montage to optimize leg responses as well. Spiral (corkscrew) needle electrodes are best suited for stimulation during craniotomies, since they are self-securing and rarely become displaced during surgery [45, 47, 49].

Typical parameters for tcMEP stimulation are: 3–8 pulses, 50–1000 μs pulse widths, and interstimulus intervals of 3.0–4.0 ms. Constant current and constant voltage stimulus generators are commercially available, with upper safety limits of 200 mA or 1000 V. However, the exact combination of pulse width and number of pulses may limit current or voltage amplitudes, so that the overall delivered charge does not exceed maximum safety limits [4, 44, 45, 50].

Because the skull has very high impedance, it is estimated that only 10–20 % of delivered current reaches the motor cortex, resulting in maximum safety limits for transcranial stimulation that significantly exceed those for direct cortical stimulation [51].

tcMEP stimulation occurs axonally, in the white matter, but the exact site of stimulation is critical for supratentorial procedures. As stimulation is increased, the latency of the D-wave shortens, which indicates stimulation occurring at an increased depth within the white matter. With high levels of stimulation, near the maximum settings of commercially available equipment, stimulation may occur as deep as the foramen magnum. This reinforces the importance of optimizing stimulation montages and minimizing stimulating charge delivered, in order to avoid stimulation occurring distal to the site of surgical manipulations [15, 52, 53].

Compound muscle action potentials (CMAPs) are typically obtained by needle electrodes in response to tcMEP stimulation. Muscle recording sites used in supratentorial procedures are generally selected according to area of representation on the motor homunculus. Areas that are well represented, such as hands and feet, are more easily activated and therefore provide more reliable responses. Commonly used muscle sites include: abductor pollicis brevis, abductor digiti minimi, brachioradialis, abductor hallucis, and anterior tibialis. Pairs of solid-gel surface electrode or subdermal needles may be used, both placed in the muscle belly of interest, approximately 2–4 cm apart. Recording is performed referentially between the 2 electrodes, to minimize electric artifacts. CMAPs should be band-pass filtered between 10 and 100 Hz, and 1500–3000 Hz [4, 45]. Although stimulus artifact may still be present with these settings, the presence of artifact is often useful to confirm the stimulus has been delivered. CMAPs, which are polyphasic waveforms with varying amplitudes, in

the absence of motor pathway deficits or muscle atrophy, range between 10 and 1000 μV. CMAP latencies vary between ~10–40 ms for cervically innervated muscles and increase in latency within a patient inferiorly for lumbosacrally innervated muscles. CMAP amplitudes are large enough that single responses are generally interpreted, as opposed to averaging techniques that are used during SSEP testing [4, 45].

The short pulses used during tcMEP stimulation are considered safe, as electrochemical injury occurs only with >1 ms pulse duration of prolonged monophasic train stimuli. Commercially available tcMEP stimulators are in accordance with the 50 mJ IEC safety limit, and therefore scalp burns due to thermal injury are exceptionally rare. Induced seizures as a result of tcMEP stimulation have a reported occurrence of 0.03 %, as seizures are very unlikely with the brief, high-frequency trains utilized. The most common tcMEP complications are bite injuries associated with jaw muscle contractions. These muscle contractions are likely mediated via the corticobulbar pathway, trigeminal nerve and/or direct jaw muscle stimulation. To minimize bite injuries, soft bite blocks are recommended to be placed between both sets of molars, though they may not necessarily eliminate injury [45, 54] (Fig. 6).

## Anesthetic Considerations

Analogous to the effect of anesthesia on SSEP recording, tcMEPs are altered by certain anesthetics [111, 112]. The neurophysiology and anesthesia team must work closely to ensure that tcMEP recording is feasible, and avoid any confounds which make CMAP interpretation uncertain. The following chart is a summary of these effects (Table 2).

tcMEP responses are more sensitive to inhalational agents than SSEP responses. In some cases, administering 0.5 MAC is tolerable for SSEP responses, but may result inability to elicit repeatable tcMEP responses. The widely recommended anesthetic for tcMEP recording is a propofol and opioid TIVA (total intravenous anesthesia) [10, 11, 45, 47, 48, 55–60].

Muscle relaxants are not recommended during tcMEP testing, although some reports indicate that low levels of relaxants may be used if they are kept constant in conjunction with the neurophysiology team monitoring train of four responses [45, 61].

## Interpretation and Application during Lesion Resection in Proximity to Eloquent Cortex

Similarly to SSEP interpretation, confounding factors may result in tcMEP changes that are unrelated to surgical maneuvers, and rostral or contralateral responses can aid in identifying these confounds.

Gradual reduction of amplitudes generalized to all muscle groups is often a result of anesthesia or what is commonly referred to as “muscle MEP fade.” This observed fade refers to the gradual progressive decrease of CMAP amplitudes, and/or increase of stimulating thresholds over the duration of time under general anesthesia. The likely cause of this phenomenon is due to decreased lower motor neuron excitability, possibly also contributed by D-wave or I-wave fade. MEP fade varies between patients, and may be absent or marked. Increments of stimulus intensity may be needed during long procedures, and it is recommended to frequently acquire MEP signals, so that this gradual fade is observed, and not attributed to significant surgically related changes [15, 48, 62, 63].

Systemic factors that will result in generalized tcMEP amplitude deterioration or loss are hypotension, drug bolus, or intracranial air if the patient is in sitting position. Limb ischemia or malpositioning can also be detected by tcMEPs, resulting in focal CMAP amplitude loss. Body or limb decreased temperature results in increased CMAP latencies. Simultaneously acquiring SSEP responses can further help identify these confounds. Depending on the time course of these systemic factors, the observed CMAP amplitude loss may appear more acutely or gradually, contributing to the “muscle MEP fade” [45, 48, 64].

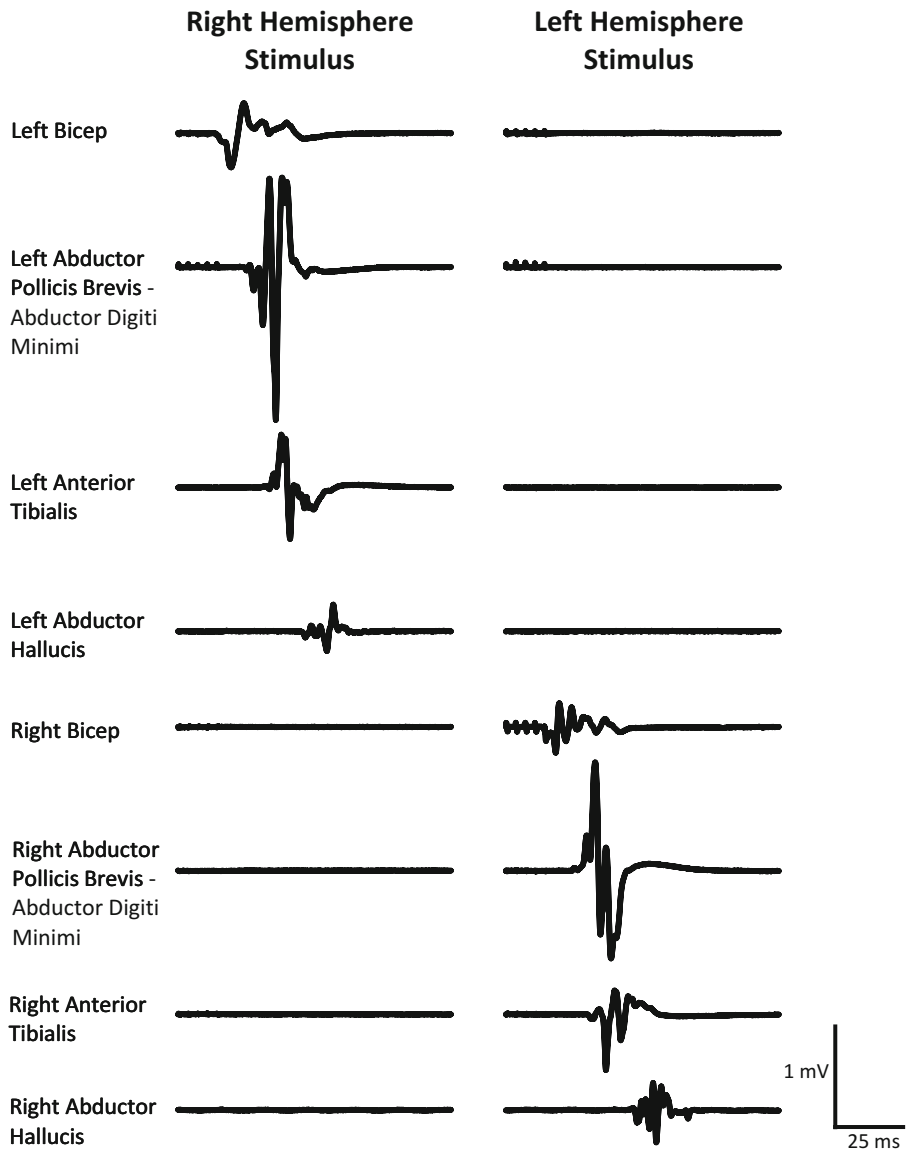


**Fig. 6** tcMEP CMAP responses in an adult patient with no motor deficit. Contralateral activation is isolated for both right and left hemisphere stimulus settings. Anodic stimulation occurred at C3 and C4 for left and right hemispheres, respectively

CMAP interpretation is dependent on the neuromuscular junction, therefore it is recommended to include a train-of-four testing modality during the use of tcMEPs. The train-of-four should be performed at a peripheral nerve site, as peripheral muscles are generally recorded during tcMEP use. The train-of-four is useful for identifying any anesthetic or systemic confounds leading to CMAP deterioration due to decreased peripheral transmission.

The following are pathologic mechanisms that may result in intraoperative deterioration of tcMEP responses: (1) cortical I-wave circuit disruption, (2) corticomotor neuron failure, (3) corticospinal tract conduction failure, (4) background

**Table 2** Anesthetic agents and their effects on tcMEP recording

| Anesthetic agent | Effects on TcMEP recording |
|---|---|
| Benzodiazepines | Significant reduction of CMAP amplitudes [10, 11] |
| Barbiturates | Significant reduction of CMAP amplitudes, disappearance of CMAPs [100] |
| Propofol | Progressive CMAP amplitude reduction [10, 11] |
| Opioids | Minimal effects [10, 11, 34, 45, 100, 101] |
| Inhalational agents | Dose-dependent reduction of cortical amplitudes Concomitant use of nitrous oxide and halogenated agents compounds amplitude reduction [10, 11, 33, 45, 102–105] |
| Etomidate | May enhance CMAP responses [10, 11, 35, 106, 107] |
| Ketamine | Negligible effect at low doses, reduction of CMAP amplitude at high doses [10, 11, 39, 45, 100, 108] |
| Dexmedetomidine | No significant effects[a] [10, 99, 109] |

[a]One case report of MEP loss associated with dexmedetomidine during pediatric spine surgery

facilitation system disruption, (5) lower motor neuron failure, and (6) peripheral conduction failure [45]. There are numerous reports suggesting interpretive warning criteria indicating tcMEP deterioration. These include:

- *Presence or Absence:* Amplitude, latency, threshold stimulus, and CMAP waveform are not analyzed, and the interpretation based solely on the absence of a CMAP response present at baseline is considered a significant change [63–65].
- *Amplitude Reduction:* Peak-to-peak amplitudes of CMAP responses are interpreted, and decreased amplitude beyond a percentage of baseline amplitude is considered significantly changed from baseline. Published reports suggest ranges between 50 and 80 % reduction should be used for warning criteria. 50 % is the most commonly accepted warning criteria for supratentorial procedures [15, 45, 66, 67].
- *Threshold Amplitude:* Current or voltage stimulus thresholds needed intraoperatively to evoke CMAP responses that are a set limit greater than baseline thresholds are considered significantly changed from baseline [55, 65, 68].

The presence or absence approach has only been suggested for use in spinal surgery, and is inadequate for supratentorial procedures [63–65]. Threshold testing requires slightly increased intraoperative testing time, and thresholds are known to vary with anesthetic depth [4, 55]. Amplitude reduction is the most commonly used criterion for supratentorial procedures [45, 66, 67]. However, it is recommended that any warning criteria decisions are discussed with the surgical team preoperatively during surgical planning, and any amplitude or threshold changes not explicitly related to known anesthetic or systemic changes are reported to the surgical team intraoperatively. However the surgical team leader must be made aware (by the neurophysiology team if not anesthesia) that anesthetic, muscle relaxant, or systemic changes have occurred or are suspected to have occurred that may jeopardize monitoring capabilities.

## Practical Limitations

As with scalp SSEP recording, tcMEP testing requires that the stimulating electrodes placed over the primary motor cortex are not in the surgical field. If this is not possible, direct cortical stimulation techniques must be used instead, discussed in Section "Direct Cortical Motor Mapping." Also analogous to scalp versus direct SSEP recording, tcMEP stimulation serves as a monitoring technique, and direct cortical methods must be employed for any localization information.

CMAP responses can have high trial-to-trial variability, especially in the presence of any preexisting motor deficits. Therefore, interpretation criteria should always account for a patient's CMAP variability observed during baseline testing. Due to this variability, signal averaging is not advanta-

geous for CMAP recording; however, it is unnecessary as the signal-to-noise ratio is typically adequate for single responses to be reliably interpreted.

As previously mentioned, the amount of voltage or current needed to stimulate transcranially is orders of magnitude greater than with direct stimulation. Although there are no electrochemical safety hazards with the tcMEP stimulus, there is contraction of the jaw and facial muscles during stimulation. Depending on the exact stimulating electrode montage and threshold intensity needed, this patient movement during stimulation can interfere with surgical manipulations. Therefore, although there is negligible delay between testing and interpretation, as opposed to SSEPs, continuous testing of tcMEP responses is not often feasible, and testing must be communicated to the surgeon so that there are no unexpected patient movements. It is recommended that tcMEP responses be obtained frequently, to account for any confounding factors, such as MEP fade, and before and after any crucial surgical maneuvers. Constant communication between the surgical and neurophysiology team is necessary, to ensure that tcMEP responses are obtained in a fashion that minimizes delay between potential surgically related injury and observed signal changes.

### Preservation or Irreversible Complete Deterioration of MEP Responses

During insular glioma and central-region tumor surgery, up to 44 % of patients might exhibit intraoperative MEP alteration [66, 69]. MEP responses with unchanged response parameters (amplitude and stimulation thresholds) correlate with no new postoperative motor deficits. The exception to this is supplementary motor area lesions; in which intraoperative MEP preservation is clinically predictive of complete or near-complete recovery of voluntary movements [70, 71]. Complete and irreversible loss of tcMEP responses is clinically predictive of a postoperative motor deficit, with a report of 42 % patients having severe permanent deficits [15].

### Reversible or Incomplete MEP Deterioration

Reversible deterioration in compound muscle action potentials is observed when intraoperative signal amplitude reduction, or complete signal loss is followed by subsequent full or partial recovery of amplitude.

There are a number of confounding factors that may affect CMAP amplitudes intraoperatively aside from those due to surgical manipulation and lesion resection. Limb pressure and malpositioning can case CMAP decrease, which can be confirmed with simultaneous SSEP recording.

Reversible deterioration or incomplete deterioration (either judged by amplitude loss or increased stimulation thresholds) are clinically correlated to postoperative motor deficits ranging from transient deficits to moderate permanent deficits [66, 67, 69, 70].

Irreversible MEP changes are more often correlated with postoperative deficits than reversible alterations, frequently with confirmatory brain MRI findings. Complete CMAP loss has been shown to significantly correlate more with subcortical MRI signal alterations, whereas CMAP incomplete deterioration correlated more often with precentral gyrus signal alterations [15, 67].

At present, although reversible or incomplete MEP deterioration lacks the sensitivity to accurately predict postoperative motor outcome, simply monitoring the presence or absence of responses is insufficient for supratentorial procedures.

## Direct Cortical Motor Mapping

Direct cortical stimulation (DCS) is a mapping and monitoring technique, in which constant current stimulation is applied directly to the cortex. Handheld monopolar, bipolar, and subdural strip or grid electrodes may all be used as stimulating electrodes. Activated pathways are identical to transcranial stimulation techniques; however, with smaller employed current fields focal activation of somatotopic axons may be elicited. Although direct cortical stimulation may be utilized during awake craniotomies with cooperative patient feedback, this chapter will only discuss methods under general anesthesia which relies on electromyographic CMAP responses.

## Stimulation and Recording

Under general anesthesia, two stimulation techniques may be employed: bipolar cortex stimulation (Penfield's Technique) and MEP mapping (Taniguchi method).

### Bipolar Cortex Stimulation (Penfield's Technique)

Bipolar rectangular pulses with 0.5–1 ms duration are delivered via a bipolar handheld probe with ~5 mm spacing or subdural grid to the exposed motor cortex at 50–60 Hz for approximately 1–4 s. Threshold intensities for eliciting a motor response are determined by starting at 3–5 mA, and increasing by increments of 0.5–2 mA. Threshold amplitudes for evoking a )motor response are typically less than 10 mA [15, 18, 24, 26, 45, 72–77].

### Multi-pulse Train Technique (Taniguchi Method)

Trains of four to nine (typically 5) monophasic anodal rectangular pulses 200–500 μs in duration with an inter-stimulus interval of 2–4 ms are delivered via a hand-held probe or subdural grid to the exposed motor cortex. Threshold amplitudes are identified by increasing amplitude by increments of 0.5–2 mA but not exceeding 25 mA. The mean threshold for motor gyrus stimulation is reported to be 6–12 mA [78]. This stimulation technique can be applied in a monopolar fashion with the return electrode in exposed temporalis muscle or scalp, or in a bipolar fashion, between two sites on a subdural grid or via a bipolar handheld probe [15, 26, 27, 45].

In both cases, it is recommended to stimulate the entire are of interest before increasing the stimulus amplitude incrementally. Penfield's technique is associated with a higher risk of induced seizure than the multi-pulse train technique. However in both cases it is recommended to place a subdural grid or strip on exposed cortex adjacent to stimulation, in order to monitor electrocorticography (ECoG) for the presence of after discharges (ADs). With either stimulating technique, although reported incidence of seizure is only 1 % it is advised to preventatively take precautions so that the surgical, anesthesia, and neurophysiology team is prepared to respond to intraoperative electrographic and/or clinical seizure, with ice cold saline or Ringers' solution quickly applied to the cortical surface [15, 26, 27, 60, 79, 113].

### Recording

Under general anesthesia motor responses to direct cortical stimulation are evaluated by subdermal needle electrodes placed in contralateral muscle groups of areas which are at the highest risk for damage, and/or visual inspection of contralateral muscle groups during stimulation. Penfield stimulation typically elicits a tonic muscle response, whereas the multi-pulse technique elicits a single CMAP response [80] (Figs. 7 and 8).

## Interpretation and Application during Lesion Resection in Proximity to Eloquent Cortex

Distorted anatomy due to lesions may make anatomical landmarks for identification of the central sulcus unreliable. Anatomical and functional imaging techniques enable the identification of the precentral gyrus, although intraoperative direct cortical stimulation remains the gold standard for functionally verifying motor cortex.

DCS is performed after central sulcus localization, when possible. The pre-central sulcus location of the largest N25 peak (which is the phase reversal of the P22 post-central sulcus peak, illus-

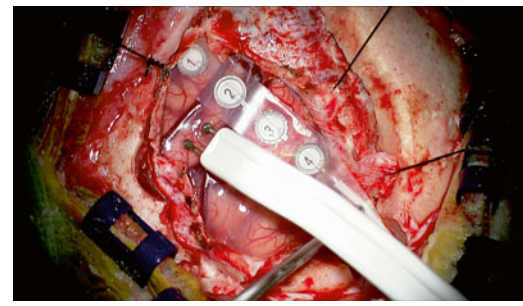

**Fig. 7** Direct cortical stimulation via handheld bipolar probe, with ECoG monitoring via subdural strip prior to resection of low-grade glioma in adult patient. Diameter of strip electrode is 6 mm

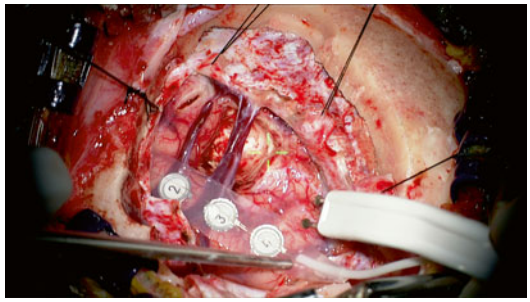

**Fig. 8** Direct cortical stimulation via handheld bipolar probe, with ECoG monitoring via subdural strip after partial resection of low-grade astrocytoma. Bipolar probe position indicates location of stimulation which evoked involuntary contralateral dorsiflexion. Diameter of strip electrode is 6 mm

trated in Figure 4) can be used as an ideal starting location to begin DCS stimulation [15, 26, 27].

The multipulse train technique is increasing in popularity, due to the decreased incidence of induced seizure, lower delivered total charge during stimulation, and more minimal stimulus artifact on ECoG recording. Furthermore, the multi-pulse technique has allowed for a more quantitative analysis of elicited responses, increasing the value of DCS as a monitoring technique as well as a mapping technique. Once DCS has successfully localized motor function, a grid or strip may be placed to stimulate and evoke CMAP responses to monitor the functional integrity of the CST during resection utilizing the multi-pulse technique, if the placement does not interfere with resection [19, 70, 78, 80–85]. An increase in stimulus-threshold of 4 mA necessary to evoke CMAP responses has been suggested as a criterion indicating significant change; however, currently there are not reports confirming or suggesting otherwise [84, 86].

When DCS is used for mapping purposes, threshold values of less than 10 mA are generally accepted as indicative of eloquent motor cortex localization, for either Penfield or multi-pulse stimulation methods.

## Practical Limitations

While under general anesthesia, motor mapping is limited to muscle groups that are monitored with electromyography, or those that are visible without disturbing the surgical drapes. With a cooperative awake patient, feedback regarding all muscle groups is available.

To maximize specificity of localization, it is important to continually use threshold or near-threshold settings, as supramaximal DCS settings may activate axons adjacent to the anodic stimulation site, decreasing specificity. When DCS is used as a monitoring tool during resection, reports have shown that only patients with significant signal deterioration or increased threshold experienced motor deficits 3 months postoperatively [82–84].

Direct cortical stimulation under general anesthesia is confined to the primary motor area. Stimulation of the supplementary motor area rarely activates involuntary CMAP responses. Intraoperative functional mapping of language, sensory, and supplementary motor area in response to direct electrical stimulation currently all require an awake cooperative patient.

Due to the great difference in stimulus amplitude parameters between DCS and tcMEP, patient movement during DCS is minimal and of less concern than tcMEP.

In the case that no CMAPs are evoked during stimulation, the function of the stimulating probe can be verified by checking for stimulation artifact on the ECoG recording montage, or stimulating the exposed temporalis and verifying a muscle twitch response. It is also possible to stimulate adjacent cortex that is not exposed when stimulating via grid electrodes, as they can be carefully slid subdurally under adjacent bone (Fig. 9). Systemic and anesthetic confounds that deteriorate tcMEP CMAPs can also deteriorate DCS CMAPs, therefore the anesthetic and troubleshooting recommendations are the same for DCS under general anesthesia as those for tcMEP.

The most likely complication of DCS is the occurrence of focal or generalized seizure. Administering bolus sedatives in response can impair continual motor mapping by decreasing neuron excitability. Instead, administering ice cold saline or Ringer's solution directly to the cortex will terminate the seizure.

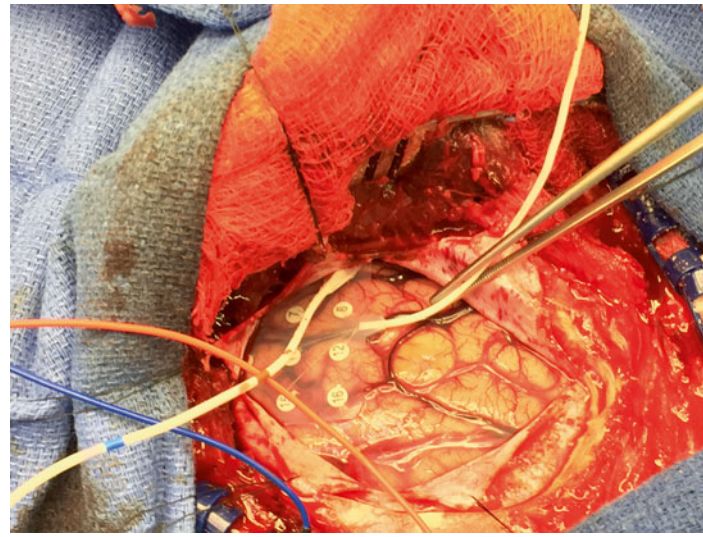

**Fig. 9** 4×4 Contact subdural grid positioned beyond the boundary of exposed cortex, underneath temporal bone for ECoG recording

## Subcortical Stimulation

During direct subcortical stimulation, white matter tracts are regularly stimulated all along the resection margin or wall during surgery of tumors in eloquent areas [110]. While sensory, speech, and language subcortical stimulation techniques all involve the cooperation of a patient under local anesthetic; subcortical motor stimulation can be performed under general anesthesia [87].

After direct cortical stimulation and mapping of the primary motor cortical areas, subcortical direct electric stimulation may be used to detect corresponding descending motor pathways. Stimulation techniques used are identical to DCS parameters for Penfield's technique or the multi-pulse train technique used for cortical stimulation, with the exception that stimulation is via the cathode.

Bipolar stimulation provides the most precise results, as the current field produced during stimulation is smaller than with monopolar stimulation; however the eloquent tissue must be situated between the two probe tips to evoke a response. Some experts prefer monopolar stimulation due to the homogeneous current field created by radial current spread [80, 84].

Subcortical stimulation can be used to estimate the distance between stimulation site and corticospinal tract (CST). Estimates of the ratio of threshold current to distance from CST during subcortical stimulation, are approximately 1.0–1.5 mA/1.0 mm. A recent report suggested that resection should be stopped when subcortical stimulation thresholds are 2 mA, and that higher thresholds indicate safe distance from CST [86, 88–90].

Subcortical stimulation used in addition to DCS monitoring during resection has shown a combined sensitivity and specificity of 66.67 and 96.84 % for prediction of iatrogenic injury in a study of 100 patients [84, 86].

## Pitfalls in the Usage of Somatosensory- and Motor-Evoked Potentials in Surgery of Eloquent Cortex under General Anesthesia

Obviously the use of these neurophysiological tools does not take the place of sound surgical experience, careful and delicate surgical technique, extensive knowledge of neuroanatomy, and particularly our newer appreciation of the subcortical white matter fiber tracts. Image guidance including the fiber tracts, functional MRI, and other modalities to preserve eloquent cortex, have shown immense value, but at present should be used in conjunction with neurophysiologic techniques, and not replace them.

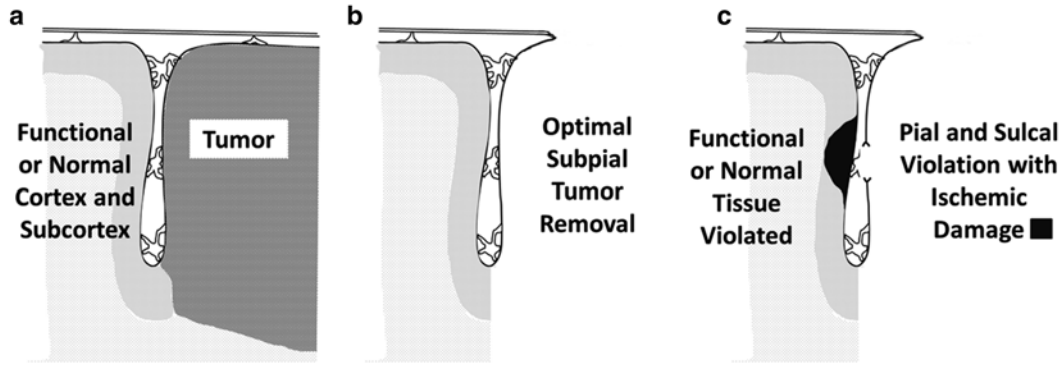


**Fig. 10** (**a**) Schematic cortical sulcus with normal or eloquent cortex on the left bank and cerebral gyrus invaded by tumor on the right. (**b**) Optimal removal of tumor on the right respecting the pial border. (**c**) Violation of the pial surface, occlusion of a sulcal artery, and ischemic injury to the normal or eloquent left cortical bank

A number of our surgical strategies and neurophysiological techniques for safe brain tumor removal in proximity to eloquent cortex come from our experience gained in epilepsy surgery. Similarly, we must be reminded of particular cautions in relation to the handling of cortical gyri and sulci, and the technique of subpial dissection. Thus eloquent cortical and subcortical tissue can be inadvertently damaged if careful subpial tumor resection is not carried out and the pial borders and vasculature in the sulci are not preserved (Fig. 10). It must be recalled that with direct cortical stimulation and SSEP recordings we are predominately only visualizing, stimulating, or recording from the crest of the particular gyrus. An equal amount or more of eloquent cortex may well be buried in the continuous cortical sulcal wall of that gyrus (Fig. 11). Similar unexpected deficits can be encountered in resections adjacent to the pre-central and post-central gyri, as eloquent cortex may occasionally continue up the other sulcal side of an adjacent gyrus whose crest would not be recognized as eloquent [91]. Additionally in the Rolandic area, the posterior angulation of the afferent primary sensory fibers to the post-central gyrus; and the pyramidal tract outflow from the pre-central gyrus through the corona radiata to the internal capsule must be appreciated and respected [91], ideally along with subcortical motor stimulation being performed (Fig. 12).

## Conclusions and Future Advancements of Somatosensory- and Motor-Evoked Potentials in Surgery of Eloquent Cortex under General Anesthesia

A number of experienced anesthesiologists are not comfortable with full general anesthesia by total intravenous anesthesia (TIVA)—being sedative/hypnotics, analgesic narcotics, with minimal muscle paralysis. For a number of good reasons they prefer to augment with inhalational agents albeit at lower percentages than routinely used for general anesthesia. However, standardized, well-accepted neuroanesthesia protocols to optimize SSEP and MEP recordings under general anesthesia are now well documented, and coordination and communication between anesthesiologists, neurosurgeons, and the neurophysiological monitoring team is essential to optimize monitoring and patient protection. Yet there is no doubt that fluctuations in anesthetic agent concentrations and the mixture of general anesthetic agents may affect neurophysiologic monitoring.

The ability for "real-time," ongoing blood concentrations of all intravenous, inhalational, and muscle paralyzing agents utilized during general anesthesia could advance neurophysiologic monitoring sensitivity and specificity. Increased understanding of the specific effects of these agents and how they may interact with each

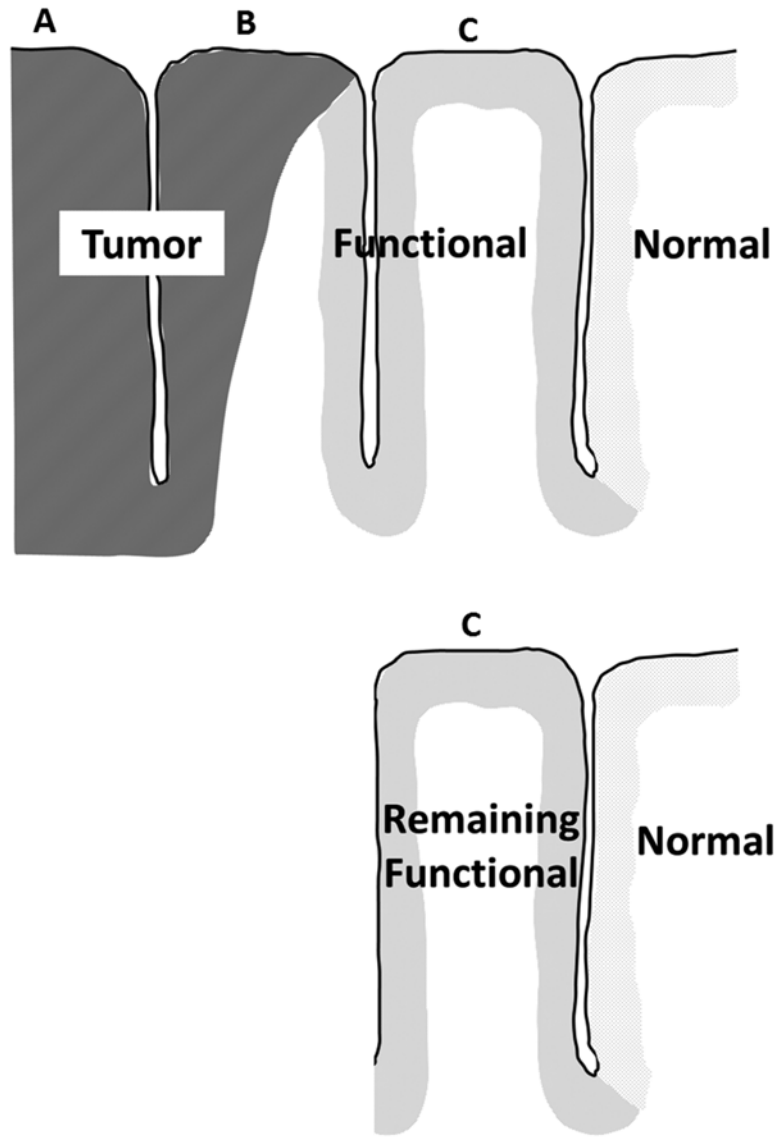


**Fig. 11** *Top*: schematic of cortical surfaces with Gyrus C having eloquent motor and sensory function revealed by surface stimulation and SSEP recording. Gyrus B is partly invaded by tumor on the left, but has eloquent cortex on its right bank not revealed by cortical surface stimulation. *Bottom*: excision of Gyrus A and B removes the right bank of B, containing eloquent function in the cortex

other would improve the ability to account for response variability due to anesthetic agents. The phenomena of MEP "fade" discussed previously with prolonged operations, may involve accumulation of drug or metabolites within muscle cells or their receptors. This information would allow the monitoring team to optimize interpretation of CMAP responses, and also likely lead to lower and better controlled dosing titrated to the individual patient. If anesthetic and muscle paralytic control could be stabilized, or become homeostatic, accurate automated quantitative waveform analysis of recorded tcMEPs and SSEPs may be possible, dramatically standardizing monitoring ability.

Cerebral cortical regions in man in general have a varied, but yet rather consistent regional cortical nerve cell and nerve fiber structural organization (i.e. pre- and post-central, primary visual, associational, etc) . There is some evidence in animals and man that each such specialized cortical area may possess a particular "neurophysiological signature" which could be used to surgically identify a particular eloquent

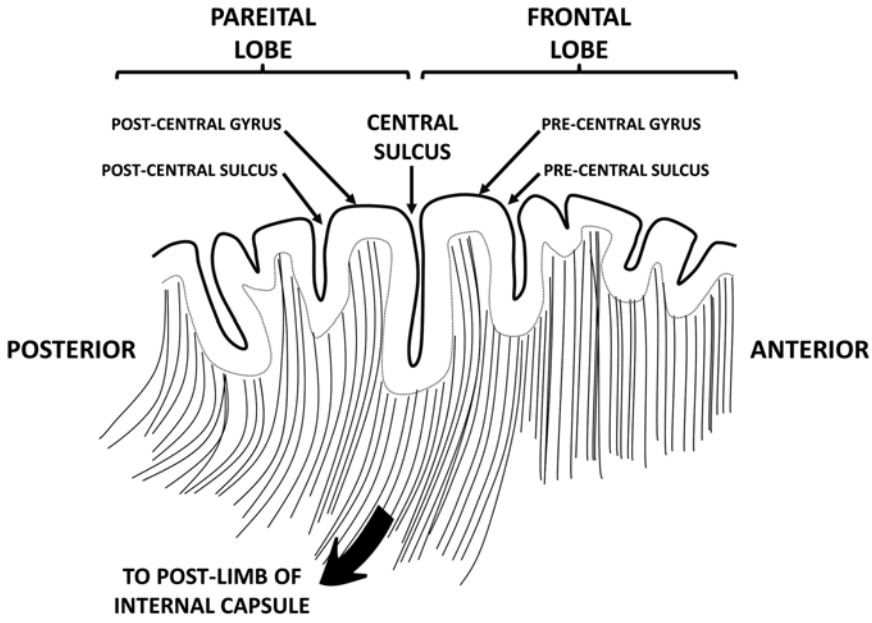


**Fig. 12** Parasagittal section through the central hemispheric region. Schematic representation of the posterior course of Rolandic cortical fibers to reach the posterior limb of the internal capsule

cortical region. Electrocorticographic (ECoG) broadband evoked responses to motor, sensory, verbal, or complex behavioral tasks in awake patients has shown promise in identifying eloquent cortical regions, which could improve the safety of subsequent tumor excision under general anesthesia. Such techniques may improve in the near future and be added to our neurosurgical armamentarium.

For the foreseeable future, somatosensory- and motor-evoked potentials under general anesthesia as an aid to cerebral hemispheric tumor surgery near eloquent cortex will likely remain a mainstay. We envision improvement in our understanding and usage of these currently accepted techniques, and better consistency in managing the variable factors in our methodologies. We also anticipate increased accuracy of automated latency and amplitude alerts, at which point: (1) all neurophysiological tests have evidence-based, agreed-upon, procedure dependent threshold warning criteria, and (2) any waveform variation due to an anesthetic agent can be accurately quantified and factored into automated algorithms.

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# Cortical Mapping with Transcranial Magnetic Stimulation

Phiroz E. Tarapore

## Background and Methodology

### Indications for Cortical Mapping

The localization of essential cortical motor and language regions is of great relevance across a wide spectrum of basic, translational, and clinical neuroscience. Retrospective localization studies relied largely on lesion-symptom mapping, in which existing injuries were correlated with clinical symptoms [1–6]. The advent of intraoperative direct cortical stimulation (DCS) mapping revolutionized this field, allowing clinicians to interrogate a region with a temporary electrical lesion. While this technique is effective, it is also highly invasive, requiring a craniotomy for cortical exposure, and is thus performed only when necessary for the surgical management of an existing lesion. A technique for noninvasive, lesion-based identification of critical motor and language sites would therefore be of great benefit to clinicians. Such a technique would also be important for neurophysiologists interested in testing cognitive models of language, including language streams [7] and connectome-based models [8].

Transcranial magnetic stimulation (TMS) is a technique that has demonstrated promise in this regard. Based on Faraday's principle of electromagnetic induction, TMS applies a brief pulse of high-strength magnetic field over the scalp which passes through the skull and induces an electrical current in the underlying brain region [9]. These pulses of current, if applied appropriately, are sufficient to depolarize a population of neurons, inducing an action potential [10]. Single TMS pulses, when delivered over the cortex, will thus briefly stimulate the underlying cortical region. Repetitive trains of these pulses, so-called repetitive TMS (rTMS), can have either an inhibitory or a stimulatory effect on cortical excitability, depending on the frequency of the rTMS trains [11]. Therefore, by altering the protocol of stimulation, TMS can cause either a temporary excitation or lesion effect in the cortex.

Furthermore, the development of *navigated* TMS (nTMS) has allowed for this technology to arrive rapidly at the forefront of noninvasive mapping modalities (Fig. 1). What sets apart the nTMS system from a nonnavigated TMS system is its demonstration, in real time, of the precise location and strength of the magnetic pulse. By integrating a frameless stereotactic navigational system (such as those used commonly utilized in neurosurgical and other procedures) with a TMS coil, one can co-register a structural MRI or CT brain scan to a subject's anatomy using fiducial markers or anatomical landmarks. This advancement allows the investigator to deliver TMS pulses with unprecedented precision under image guidance [12–15].

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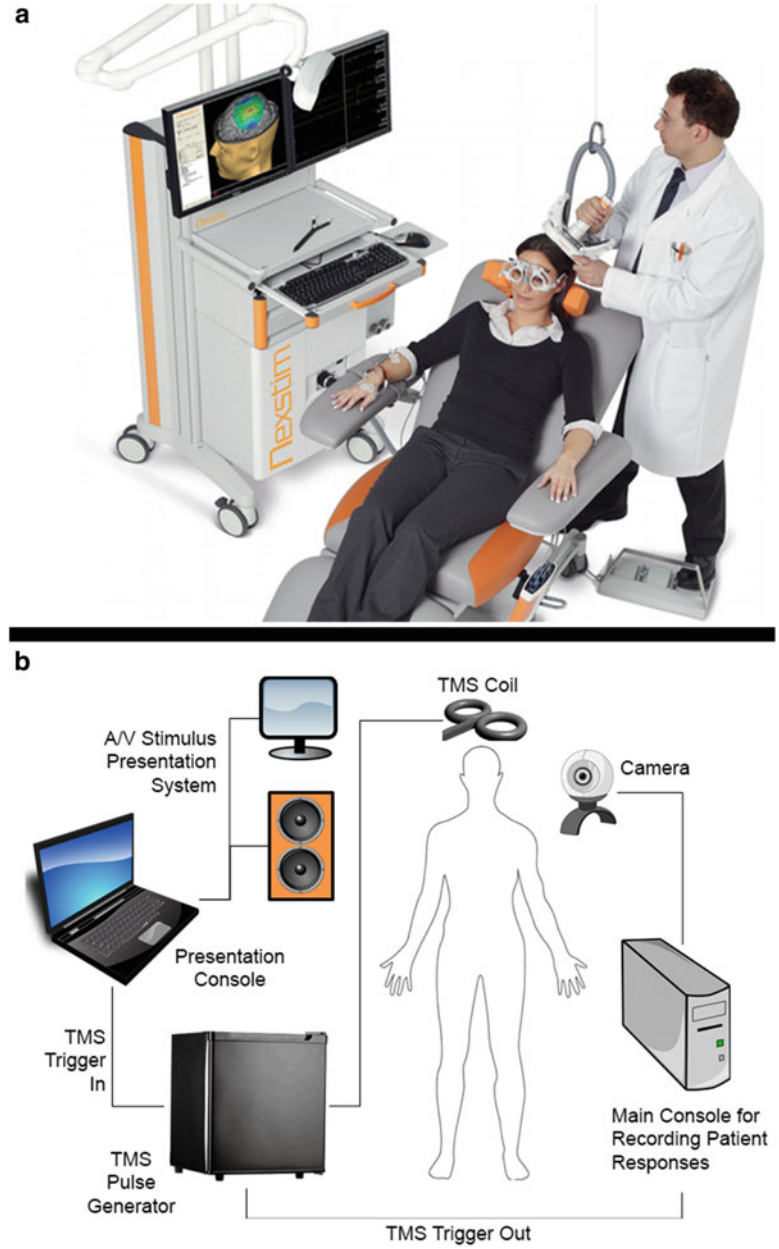


**Fig. 1** (**a**) A modern navigated TMS system complete with navigation unit, real-time field strength calculation, and heads-up display (courtesy Nexstim Oy, Helsinki, Finland); (**b**) A schematic of the key components in a TMS-based speech mapping setup. Note the presence of two unique computers: one controls the presentation software and triggers the TMS pulses timelocked to the stimuli; the other records patient responses and correlates those responses with the cortical location of the associated TMS pulse train

Furthermore, in some nTMS systems, the strength and directionality of each TMS pulse is calculated on-the-fly according to a dynamic spherical model which takes into account the preset parameters of stimulation as well as the subject's scalp/skull thickness [16, 17]. As a result, when the stimulation coil is positioned over the subject's scalp, the investigator can visualize the targeted cortical region, the strength and orientation of the magnetic dipole, and the cone of activation generated by the magnetic pulse (Fig. 2).

nTMS therefore allows the investigator, for the first time, to pinpoint precisely the cortical region that is being targeted. This capacity for accurate localization suggests a number of novel applications for TMS. In particular, it offers the possibility of mapping essential cortical regions associated with motor and language function.

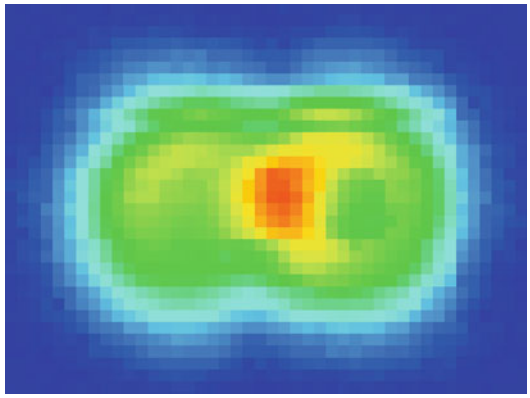

**Fig. 2** A heat-map of magnetic field strength as generated by a figure-of-8 TMS coil. Note the central area (*red*) reaches >2 Tesla in strength

Prior studies [18–24] have examined the use of repetitive TMS to cause speech arrest and lateralize language (see below for details). However, these efforts were not stereotactically guided, and showed repetitive TMS to be an unreliable technique for determining language laterality, largely because of a high false-positive rate for speech arrest sites on the supposedly nondominant hemisphere. It should be noted that most of these studies did report finding dominant-hemisphere positive language disruption sites in almost all their subjects (see Table 1, "# Pts with +SA").

## Prior Studies of Motor Cortex Using TMS

The use of nTMS for motor mapping has become a widely accepted method of generating preoperative motor maps. In the first study of nTMS-based motor mapping in the preoperative context, Picht et al. [25] demonstrated how nTMS might be utilized to generate high-resolution maps of peri-Rolandic regions in patients undergoing surgical resection of eloquent neoplasm. These results were confirmed and augmented by Tarapore et al. [26], who showed that nTMS yielded more accurate motor maps than magnetoencephalography (MEG), another noninvasive preoperative mapping technique. Since these initial studies, the validity and utility of nTMS-based motor maps has been widely confirmed as one of the most accurate preoperative motor mapping modalities [27, 28].

## Prior Studies of Speech Cortex Using TMS

Although the use of nTMS for language mapping is in its infancy, in the last 3 decades, several eminent research groups have examined TMS as a technique for studying the lateralization of language function [18–24]. In the first reported study of rTMS and the interruption of language function, Pascual-Leone et al. showed that speech arrest could be obtained in all 6 of 6 test subjects. Subsequent studies by Michelucci, Valzania [19] and Jennum, Friberg [20] had less convincing results, finding speech arrest sites in 50 and 67 % of their study subjects, respectively. Wassermann, Blaxton [21] showed that rTMS of left-sided targets would preferentially interfere with object naming. Finally, Epstein, Woodard [24] showed that rTMS was inferior to the Wada test in determining language laterality. One other report of particular significance was that of Epstein and colleagues, which showed that low-frequency repetitive TMS (4–5 Hz) can be equally effective as high-frequency repetitive TMS (15–30 Hz) in causing language disruption, because most subjects are unable to tolerate the discomfort of high-frequency repetitive TMS [22].

## Strengths and Weaknesses of These Prior Studies

### Navigated vs. Unnavigated

Although TMS technology has been around for more than 5 decades, the integration of TMS with a neuronavigation system is a relatively recent development [13, 14]. By co-registering identifiable anatomic points on the patient's MRI with those same points on the patient's head, one can "teach" the system the exact location of the patient's head in 3-dimensional space. In this way, the MRI scan is precisely related to the actual brain, and one can target specific points on the cortical surface accurately and reproducibly [12]. Only in the last few years have reliable,

**Table 1** Prior publications on TMS-based language localization

| | Date | # Pts | # Pts with +SA | rTMS freq (Hz) | Train length (s) | Task | Primary pathology | Coil | Design |
|---|---|---|---|---|---|---|---|---|---|
| Pascual-Leone | 1991 | 6 | 6 | 25 | 10 | Counting | Epilepsy | CRRMS | 15 Positions bilat (10/20), c/w IAT |
| Michelucci | 1994 | 14 | 7 | 16–20 | 6–10 | Counting | Epilepsy | CRRMS | 9 Positions bilat (10/20), c/w IAT |
| Jennum | 1994 | 21 | 14 | 30 | 1 | Counting, reading | Epilepsy | MagPro biphasic | 4 Positions bilat (10/20), c/w IAT |
| Wassermann | 1999 | 14 | 13 | 15, 5–18 | 2–3 | Naming, reading | Epilepsy | CHSMS | 1 cm grid, c/w IAT in 10 pts. |
| Epstein | 1996 | 5 | 4 | 4 | 1–5 | Counting | None | CHSMS | Continuous over lat frontal region |
| Epstein | 1999 | 10 | 10 | 4 | 2–5 | Counting | None | Custom circular | Continuous over lat frontal region |
| Epstein | 2000 | 17 | 16 | 4 | N/A | Counting | Epilepsy | Custom circular | Continuous over lat frontal region |

commercially-available navigated TMS systems become available outside the laboratory.

The advantages of integrated navigation are many. First and foremost, it allows for accurate targeting of a particular cortical region: cortical anatomy can vary from patient to patient and, without navigation, the cortical region being stimulated is at best an educated guess. Second, navigated TMS delivers more consistent magnetic field strength: with new algorithms, the magnetic field strength incident on a cortical region can be calculated in real time [16, 17]. Third, navigation allows for very high inter-session reliability: The co-registration process is repeated at the beginning of every session and, unless there is significant change in the patient's anatomy, every session is set up and targeted in the same way. Navigated TMS has been verified in numerous studies as safe, reliable, and more accurate than nonnavigated techniques [15, 26]. Successful mapping requires that a specific cortical region be targeted. Therefore, the ability to navigate accurately to that target is of paramount importance.

Image guidance is a critical component of any modern TMS-based language mapping. Precise targeting of the stimulus pulse is clearly important, but we have found that the orientation of the dipole is also critical. In fact we have noted on several occasions that small rotations of just 10–15° can alter the amplitude of a motor evoked potential or the positivity of a language site. In general, to maximize patient comfort, it is ideal to maintain the dipole in perpendicularity with fibers of the temporalis muscle and the adjacent sulcus.

### Coil Orientation

Two other improvements in the current technique are the use of the figure-of-8 coil and the ability to optimize the electrical field strength in real time. A figure-of-8 coil offers improved ability to focus the magnetic field on a small cortical region. Relatedly, the navigated system allows the operator to visualize in real time the theoretical field strength for a proposed stimulation pulse given the angle of the coil and the targeted cortical region. It is thus possible to maximize the effective cortical depolarization for a given stimulator output intensity, thus ensuring improved consistency between pulse trains (Fig. 3).

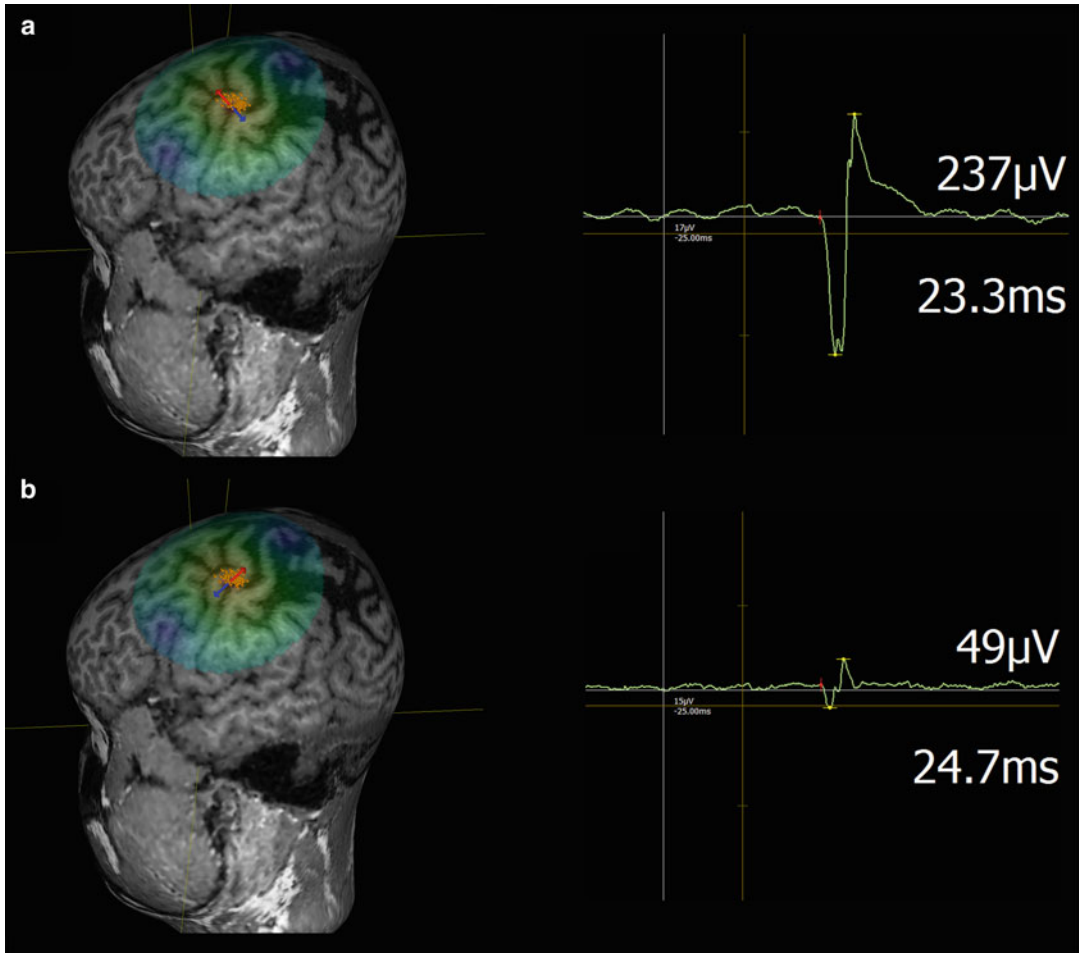


**Fig. 3** An example of the effect of magnetic dipole orientation on motor-evoked potential (MEP). In (**a**), the MEP for extensor pollicis brevis is 237 μV, while in (**b**), with 90° rotation, the MEP for the same muscle is 49 μV. Both pulses were of the same intensity

### Stimulator Settings

Another improvement in the modern TMS protocol is the change in stimulator parameters. These improvements have been particularly relevant in speech-mapping protocols. The initial TMS language studies utilized high frequencies of 15–30 Hz with long trains of up to 10 s in their stimulation protocols. These parameters, in addition to being intensely uncomfortable to subjects, would not be approved by most modern ethical review committees because of the risk of provoking seizure. Indeed, Wassermann and colleagues chose to change the stimulation protocol in the midst of their study when it became known that low frequency stimulation was equally effective [21].

## Clinical Practice

### Patient Selection: Inclusion and Exclusion Criteria

As with any procedure, a successful outcome relies first on appropriate subject selection. Motor mapping should be considered in any case of lesion involving peri-Rolandic cortex, including the supplemental motor area and somatosensory cortex. Speech mapping should be considered in any case of a lesion involving eloquent or peri-eloquent speech regions including dominant temporal, inferior and middle frontal, supramarginal and angular gyri (Fig. 4). For practical purposes the "lesion" is

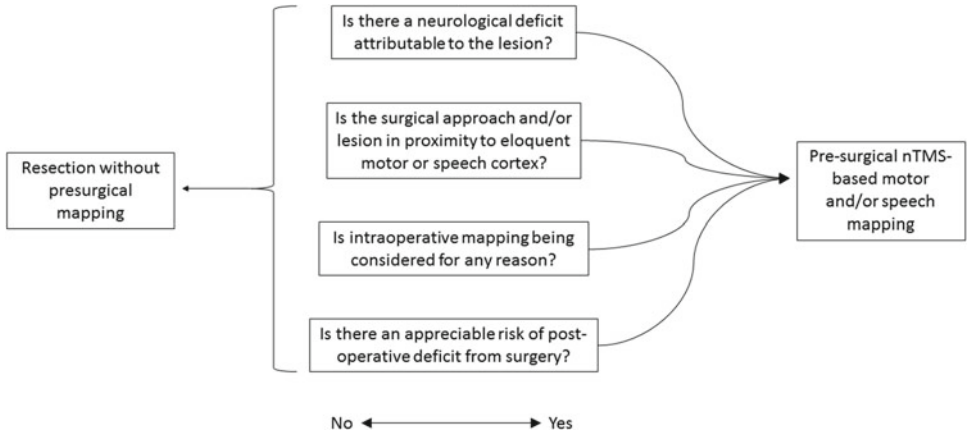


**Fig. 4** An algorithm for determining whether to employ nTMS motor and/or speech mapping in the surgical management of lesions in eloquent and peri-eloquent cortex

defined broadly: it may be neoplastic, as with primary glial neoplasms, electrophysiologic, as with epileptic foci determined by EEG or MEG, ischemic or hemorrhagic cerebrovascular accidents, or any other intracranial abnormality which is perceived to threaten the aforementioned areas.

Although the repetitive TMS protocol is well tolerated, there are contraindications to its application. These include the following:

- Implanted metallic parts of implanted electronic devices, including pacemakers, defibrillators, or implant medication pump.
- Pregnancy.
- History of uncontrolled epilepsy with >1 seizure per day.
- Implanted brain stimulator.
- Aneurysm clip or other metal in body.
- Scalp wounds or infection.

## Patient Preparation

### What to Expect

Prior to starting the mapping, all subjects must be prepared for the experience with a short verbal description of the expected sensations associated with single-pulse and repetitive nTMS. These sensations should be explicitly defined as muscle contraction, tingling, and occasional discomfort. Subjects should be encouraged to give feedback about the level of discomfort associated with the nTMS mapping process so that the stimulation intensity could be decreased if necessary. They should be also encouraged at multiple points to ask for a break if needed, and to opt out of the mapping altogether if they feel any significant discomfort. Finally, with speech mapping, subjects should be prepared for a possible speech arrest with an explanation of the purpose of mapping, a basic description of the underlying neurophysiological processes, and an assurance that any language disturbance is a result of the stimulation and would spontaneously resolve.

### Time of Procedure

The procedure should take approximately 45–90 min, depending on the size of the mapped region and the experience of the operator. It is recommended to keep study duration under 1 h, as this seems to represent a limit in the ability of the patient to cooperate with sometimes demanding cognitive tasks associated with language mapping.

### Imaging Requirements

The patient must undergo a high resolution, thin-slice MRI scan prior to nTMS mapping. The navigation will be based off this scan. Optimal

slice thickness is 1.5 mm, with matrix size 256 × 256 × (108 – 140), and field of view = 260 mm × 260 mm with skin-to-skin coverage including the nasion and preauricular points. Each nTMS imaging session involves aligning the MRI images to the subject's head via the MRI to head co-registration process.

Using the bridge of the nose and the tragus of the ear, landmarks that are visible on both the subject's MRI and the head, the 3D-locations of the landmark are measured using a digitizing pen with an optical tracking system (Fig. 5). This registration allows for real-time monitoring of the coil position without restraining the subject's head during the TMS procedure [29]. The optical tracking system uses 2 cameras to triangulate the location in 3D space of infrared reflectors attached to the coil and subject's head. The mapping surface should be located between 23 and 28 mm deep to the scalp. This "peeling depth" will vary amongst subjects and must be set individually.

## Current Protocol for Navigated TMS Motor Mapping

By far, the most widely used protocol for TMS motor mapping consists of single pulses, with an inter-stimulus interval of at least 3 s but as long as needed for targeting purposes. The pulses are typically triggered by way of a foot pedal which is controlled by the operator. After registering to an anatomical scan, the operator proceeds to move the coil around the patient's head, focusing on the cortical regions that are of interest. It is helpful to have an integrated electromyography (EMG) capability, to identify motor evoked potentials in real time. EMG also allows the operator to use a lower stimulator intensity, because EMG can detect much smaller MEPs than the naked eye. Finally, multichannel EMG allows monitoring and recording from several muscle groups, thus allowing the operator to focus on the mapping instead of on interpreting the EMG in real time.

In contrast to speech mapping, motor mapping is a passive study. Subjects need only lie still in a comfortable position; they may even be asleep or under pharmacological sedation. In this regard, nTMS-based motor mapping has an advantage over fMRI- and MEG-based methods, which require active subject participation. nTMS can therefore be used for motor mapping in very young patients (as young as 3 years) or in patients who are impaired and unable to participate in an active motor task.

### Case Example: Motor Mapping to Optimize Approach

Commonly, motor mapping in the preoperative period is useful for surgical planning. In this case, a 51 year-old man with a history of esophageal adenocarcinoma presented with progressive right hand discoordination and weakness. MRI demonstrated an expansile enhancing lesion in the left frontal lobe that was centered in the precentral gyrus. Preoperative DTI demonstrated motor fibers completely surrounding the lesion (Fig. 6a). He was referred for nTMS-based motor mapping to determine if indeed the motor tracts were split around the lesion and, if so, to identify the safest approach to the tumor.

The nTMS-based motor map identified hand and forearm hotspots posterior to the lesion, but did not confirm any active sites anterior to the lesion (Fig. 6b). These findings were confirmed in the operating room with direct cortical mapping (Fig. 6c). Because of the agreement between pre- and intraoperative maps, the decision to take an anterior approach was easily made, and the tumor was removed completely (Fig. 6d). Postoperatively, the patient's hand function was improved and, at 6-week follow-up, his function was back to normal.

### Case Example: Motor Mapping to Evaluate the Safety of Surgery

In some situations, the clinical question is not what kind of approach to take, but whether to offer surgery at all. In this case, a 26 year-old man with epilepsy, prior resection, and recurrent seizure was being evaluated for a repeat surgery with extension of resection. He had full strength on his right side, but had significant weakness and discoordination of his left upper extremity. Per his report, this weakness had started after his

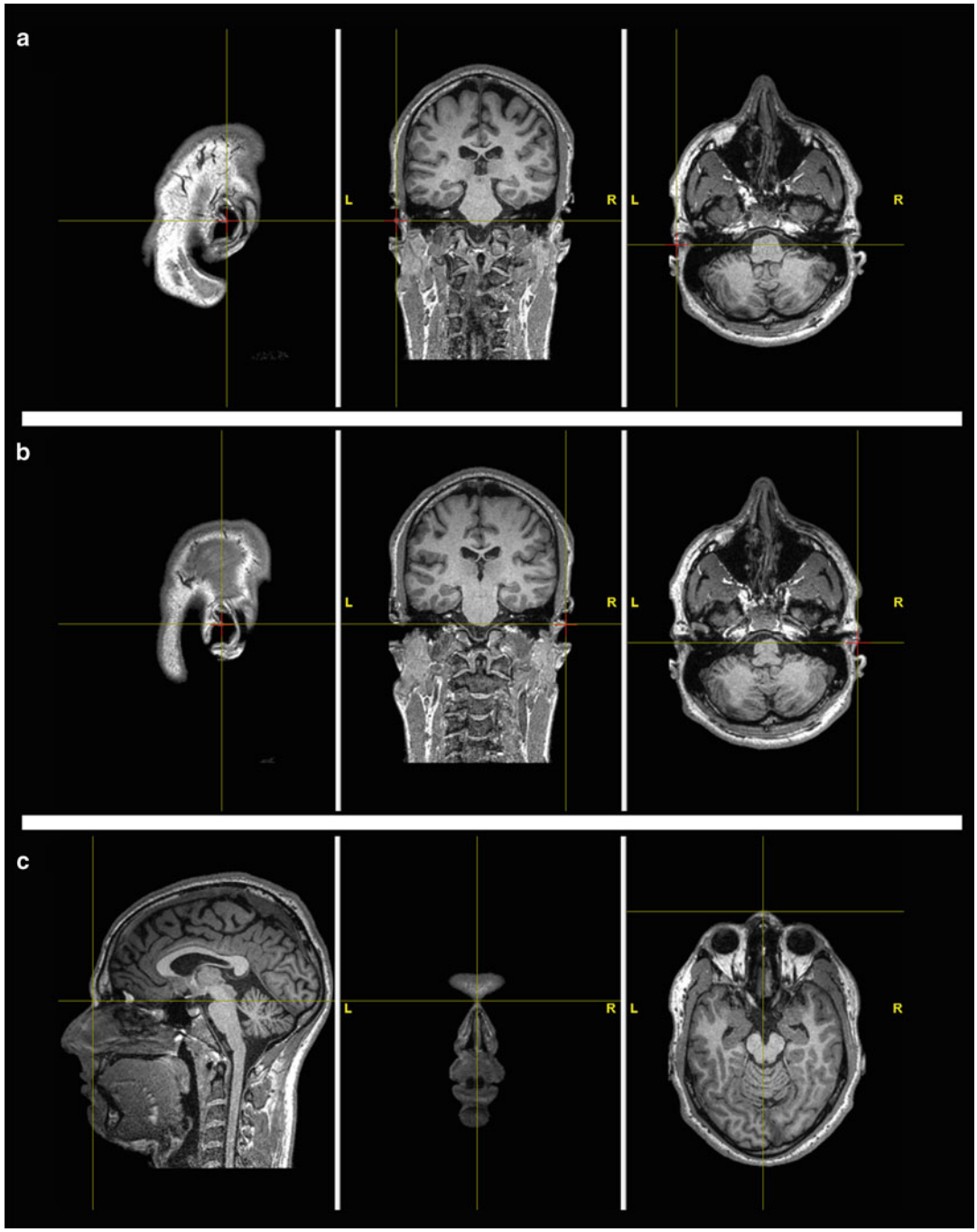


**Fig. 5** The sagittal, coronal, and axial cuts of commonly used registration points (marked with a *red cross*). In (**a**) is the left crus of helix, in (**b**) the right crus of helix, and (**c**) the nasion

prior resection and had been improving over the last 10 years. He was referred for nTMS-based motor mapping to evaluate the likelihood of worsened deficit with an extended resection.

As can be seen from the motor map (Fig. 7), this patient's right-sided motor system was located along his remaining precentral gyrus. While he still had some hand function in the superior portions of

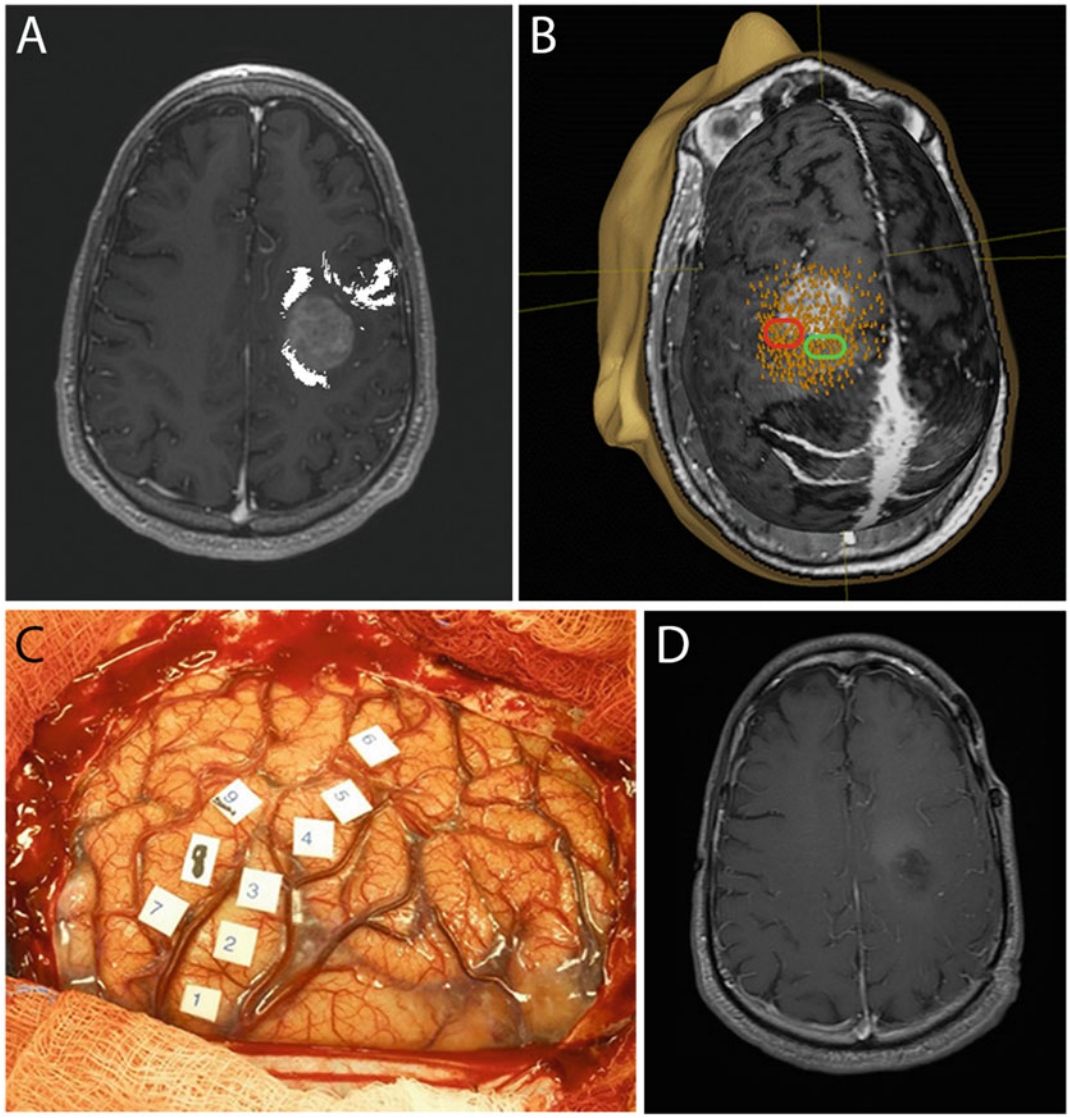


**Fig. 6** Case 1, Motor mapping to optimize approach. (**a**) MRI with superimposed motor tractography as determined by DTI; (**b**) nTMS motor map with APB (*green*) and ADQ (*red*) hotspots; (**c**) intraoperative motor map with 1–3 representing hand and 4–6 representing face motor hotspots; (**d**) postoperative MRI showing total resection

the motor strip, he also had strong hand responses in more inferior distributions, overlying what would typically be his face motor cortex. This redistribution of motor function, a result of synaptic plasticity, is most commonly found in younger patients who have had many years to recover from a surgery or neurological injury [30]. The map clearly demonstrates that the patient is at high risk of worsened deficit with repeat resection.

## Current Protocol for Navigated TMS Speech Mapping

The most widely used protocol for TMS speech mapping consists of a train of ten pulses at 5 Hz lasting a total of 2 s. The inter-stimulus interval is maintained at 3–5 s, with the cue (if visual) being visible for 1 s less than the total inter-stimulus interval. The rTMS pulse train should be stimulated

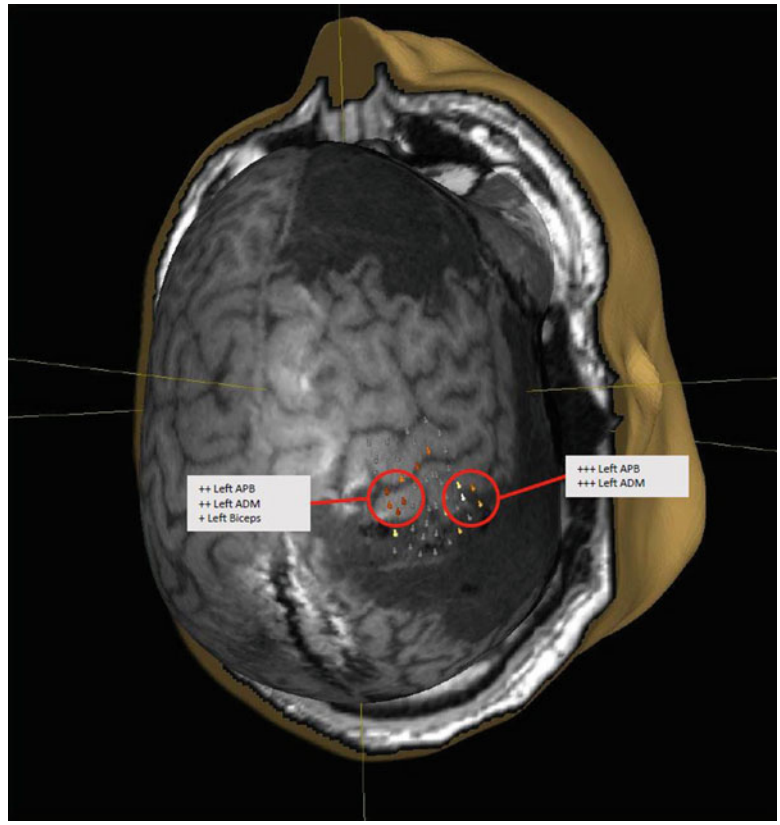


**Fig. 7** Case 2, Motor mapping to evaluate the safety of surgery. nTMS map demonstrating robust motor hotspots corresponding to APB, ADM, and biceps in the precentral gyrus, adjacent to the prior resection cavity

by an electronic trigger, with the pulse train starting at the onset of the task stimulus.

Many tasks may be used during speech mapping. The most common is object naming, perhaps because it is also the most commonly used task in the operating room during DCS mapping of speech function. Early studies of TMS speech mapping, however, suggest that the usage of a battery of "region-specific" tasks may yield better results than a single task (see below: "Region Specific Tasks"). Other tasks that may be useful in this regard are counting, verb generation (with auditory or visual cue presentation), word reading, auditory word repetition, word/nonword categorization, and free description.

As the sequence of cues is presented, the investigator moves the coil systematically around the region to be mapped, delivering a single train at each relevant point, and following a grid with 1 cm raster (Fig. 8). Each session should continue until every grid point has been covered once. If the subject is demonstrating discomfort during mapping, the investigator can alternate between more uncomfortable and less uncomfortable sites within the region of interest so that the subject is not confronted with multiple uncomfortable trials in a row. If the subject is still unable to continue due to discomfort, stimulator intensity may be reduced by 10 % at a time until the subject is able to continue. Note must be made of the intensity used during mapping in case the results become questionable due to very low intensity (i.e. <70 % RMT). In most cases, three mapping runs are adequate to achieve a reliable language map.

## Case Example: Speech Mapping to Guide Task Selection and Surgical Planning

This 28-year-old man presented with progressive word-finding deficits. His primary language was Tagalog and his secondary language was English; his word-finding difficulties occurred primarily

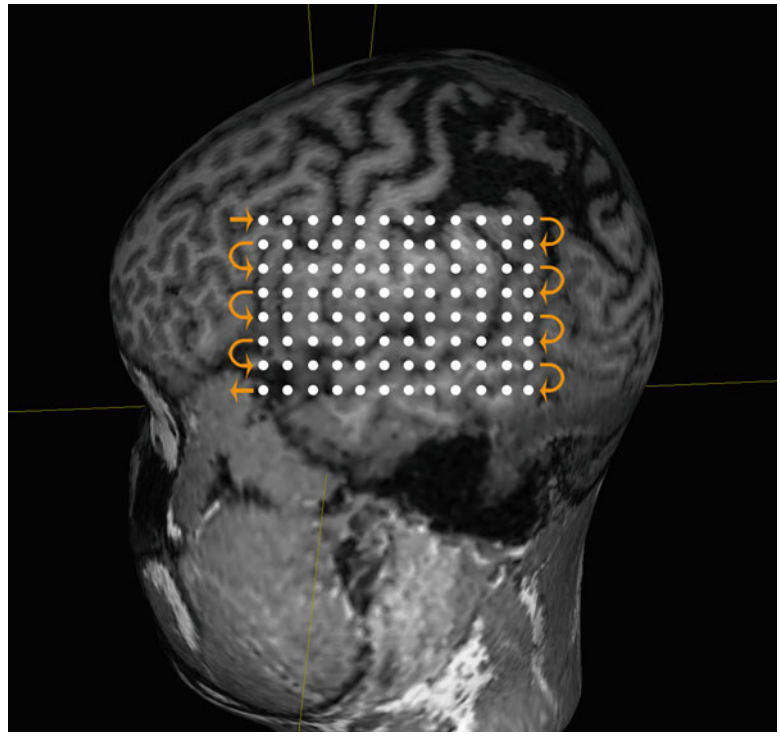

**Fig. 8** A sample pattern covering the left fronto-temporal region during a typical speech mapping session. The grid utilizes a 1 cm raster

in English. MRI demonstrated a non-enhancing left temporal mass consistent with a low-grade glioma (Fig. 9a). Given the location of the lesion and his existing deficit, he was referred for preoperative nTMS-based speech mapping.

During the speech mapping session, it quickly became evident that his anomia was too profound to allow for speech mapping in English. Object-naming was subsequently performed in Tagalog, and his baseline error rate improved to the point where nTMS testing was possible. The resulting speech map demonstrated speech arrest in the posterior portion of the superior temporal gyrus (Fig. 9b). Intraoperative mapping corresponded with the preoperative nTMS map (Fig. 9c). He went on to have a gross total resection of his tumor; his anomia improved postoperatively (Fig. 9d). This case illustrates an additional benefit of noninvasive preoperative mapping: limitations in the testing paradigm and the patient's performance can be identified in a stress-free environment. The tasks can then be optimized without the time pressure of the operative room so that the best possible preoperative map is obtained.

## Analysis of Data

Analysis of TMS motor mapping data can take place both during the study (online) and after its completion (offline). The locations of cortical stimulation points are recorded along with their resulting MEPs. The operator must go through each of these points, examining the MEPs, and identifying cortical 'hotspots,' the stimulation of which is associated with MEPs in a particular muscle. Finally, these hotspots are superimposed on the anatomical scan and reported to the clinician.

The analysis of TMS speech mapping data is often more complicated than that of motor data. Language errors are often subtle, and involving a speech and language pathologist is often the best way to achieve the most accurate categorization of speech errors. Additionally, the use of audio-visual recording equipment to capture every speech mapping session is essential to getting the most accurate and detailed speech maps. In many cases, speech errors are so subtle that it is only after multiple viewings of a particular trial with

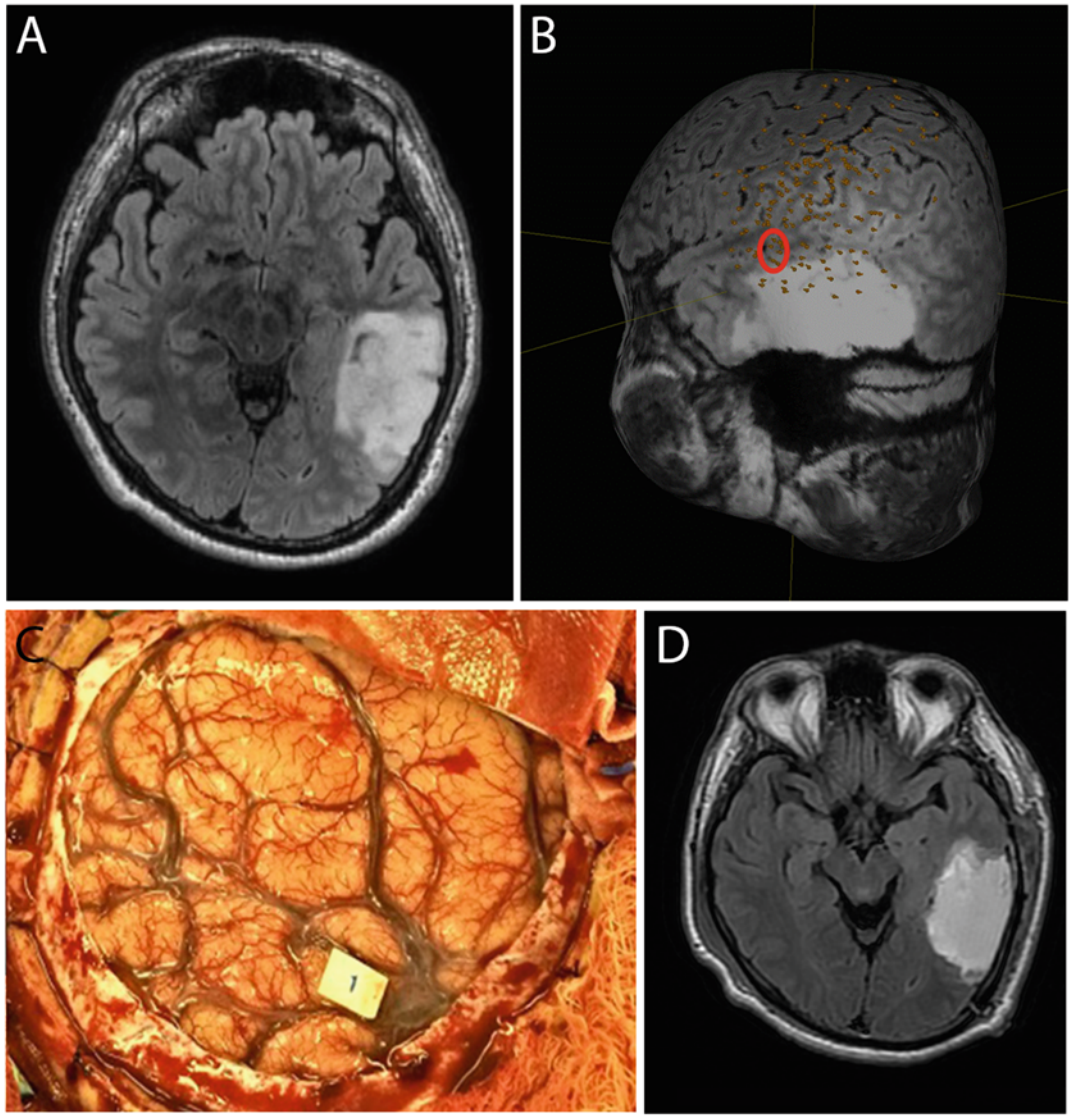


**Fig. 9** Case 3, Speech mapping to guide task selection and surgical planning. (**a**) MRI of the left temporal infiltrating lesion; (**b**) nTMS speech map with speech arrest hotspot (*red*); (**c**) intraoperative speech map with 1 representing the speech arrest locus; (**d**) postoperative MRI showing total resection

direct comparison to baseline that an error can be picked up. Louimis and colleagues found, in a series of four patients, that results were more accurate and reproducible using this system [31].

Equally important to identifying the speech errors is tabulation of their location. Once the TMS sites with associated errors have been identified, those sites must be recorded and shared, both for the patient's own surgery and for future publication of results. The easiest method for transferring TMS speech maps to the operating room is by exporting the patient's map as a DICOM stack. Most navigated TMS systems allow for native exporting of the results to a DICOM stack, and this facility should be utilized where possible.

The usage of TMS motor and speech maps for research purposes poses more of a challenge.

To be of use in most research applications, each patient's map must be standardized, and the results tabulated into an aggregated database. In this fashion, the results of many patients, often with multiple modalities of imaging, may be compared against each other. There are many methods for achieving anatomical standardization, and a detailed discussion of these is beyond the scope of this chapter. One of the most common methods uses the toolbox Statistical Parametric Mapping 8 (SPM8) for MATLAB. SPM8 can standardize the brain to the Montreal Neurological Institute atlas template. In cases where tumor growth or per-tumoral edema distorts the brain anatomy, it may be necessary to place reference points manually on identifiable anatomic structures such as the Sylvian fissure, inferior frontal sulcus, superior temporal sulcus, and central sulcus to assist the normalization procedure.

Once normalized, the maps may be superimposed on any standardized cortical atlas; a freely available and highly featured such atlas is Freesurfer (Fig. 10). The Freesurfer standardized brain, nicknamed "Bert," can be modified to display standard cortical regions, thus easily representing the anatomic location of points on the map. Another reference system, commonly used by neurosurgeons, is the standard 1 $cm^2$ grid superimposed on the standardized lateral view of the cortex (Fig. 10). While this method of representation lacks any anatomic reference, it offers a categorization system of higher granularity. For example, while several points might fall on the MNI superior temporal gyrus and be lumped together, the grid system divides the same area into more than 12 individual boxes. Each of these representation systems has its advantages and disadvantages. Once standardized, it is a trivial step to represent each map using either one of these systems.

## Safety

### Single Pulse TMS

Single pulse TMS is associated with minimal adverse effects according to the NIH Consensus Conference and subsequent safety guidelines [32, 33]. Seizure has been reported in two cases [34, 35] in the literature, both of which occurred in the setting of pro-epileptogenic medications. Given the widespread application of single pulse TMS in clinical and research investigations, the total number of patients who have received single pulse TMS likely numbers in the tens of thousands. Care must be taken to appropriately screen candidates for pro-epileptogenic medications and a history of poorly controlled seizure; if attention is paid to excluding such patients, the risks associated with single pulse TMS appear to be minimal (see below, Inclusion and Exclusion Criteria).

### Repetitive TMS

In the report of the NIH Consensus Conference [32], repetitive TMS (rTMS) was recognized to be associated with potentially more frequent (although still rare) adverse effects than single-pulse TMS. The frequency of adverse effects was noted to increase in parallel with the frequency (Hz) and intensity (% of motor threshold) of the rTMS trains used. The workshop issued safety guidelines where 10 Hz rTMS was considered safe for use in the nonmedical setting. These guidelines have been reassessed and updated with no change to the safety recommendations [33]. Protocols using 10 Hz stimulation are commonly in use for treatment of depression in the nonmedical environment, and rTMS devices are FDA-approved for rTMS-based mapping of speech and language. Furthermore, there is good evidence that no deleterious cognitive effects result from the standard rTMS speech mapping protocol [36]. There are also potential risks of microvascular changes, seizures, and hearing loss, as described below.

## Tolerability

Optimizing subject comfort is of great importance to make nTMS a viable modality for motor and language mapping. Single pulse TMS for motor mapping is well tolerated in the vast majority of patients. With rTMS protocols for speech mapping, however, the inherent issue is that the majority of language sites fall in the inferior frontal

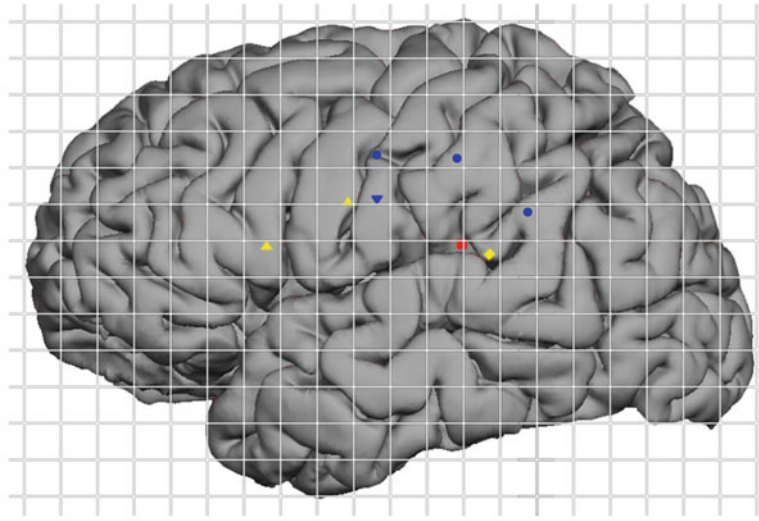

**Fig. 10** A completed speech map superimposed on a template brain ("Bert," from Freesurfer). Different types of speech errors may be represented with unique markers to allow for visual representation of a complete speech mapping session. In this case, the red circle represents a site of speech arrest, the blue circles represent anomia, and the yellow triangles represent hesitation. Note the parcellation both based on anatomic gyrus and a grid with 1 $cm^2$ raster

and temporal regions, underneath the temporalis muscle and facial nerve. In targeting these regions, the magnetic pulse must travel through the muscle fibers; in so doing it triggers a brief but powerful spasm of the temporalis muscle. It can also depolarize the facial nerve, resulting in similar contractions of the orbicularis oculus muscle. Thus, in an rTMS train of ten pulses at 5 Hz, the subject can experience a jaw-rattling sensation, the description of which ranges from "uncomfortable" to "painful." One may mitigate this effect by maintaining the dipole of our induced field in perpendicularity to the temporalis muscle fibers. Nevertheless, half of subjects required some reduction in the stimulation intensity.

Not only is the jaw contraction unpleasant for the subject, but it can also confound the examiner's ability to distinguish true speech errors from subject withdrawal. Indeed, this side effect is the reason why we chose not to use dysarthria as a specific type of speech disturbance; it was often impossible to differentiate between true dysarthria from cortical disruption and "secondary" dysarthria from temporalis interference. Thus, when a questionable site was encountered, it is important to repeat stimulation; eventually, with a few repetitions, the vast majority of sites will resolve themselves as speech arrest or as temporalis interference.

## Limitations

While navigated TMS mapping is a promising new modality, there are several limitations that bear mentioning. The first of these relate to the precision of the navigation itself. The tolerance of registration on most modern nTMS systems is estimated at 2–3 mm; given that the guidance system is not frame-based it is possible that the actual error is higher. Care must therefore be taken to ensure that preoperative maps match up with anatomical landmarks in the operating room: gyri and sulci, for example, and blood vessels can be used to ensure an accurate co-registration between the preoperative and the intraoperative findings.

Single pulse TMS for motor mapping, as described above, has been shown to be highly accurate. Limitations with this modality are similar to that of intraoperative cortical stimulation:

namely, that cortical and subcortical lesions can interfere with the cortico-spinal tract, making MEPs difficult or impossible to obtain. In the majority of these cases, patients will demonstrate signs of clinical weakness as well. This limitation can in fact be of great use; if preoperative mapping yields a difficult or unobtainable map, intraoperative cortical stimulation will likely encounter the same difficulty. Additionally, if motor maps of inferior motor cortex are required, patients may complain of discomfort from associated temporalis contractions. In general, this discomfort is less than with rTMS because of the differences in protocol.

An inherent limitation in the specificity of nTMS for speech mapping is transsynaptic excitation of downstream (and, possibly, upstream) neuronal units. Neurophysiological and neuroimaging studies have shown that repetitive TMS of a given brain region induces distributed activation of neural circuitry via transsynaptic spread, which follows established functional networks [37–39]. Thus, behavioral effects may be a result of activation not in the target region but in a distant, functionally connected region. The "overcalling" seen in many nTMS validation studies is likely a result of this limitation. Nevertheless, it should be pointed out that the overall nTMS language map does reflect the distribution of DCS language sites in both of the published series to date [40–42]. Additionally, it seems to correlate with prior studies of un-navigated rTMS mapping of language sites.

Another inherent limitation to both motor and speech maps is the spread of the magnetic field itself. The figure-of-8 coil used in most modern systems generates a conical magnetic field. The field is therefore roughly circular at the cortical surface with a diameter of about 2 cm (and greatest intensity at the center with a sharp fall-off at the edges) and tapers toward its apex which occurs approximately 4.5 cm from the coil surface. As a result, the magnetic pulses might disrupt subcortical white matter tracts, while the overlying cortex is inappropriately identified as a site of motor function or language disruption.

Furthermore, a given neuron's orientation, volume, axonal and dendritic organization, and innate threshold affect the likelihood of a magnetic pulse generating an action potential [43]. Thus, nTMS positive sites are not "points"—that is a misnomer; it is more accurate to say that they are regions, and to be aware that closely approximated regions of positivity on the map may all be associated with a single eloquent cortical site.

Finally, the basic parameters of nTMS stimulation, particularly with regard to speech mapping, should be examined more systematically and thoroughly. It is possible that relatively small adjustments in the frequency or number of pulses could improve results. Similarly, the timing of the onset of the pulse train is potentially important. In one published series, the pulse train was initiated just before the presentation of the stimulus in an object naming task, largely because that is the protocol used for DCS [42]. It is possible, however, that initiating the pulse train with, or just after the stimulus might improve the specificity of nTMS mapping. These variations in task and parameter must be methodically explored in future studies of nTMS protocols.

## Conclusion

nTMS is a useful modality for generating motor and language maps noninvasively. It is thus of immediate interest in the clinical management of subjects with eloquent brain tumors; it also has wide-ranging implications in basic science and translational studies of cortical language representation and physiology.

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# Practical Application of Preoperative and Intraoperative Cortical Mapping in Surgery

Sepehr Sani, Carter S. Gerard, and Richard W. Byrne

**Core Messages and Summaries for the Clinician**

1. While anatomical and functional imaging are helpful in localizing the relationship of lesions to eloquent cortical regions, the high temporal and spatial resolution of cortical mapping during resection render this technique the gold standard for ensuring maximal extent of safe resection of intrinsic brain tumors and epileptogenic lesions.
2. The key to success of cortical stimulation mapping is its rigorous and consistent methodological application throughout the operation and in between operations.
3. Despite high temporal and spatial resolution, cortical stimulation mapping has limitations that may lead to a more limited resection.

## Introduction

While concrete knowledge of classical anatomic descriptions of cortical language and motor locations is mandatory for each neurosurgeon, in many cases it is not sufficient for localizing eloquent cortices. Even in the normal brain, language function localization can be highly variable [1–6]. Further distortion of eloquent cortex can occur due to nearby pathology including tumors, epileptogenic foci, or vascular lesions [7–9]. Although the uses of neuronavigation and functional neuroimaging have improved localization, these techniques only reveal areas that are involved in language or motor function, but not critical to it. While intraoperative cortical stimulation mapping was first described over 80 years ago [10], it remains the gold standard for in vivo identification of eloquent cortex allowing the neurosurgeon to maximize resection while minimizing risk to the patient [11–13].

## Indications

When evaluating patients for cortical stimulation, preoperative imaging is reviewed and the pathology can be classified into three groups: presumed eloquent location, near-eloquent location, and non-eloquent location. We define topographic regions of the brain with presumed

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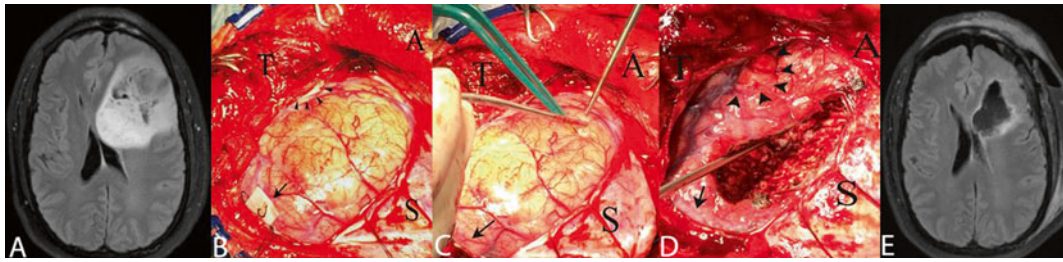


**Fig. 1** (**a**) Shows a well-defined left frontal lesion with involvement the dominant frontal operculum (language) and posterior frontal cortex (motor). (**b**) After mapping, language (*small arrows*) and motor (*large arrow*) areas are marked. (**c**) The resection is begun away from eloquent cortex and taken toward functional areas. (**d**) The final resection was taken within 5 mm of motor cortex and was stopped when the patient developed new subtle language deficits. (**e**) Postoperative MRI shows a small area of residual tumor involving white matter beneath Broca's area corresponding to the intraoperative finding. *A* anterior, *T* Temporal, *S* Superior, *Arrowheads*—Broca's expressive language area; *Arrow*—primary motor hand area

eloquence similar to previously published studies [14–20] and includes the primary sensorimotor cortex of the pre- and postcentral gyri, Werniecke's area (posterior portion of the superior temporal gyrus and the inferior parietal lobule), Broca's area (inferior posterior dominant frontal lobe), the calcarine visual cortex, the basal ganglia, internal capsule, thalamus, and the white matter paths of each. If any part of the lesion is found to infiltrate these regions (Fig. 1a) it is regarded as being located in presumed eloquent brain; if it approaches, but does not clearly involve these regions it is considered near eloquent and if it is situated in a separate anatomic location it is considered non-eloquent.

The classification of a lesion as located in eloquent, near-eloquent (E), or non-eloquent (NE) brain has ramifications for the operative strategy used. While lesions distant from eloquent anatomic structures do not require further preoperative functional investigation, it is prudent to consider preoperative functional imaging in lesions involving eloquent and near eloquent brain to help define the critical structures within the proposed operative field. Patients with pathology within the areas considered to be eloquent or near eloquent cortex may benefit from intraoperative cortical stimulation. If language mapping is required a patient must be without major dysphasia or confusion (Table 1), and have the ability to tolerate an awake craniotomy.

**Table 1** Relative contraindications for awake craniotomy

| |
|---|
| • Uncooperative patient |
| • Pediatrics—<10 years old |
| • Extreme obesity |
| • Airway concerns |
| • Extreme mass effect (consider staging) |
| • Significant dysphasia |

## Integrating with Functional Imaging

While the use of functional MRI allows the surgeon to better assess the relationship of a lesion to eloquent cortex, there are considerable limitation, especially when mapping language areas. Several recent studies have shown relatively reliable motor cortex mapping when compared to intraoperative stimulation [1, 21–23]. However, while fMRI has largely replaced Wada test for language lateralization, fMRI does not allow for precise localization of language which is reflected by the wide range of reported results in the literature. A review of five studies showed language mapping sensitivity from 59 to 100 % and specificity from 0 to 97 % when compared to intraoperative stimulation [2, 24]. Various authors have used newer noninvasive technologies for anatomic mapping such MEG and TMS [25–28]. Advanced preoperative functional imaging may serve two important purposes:

1. Neuroplasticity may induce migration of functional activity to other neighboring regions in tumor-infiltrated brain, which is why minimal or no neurological deficits are seen in some patient with slow growing low grade gliomas. Thus a better understanding of the true functional eloquence of the anatomically eloquent region under investigation is gained. This finding has redefined the term "eloquence" and indeed resulted in a greater number of tumors being resected that were previously considered as being part of anatomically eloquent cortex.
2. It enables the surgeon to understand the most dangerous regions of the tumor with regard to neurological morbidity and estimate the extent of safe resection prior to the operation [29–31]. This can aid discussions with the patient and multidisciplinary care-providers considering adjuvant and neoadjuvant treatment options.

## Preoperative Preparation

### The Patient

In preparation for surgery, a thorough understanding of the patient's baseline neurocognitive status is needed. We consider formal neuropsychological evaluation of patients with lesions involving or near the speech cortex. Often there are "silent" deficits present preoperatively that may go unnoticed [32]. Furthermore, identification of cognitive deficits may guide the resection approach and extent irrespective of pure motor or language findings in addition to monitoring postoperative recovery [33, 34].

The cornerstone of a successful cortical mapping assisted resection is patient cooperation in the awake setting. This is particularly important in language mapping. During the preoperative clinic visit, a detailed rehearsal and review of expectations during the awake portion of the operation can be very helpful in allaying patient anxiety and ensuring a cooperative patient (Table 2).

If language mapping is anticipated, preoperatively the patient is extensively counseled on the nature of intraoperative testing and undergoes a baseline language evaluation as follows: the patient is asked to count from 1 to 50, name objects seen on a computer generated slide show, read single words projected on a computer screen sequentially, repeat complex sentences, and write words and sentences on paper. Language deficits are classified as anomia when the patient is unable to name an object but able to repeat sentences and has fluent speech . Alexia is defined as retention of the ability to write spell, but with reading errors. Aphasia may be expressive, receptive, or mixed. Mild language errors such as paraphasic errors are not considered in resection planning. Patient should have 80 % language comprehension preoperatively in order to be considered for awake speech mapping.

**Table 2** Preoperative evaluation for awake craniotomy

| |
|---|
| • Medical evaluation |
| • ICP control—dexamethasone, mannitol |
| • Anticonvulsant |
| • Speech, motor evaluation |
| • Consider fMRI, DTI (cases where mapping may fail, subcortical cases) |
| • Image guidance MRI |
| • Anesthesia evaluation and discussion of expectation |

### Equipment

The following is a listing of the standard material and equipment used at the senior author's institution for cortical and subcortical brain mapping during resection operation:

(a) Image guidance for anatomical localization and verification.
(b) Electroencephalographic (EEG) monitoring of cortical surface by placement of an electrode strip or grid on the cortical surface to monitor after-discharges during stimulation.
(c) Appropriate EEG cables and strips or grids. 1–2 six contact strips are placed adjacent to the stimulated area.

(d) Cortical stimulation probe and box with power source verified (e.g. Ojemann Cortical Stimulator (Radionics Corp., Burlington, MA) or another commercially available probe).
(e) Counted and linked map tags for cortical identification during mapping.
(f) Cold saline or Ringer's solution for irrigation to abrogate an induced seizure during stimulation.
(g) Neuropsychological assessment team with naming cards for speech mapping.
(h) Dedicated and experienced neuroanesthesiologist.

## Anesthetic Considerations

For general anesthesia, a routine cranial neuroanesthesia protocol is followed. Pharmacological paralysis and high concentrations of inhalation anesthetic agents are avoided. In awake craniotomy cases, the following regimen is employed: Before incision, midazolam (2 mg; avoided if EEG to be recorded) and fentanyl (50–100 mcg) are administered. During surgery, either propofol (50–100 mcg/kg of body weight per minute; avoided if EEG to be recorded) or dexmedetomidine (0.2–0.7 mcg/kg/h) and remifentanil (0.05–0.2 mcg/kg/min) are given. Local anesthesia is given along the Mayfield pin sites as well as a circumferential scalp field block. A mixture of 0.5 % lidocaine, 0.25 % Marcaine (bupivacaine hydrochloride), and epinephrine (1/200,000) are used. Once the craniotomy is performed, intradural injections along either side of the middle meningeal artery are given in cases involving the middle fossa. Anesthetic agents are discontinued at this time until mapping is completed. Painful portions of the operation, such as early portions of the exposure and dural opening are managed by sedation, patient reassurance, and transient increase in propofol infusion rate. In cases that require additional sedation, supplementary boluses of propofol (0.5 mg/kg) are given and the infusion rate may be increased to 125 mcg/kg/min. Nausea or vomiting can be controlled with intravenous droperidol (1.2–2.5 mg) or metoclopramide (5–10 mg). The patient is asked to hyperventilate before dural opening. Once mapping is complete, sedatives are restarted. Intraoperative seizures due to cortical stimulation have been reported in up to 24 % of cases [35, 36]. Epilepsy patients are at particularly increased risk of intraoperative seizures due to decreased anticonvulsant levels. These seizures, whether focal or general, are usually transient and can be suppressed by application of local ice-cold Ringer's solution and a bolus of intravenous propofol (1 mg/kg) [37]. If airway control is of concern, tracheal intubation may be necessary.

## Preparations and Positioning

Patient comfort is paramount in cortical mapping operations, Often during longer operations in an awake patient, hip or neck pain can cause more discomfort than the actual surgery. Extra padding of all pressure points is essential. The neck position should look comfortable. Side positioners should be placed on both sides along with safety straps and the patient should be securely taped to the bed. Wrists should be secured with restraints. The drapes need to be elevated to allow direct visualization for seizures, airway concerns, testing such as object naming, and to avoid claustrophobia.

After positioning, monitors are attached, an indwelling urinary catheter is inserted, and oxygen delivery via nasal cannula is provided. Usually the semilateral position is preferred using a padded roll for back support. The semisitting position may be needed for some cases involving motor or sensory cortex. Medications such as mannitol and dexamethasone, as well as antibiotics are given prior to making the incision.

## Craniotomy Considerations

The draping is performed accordingly to allow the anesthesiologist and examiner the full view of the patients face as well as contralateral arm and

**Table 3** Intraoperative troubleshooting

| |
|---|
| • Apnea |
| • Coughing |
| • Swelling |
| • Low level after discharge |
| • Seizure |

leg for intraoperative monitoring of the patient's neurologic and respiratory status (Table 3). A localized craniotomy is performed using standard neurosurgical technique with the assistance of neuronavigation. A tailored craniotomy is preferred, including the underlying lesion or seizure focus, along with exposure of surrounding areas. The patient remains under heavy sedation until the craniotomy is complete. Ideally the patient awakens as the dura is opened. Pain upon awakening can be addressed with local anesthetic. Often pain is related to the temporalis muscle which is difficult to block. Releasing traction on the muscle can relieve pain.

In case of an occipital focus, a generous craniotomy is preferred with exposure of the occipital, occipital-parietal, and posterior temporal language areas for testing. After the durotomy, neuronavigation is used to identify the cortical margins of the lesion. Expected locations of the central sulcus and sylvian fissure are also identified. All margins and landmarks are labeled on the cortical surface.

## Stimulation Mapping

### Somatosensory Evoked Potential Recordings

Evoked potential recording can be used to localize the central sulcus [38, 39]. This is particularly helpful in cases in which underlying lesions have distorted normal anatomy. The technique is performed by placing an electrode strip perpendicular across the proposed location of central sulcus. A contralateral suprathreshold median nerve stimulation is made, an N20 wave is recorded over the hand somatosensory cortex, and a phase reversal is observed across the fissure. This process is performed several times as the strip is moved along the sensory-motor cortex. Recording is usually begun 3–4 cm above the sylvian fissure medial. Two or three recordings are usually needed to localize the central sulcus. The hand region is the most readily identifiable area and is generally localized to 4–6 cm above the sylvian fissure. Once identified, the sulcus is labeled accordingly and the strip is removed. Continuous SSEP or motor evoked response can be continued through the operation. Evoked potential recording can be performed in the awake patient or under general anesthesia.

### Electrocorticography

In patients with intractable epilepsy, electrocorticography may be used in order to identify the abnormal interictal spikes. It may be helpful to have a neurophysiologist or epileptologist with neurophysiology expertise in the operating room for recording interpretation. An electrode grid is laid over the cortical area of interest and several minutes of electrocortical activity are recorded. Areas with abnormal interictal spikes are marked [18]. Surgical resection of these areas depends on their functional importance based on motor or language mapping. Electrocorticography is also employed in monitoring of after-discharges during sensorimotor or language mapping as described in the succeeding section.

### Sensorimortor Stimulation

Cortical mapping begins with a function check by stimulating the temporalis muscle, if exposed, and confirming visual contraction. If no contraction is seen up to 10 mA of stimulation, a systemic check is done (cable connections, paralytic levels, stimulation parameters, battery, etc.) It is important to remember that the bipolar stimulators are designed to be used in only five cases and are then replaced in order to avoid potential disconnection. The localization of pre- and postcentral gyri are confirmed by direct cortical stimulation after identification with evoked potentials. Detailed somatotopic mapping is also possible with cortical stimulation. This technique is used when the lesion or seizure focus is close to or involves sensorimotor locations. Stimulation is performed using an Ojemann Cortical

Stimulator (Radionics Corp., Burlington, MA). Primary sensory cortex is mapped with the patient awake. Stimulation parameters of 1–2 mA initially, with a frequency of 60 Hz and a pulse duration of 1 ms are used. Cortical patches of 1 cc are stimulated sequentially with rest periods between stimulations. The probe is applied to the cortex for 3 s duration and the patient is asked to report the onset and location of any perceived paresthesias. Stimulation starts in the suprasylvian portion of the sensory gyrus and advanced superiorly, thereby sequentially identifying the tongue, lip, and hand sensory areas. If the operation is being performed under general anesthesia, only motor mapping is possible [18]. Stimulation parameters remain the same, but usually a higher threshold of initial stimulation is used (3–6 mA). Stimulation intensity increases until contralateral movement is observed by the anesthesiologist or the examiner. Amplitudes greater than 10 mA are not recommended in motor cortex stimulation. Stimulating different areas in sequence rather that immediately adjacent areas, and using pauses of at least 10 s between stimulations may reduce the risk of intraoperative seizures. Congruent with sensory mapping, stimulation is initiated in the suprasylvian region in 1 cm patches and moves superiorly along the gyrus until somatotopic mapping of tongue, lips, thumb, hand, and arm are obtained sequentially. If mapping of motor leg region is needed, stimulation is given through a strip electrode that is inserted in the interhemispheric fissure. Seizures, focal and general, can occur during motor mapping and have been reported in up to 24 % of cases [35, 36]. They are usually transient. Application of ice cold Ringer's solution for 5–10 s is often effective at breaking the seizures. A bolus of intravenous propofol (1 mg/kg) [37] can also be given as adjunct to stop the seizure. Areas stimulated are labeled by the linked map tags that are connected to the surgical drapes. A picture may be taken at the end of mapping and the tags are removed.

## Language Mapping

Language mapping is done in the awake patient when the lesion involves the dominant perisylvian frontotemporal region. Preoperative language evaluation and counseling has been described earlier in this chapter. Intraoperative language mapping is not useful in patients with significant language deficits. Intraoperatively, Broca's area is identified by stimulation induced speech arrest. Mapping is initiated at stimulation parameters of 1.5–3 mA, frequency of 50–60 Hz, and pulse duration of 1 ms. Once identified, cortical patches of 5 mm are stimulated sequentially with rest periods between stimulations. The probe is applied to the cortex for 1–3 s and the patient is monitored. Each cortical patch is tested up to three times. Electrocorticography is monitored to determine the threshold for after-discharges. It is important to keep all stimulation below this threshold and meticulously monitor for after-discharges as they can produce false localizing results during mapping and may lead to a clinical seizure. For each site, the patient can be tested for counting errors, object naming errors, and word reading errors as they are presented on naming cards. A cortical area is considered positive for language function if the patient is unable to count, name objects, repeat words, or read words in two out of three stimulations [40]. Positive sites are labeled by sterile labels on the cortex (Fig. 1b) and marked using neuronavigation. It is also important to move to a different area of the cortex after completing stimulation in order to prevent summation and subsequent seizure activity. Usually no more than 25–30 sites are tested around the intended resection site to delineate the positive language areas. All positive language areas, vascular supplies, and white matter connections must be preserved during resection with a margin of 1 cm [41–44]. In anterior temporal resections of the dominant hemisphere, resections within 2 cm of a positive language area, particularly stimulation-induced anomia, will produce a mild but identifiable general language deficit observed on an aphasia battery administered 1 month after the operation [45].

If all tested areas are negative for language errors and the mapping team is confident in the equipment and technique (stimulating up to after-discharge), wider cortical exposure is not necessary and the resection can be carried out based on delineated margins of the lesion or

seizure focus. The cortical incision is made in a "silent" area first and resection is carried out (Fig. 1c). Subcortical stimulation may be performed to preserve essential white matter. This typically requires higher levels of stimulation. Once mapping is completed, additional anesthetic agent may be given for patient comfort. It may be difficult to distinguish the mechanism of speech arrest during stimulation of the inferior prefrontal cortex as this area is intimately involved in both language and motor function. Speech arrest can be attributed to a stimulus disturbance of language function or arrest of motor activity. Indeed a combined language and motor function in these cortical areas has been suggested [46, 47]. These areas, when encountered, should be marked as eloquent cortex and preserved, as their resection will lead to postoperative language deficits.

## Stimulation Pitfalls

Although identification of the eloquent areas of cortex by stimulation mapping is considered the gold standard, this technique is not without limitations. Indeed a positive cortical finding during stimulation may reflect retrograde activation of another area through network activity. Another issue is that an area that is found to be positive by stimulation may be redundantly represented (whether as a function of the original network or due to plasticity secondary to the underlying pathology) and hence amenable to resection.

Another issue worthy of mention is negative mapping. This technique has been reported as an alternative to positive mapping with the advantage of a more limited craniotomy, exposure, and operative time [19, 48–50]. This technique is of great value for the experienced practitioner. However, the caveat lies in the potential for false negative findings in less experienced centers. Technical issues, suboptimal patient cooperation, or insufficient levels of stimulation can skew negative mapping results and result in resection of potentially eloquent areas. Furthermore, in operations involving seizure foci or lesions (such as low grade glioma) that do not have visible anatomical borders, the extent of resection is defined by the borders of positive mapping, not negative mapping. In most cases, however, negative mapping is adequate for safe resection in and around eloquent centers, and remains a significant advance in clinical management.

## Subcortical Stimulation Mapping

Once resection continues past the cortical surface, it is possible and sometimes necessary to continue stimulation mapping. Subcortical stimulation mapping (SSM) refers to stimulating the descending (or ascending in case of primary sensory cortex) white matter network tracks that connect various cortical structures to each other to deep nuclei as well as stimulation of the basal ganglia or thalamic areas. The technique is the same as cortical mapping but stimulation parameters are generally higher than cortical mapping. The resection is carried out incrementally using anatomic landmarks and neuronavigation, with frequent confirmation by SSM before proceeding to the next area. It should be emphasized that subcortical white matter tracks are as eloquent as the cortical structures (Fig. 2). Preservation of theses essential tracks is especially challenging due to the poorly defined borders of subcortical anatomy and the tendency of adjacent pathology to distort the expected trajectory of the white matter.

## Surgical Endpoints

The goal of stimulation mapping is to allow the surgeon maximal extent of resection with preservation of neurological function. Upon completion of mapping, resection starts from the least eloquent area and proceed to the most eloquent area. In the awake patient, continued motor and speech assessment will alert the surgeon to any new deficits. These assessment should increase in frequency as needed as the operation proceeds toward mapped eloquent areas.

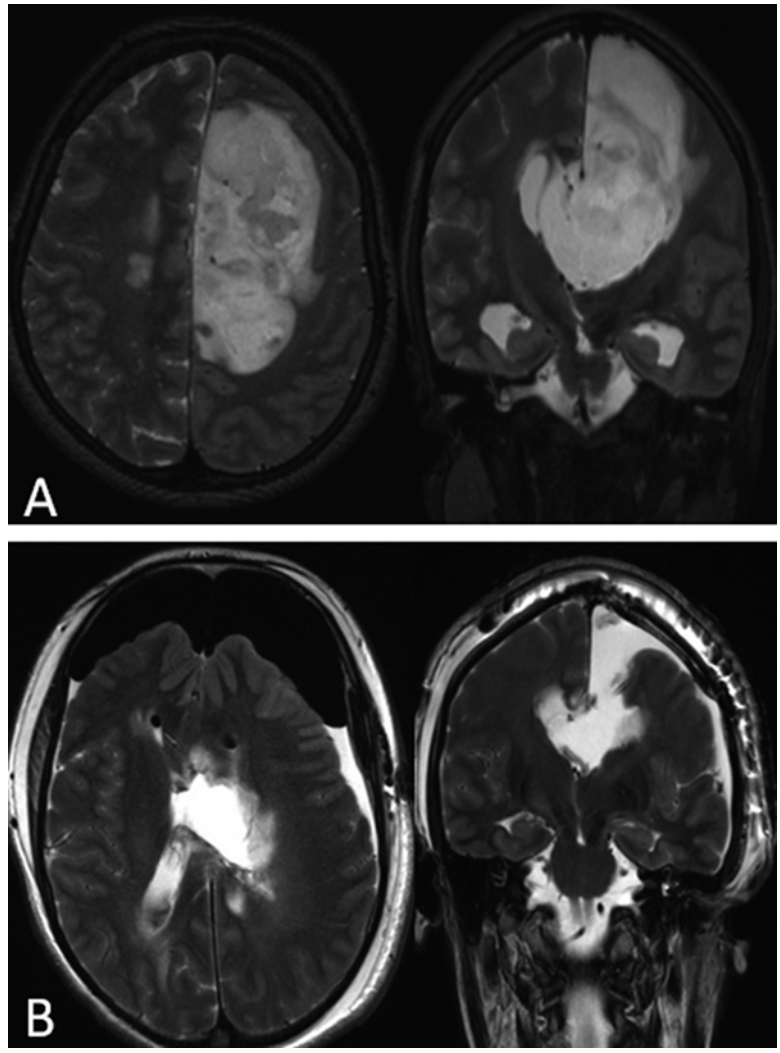


**Fig. 2** A 29-year-old female presented with progressive headaches, nausea, and right-sided weakness is found to have a large left frontal-parietal lesion. MRI reveals a lesion expanding F1 with extension into the lateral and third ventricle (**a**). Due to involvement of the supplemental motor area and the significant mass effect, the surgery was performed asleep with stimulation. After cortical mapping, resection began anteriorly and proceeded posteriorly. The resection was stopped when subcortical stimulation produced leg activity at 6 Ma. Pathology was consistent with diffuse astrocytoma, WHO grade II and postoperative imaging showed significant improvement in mass effect (**b**). The patient initially developed a supplementary motor syndrome that completely resolved 6 weeks postoperatively

Resection involving motor cortex or subcortical areas should stop at least 1 cm from identified eloquent areas [51]. Resection can be continued to the pre or post central sulcus if there are clearly identified and white matter is spared. Low grade gliomas often respect gyri. The tumor can expand gyri, pushing into presumed functional areas without infiltrating. They appear to occupy eloquent regions, but often only displace. They can then be identified by counting the gyri. It has been the senior author's experience that stopping the resection when the patient's motor examination is 3/5 or mild dysphasia will result is an intact patient at 6 weeks follow up unless there is a vascular injury or descending white matter has been interrupted. Alternatively for continuous motor mapping a six contact strip can be placed on the precentral gyrus for continuous motor stimulation mapping. Continuous, repeated assessment of an awake patient while operating in or near eloquent cortex remains the safest way to maximize resection and preserve function. When operating around language areas, resection should stop 1 cm from any identified speech area or if there is any change in language testing (Fig. 3).

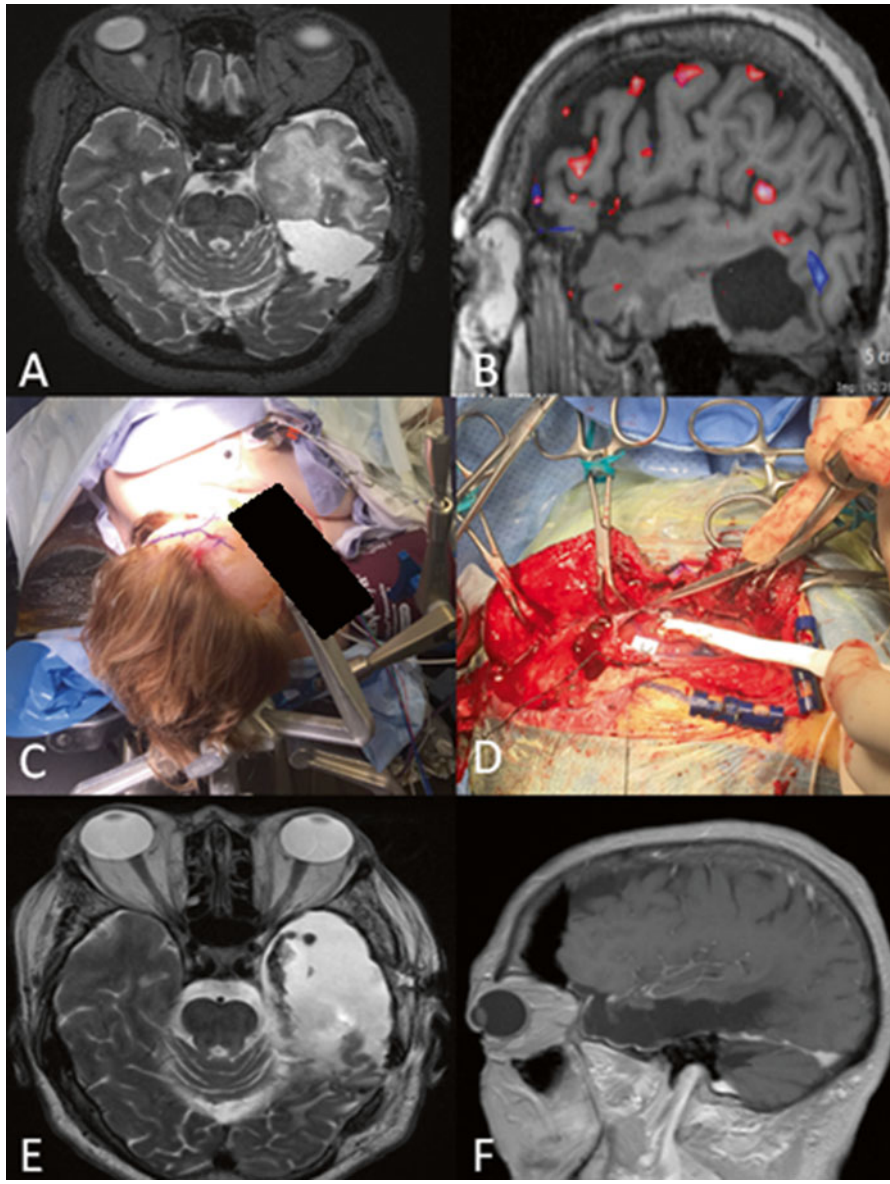


**Fig. 3** A 63-year-old female with a history of left temporal anaplastic oligodendroglioma with 1p/19q deletions s/p resection 10 years earlier presents for evaluation due to radiographic progression on serial imaging (**a**). Functional MRI showed bilateral speech with activity at the superior posterior border of the existing resection cavity (**b**). The patient was taken to the OR for awake craniotomy for speech mapping (**c**). Intraoperative speech mapping produced arrest during inferior parietal stimulation (**d**). The surgery was completed without development of deficits. Postoperative imaging showed a gross total resection of the tumor, including 8 cm of dominant temporal lobe (**e**, **f**)

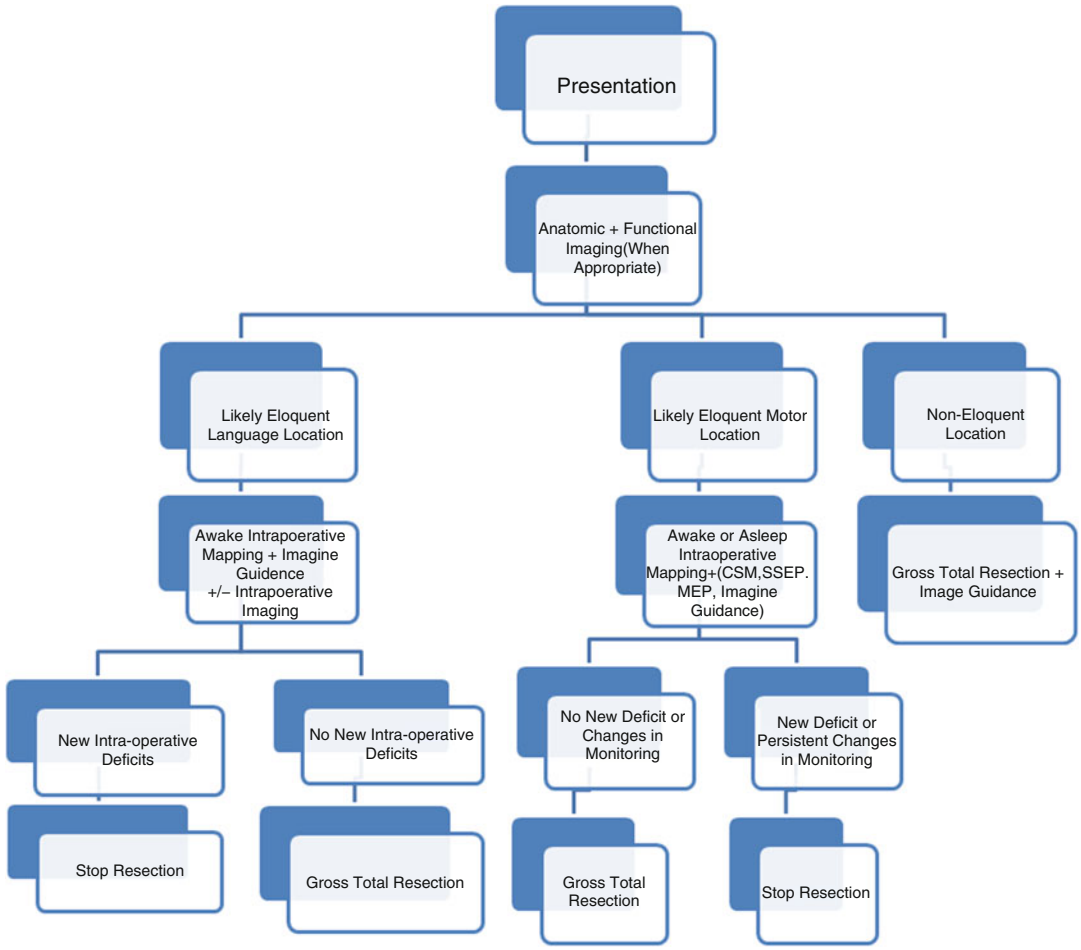


**Fig. 4** Shows the treatment paradigm for patients with focal intracranial lesions who require surgical intervention

## Summary Algorithm

Shown below (Fig. 4) is a summary of the algorithm used at the senior author's institution to aid in communicating the surgical paradigm for treatment starting with diagnosis of an intracranial lesion.

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# Epilepsy Surgery in Eloquent Cortex

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**Summary of Key Points**

- Surgical treatment of epilepsy involving the eloquent cortex is challenging due to potential postoperative neurological deficits.
- Potential benefits in seizure control after surgery must be weighed against new neurological deficits that can negatively affect the patient's quality of life.
- Commonly utilized surgical techniques include en-bloc resection, endopial resection (intervascular endopial gyral emptying), multiple subpial transections (MST), and NeuroPace.
- Arteries and veins supplying eloquent cortex must be preserved during resection to minimize neurological deficit related to vascular complications.
- Intraoperative or extraoperative cortical mapping is essential to delineate functional areas and outline borders of safe resection.
- A solid understanding of functional anatomy and meticulous surgical technique to preserve vasculature are essential to ensure success.
- Detailed and thorough preoperative discussion regarding expectations of surgical outcome and possible neurological deficit is essential.

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## Introduction

Surgical management of medically refractory epilepsy in eloquent areas of the brain is challenging because there is often a trade-off between extent of seizure focus resection and potential postoperative neurological deficits. Complete resection of the seizure focus in eloquent cortex offers the best postoperative seizure control, but this approach also carries the highest risks for new neurological deficits. Other approaches such as multiple subpial transection (MTS) and NeuroPace carry much less risk for significant postoperative deficits, but the seizure control rate is lower. The advantages and disadvantages of each approach must be carefully considered and discussed with the patients and their family, and

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the optimal surgical approach may be different for each patient depending on seizure frequency, severity, and existing neurological deficits. The goal of surgery should be to achieve maximal seizure control without causing unacceptable deficits in order to maximize the patient's quality of life postoperatively.

In this chapter, we will focus on the surgical treatment of epilepsy involving the rolandic and perirolandic regions. The various surgical techniques, the surgical outcome, and complication avoidance are discussed. Other important aspects such as seizure focus localization, preoperative functional mapping, and intraoperative cortical mapping are discussed in detail in other chapters of this book and thus will not be discussed extensively in this chapter.

## Historical Perspective

Surgical treatment of epilepsy began with the birth of modern neurosurgery in the nineteenth century [1]. The electrical theory of epilepsy was first presented by Robert Bentley Todd, an Irish physician who was also credited with "Todd's paralysis," at a Lumleian lecture he presented to the Royal College of Physicians in 1849 [2]. John Hughlings Jackson, known for "Jacksonian seizures," suggested using the term "epilepsy" to describe sudden and temporary loss of neural function in 1866 [2]. Based on Jackson's clinical observations, Eduard Hitzig and Gustav Fritsch performed experiments on dogs in 1870, in which they demonstrated that electrical stimulation of specific parts of the cerebral cortex elicited muscle contractions in the contralateral limbs; these findings were published in their landmark paper entitled 'On the Electrical Excitability of the Cerebrum' [3], which provided the first experimental evidence of the electrical theory of epilepsy. Jackson then formally defined "epilepsy" as "occasional, sudden, excessive, rapid, and local discharges of gray matter" in 1873 [2, 4].

Utilizing this localization theory, William Macewen successfully diagnosed a left frontal lobe lesion in a boy who presented with right side motor seizures in 1876. Unfortunately the patient did not undergo surgery and subsequently died; a subsequent autopsy revealed that there was indeed a left frontal abscess "about the size of a pigeon's egg." In 1879, Macewen successfully performed the first cranial surgery where the "motor phenomena were the sole guides to the cerebral lesion" in a boy with posttraumatic seizure and subdural hematoma [5]. The most well-recognized early epilepsy surgery, however, was done by Sir Victor Horsley in 1886 when he successfully treated a patient with focal seizures from cortical scar secondary to a depressed skull fracture at the National Hospital for Paralysed and Epileptic, Queen Square, London, England [6]. Following Horsley's success, a host of important epilepsy surgeons emerged including Fedor Krause, Otfrid Foerster, Theodor Kocher, Walter Dandy, Harvey Cushing, Wilder Penfield, Percival Bailey, and many others who contributed greatly to the field of epilepsy surgery [1].

Today, advanced medical technology and improved surgical techniques make epilepsy surgery much safer than 100 years ago. However, accurate localization of seizure focus and solid understanding of functional anatomy remain the key components to a successful surgery, especially when eloquent cortex is involved. Successfully surgical outcome requires multidisciplinary collaboration among the epileptologist, neurophysiologist, neuropsychologist, anesthesiologist, and the epilepsy surgeon.

## Anatomical Considerations

The rolandic and its adjacent regions contain highly eloquent areas of the brain responsible for sensorimotor and speech functions. Inadvertent injuries to structures in these areas can have devastating impact on the patient's quality of life. Therefore, a solid understanding of the anatomy in this region is a must for a successful surgical outcome. Detailed cortical anatomy of the eloquent cortex is discussed in a separate chapter. A brief overview of the pertinent cortical, vascular, and functional anatomy is presented in this section.

The central sulcus and the sylvian fissure are the most consistent and apparent anatomical

structures in the lateral convexity of the brain. The central sulcus separates the precentral gyrus from the postcentral gyrus. These two gyri are often connected inferiorly by a gyral bridge at the sylvian fissure referred to as "inferior pli de passage" or "rolandic operculum." The motor and sensory cortices are organized in such a way that their functional homunculi are reciprocal: feet and leg are represented in the medial aspect in the midline, arm and hand areas are situated more laterally, and the head/neck/tongue is represented in the most lateral and inferior region.

One key concept to consider is that the shape of the central sulcus is usually sinusoidal with three bends; the middle bend, with its convexity facing posteriorly, represents the hand area in the corresponding portions of the motor and sensory cortex. Because of these bends, the primary motor cortex forms as the well recognized "omega sign" on MRI; the middle bend, which its convexity facing posteriorly, represent hand motor area. This is important because below hand motor, facial movement is innervated bilaterally and resection of this area usually does not cause a significant deficit other than drooping of the contralateral corner of the mouth. The primary sensory cortex lies just posterior to the central sulcus and consists of Brodmann's areas 3, 1, and 2 in anterior to posterior direction. Injury to the primary sensory cortex will result in decreased two-point discrimination and loss of proprioception in the corresponding areas of the body. Impairment of the hand and feet areas can impair dexterity and ambulation, where injuries to face and tongue areas may have little clinically significant consequence.

The most important vascular structures in the rolandic region include the precentral sulcus artery, the central artery, vein of Trolard, and variable central veins, which are responsible for the arterial supply and veinous drainage of the rolandic cortex. Other MCA cortical branches and smaller cortical veins can also be important vascular supplies for this region and damage to these vessels can cause loss of motor and sensory functions of the vascular territory. Therefore, all central area arteries and veins of significant size must be preserved unless en-bloc resection is the goal and loss of function is expected postoperatively.

Cortical stimulation has enhanced our understanding of language dominance and confirmed the location of Broca's and Wernicke's area in addition to other sites vital to language [7, 8]. Classically, the left hemisphere is dominant in 90–95 % of the population, with the remaining 5–10 % has bilateral or right sided language function [9, 10]. Multiple factors have been found to contribute to atypical language dominance including left handedness and injury in early childhood to the left hemisphere [11].

While fMRI has largely replaced Wada test for language lateralization, fMRI does not allow for precise localization of language which is reflected by the wide range of reported results in the literature. A review of five studies showed language mapping sensitivity from 59 to 100 % and specificity from 0 to 97 % when compared to intraoperative stimulation [12, 13]. Various authors have used newer noninvasive technologies for language mapping such MEG, TMS, and Diffusion-weighted imaging [14–16]. While preoperative language mapping is vital for patients who cannot tolerate an awake craniotomy i.e. pediatric cases [17–19], awake craniotomy with cortical mapping is ideal for identifying language areas and enhancing safe resections [20, 21].

## Seizure Focus Localization and Preoperative Planning

Accurate seizure focus localization is essential for favorable surgical outcome in epilepsy surgery, but it is even more important when eloquent cortex is involved given the potential neurological function at stake. Many seizure focus localization techniques are available including scalp EEG, invasive intracranial recording with subdural grids and depth electrodes, MRI, PET, SISCOM, MR spec. Functional MRI can be useful for noninvasive preoperative brain mapping. Functional MRI can be reliable in localizing sensorimotor cortex, but it has poor positive predictive value in localizing essential speech function and thus cannot yet be substituted for intraopera-

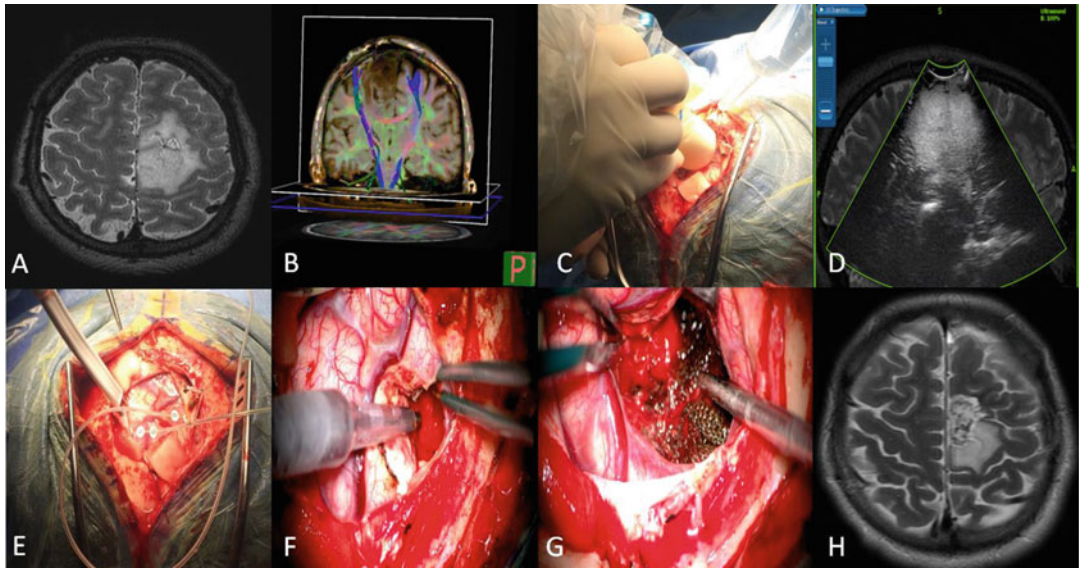


**Fig. 1** A 25-year-old male s/p open biopsy of a left frontal-parietal glioma (Grade III) is referred for evaluation due to epilepsy partialis continua (**a**). Further imaging confirms involvement and some posterior displacement of the corticospinal tracts (**b**). The patient is taken to the operating room for awake craniotomy due to involvement of eloquent cortex. After the craniotomy is performed, ultrasound merged with MRI is used to further delineate the lesion (**c** and **d**). The area is stimulated and the hand motor area is noted (**e**). The resection is started anteriorly, away from eloquent cortex, and proceeds posteriorly (**f**). The resection is stopped when subcortical motor stimulation was positive at 4 mA at the posterior edge of the cavity (**g**). Postoperative imaging shows resection to the limit of the precentral gyrus (**h**)

tive or extraoperative cortical mapping. All of these preoperative evaluation modalities are discussed in detail in other chapter and are not repeated here.

## Surgical Techniques

Cortical mapping is essential to accurately identify functional areas in eloquent cortex to guide extent of resection. Specific techniques of cortical mapping are discussed elsewhere in this text. One key point for cortical mapping is that resections up to 1 cm from eloquent cortex are usually well tolerated without causing permanent morbidity [20]. However, a recent study investigating a series of low grade glioma patients have suggested resections in the eloquent cortex without leaving a margin may cause a higher incidence of transient deficits, but not permanent deficits [22]. Therefore, it may be reasonable in some cases to trade transient deficits for better seizure focus resection and long-term seizure control. In fact, resection of the gyri adjacent to the pre or postcentral gyrus may be performed safely as long as the pial border and vasculature are preserved (Fig. 1). Occasionally, in patients with debilitating seizures with non-lesional foci in eloquent cortex, such as epilepsia partialis continua, who fail other interventions may ultimately benefit from resection despite new and permanent deficits.

In patients with frequent and severe epilepsy, who may already have signs of atrophy and existing severe sensorimotor deficit, en-bloc resection of the seizure focus in eloquent cortex may be considered to gain maximal seizure control. En bloc resection consists of complete removal of the cortical tissue along with the arterial supply and venous drainage.

Endopial resection consists of selectively removing the seizure focus while preserving the pia, arachnoid, the underlying white matter, and the vascular supply to minimize postoperative deficits from white matter or vascular injuries. To

perform endopial resections, the area of resection should be clearly outlined after ECoG recording and cortical mapping. The pia of the cortex of intended resection is cauterized with a bipolar and cut with a microscissor. The tissue aspirator is then used to remove the brain tissue under the pia. The aspirator should be set on high selectivity and low suction to prevent inadvertent breach of pia and injury to blood vessels. Multiple pia windows can be created in between the cortical vessels to achieve complete resection of the identified seizure focus while preserving the bypassing blood vessels. The endopial resection technique is essential to minimize collateral damage that can cause additional deficits from vascular injuries.

Multiple studies have shown epilepsy surgery to produce positive outcomes with a relatively low risk to the patient [23–30]. While the complication rate is intuitively higher when working in and around eloquent cortex, evaluation of the literature will prove difficult due to the heterogeneity of cases and timing of postoperative assessment. When there is a lesion in or around eloquent cortex negative mapping and resection can ensure limited permanent deficits [21, 31, 32]. However, when the lesion arises from eloquent cortex, permanent deficits may be expected. Delev et al. reported a 28 % permanent deficit rate for foci resections involving the roldic cortex. [33].

## Multiple Subpial Transections

Multiple subpial transection is a surgical technique used to disrupt synchrony of seizure foci by disputing horizontal oriented fibers, while minimizing functional disruption of afferent and efferent fibers, which run vertical [34–36]. At the same time, seizures in part spread horizontally through the gray matter. The goal of this surgery is to inhibit synchronization and spread of the seizure focus while minimizing damage to the cortex. The first large series of multiple subpial transection was reported 1989 [37], the technique can be used in eloquent cortex when permanent deficits are not acceptable. MST may be used to treat patients with epileptogenic lesions of the speech, motor, or primary sensory cortex.

MST may be performed under general anesthesia following extraoperative subdural grid mapping or awake if intraoperative language mapping is planned. A standard craniotomy is performed to ensure adequate exposure for functional mapping and ECoG. If subsequent testing reveals the seizure focus to reside in eloquent and noneloquent cortex, surgical resection may be performed in the noneloquent cortex to within 1 cm of language cortex and to the border of sensory and motor cortex [38, 39]. White matter pathways and vascular supplies are preserved. If repeat ECoG does not show significant resolution of the interictal activity or if the primary residual focus lies within eloquent cortex, MST may be performed at the apex of the implicated gyri. Transections are made in the direction perpendicular to the long axis of the gyrus. If resolution of the seizure focus is seen with ECoG, no additional transection is performed.

A pliable wire that is bent into a 4-mm blunt hook is used to carry out the transection. The hook of the subpial transector (Whisler-Morrell Subpial Transector, Redman Neurotechnologists, Lake Zurich, IL) measures 4 mm, the average depth of gray matter in the neocortex [36]. Prior to transection, the gyral and microgyral patterns are closely inspected. The surrounding and bypassing vessels are defined. Once ECoG has been performed, the transections are started at the apex of the targeted gyrus in order to avoid interference from subsequent subarachnoid bleeding. The transection is begun by opening a hole in the pia at the edge of a sulcus with a 20-gauge needle. The transector enters the gray matter through this opening, and then is advanced in a straight line across the vertex of the gyrus in a direction perpendicular to the long axis of the gyrus. The hook is then withdrawn along the same path, with the tip of the hook visible just below the pia [40–42]. The next transection line is made parallel to and 5 mm from the first. Great care must be taken to note the course of the major blood vessels, particularly around the sylvian and interhemispheric fissures. When transections must be performed in the depths of a sulcus or fissure, the hook is inserted upside down, with the tip pointed away from the pial surface. This lessens the likelihood of damag-

ing a vessel in the sulcus or fissure. The obtuse angle of the hook also helps lessen the likelihood of injury to vessels. In cases of perisylvian-onset epilepsy, it is often useful to open the sylvian fissure to record from the depths of the fissure and transect under direct vision. In some cases, transection at 5-mm intervals is not possible because of microgyral patterns or a large confluence of vessels that may cover the area to be transected.

During the early postoperative period, most patients who undergo MST in eloquent cortex have subtle, transient deficits corresponding to the area transected. These deficits are most evident in the first week after surgery. As the edema and microhemorrhage resolve, most patients return to their baseline function within 6 weeks [43].

The results of MST in the literature must be separated into cases of MST alone and MST with concomitant resection. Spencer et al. performed a meta-analysis on 212 patients who underwent MST at six epilepsy centers [44]. In cases of MST alone without resection, they reported rates of excellent outcome with regard to seizure control of 71 % for generalized epilepsy, 62 % for complex partial epilepsy, and 63 % for simple partial seizures. However, it is more common to use a combination of MST and resection as seen in the series of Morrell and Whisler [37], as it is rare for a seizure focus to lie entirely in eloquent cortex. A total of 82 % of patients in this category were seizure free or had a significant reduction in their seizures (Engel's class I to III) Although the majority of patients exhibited worthwhile improvement, the initial report by Morrell of 52 % being free of seizures was not sustained later in the series [37]. The meta-analysis reported by Spencer and coauthors showed similar results for patients who underwent resection with MST. The patients had marked seizure reduction (>95 % reduction) reported in 87 % of patients with generalized seizures, 68 % of patients with complex partial seizures, and 68 % of patients with simple partial epilepsy [44]. However, long-term results are not as favorable in other series, with 18.5 % seizure recurrence rate with 5 years of follow-up [45, 46]. This phenomenon has also been described in patients who have undergone resective epilepsy surgery.

## Responsive Neurostimulation System

When a non-lesional seizure focus is located entirely in eloquent cortex (Fig. 2), MST or a stimulation procedure, such as VNS or Responsive Neurostimulation (RNS), are the only surgical options [47–49]. Currently, the only commercially available Responsive Neurostimulation system is NeuroPace (NeuroPace, Mountain View, CA, USA). NeuroPace is a closed looped system that is designed to detect and interrupted electrical activity at the seizure focus at onset. The NeuroPace system was approved by the FDA as an adjunctive therapy for treatment of seizures in adult patients with partial onset seizures, who have no more than 2 epileptogenic foci, are refractory to ≥2 antiepileptic medications, and currently have frequent and disabling seizures [50]. The system includes one or two either depth and/or cortical electrodes/strips that can be used for recording and stimulation, along with a neurostimulator that is implanted in the skull. The NeuroPace system is unique when compared to other stimulation devices, such as VNS or DBS, in direct contact with the site of seizure onset. No cortical resection is performed, thus eliminating neurological deficit associated resection in the eloquent areas. The use of RNS also enables long-term recording, improved foci localization, and may result in successful resection [48].

Morrell et al. [51] published a large multicenter, randomized, double blinded, controlled trial of responsive stimulation system (NeuroPace) in patients with refractory partial-onset seizures. The trial included 191 patients treated with either subdural or depth electrodes at one or two seizure foci. During the randomized blinded stimulation period of 3 months, the seizure reduction in patients receiving stimulation was (37.9 %) compared to the seizure reduction (17.3 %) seen in patients receiving sham stimulation [51]. As in patients treated with vagal nerve stimulation, seizure control improved over time with an ultimate seizure reduction of 53 % at 2 years [52]. Long-term follow-up also revealed a comparable serious adverse effect rate compared

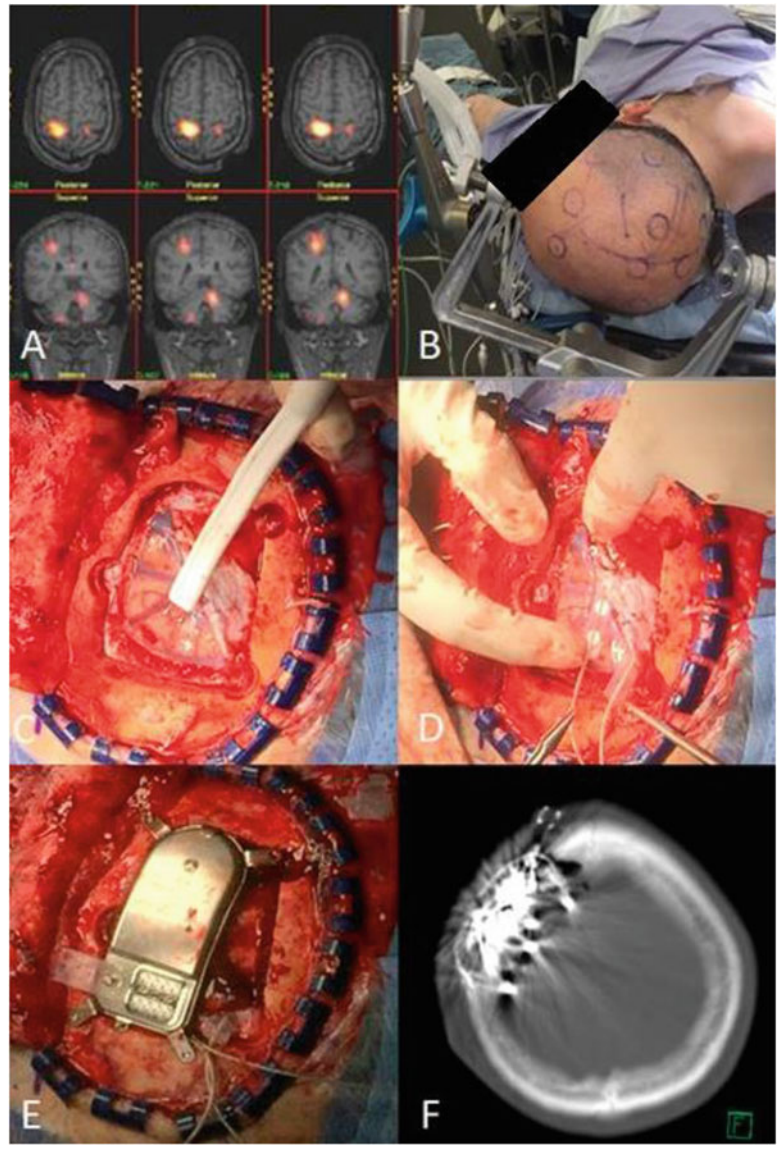


**Fig. 2** A 48-year-old male with refractory partial motor seizures involving the left arm and leg with negative MRI is found to have hyperperfusion of the right precentral gyrus on SISCOM (**a**). The patient was consented and taken to the operating room for placement of a responsive stimulation system. After intubation, the patient is registered for neuronavigation and positioned for a right paracentral frontal-parietal craniotomy (**b**). At 4ma of stimulation hand motor activity is noted (**c**). Two four contact subdural electrode are introduced over the target area (**d**). Once the leads are secured, the generator is placed over the craniotomy defect (**e**). Postoperative CT is performed with a level gantry to verify lead position (**f**)

to patients undergoing DBS or respective epilepsy surgery. The most common complications were infection, with a 9.4 % infection rate over 5 years [52].

Multiple series have reported responsive stimulation to be a safe and effective therapy for a select group of epilepsy patients [50, 51, 53, 54]. This is an especially attractive option for lesions within eloquent cortex. In addition to seizure reduction, RNS systems allow for long-term recording of seizure activity that may result in curative resection [48].

## Conclusion

Surgical management of medically refractory epilepsy in eloquent cortex continues to be a challenge for even the most experienced surgeon. While complete resection of the seizure focus

may offer the best postoperative seizure control, permanent deficits may result in a worse quality of life despite seizure freedom. It is important for the surgeon to understand the relevant anatomy, preoperative evaluations, and surgical options in order to offer each patient seizure reduction or cure with minimal morbidity to vital functions.

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# White Matter Tracts

Timothy D. Miller Jr., Jordan M. Komisarow, and Allan H. Friedman

## Introduction

While neurosurgeons have paid a great deal of attention to the anatomy of the cortex, less attention has been paid to the anatomy of the cerebral white matter. Where the cortical gray matter is conveniently divided into discrete segments by fairly regular sulci, the white matter appears to be amorphous. The named white matter tracts seem to define predominant directions of axon flow. Most of these tracts contain multiple subcomponents as demonstrated by a recent report on Meyer's loop [1]. The anatomy of several "eloquent" tracts has been elucidated through clinical pathologic correlation, anatomic dissections, imaging studies, and intraoperative electrical stimulation. As with the cerebral cortex where certain input and output areas have been found to be essential and designated eloquent, certain white matter pathways have also been found to be essential for basic neurological functions [2, 3].

The first recognition of a major fiber bundle is attributed to Galen, who described the corpus callosum [4]. Carl Wernicke postulated a pathway connecting the posterior temporal language area he described and the area of speech production described by Paul Broca [5].

Wernicke's pathway was postulated to relay through the insula. He conjectured that a lesion of this connection would be manifested by normal speech and comprehension, but with paraphasic errors as Broca's area was no longer monitored by Wernicke's area. Based on post mortem examinations, Dejerine delineated the role of white matter lesions in patients with normal vision, normal speech, but an inability to read [6].

In the early 1800s, German anatomist Johann Christian Reil, using gross fiber dissection, described a group of fibers connecting the temporal, parietal, and frontal lobes that passed around the sylvian fissure [7, 8]. A few years later, Burdach reported a detailed anatomic dissection of these fibers and coined the term arcuate fasciculus. Joseph Dejerine confirmed Burdach's finding in describing the connection as Burdach's arcuate fasciculus [6].

In the 1960s, the importance of disconnection syndromes was resurrected and brought to the attention of clinical neurologists by Norman Geschwind [9–11]. He demonstrated the anatomic basis of apraxias, a state in which a person with normal motor, sensory, and cognitive function cannot perform specific skilled movements. He described a patient who, following an infraction of the anterior 80 % of his corpus callosum could not follow commands with his left hand that he readily performed with his right hand.

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The patient was able to flawlessly imitate the movements with his left hand.

The axonal bundles comprising the white matter pathways can be grouped into stereotypic types [12]. U fibers are short association fibers that connect adjacent gyri. Neighborhood association fibers link cortical regions in the same hemisphere. Commissural fibers pass to the contralateral hemisphere. Striatal fibers connect the cortex with the striatum, and thalamic fibers link the cortex with the thalamus. Projection fibers terminate in the brainstem, cerebellum, and spinal cord. While there is a fair bit of fascinating work being done on many of the tracts, this chapter will focus on the association, striatal, thalamic, and projection tracts whose function has been demonstrated to be essential for basic neurological function.

## Methods of Determining Fiber Tracts

The earliest descriptions of fiber tract anatomy relied on fiber tract dissections [13]. In the late 1800s histological methods were developed. Histological methods that took advantage of degenerating myelin's propensity to stain with osmotic acid were described by Marchi in 1886 [14]. The tract of interest would be lesioned and followed on consecutive histologic sections with the degenerating myelin staining black. Because the stain was capricious and expensive, it was replaced with the silver techniques of Glee and Nauta which also stained degenerating axons [15, 16].

In the 1970s autoradiography proved to be an excellent histological method for demonstrating fiber tracts in vitro. Axonal transport of radiolabeled materials is used to demonstrate white matter pathways [17, 18]. Small volumes of radiolabeled amino acids such as H3-Leucine or Proline are injected into the brain and after a period of days, the animal is sacrificed. Proteins are principally synthesized in the neuronal area so that axons passing the injection site should not be labeled. The animals are sacrificed and their brains are fixed and sectioned. Autoradiography is then used to demonstrate the distribution of the labeled amino acids. Several associate pathways have been demonstrated in monkeys using this technique [17, 19–21].

### Fiber Tract Dissection

Fiber tract dissection is an old technique. Presently most authors use the technique described by Klingler and resurrected by Yasargil and Ture [22–25]. In this technique, the brains are fixed in formalin and the pia and blood vessels are removed. The brains are frozen at −20 °C for 2–4 weeks and then slowly defrosted. The crystallization of the water and the formalin disrupts the grey matter and spares the white matter tracts. The disrupted grey matter is scraped from the brain using dissectors made from split wooden tongue depressors. Those dissectors are also used to peel away the short "U" fibers. The white matter tracts are delineated by gently teasing their edges off the bundles with these blunt dissectors under low power magnification, 3.5–10×. Separation of the bundles often requires the use of thin steel dissectors. Martino et al. modified this technique, preserving the relevant cortex so that the relationship of the white matter tracts to the cortical landmarks could be appreciated [26].

### Diffusion-Weighted Imaging

Diffusion-weighted or -tensor imaging (DTI) measures the movement of water molecules. In a free-standing pool of water, molecules diffuse in all directions at a constant rate determined by temperature of the water. In the brain, the diffusion is impeded by macromolecules, organelles, and cell membranes. The homogeneous orientation of axons and myelin in fiber tracts directs the water molecules to preferentially diffuse in the direction parallel to the fibers. This asymmetric diffusion, termed anisotropy, is the basis of DTI. The rate of diffusion is measured in multiple directions to determine the net magnitude and direction of the water molecules in each voxel (conventional DTI has difficulty resolving crossing fiber tracts). More sophisticated techniques such as high angular resolution diffusion-weighted imaging, Q-ball imaging, and diffusion spectrum imaging have been developed to trace out the crossing and merging fibers that can occupy a given voxel [27–30]. Spherical decon-

volution has the ability to identify and quantify the orientation of different fiber tracts within the same voxel. Fiber tracts delineated by this method have correlated with maps constructed from axon tracing studies [31]. DTI tractography constructs fiber tracts by linking voxels [32, 33]. Several strategies have been proposed to tease the fiber tracts out of the DTI data [34]. The tracts derived from DTI tractography are dependent on data acquisition, cut-off values for thresholds, modeling, and the software being used [35–37]. Strategies are lumped into deterministic tractography which assigns a predominant direction to each voxel and links voxels with a similar direction, and probabilistic tractography which calculates a probability of direction of diffusion for each voxel and links voxels based on the probability of a water molecule passing from one voxel to the next [38]. Fiber tracts can be determined by choosing a single region of interest (ROI) and constructing all fiber tracts that pass through that region, or by choosing two or more regions of interest and constructing all tracts that pass through those regions [32, 39]. When two regions are chosen to define a fiber bundle, fibers from within that bundle but traveling outside one of the chosen regions of interest will be lost [40]. In clinical practice, it is common to choose a region of interest adjacent to a region of cortex whose function has been determined by a functional MRI scan. Edema diminishes flow within a given voxel but preserves the direction of the flow [41, 42]. Disruption of the fiber tracts by infiltrating tumor diminishes the preferential direction of the flow. Fiber tracts are poorly visualized at their connection with the cortex. DTI has proven very useful in clinical practice [42, 43].

## Methods of Electrical Stimulation

### History

Electrical stimulation of the brain has been of interest since the late 1800s [44, 45]. While several neurosurgeons including Cushing published case studies using electrical stimulation for cerebral localization, the technique appears to have been first used on a regular basis by Foerster and popularized in North America by Penfield [46–48].

### Clinical Results

Electrical stimulation of the brain during surgery has become a regular part of the neurosurgeon's armamentarium and is used to guide tumor resection in many centers. Awake surgery is well tolerated by patients [49–52]. The value of intraoperative mapping in preserving function and improving resection grade has been reported by a number of surgeons [52–57]. A literature review of 90 reports published between 1990 and 2010 demonstrated a significant decrease in postoperative neurological deficits and a significant increase in the rate of gross total resections when intraoperative cortical stimulation was used [53]. However, direct stimulation is not infallible. Roessler notes that technical problems occur in 13.6 % of patients with cortical mapping [58]. Despite negative mapping, permanent deficits may still occur [59]. Sanai et al. reported that in their series of 250 patients with dominant hemisphere tumors, transient language deficits developed in 20.3 % of frontal lobe resections and 9.3 % of temporal resections in patients despite no positive language sites being detected at the site of resection prior to resection [52]. Four (1.4 %) patients had a persistent neurological deficit. Whether these deficits are a result of ischemia, function confined to a sulcus, damage to white matter tract, or some other mechanism remains uncertain.

### Traditional Method of Electrical Stimulation

Bipolar stimulation at a constant set frequency has been the traditional mode of cortical and subcortical mapping [60, 61]. The tines of the stimulation probe are traditionally spread 5 mm. Most surgeons stimulate with 50–60 Hz with a pulse width of 1–2 ms delivered by a constant current generator with a variable output of 1–9 mA stimulating for up to 5 s [62]. Such stimulation has

been shown using optical imaging to activate 2–3 mm of cortical tissue [63]. A constant current generator is preferred because the current delivered will not vary with tissue impedance. Biphasic stimuli were employed to mitigate the adverse effects of electrical stimulation but with better constant current generators, monophasic stimulation appears to be safe [64, 65]. The surgeon begins stimulation at 2 mA and releases the current until there is a functional response or until after discharge is seen on EEG. Many surgeons monitor the cortical EEG for after discharge or spread of epileptiform activity to adjacent cortex. The stimulation current is increased until tonic motor movement, speech arrest, or after discharge is detected. At our institution, we stimulate the motor cortex that is either exposed by the craniotomy flap or sought out with a multi-contact strip slid under the dura to a nonexposed cortical surface to determine a stimulation threshold. While older techniques called for large craniotomies to include an eloquent area of brain in the operative field, most surgeons use "negative mapping" in the field of resection [52, 59].

Cortical and subcortical stimulation can be employed to map various neurological functions but is most commonly used to localize brain critical for motor and language function [66]. When mapping for motor function, stimulation results in tonic muscle contraction, although interference with motor function has been reported with subcortical stimulation [67]. Multichannel electromyography can be used to detect motor movement as well [68]. When mapping for language function most authors have the patient name the objects shown on a computer screen or flash cards or read sentences while the brain is being stimulated. Stimulation of language-sensitive tissues can result in speech arrest, dysarthria, or semantic or phonemic paraphasic errors [56, 69, 70].

Stimulation of the arcuate fasciculus usually results in phonological paraphasias but semantic paraphasias and articulating difficulties have been reported. Phonological paraphasias indicate the substitution of word or nonword maintaining most of the phonemes of the original word. For example, rat or bat can be substituted for cat. Stimulation of the superior longitudinal fasciculus results in dysarthria or articular disorders. Stimulation of the inferior fronto-occipital fasciculus produces semantic paraphasias. Semantic paraphasias substitute a word of the same linguistic class as the intended word. For example, cow for horse. Stimulation of the subcallosal or aslant fasciculus induced hesitation dysarthria or anarthria.

## Methods of Stimulation

While bipolar stimulation at 50–60 Hz is most commonly used for cortical and subcortical stimulation, monopolar stimulation and short bursts of high frequency stimulation have been described [71, 72]. Short train stimulation of five pulses at 250–500 Hz repeated every 2–3 ms have been used to stimulate cortical and subcortical motor and language structures [73, 74]. Short train stimulation is thought to be less likely to evoke seizures, but all investigators have not correlated these findings [75, 76].

Monopolar stimulation results in a current that diffuses in all directions and falls off proportional to distance from the electrode. Bipolar stimulation results in a current that runs between the two poles and falls off proportional to the distance squared. Thus monoplar stimulation is more likely to trigger action potentials at a greater distance.

With monoplar stimulation, anodal stimulation is reported to be superior in stimulating motor cortex but cathodal stimulation is superior in stimulating white matter [75–78]. Monopolar stimulation has been demonstrated to be effective in eliciting motor responses. The amperage required to elicit a motor response is proportional to the distance between the stimulating electrode and the motor fibers. The Stimulation of the white matter at 5 mA indicates that the probe is within 5 mm of motor fibers [73, 79]. When mapping language using monopolar short train stimulation, it is important to synchronize the presentation of the object to be named with the onset of the stimulus or 300 ms after the object presentation [79, 80]. When the object presentation and stimulation are out of phase, the patient may be able to name objects accurately

even though language associated structures are being stimulated.

Szelenyi et al. compared bipolar and monopolar stimulation using Penfield's standards of 50 Hz and short train high frequency stimulation in stimulating the subcortical motor fibers in 20 patients undergoing tumor resection [59, 75]. The pulse width for each technique was 0.5 ms. For the short train technique, five pulses are delivered with a 4 ms interval. The train is repeated every 2 s. They found that monopolar stimulation using short trains at a high frequency resulted in stimulation of motor fibers at lower amperage than the combinations of stimulating frequently and number of pulses. They found that the type of probe used, monopolar vs. bipolar, was more important than the configuration of stimulus. Motor evoked potentials were elicited in 39 of 42 stimulation attempts using the monopolar probe but in only 23/42 attempts using the bipolar probe. They also found that while the short train high frequency stimulation technique elicited motor evoked potentials in a greater number of patients and at a lower threshold than constant frequency stimulation, the difference did not reach statistical significance. The field produced by monopolar stimulation is more radiant than that produced by bipolar stimulation and thus will stimulate motor fibers at a greater distance.

Kombos et al. compared bipolar stimulation of the motor cortex at 50 Hz with short train stimulation at 500 Hz in 35 patients undergoing tumor resection. They found that monopolar stimulation was more likely to only elicit movement from motor cortex stimulation but bipolar stimulation was more sensitive in mapping function in the premotor as well as motor cortex [60].

### Newer Techniques

Raabe described using an insulated suction aspirator to continuously provide short train monoplar stimulation at its tip while dissecting tumor close to the motor system in 89 patients. Motor evoked potentials were monitored. An increase in motor threshold stimulus of 4 mA was considered a warning sign of impending damage as was a reduction in stimulus threshold by the sucker/aspirator stimulator of 1–2 mA. Two patients developed postoperative deficits, both of whom had suffered a stroke [81].

## Anatomy

### Optic Radiations

The optic radiations begin in the lateral geniculate a short distance posterior to the anterior choroidal point of the temporal lobe [82]. They then pass through the temporal stem below the inferior fronto-occipital fasciculus (IFOF) [83, 84]. Using the Klingler method, Parraga and others have demonstrated the optic radiations [82, 84, 85]. The fibers of the optic radiation lie in the posterior thalamic bundle passing under the lentiform nucleus as the most posterior part of the internal capsule. In the temporal stem they lie in a plane below the IFOF [84]. Above the tail of the caudate the fibers pass over the junction of the temporal horn and the atrium of the lateral ventricle where the fibers diverge into the anterior, central, and posterior bundles. All three bundles join the sagittal striatum along with the IFOF and fibers of the anterior commissure [1].

The anterior bundle passes over the temporal horn of the lateral ventricle beyond its tip and then doubles back over the lateral wall of the temporal horn and along the atrium to the inferior calcarine fissure. It should be noted that the temporal loop is composed of various projection fibers and is not exclusively composed of the optic radiations [1]. The optic radiations are separated from the atrium by the tapetum and separated from the roof of the temporal horn by the tapetum and tail of the caudate [31]. The central bundle passes laterally over the temporal horn and abruptly turns backward over the atrium to end in the occipital pole. The posterior loop courses posteriorly forming the lateral wall and part of the roof of the atrium in the occipital horn of the lateral ventricle, and then continues to the superior calcarine fissure. The optic radiations lie above the level of the inferior temporal sulcus [86, 87]. They maintain a retinotopic organization with the anterior bundle mediating superior

peripheral vision, the posterior bundle mediating inferior peripheral vision and the central bundle representing foveal vision. The anatomy of the optic radiations influences neurosurgical trajectories [88, 89].

### DTI

The anatomy of the optic radiations can be demonstrated with DTI. Sherbondy et al. demonstrated the course of the optic radiation in eight volunteers using DTI [90]. They found a good correlation between the DTI reconstructed optic radiations and anatomic landmarks defined using fiber tract dissections. This technique has been used to determine the relationship of the optic radiations and lesions prior to surgery [91–93].

### Optic Radiations Stimulation

Stimulation of the optic radiations adjacent to the lateral ventricle may result in phosphenes (flashing lights), a focal loss of vision, or rarely, visual hallucinations [94, 95]. In our experience, focal loss of vision is the most common manifestation.

Gras-Combe et al. described a method for testing visual fields during awake surgery [85]. The patient views a screen divided into four quadrants. Single objects are presented in two of the quadrants. One image is presented in the visual quadrant being tested by intraoperative stimulation and the second object is presented in the diagonally opposite quadrant. With electrical stimulation of the optic radiations, the positioned object in the quadrant being tested will not be seen. When applied to 14 patients, Gras-Combe et al. were able to produce temporary visual deficits in all patients with electrical stimulation and avoided a postoperative hemianopsia in 13 of the patients. Seng et al. used this test in eight patients undergoing operations for low-grade gliomas involving the sagittal striatum. The optic radiations were detected by electrical stimulation in five of the eight patients. All patients had persistent postoperative right superior quadrantanopsia but none had a hemianopsia [96]. Even when the optic radiations are detected by electrical stimulation, the patient may develop a partial visual deficit. Whether this is due to disruption of blood supply to the optic tract is not known. Resection of the anterior temporal lobe including the lateral wall of the temporal horn and Meyer's loop will result in a variable degree of contralateral upper quadrantanopsia [86].

## Subcallosal and Aslant Fasciculus

### Anatomy

The subcallosal fasciculus, or Muratoff's bundle, links the supplementary motor cortex with the caudate nucleus [97, 98]. It passes around the lateral angle of the frontal horn of the lateral ventricle [99]. This tract has been demonstrated using DTI in humans [100, 101] Interruption of this fasciculus produces elements of a supplementary motor syndrome. Lesions of the subcallosal fasciculus cause impaired initiation and preparation of speech. Naeser et al. studying stroke patients, noted severe non fluid aphasia in patients with lesions of the subcallosal fasciculus [102]. Stimulation results in transcortical motor aphasia [56]. Patients have impaired spontaneous speech but intact repetition [61]. Duffau et al. demonstrated transient transcortical motor aphasia in 16 patients with tumors of the middle frontal gyrus when stimulating the subcallosal fasciculus. This pathway was the deep limit of the resection [56].

It is not clear what speech difficulties arise from lesions of the subcallosal fasciculus and which arise from lesions of the more recently described aslant fasciculus. The aslant fasciculus was originally described as connecting the pars opercularis and posterior pars triangularis to the anterior cingulate, supplementary, and pre-supplementary motor area. This fasciculus runs a path adjacent to the subcallosal fasciculus [103–105].

Using DTI, Thiebaut de Schotten found that the frontal aslant tract connects the ventral premotor inferior frontal gyrus and pars opercularis with the supplementary motor area and pre-supplementary motor areas of the superior frontal gyrus [31, 106]. The Superior origin of this tract is not consistently agreed upon in the literature, with some authors finding connections to the medial and lateral superior frontal gyrus and others only finding connections to the lateral posterior

superior frontal gyrus [74, 107]. Kinoshita et al. defined a tract connecting the lateral superior frontal gyrus to Broca's area in eight cadaver hemispheres using fiber dissection as well as in 49 normal right-handed patients using DTI [107]. Fuji et al. stimulated the posterior superior frontal gyrus and white matter in the posterior frontal lobe eliciting speech arrest in four patients and difficulty initiating speech in a fifth [108].

## Superior Longitudinal and Arcuate Fasciculus

Historically the superior longitudinal fasciculus (SLF) was not distinguished from the arcuate fasciculus. These two fascicular tracts run a somewhat parallel course and will be discussed together, although each has unique cortical connections and probably unique function. The SLF is sometimes referred to as the indirect component, and the arcuate fasciculus as the direct component.

Deciphering the anatomy of the SLF and arcuate fasciculus through the literature can be confusing as the anatomy is species-specific and varies with the technique used to define the fibers.

Schmahmann et al. used diffusion spectral imaging, a MRI-based diffusion tensor technique which can resolve crossing fibers within a single voxel, to investigate long white matter tracts in rhesus monkeys, verifying his results using autoradiography. He defined SLF I as a tract linking the dorsal premotor and prefrontal cortex with the medial and dorsal parietal lobe. SLF II connected the dorsal inferior parietal lobe, approximating the angular gyrus in humans, with the dorsal premotor and prefrontal cortex. The frontal destination of this tract is inferior to the destination of SLF I. SLF III extends from the rostral inferior parietal lobe to the ventral premotor and prefrontal cortex, inferior to the destination of SLF II. They found that the arcuate fasciculus connected the posterior superior temporal lobe to the mid dorsal premotor and prefrontal cortex approximating the connection of SLF II [19, 97]. Petrides and Pandya used autoradiography to demonstrate the long associative fibers connecting the frontal and parietal lobes in the rhesus monkey. Their findings were consistent with those of Schmahmann et al. [17, 20].

The anatomy of the SLF and arcuate fasciculus complex in humans is different from that seen in monkeys [109, 110]. Further confusion arises from the fact that different authors use different nomenclature for defining the components of the SLF/arcuate fasciculus fiber tracts. What is referred to as the anterior or horizontal limb of the SLF in humans connects the inferior parietal lobe, predominantly the supramarginal gyrus, with the ventral premotor and posterior inferior and middle frontal gyri. In humans, distinct SLF II and III tracts are sometimes seen as distinct, but more often are grouped into the horizontal limb of the SLF [109]. The posterior or horizontal limb described in humans connects the mid posterior temporal lobe with the inferior parietal lobe, predominantly the angular gyrus. There does not seem to be a fiber tract in monkeys that correlates with the posterior/horizontal limb that is so well defined in humans, although the vertical limb of the inferior longitudinal fasciculus described in monkeys may include a rudimentary analog of this limb [109, 111]. Gierhan and others have adopted the monkey nomenclature to humans [39, 112], and have added a fourth fiber bundle designated SLFtp to describe the fibers connecting the inferior parietal lobe to the temporal lobe [39, 109, 113]. Two components of the SLFtp have been described. Parker et al. described a fiber bundle passing from the supramarginal gyrus to the superior temporal gyrus and Martino described a path connecting the angular gyrus to the middle temporal gyrus [114]. Electrical stimulation eliciting corticocortical evoked potentials demonstrate bidirectional connectivity between Broca's area and both the superior temporal gyrus and inferior parietal lobe [115].

### Fiber Dissections

Martino et al. dissected twelve postmortem human hemispheres using a modified Klingler method to demonstrate the trajectory and the cortical connections of SLF I (anterior limb), SLF II (posterior limb), and the arcuate fasciculus [116].

He found that the anterior segment of the SLF terminated in the supramarginal gyrus and posterior temporal gyrus in 82 % of hemispheres and in one hemisphere connected to the angular gyrus. In the frontal operculum the bundle terminated in the precentral gyrus in 73 % of hemispheres. The posterior segment connected to the posterior middle temporal gyrus in all hemispheres. It connected to the angular gyrus in 88 % of hemispheres and the supramarginal gyrus in 12 % of hemispheres. The arcuate fasciculus connects to the inferior temporal gyrus in all hemispheres and the middle temporal gyrus in 83 % of hemispheres. Anteriorly the arcuate fasciculus connects to the ventral precentral gyrus in 75 % of hemispheres and to the posterior inferior frontal gyrus in 75 % of hemispheres and to the posterior middle frontal gyrus in 58 % of hemispheres. In three hemispheres, the exact frontal connections could not be determined. It should be noted that connections of the arcuate fasciculus extend beyond the classical Broca's area to include middle frontal gyrus and inferior precentral gyrus, passing dorsal to the internal capsule around the posterior circular sulcus and reaching the posterior, inferior, and middle temporal gyri.

De Benedictis et al. dissected ten human cadaver hemispheres to determine the anterior terminations of the SLF and arcuate fasciculus. They found that the anterior limb of the SLF terminated in the inferior frontal gyrus, the middle frontal gyrus, and the ventral premotor cortex. The arcuate fasciculus was found to terminate in the middle and inferior frontal gyrus, including the opercular and posterior triangular gyri [117].

In their three-dimensional atlas Fernandez-Miranda et al. [22] demonstrated the two superficial components of superior longitudinal fasciculus and the arcuate fasciculus by fiber dissection. They noted that the posterior component connected the posterior middle and superior temporal gyri to the inferior parietal lobe and the anterior component connected the inferior and middle frontal gyri with the inferior parietal lobe.

Yagmurlu et al. divided the horizontal limb of the SLF into SLF II, which connected the middle frontal gyrus with the angular gyrus, and SLF III which connected the supra-marginal gyrus to the pars opercularis [109]. They also divided the arcuate fasciculus into a dorsal segment connecting the inferior and middle temporal gyri to the inferior and middle frontal gyri, and a ventral segment connecting the superior and middle temporal gyri to the inferior frontal gyrus.

## DTI

Early DTI studies described the superior longitudinal fasciculus and arcuate fasciculus as a single white matter path [98, 101]. The complexity of the SLF/arcuate fasciculus was demonstrated by Schmahmann and Pandya using a high resolution DTI technique, diffusion spectral imaging, in Rhesus monkeys as noted above.

Catani et al. [118] used DTI to define the language tracts in 11 right-handed healthy males. They defined three tracts. The arcuate fasciculus was found running from the ventrolateral posterior frontal lobe, coursing above the insula and terminating in the posterior, superior, and middle temporal gyri. They also found two tracts running lateral to the classic arcuate fasciculus: an anterior segment connecting the posterior inferior frontal gyrus with the inferior parietal lobe and a posterior segment connecting the inferior parietal lobe with the superior posterior temporal lobe. Gharabaghi et al. [119] found similar pathways in the right hemisphere although using DTI multiple investigators have demonstrated this pathway to be larger on the left than on the right [120, 121].

Makris et al. described four separate components of the dorsal system in humans [122]. Using DTI they could demonstrate the bodies of the fasciculi. Because DTI has difficulty separating the long projection fibers from the U fibers close to the cortex, the cortical attachments were extrapolated but not clearly visualized. Superior longitudinal fasciculus I connected the superior parietal lobule and the premotor and dorsolateral prefrontal region. The fibers run in the dorsal medial white matter under the superior frontal gyrus. Superior longitudinal fasciculus II located in white matter above the insula extended from the angular gyrus to the posterior middle frontal gyrus. Superior longitudinal fasciculus III extends

from the supramarginal gyrus to the inferior frontal gyrus and resides in the frontoparietal opercula. Superior longitudinal fasciculus IV or the arcuate fasciculus begins in the superior temporal gyrus and passes around the caudal sylvian fissure and connects to the same caudal lateralprefrontal area as superior longitudinal fasciculus II. The vertical SLFtp was not noted in their report.

The exact frontal connection of the anterior limb of the superior longitudinal fasciculus in the frontal lobe is debated with various authors noting connections with the ventral precentral gyrus, middle frontal gyrus, pars opercularis, and pars triangularis. It is commonly believed that the arcuate fasciculus is primarily connected to the pars opercularis and pars triangularis, but recent literature indicates that the termination of the ventral stream is predominantly in the ventral precentral gyrus and the pars opercularis [116, 123–125]. Bernal and Altman using DTI found that in twelve patients studied, the arcuate fasciculus connected to precentral gyrus with much sparser connections than with the inferior frontal gyrus [126]. Frey et al. found components of the arcuate fasciculus connecting to the posterior middle frontal gyrus (Brodmann's Area 8), the dorsal preprecentral gyrus (Brodmann's Area 6), and the pars opercularis (Brodmann's Area 44) [112].

Along with the dissections discussed above, Martino et al. reconstructed the anterior/horizontal/vertical SLF and the arcuate fasciculus in three healthy volunteers using DTI [116]. The anterior horizontal SLF was found to terminate in the supramarginal gyrus in all hemispheres, the posterior temporal gyrus in 50 % of hemispheres and the angular gyrus in 33 % of hemispheres. In the frontal operculum, it was connected to the precentral gyrus of all hemispheres and to the posterior inferior frontal gyrus in 33 % of hemispheres. The vertical limb of the SLF terminated in the posterior middle temporal gyrus in 80 % of hemispheres, the inferior temporal gyrus in 40 % of hemispheres and the superior temporal gyrus in 20 % of hemispheres. Superiorly the vertical limb terminated in the angular gyrus in 80 % of hemispheres and the supramarginal gyrus in 60 % of hemispheres. The arcuate fasciculus connected to the middle temporal gyrus in all hemispheres and to the inferior temporal gyrus in 40 % of hemispheres. In the frontal operculum, the arcuate fasciculus connected to the ventral precentral gyrus in 80 % of hemispheres, the posterior inferior frontal gyrus in 68 % of hemispheres and the posterior middle frontal gyrus in 20 % of hemispheres.

Similarly using DTI, Glasser and Rilling found that the arcuate fasciculus connected to the posterior middle temporal gyrus [124].

Theibaut de Schotten et al. compared human white matter tracts connecting to the frontal lobe determined by spherical deconvolution DTI with monkey tracts demonstrated by autoradiography [31]. In humans they found SLF I to connect the superior parietal lobule to the posterior superior frontal lobe. SLF II originated from the anterior interparietal sulcus and angular gyrus and connected to the posterior superior and middle frontal gyrus, and SLF III connected the inferior parietal lobule with the posterior inferior frontal gyrus. They found that a small component of the arcuate fasciculus linked the posterior superior gyrus with Broca's area (BA 44,45), but the largest component linked the middle and inferior temporal gyri to the inferior precentral gyrus (BA 6) and the posterior middle and inferior frontal gyri (BA8,9,44) . The SLF connections to the frontal lobe, SLF I, II, III, appear to be conserved between monkeys and humans. The authors did not investigate the vertical limb of the SLF. In monkeys the arcuate fasciculus terminates in the superior temporal gyrus and there are no connections to the middle or inferior temporal gyri as there are in humans.

In summary, Wernicke's arcuate fasciculus is composed of two segments, the multicomponent superficial SLF which connects the frontal, inferior parietal, and temporal lobes and the deeper single component arcuate fasciculus which directly connects the temporal and frontal lobes. Neither system has major connections with the classical Wernicke's area terminating predominantly in the middle and inferior temporal gyri. The frontal connection is to BA6, 44 and 8 with little evidence for a major connection with the pars triangularis (BA 45).

Superior longitudinal fasciculus I has been demonstrated by DTI in humans to extend from

the superior parietal lobule and precuneatus to the superior frontal gyrus and cingulum [106].

## Function

Patients with lesions confined to the arcuate fasciculus would be expected to have relatively preserved spontaneous speech and comprehension but impaired repetition.

The arcuate fasciculus was postulated to be essential for verbal repetition. Normal repetition has been reported with lesions of the arcuate fasciculus and impaired repetition has been reported when the arcuate fasciculus is intact. Berthier et al. suggests that variability in anatomy and lateralization may explain normal repetition in the setting of apparent arcuate fasciculus lesions [127, 128].

Theoretically, lesions of the anterior and posterior components of the superior longitudinal fasciculus would be expected to produce the transcortical motor and sensory aphasias proposed by Lichtheim [129–131]. With lesions of the anterior limb of the SLF the patient manifests good comprehension and repetition, but fluency is reduced. With lesions of the posterior limb of the SLF, the patient demonstrates good fluency and repetition, but diminished comprehension. It should be noted that anterior transcortical aphasia is most often associated with lesions disrupting the subcallosal or aslant fasciculus. Posterior transcortical aphasias is associated with disruption of connections between the left temporal phonology and lexical-semantic processing areas [130, 132]. Disruption of the SLFtp disconnects these two areas. Galantucci et al. demonstrated that the temporoparietal branch of the SLF was selectively more damaged in a variant of primary progressive aphasia associated with phonological deficits using DTI [113]. McCarthy and Warrington describe three patients demonstrating the difference between conductive and transcortical aphasias [133]. Two patients had a marked deficit in speech production during repetition tasks but spontaneous speech was intact, and one patient had intact repetition but poor spontaneous speech. Sanai et al. noted a 13 % incidence of immediate postoperative language difficulty following radical resection of parietal lobe gliomas when subcortical language mapping was not performed [52].

Intraoperative electrical stimulation of the frontoparietal limb of the SLF is associated with dysarthria, buccolingual apraxia, or anarthria [56, 99, 134, 135]. Intraoperative stimulation of the arcuate fasciculus along its frontal or temporal course results is phonological paraphasias [136]. Phonological paraphasias are the substitution of a word with another word that sounds similar or the substitution of a word with a "nonword" which preserves most of the syllables of the intended word. Duffau et al. demonstrated that stimulation of the arcuate fasciculus was associated with phonemic paraphasias in 62 patients with tumors extending from the inferior frontal area through the posterior temporal lobe [56]. Stimulation of the frontoparietal limb of the SLF resulted in anarthria or dysarthria in five patients. Stimulation of the supplementary motor area, anterior insula, and lentiform nucleus elicit dysarthria, slowness of speech, or anarthria [101]. This pathway can determine the deep limit of the resection in patients with inferior frontal, inferior parietal, or insular tumors and the posterior limit of resection in patients with temporal tumors [56].

The superior longitudinal fasciculus also appears to be involved with spatial orientation [106, 137]. Current thinking divides the dorsal visual stream into two components, the dorsal–dorsal stream and the ventral–dorsal stream [138]. The dorsal–dorsal stream, which includes SLF I is involved with the patient's interaction with the environment. Lesions of SLF I results in optic ataxia disorder in visually guided movements toward a goal. The patient knows the location of the object but has difficulty executing planned movements [139, 140]. The ventral–dorsal stream which includes the horizontal component of the SLF is involved with perception of space and recognition of action made by others. The patients with damage to the ventral–dorsal stream have neglect on the contralateral side. It also plays a role in action organization [141]. Damage to the nondominant arcuate fasciculus is associated with tone deafness [142].

The arcuate fasciculus and SLF are part of the so-called mirror system. The mirror system has

been postulated to take part in motor learning, rapid intuitive thinking, and reading of other's interactions and emotions [143, 144]. While the mirror system reads the emotions and interactions of others, it does not derive others' motivations. This seems to be the function of the medial frontal parietal system.

## Middle Longitudinal Fasciculus

Schmahmann et al. defined the middle longitudinal fasciculus in rhesus monkeys using autoradiographs and DTI as traveling in the white matter below the superior temporal gyrus connecting the inferior parietal lobe, including the caudal cingulum with the length of the superior temporal gyrus to the tip of the temporal lobe [19, 97].

Martino was able to identify the middle longitudinal fasciculus in a single hemisphere using fiber tract dissection. He found that the tract traveled deep to the arcuate fasciculus and connected the superior temporal gyrus to the inferior parietal lobe [114].

Maldonado et al. used fiber dissection techniques in 18 human cadaver hemispheres to delineate the middle longitudinal fasciculus [25]. The tract passes deep to the superior temporal gyrus medial to the arcuate fasciculus and lateral to the inferior fronto-occipital fasciculus and the sagittal striatum. They found that the fibers ran horizontally in the base of the temporal operculum along the entire superior temporal gyrus and connected with the dorsal occipital lobe posterior to its junction to the parietal lobes. No connections were seen to the angular gyrus.

Makris et al. delineated the middle longitudinal fasciculus using DTI in four human volunteers. They found that the middle longitudinal fasciculus connected the inferior parietal lobule, especially the angular gyrus, with the entire superior temporal gyrus [145].

Combining EEG, DTI, and fMRI in 33 volunteers passively listening to sentences, pseudosentences, and reversed sentences, Saur et al. concluded that the middle longitudinal fasciculus was involved in semantic processing [125].

The MLF has been hypothesized to participate in language comprehension in the dominant hemisphere and spatial attention in the nondominant hemisphere. De Witt et al. stimulated the middle longitudinal fasciculus in the left dominant hemispheres of eight patients undergoing resection of a glioma in the superior temporal gyrus [146]. No patient demonstrated difficulty with picture naming with intraoperative stimulation of the middle longitudinal fasciculus. No patient demonstrated a postoperative neurological deficit despite the fact that the middle longitudinal fasciculus was partially resected in all cases.

## Inferior Longitudinal Fasciculus

The inferior longitudinal fasciculus connects the occipital lobe and posterior basal temporal lobe with the anterior temporal lobe. It runs lateral and inferior to the lateral wall of the temporal horn just lateral to the optic radiations [147]. Schmahmann et al. used radioisotope and DTI to define the inferior longitudinal fasciculus in rhesus monkeys. They demonstrated connections between the inferior parietal lobe, the extrastriate occipital lobe, and the inferior and basal lateral temporal lobe [19, 97].

Martino using fiber tract dissection demonstrated that the tract connects the anterior portion of the inferior temporal gyrus and temporal pole with the superior and middle occipital gyri [114]. It also connects the fusiform gyrus into the inferior occipital gyrus [26].

Using DTI, Catani et al. demonstrated a distinct pathway passing from the extrastriatal occipital lobe [40, 148]. Posteriorly two branches were identified, one arising from the dorsolateral occipital lobe and a second from the cuneatus, posterior lingual, and fusiform gyri. These branches merge as they run forward parallel to the optic radiations and lateral to the temporal horn of the lateral ventricle. They distribute to the three anterior lateral temporal gyri and the uncus and parahippocampal gyrus.

DTI studies have demonstrated that the visual world form area in the left posterior occipital temporal sulcus, an area essential for reading, is

connected to the occipital lobe by the inferior longitudinal fasciculus [149].

In one study, intraoperative electrical stimulation demonstrated that the anterior inferior longitudinal fasciculus is not essential for picture naming during awake craniotomies for low-grade gliomas in 12 patients [150]. Other studies demonstrate that the inferior longitudinal fasciculus is involved in reading, face recognition, and visual object recognition [151–154]. With loss of visual recognition, the patient can name an object but is unable to describe its purpose. A patient with such a deficit can name a stop sign but cannot describe what it indicates.

Disruption of white matter connections between the occipital lobe and occipitotemporal sulcus results in alexia, an inability to read [149, 155]. Seng et al. were able to induce a temporary alexia in three patients undergoing resection of a left posterior temporal low-grade glioma by stimulating the basal area of the resection cavity corresponding to the inferior longitudinal fasciculus [96]. The inferior longitudinal fasciculus also connects the occipital lobe with the infratemporal fusiform face area. Disruption of this pathway leads to prosopagnosia [153]. Several authors have noted the inferior longitudinal fasciculus has also been associated with object recognition [146, 151, 153].

It has been suggested that the inferior longitudinal fasciculus and uncinate fasciculus constitutes an indirect language pathway parallel to the inferior fronto-occipital fasciculus [142, 150, 154].

## Uncinate Fasciculus

The uncinate fasciculus connects the anterior temporal lobe with the orbital and polar segments of the frontal lobe passing through the temporal stem anterior and ventral to the inferior fronto-occipital fasciculus [26, 83, 84, 156]. In the temporal lobe, the uncinate fasciculus connects to the uncus, the entorhinal cortex, the perirhinal cortex, the temporal pole, and the anterior, middle, and superior temporal gyri [26]. The fibers connect to the anterior and orbital frontal lobe, Brodmann's areas 10, 11, 47, and possibly 45. The caudal frontal cortex connects to the entorhinal and perirhinal cortex and the rostral orbital cortex to the anterior temporal lobe in the rhesus monkey [157]. The uncinate fasciculus passes through the temporal stem posterior to the insula and anterior inferior to the inferior fronto-occipital fasciculus. Thiebaut de Schotten using spherical DTI found that the uncinate fasciculus connected the temporal pole, uncus, paraphippocampal gyrus, and amygdala with the lateral orbital frontal cortex, cingulum, and frontal pole [31]. The uncinate fasciculus has been associated with semantic processing, episodic memory, and emotional processing. A recent theory proposes that the uncinate fasciculus conveys mnemonic associates such as the association of a name with a face and a voice that influence lateral frontal lobe decision making [31, 158]. Another theory is that the inferior longitudinal fasciculus and uncinate fasciculus constitute an indirect language pathway running parallel to the inferior frontal occipital fasciculus [159]. Stimulation of the uncinate fasciculus at the time of surgery does not interfere with language function [136], although removal of the uncinate fasciculus is associated with difficulty in recalling proper nouns [160].

## Inferior Fronto-Occipital Fasciculus

The inferior fronto-occipital fasciculus (IFOF) is a complex group of fibers that travels in the inferior sagittal striatum and temporal stem to connect the superior parietal lobe, occipital cortex, and temporobasilar area with the frontal lobe. The inferior fronto-occipital fasciculus was described by Curran and Dejerine [161]. This fascicle was not demonstrated in the excellent study of monkeys performed by Schmahmann and Pandya [19]. In monkeys, fibers entering the extreme capsule from the caudal parts of the orbital cortex, the ventro-lateral prefrontal cortex, and the frontal pole terminate in the middle superior and caudal inferior temporal region. Thus there is an analogous pathway in the monkeys and humans, although in the monkey, the fiber tract does not contain the robust occipital connections seen in humans [19].

## Dissections

Martino et al. reported on 14 hemispheres dissected using the Klingler fiber dissection technique [162]. They defined the inferior fronto-occipital fasciculus posterior to its passage through the external capsule. They noted that the inferior fronto-occipital fasciculus was composed of a superficial and a deep component. The superficial component received fibers from the superior parietal lobe and posterior portion of the middle and superior occipital gyri, joined the superior part of the sagittal striatum on the lateral surface of the atrium and continued over the roof of the temporal horn. The deep component receives fibers from the posterior portion of the lateral surface of the inferior occipital gyrus and the posterior temporobasal area, including the fusiform gyrus, temporo-occipital sulcus, and basal inferior temporal gyrus, and passes lateral to the temporal horn superficial to the optic radiations. At the level of the temporal horn, the inferior fronto-occipital fasciculus runs medial to the inferior longitudinal fasciculus. Dissecting four additional hemispheres, Martino demonstrated the relationship of the IFOF to the medial and inferior longitudinal fasciculi, the SLF, arcuate eminence, and optic radiations [117].

Sarubbo et al. defined the anterior destination of the inferior fronto-occipital fasciculus in an elegant set of dissections of ten hemispheres using a modified Klingler technique. From posterior to anterior, the fibers travel in the inferior sagittal striatum, above the temporal horn of the lateral ventricle, and in the temporal stem superior–posterior to the uncinate fasciculus beneath the ventral claustrum to constitute the posterior 2/3 of the ventral external capsule. The fibers then fan out to their destinations in the frontal lobe. Like Martino, they found that the inferior fronto-occipital fasciculus was composed of superficial and deep layers. The superficial layer connects to the pars triangularis and pars orbitalis of the inferior frontal lobe. The deeper component can be divided into three sub-tracts. The posterior component connects to the middle frontal gyrus and dorsolateral prefrontal cortex. The middle component connects to the middle frontal gyrus and lateral orbitofrontal cortex. The anterior component connects to the orbitofrontal cortex and frontal pole [40].

De Benedictis used the Klingler technique to define the frontal terminations of the IFOF in ten hemispheres. They noted a superficial and a deep fascicular bundle. The superficial bundle terminated in the pars triangularis and adjacent orbital cortex. The deep component terminated in dorsolateral prefrontal cortex, the middle portion of the middle frontal cortex, the lateral and anterior orbital cortex and frontobasal cortex [117].

## DTI

Catani et al. used DTI to delineate the inferior fronto-occipital fasciculus. They found that the inferior fronto-occipital fasciculus connects the inferolateral and dorsolateral frontal cortex with the posterior temporal and occipital cortex. The fibers narrow in the ventral external capsule and fan out anteriorly to the inferior and dorsal frontal lobe and posteriorly to the lateral occipital lobe, middle and inferior temporal gyri, lingual and fusiform gyri, and the inferior parietal lobe [101, 118].

Thiebaut de Schotten found that the inferior fronto-occipital fasciculus connected the inferior and basal occipital lobe with the inferior frontal gyrus, the medial fronto-orbital region, and frontal pole [31]. Some fibers were followed as high as the superior frontal gyrus.

Sarubbo et al. investigated the inferior fronto-occipital fasciculus in a single patient using DTI performed in a 4T MRI scanner. They found evidence for fibers that contributed to the superficial portion of the inferior fronto-occipital fasciculus, originating in the anterolateral inferior occipital gyrus and adjacent middle occipital gyrus and terminating in the inferior frontal gyrus [40]. The anterior deep component originated from the medial posterior portion of the inferior occipital gyrus at the border of the fusiform gyrus. The middle and posterior components originate from the anterolateral inferior occipital gyrus and adjacent inferior temporal gyrus. The streams of fibers converged as they ran forward over the temporal horn through the extreme capsule. The

fibers originating from the medial part of the inferior occipital gyrus and adjacent fusiform gyrus terminated in the orbital frontal cortex. Fibers terminating in the middle frontal gyrus and dorsolateral prefrontal cortex originate in the lateral inferior occipital lobe and adjacent posterior temporal lobe [40]. Similar anatomy was described by Lawes et al. based on DTI performed on 15 healthy males [105].

The exact relationship of the frontal connections of the ventral and dorsal language streams remains to be defined. Using high angular resolution diffusion imaging in twelve human volunteers, Frey et al. demonstrated that while superior longitudinal fasciculus/arcuate fasciculus connects to ventral premotor and pars operculum, pars triangularis connects to the superior temporal gyrus by fibers that pass through the extreme capsule [56, 112]. By the placement of their posterior region of interest for their fiber tracking, the authors may have inadvertently missed fibers traveling to the occipital lobe, and that the fiber's connections to the pars triangularis in humans are part of the inferior fronto-occipital fasciculus [39, 56, 112]. Similar connections have been demonstrated in the monkeys where the ventral premotor area and Brodmann area 44 connect superior longitudinal fasciculus III, but Brodmann area 45 connects to the superior temporal gyrus by fibers that run through the extreme capsule [17, 19, 20, 163, 164]. Several authors have found that the phonological system of the SLF/arcuate fasciculus connects to Brodmann's areas 44, 6, 8, and the IFOF mediating semantic function connects to Brodmann's areas 47, 45, and 46 [39, 165]. The exact contribution of each of the two systems to Brodmann's 47 is debated [31, 125]. De Benedictis, using fiber tract dissections, found overlap of the ventral and dorsal systems in Brodmann's areas 47, 6 [117]. In summary, it appears that the SLF/arcuate system connects to the more posterior inferior and middle frontal lobe and the IFOF connects to the more anterior of the SLF/arcuate connections.

## Function

Duffau et al. demonstrated that semantic paraphasias could be elicited by stimulating the inferior fronto-occipital fasciculus along its entire pathway [56, 70, 136]. Semantic paraphasias (as opposed to phonological paraphasias discussed earlier) are perturbations of the word's meaning. The substituted word is generally related to the intended word, being of the same category (dog instead of cat). In a series of articles Duffau et al. noted semantic paraphasias could be produced when stimulating along the entire length of the inferior fronto-occipital fasciculus [56, 70, 136]. Semantic paraphasias were induced along the sagittal striatum adjacent to the atrium of the lateral ventricle, under the superior temporal sulcus, beneath the insula in the ventral most portion of the external capsule, under the inferior frontal sulcus lateral to the caudate nucleus, and beneath the anterior most part of the superior limb of the circular sulcus [56, 70, 146]. Operating on eight patients with low-grade gliomas abutting the sagittal striatum, semantic paraphasias could be evoked in all patients when stimulating the upper part of the cavity corresponding to the IFOF [96]. In 17 patients with Gliomas of the frontal lobe, temporal lobe, or insula, semantic paraphasias could be elicited by stimulating the cortex superior or inferior to the posterior superior temporal sulcus, over the posterior middle frontal gyrus, or within the orbitofrontal cortex. Semantic paraphasias could be provoked stimulating under the superior temporal sulcus, under the anterior insula (extreme capsule), under the inferior frontal sulcus, and lateral to the head of the caudate. This fasciculus can mark the deep limit of resection in tumors of the temporal lobe, insula, inferior frontal gyrus, or middle frontal gyrus.

Moritz-Gasser et al. electrically stimulated the inferior fronto-occipital fasciculus in eight patients undergoing left temporo-occipital tumor resections while the patients were assessed for visual naming, semantic fluency, phonological fluency, and nonverbal semantic association [159]. Verbal semantic processing was tested by standard naming tasks, and nonverbal semantic processing was tested using a semantic matching test, (Pyramid and Palm Trees Test, PPTT). This test evaluates the patient's ability to access meaning from pictures and words, and does not rely on language production or comprehension. The semantic testing was designed to determine an

impairment at the cognitive level of semantic processing. The patient is shown one of 52 black and white pictures. For each target picture, two additional pictures are shown, one of which has a semantic link to the target picture. For example, if the target picture is a hand, the choices would be a picture of a glove and a shoe. Choosing the glove would be the correct answer. Stimulation of the inferior fronto-occipital fasciculus resulted in semantic paraphasias during naming tasks in all patients. During the nonverbal tasks, the patients became unaware of the semantic content of the pictures being shown and could not associate the pictures that were semantically linked. The authors interpreted this to mean that the inferior fronto-occipital fasciculus is important not just for semantic language processing but for awareness of semantic knowledge.

Stimulation of the white matter of the dorsolateral frontal lobe superior to Broca's area may impair cross modality semantic function [166]. Khan et al. demonstrated that stimulation of the inferior fronto-occipital fasciculus in the sagittal striatum or below the insula may produce perseveration [167].

## Cingulum

The cingulum is a long fiber bundle that connects regions of the brain involved with decision making, executive function, and emotion processing. Heilbronner and Haber studied the cingulum in nonhuman primates using tracer injection techniques [168]. They demonstrated that the cingulum consisted of a number of sub-bundles stretching from the area ventral to the genu of the corpus callosum to the region medial to the cingulate cortex and out to the medial inferior temporal lobes. Bundles of fibers leave the cingulum to connect to the cingulate cortex, striatum, anterior thalamus, amygdala, and adjacent cortex, especially in the orbital, dorsomedial and ventrolateral frontal lobes, precuneatus, retrosplenial cortex, and prosubiculum.

The part of the cingulum which connects the anterior cingulate cortex to the precuneatus is associated with inference based thinking [143]. In terms of thinking fast and thinking slow, the superior longitudinal fasciculus is involved in quick decisions and the medial frontal parietal circuits are more associated with thoughtful mentation [169]. The cingulum is a key pathway in the default network, the circuit that is postulated to organize thought not driven by external stimuli [170, 171]. DTI studies demonstrate abnormalities in the rostral dorsal cingulum in bipolar disorders and the subgenual cingulum in severe depression [172, 173].

## Motor Tracts

The corticospinal tract originates from Brodmann areas 4, 6 and the parietal lobe. Face fibers emanating from the posterior frontal lobe are anterolateral to the hand fibers which are anterolateral to the leg fibers. At the level of the superior limb of the circular sulcus which surrounds the insula, the motor fibers lay deep to the sensory face cortex and under the tip of the anterior long gyrus of the insula [174]. The fibers enter the posterior limb of the internal capsule between the globus pallidus and the thalamus with the face fibers at the genu anterior to the hand and leg fibers.

### Stimulation

Skirboll et al. reported on 20 patients with functional motor tracts within low- and high-grade tumors, defining the tracts using bipolar electrical stimulation. While immediate new deficits were noted in 73 % of patients following surgery, only one patient had persistent leg weakness [175].

Keles et al. demonstrated the utility of electrical monitoring by performing monitoring during cortical and subcortical stimulation of the internal capsule and corona radiata [176]. They reported on 294 patients who underwent subcortical mapping using bipolar 60 Hz stimulation. Sixty (20.4 %) of patients developed new motor deficits with 23 (38 %), 12 (20 %), and 11 (19 %) recovering to their preoperative state at 1 week, 4 weeks, and 3 months following surgery, respectively. Fourteen (4.8 %) of patients had a permanent deficit. As

expected, patients whose motor pathways were identified by electrical stimulation were twice as likely to have a postoperative deficit.

Mikuni et al. reported using subcortical bipolar train-of-five stimulation when operating on 40 patients with tumors within 2 cm of their pyramidal tracts. They were able to preserve motor function in all patients [177].

Eisner et al. operated on ten patients using subcortical bipolar stimulation to resect subcortical lesions close to motor fibers. No new permanent deficits were recorded [178].

Carrabba et al. reported operating on 146 patients with gliomas approximating the motor fibers. The motor cortex was identified by intraoperative bipolar stimulation in 133 (91 %) patients and the motor fibers were identified in 91 (62.3 %) of patients. Sixty-two (45.5 %) had a new subcortical postoperative motor deficit following the surgery. Deficits persisted in eight (5.4 %) of patients examined 1 month following the surgery. This group also noted the identification of subcortical fibers was associated with a greater risk of weakness [179].

Duffau et al. demonstrated that stimulating beneath the mouth motor/sensory cortex, the final pathway for speech production, resulted in anarthria [99]. These fibers can represent the deep and posterior limit of resection in tumors of the frontal precentral region [56].

## Comparison of Monkey and Human Studies

Detailed anatomy of white matter tracts have been worked out in monkey brains using autoradiography. Of course, this method is not applicable to human studies which rely on DTI and cadaver dissections. Many of the tracts found in monkeys are also found in humans, but the inferior fronto-occipital fasciculus which is so important in human language has not been demonstrated in monkeys [31, 111]. An analogous tract with similar frontal lobe connections passing through the extreme capsule and entering in the superior and middle temporal gyrus has been demonstrated [180]. While some tracts such as the superior longitudinal fasciculus I, II, III, cingulum, and uncinate fasciculus appear to be preserved, the inferior temporal and occipital connections of the superior longitudinal fasciculus, arcuate fasciculus, and inferior fronto-occipital fasciculus demonstrated in humans have not been demonstrated in monkeys [31, 181]. Thus the greatest discrepancies are found in the posterior temporal and extra striatal occipital areas, regions associated with language function.

## Plasticity

While plasticity has been demonstrated within the cortex, the white matter tract function seems to be more fixed [2]. Several stroke studies have noted more severe and prolonged deficits following white matter injury [102, 182].

Plasticity is not seen in the unique input and output areas of the cortex such as Brodmann's area 4 for motor function or area 17 for vision, but is present in the cortex involved with higher order processes that utilize short and long-range networks. Thus there is little plasticity in Brodmann's area 4, but there may be plasticity in the premotor areas. Similarly, there seems to be little plasticity in the white matter pathways connecting those input and output areas of cortex or important hubs such as Wernicke's and Broca's areas [2, 3].

## Language Function

Connections between the inferior frontal and posterior temporal language areas converging on the insula was postulated by Wernicke to account for patients with conduction aphasia [5]. He described a patient who had normal comprehension and relatively good language production, but who could not repeat. He attributed the patient's paraphasias to the inability of the temporal lobe to monitor the frontal lobe. The identification of perisylvian fibers connecting the frontal, parietal, and temporal lobes is attributed to Reil and Burdach and confirmed by Dejerine [6, 7, 12, 13].

Geschwind et al. [10, 11] resurrected the idea that conduction aphasia resulted from a lesion of the white matter connection between the frontal and temporal speech areas or an intermediate region of association cortex which served as a relay station between the two. Hickok and Poeppel proposed a dual track system similar to the ventral and dorsal tracts used to describe the visual system [183].

Each pathway has been proposed to mediate different language information with the dorsal pathway predominantly involved in language production and the ventral pathway predominantly involved in language understanding. While this partition is useful, it is far too simplistic as patients with dorsal lesions clearly have difficulty in understanding and patients with ventral lesions can have difficulty initiating speech.

Each pathway has been postulated to contain direct and indirect connections. The dorsal pathway's direct connection is the arcuate fasciculus and indirect connection is the limbs of the superior longitudinal fasciculus, SLF II, III, tp. The inferior fronto-occipital fasciculus is the direct connection of the ventral pathway, and the inferior longitudinal fasciculus and the uncinate fasciculus.

## Validation of DTI with Intraoperative Stimulation

Early reports of DTI reported results of fiber tracking in normal individuals, and then as part of preoperative MRI assessment. Holodny et al. reported the ability of DTI to demonstrate the corticospinal tract in eight patients harboring intracranial tumors, two extrinsic and six intrinsic [184]. In the two cases of extrinsic and in five out of six intrinsic tumors, the corticospinal tract was displaced. In the final case, the corticospinal tract was displaced and infiltrated. Mori et al. noted the effect of brain tumors on two white matter tracts, the superior longitudinal fasciculus and the corona radiata in two patients harboring anaplastic astroctyomas using DTI. In one patient, the white matter tracts were displaced and in the second, the white matter tracts were infiltrated [185]. Clark et al. reported using DTI to follow white matter pathways in four patients who had brain tumors. They found that they could track white matter pathways through areas with an increased T2 signal. They also demonstrated that white matter pathways could be disrupted or displaced by intrinsic brain tumors [186]. Hendler and colleagues [187], used a combination of functional MRI and DTI for pre-op planning in 20 patients with lesions approximating the motor and sensory pathways, and Mamata et al. established the feasibility of performing intraoperative DTI using an intraoperative 0.5 Tesla magnet [188].

In their initial experience with intraoperative DTI, Nimsky et al. compared the position of the corticospinal tract as determined on pre- and intraoperative DTI in 19 patients (17 of whom underwent craniotomies) [44]. The pyramidal tract was seen to shift up to 8 mm in a postoperative follow-up study. They also reviewed their experience using pre and intraoperative DTI to demonstrate the course of white matter tracts in 37 patients undergoing glioma surgery [189]. They noted that fiber tracts adjacent to mass lesions could be displaced up to 20 mm when compared to the tracts in the unaffected hemisphere. In 34 of the 37 patients, significant intraoperative shifting of the white matter tracts up to 15 mm was noted. The amount of preoperative shift was proportional to the tumor's size but the direction of the intraoperative shift could not be predicted.

Preoperative fiber tract mapping with DTI improves operative results. In 2007, Wu et al. performed a randomized study of surgery with and without preoperative mapping of the pyramidal tract in 238 patients. The authors found an improvement in extent of resection in patients harboring high-grade tumors and a decrease in postoperative motor deficits (32.8 % vs. 15.3 %) in patients who had preoperative MRI tractography [190]. Ius et al. reported on 190 patients who underwent craniotomy for low-grade gliomas, of which 117 had preoperative fMRI/DTI. Patients having preoperative DTI enjoyed a greater extent of resection and postoperative survival [2].

Several authors have compared DTI depictions of fiber tracts with intraoperative detection of fiber tracts using electrical stimulation. Kinoshita et al. compared preoperative DTI-based tractography of the corticospinal tract with intraoperative electrical stimulation [191]. The fiber tracing demonstrated the relationship between the tumor and the corticospinal tract and tailored the electrical stimulation, saving operative time. The authors concluded that the DTI-based tractography underestimated the size of the corticospinal tract. Kamada et al. compared preoperative DTI-based tractography of the corticospinal tract with intraoperative electrical stimulation using a monopolar train-of-five technique in six patients. In the three patients in whom the distance between the corticospinal tract and the tumor was less than 1 cm, intraoperative electrical stimulation confirmed the position of the corticospinal tract as predicted by preoperative DTI. In the three patients in whom the corticospinal tract was greater than 1 cm, electrical stimulation failed to elicit movement [192].

Berman et al. compared the location of DTI-determined pyramidal targets with motor tracts determined by intraoperative stimulation in 16 patients undergoing surgery for intraparenchymal brain tumors. The mean distance between the positive stimulation sites and DTI determined tracts was 8.7 ± 3.1 mm [71, 193].

Bello et al. reported their experience in correlating DTI-based tractography of motor and language tracts with intraoperative subcortical bipolar stimulation. In 34 patients with tumors adjacent to motor fibers, the DTI-predicted location for motor fibers was confirmed with a sensitivity of 95 % and a specificity of 100 %. In 33 patients with tumors adjacent to the superior longitudinal fasciculus, the DTI-based tractography of the superior longitudinal fasciculus was compared with the results of intraoperative subcortical mapping and found to have sensitivity 98.2 % for superior longitudinal fasciculus and 88.6 % for inferior fronto-occipital fasciculus for language function. Phonemic paraphasias were found at 169 subcortical sites corresponding to the superior longitudinal fasciculus as depicted on DTI tractography. Semantic paraphasias were evoked by electrical stimulation in 26 sites in the vicinity of the inferior fronto-occipital fasciculus. Twenty-three sites corresponded to the tract as demonstrated by DTI tractography. Interestingly, semantic paraphasias were elicited in nine sites corresponding to the uncinate fasciculus. The authors subsequently updated their series to 230 patients [194]. They noted that DTI did not localize the corticospinal tract close to the motor cortex. They also noted a high rate of temporary postoperative deficits even with intraoperative mapping when the DTI fiber tractography demonstrated that the fiber tracts were displaced or infiltrated [45].

Okada et al. used bipolar subcortical stimulation to confirm the location of corticospinal tract as demonstrated by preoperative DTI fiber tractography [195]. They found a good correlation between the predicted position of the corticospinal tract and intraoperative stimulation in four patients, but in three additional patients where the corticospinal tract was expected to be close to the resection cavity, no movement could be stimulated. In a subsequent report from this institution, Mikuni et al. reported to be able to stimulate the corticospinal tract in 18 of 20 patients in whom the corticospinal tract was located within 1 cm of the resection cavity [177]. They reported that when the fiber tracts were disrupted on DTI, they could not stimulate a subcortical motor response.

Leclercq et al. compared preoperative reconstructions of the inferior fronto-occipital fasciculus, subcallosal fasciculus, premotor tracts, and arcuate fasciculus with the results of intraoperative bipolar subcortical electrical mapping in ten patients. 17 of 21 positive stimulation sites were within 6 mm of DTI-tractography demonstrated tracts while four positive stimulation sites were not in the vicinity of DTI-demonstrated tracts. In three cases, the stimulation was at the depth of the opercular-insular sulcus and thus could have resulted from stimulation of fibers of the extreme capsule. In the remaining case, the stimulation was probably of the arcuate fasciculus that was interrupted by the tumor [69]. Gonzalez-Darder et al. compared DTI tractography with subcorti-

cal stimulation during the resection of 17 gliomas located in or close to the motor cortex or motor fibers. Fifty-five positive stimulation sites were identified in 13 patients at a distance averaging 7.3 mm (1.8–13.4 mm) from the position of the corticospinal tract determined from preoperative DTI tractography [196].

Ohue et al. evaluated the accuracy of DTI tractography in defining the corticospinal tract using intraoperative bipolar train-of-five subcortical stimulations in 32 patients. Postoperative MRI scans including DTI tractography were performed. Postoperative DTI tractography showed a shift in the corticospinal tract in 26 (81 %) of patients ranging from 1.7 to 23.6 mm and a distance from the resection cavity to the corticospinal tract of 1.7–18.9 mm in the 28 patients with positive intraoperative stimulation. There was a correlation of 1 mA/1 mm between the minimum amperage for stimulation and the distance to the corticospinal tract. This is surprising as bipolar stimulation was being used [57]. Zhu et al. compared the location of the corticospinal tract determined by preoperative DTI with intraoperative subcortical mapping in 58 patients. They found a 2–14.7 mm (5.2 ± 2.2 mm) disparity between the two methods demonstrating that preoperative DTI cannot replace intraoperative subcortical mapping [61].

## Results of Intraoperative Subcortical Stimulation

Several authors have reported their postoperative results following craniotomy with subcortical mapping. Mikuni et al. reported using a train-of-five bipolar stimulation and intraoperative navigation with preoperative DTI tractography in 40 patients. They were able to stimulate the corticospinal tract in 18 of 20 patients whose corticospinal tract was estimated to be less than 1 cm from the lesion, but only 3 of 15 patients whose lesion was 1–2 cm from the lesion. Two patients had improvement in their preoperative weakness and two patients had new temporary weakness. No patient suffered permanent weakness following surgery [177].

Skirball et al. reported operating using cortical and subcortical stimulation on 26 patients in whom functional white matter tracts lay within the tumor. Although 19 had new deficits immediately following the surgery, 3 months after surgery, only one had persistent leg motor weakness and two had persistent hand numbness [175].

Gonzalez-Darder et al. operated on 17 patients with lesions close to the motor cortex (12 patients) or the motor fibers (5 patients) employing preoperative DTI tractography and intraoperative subcortical stimulation. Ten patients (58.6 %) of patients had preoperative weakness. Twenty-four hours after surgery 12 patients (70.6 %) had deficits. One month after surgery eight patients (47.1 %) had motor deficits with only one having a deficit impairing daily activities. The authors found a positive correlation between risks of motor deficit and estimated distance to corticospinal tract [196].

Ohue et al. used preoperative DTI tractography and intraoperative subcortical electrical stimulation to guide resection in 32 patients harboring intrinsic gliomas close to motor fibers. Twenty-one patients manifested motor weakness immediately after surgery, with all patients returning to their preoperative strength or better 1 month following surgery. Fourteen patients had a total tumor resection with an overall mean rate of resection of 93.1 % [57].

Bello et al. reported results of subcortical mapping when operating on 88 gliomas suspected to be close to white matter tracts involved with language [197]. Language tracts were identified in 57 % of patients. Stimulation of the periventricular white matter caused dysarthria, the head of the caudate perseverations, anterior border of the ventricle anomia, anterior border of the insula phonemic paraphasias, at the tip of the temporal lobe semantic paraphasias, and along the lateral border and roof of the temporal horn anomia. Stimulating deep to the parietal lobe caused phonemic paraphasias except under the inferior border where semantic paraphasias were elicited. Identification of language tracts was associated with postoperative deficits in 67.3 % of patients which resolved in all but 2.3 % of cases. The same group 1 year later reporting on

64 patients noted that 94 % of patients whose motor tracts and 90 % whose language tracts that were identified by electrical stimulation, at 1 month follow-up 88 % of patients with language lesions and 89 % of patients with motor lesions had normal exams [194]. In a follow-up report employing continuous motor mapping (MEP) monitoring and cortical and subcortical mapping with bipolar 60 Hz in 230 patients, of 157 cases with intraoperative cortical mapping of the corticospinal tract, 109 had immediate postoperative deficits. Of 140 patients who had attempted mapping of the superior longitudinal fasciculus, 118 manifested postoperative deficits, and of 113 who had attempted mapping of their inferior fronto-occipital fasciculus, 105 had an immediate postoperative deficit. The deficits occurred in the majority of patients whose preoperative DTI demonstrated infiltration or displacement. All deficits resolved by 1 month post-surgery.

Keles et al. reported using subcortical motor stimulation in the resection of 294 gliomas located within or adjacent to motor pathways. Sixty (20.4 %) incurred new motor deficits which resolved in all but 14 patients at the end of 3 months. Zhu et al. used preoperative DTI and intraoperative monopolar 60 Hz constant current stimulation of the corticospinal tract to operate on 58 patients with gliomas. Seventeen patients (29.3 %) suffered postoperative worsening of contralateral motor function which persisted for 1 month in six patients (10 %) [176].

Fujii et al. used bipolar stimulation to map the aslant fasciculus in five patients with left frontal gliomas [108]. Stimulation of the aslant pathway resulted in hesitation of speech initiation or speech arrest defining the deep posterior limit of the tumor resection. No patient had a language deficit when tested 10–14 days following surgery.

Duffau and his colleagues have a series of publications reporting their experience with cortical and subcortical mapping during glioma resection. In 2002, Duffau et al. reported on early results of subcortical mapping of language fibers in 30 patients with left hemisphere gliomas [61]. They noted that stimulation of the subcallosal fasciculus produced disorders of initiation of speech, the periventricular white matter produced dysarthria, and the arcuate fasciculus produced anomia. Twenty-seven had postoperative deficits which completely recovered in 3 months except for a mild reduction in spontaneous speech in three of the patients with a postoperative supplementary motor syndrome and some mild sensory deficits in the patients with retrocentral lesions. That same year they also reported their experience using subcortical mapping to guide their resection of 14 gliomas involving the nondominant striatum. Ten patients had a postoperative motor deficit that resolved in all but one within 3 months [198].

In 2003, Duffau et al. reported on 103 patients in whom subcortical mapping was used in the resection of their low-grade gliomas. Eighty percent of patients had immediate postoperative worsening of their neurological function with 94 % recovering over the next 3 months. Eight patients had mild persistent weakness or delay of spontaneous speech [199].

A 2005 report focused on 17 patients with lesions adjacent to the semantic system. Semantic paraphasias were generated with electrical stimulation below the posterior superior temporal sulcus, in the anterior external capsule beneath the anterior-inferior insula, or beneath the lateral orbitofrontal and dorsolateral prefrontal cortex [70].

In 2008, Duffau et al. reported on their results operating 115 patients with grade II gliomas with intraoperative language mapping [56]. They demonstrated that stimulating the arcuate fasciculus results in phonemic paraphasias; stimulation of the inferior fronto-occipital fasciculus results in semantic paraphasias; stimulation of the fronto-parietal portion of the superior longitudinal fasciculus results in dysarthrias and anarthria, and stimulation of the subcallosal fasciculus results in difficulty initiating speech, and stimulation of the periventricular white matter medial to the motor strip results in anarthria. All patients had postoperative deficits with 113 returning to baseline within 3 months. Two patients had residual hemiparesis secondary to lenticulostriate artery injury.

## Monitoring

Intraoperative neurophysiology includes not only electrical stimulation but also on-line continuous assessment of motor and sensory pathways.

The central sulcus can be detected by recording sensory evoked potentials across the cortex. The evoked potential will have opposite polarity when simultaneously comparing evoked potentials recorded from the precentral and postcentral gyri. Using this technique, the central sulcus can be localized in 95 % of patients [60, 68].

Motor evoked potentials can be used to monitor function while the tumor is being resected [74, 200–202]. Decreases in amplitudes of greater than 50 % or increases in threshold stimulation of 20 % or 4 mA have been defined as warnings of impending neurological deficits.

Seidel et al. compared intermittent subcortical motor mapping and continuous motor evoked potentials for their efficacy in predicting permanent neurological damage in 100 consecutive patients undergoing tumor resection [201]. They found that significant changes in motor evoked potentials were most predictive of a permanent deficit but that a lowering of stimulation threshold below 3 mA provided a warning prior to incurring a deficit.

Sala et al. used continuous motor evoked potentials and monopolar train of five cortical and subcortical tract mappings in operating on 51 patients with gliomas close to the motor fibers. Eight patients lost motor evoked potentials during the surgery but the motor evoked potentials were restored by intraoperative interventions. Twenty-four percent of the total population had a mild worsening of their motor function in the immediate postoperative period. No patient who had restoration of the motor evoked potentials had a significant postoperative motor deficit [76].

## Conclusion

The early combined efforts of neurologists, neurosurgeons, neuro-anatomists, and neuropathologists paved the way for neurosurgeons today to utilize preoperative and intraoperative testing for identification and preservation of the critical white matter pathways. Our understanding of the function of these tracts has blossomed over the past half century, with novel functions assigned and new insights gained. Awake craniotomy with electrical stimulation allows surgeons to localize essential white matter tracts in real time. DTI provides the surgeon with an idea of displacement of white matter tracts prior to surgery. Both DTI and intraoperative mapping have proved useful to the surgeon in minimizing postoperative neurological deficit. Advances in neuro-imaging and newer imaging techniques can provide useful information prior to surgery but at the time of this writing, intraoperative stimulation and mapping remains the best method for preservation of function while also allowing maximum possible tumor resection.

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# Intraoperative Cortical Stimulation and the Value of Negative Mapping

Nader Sanai and Mitchel S. Berger

## Basic Principles

Direct cortical stimulation has been employed in neurosurgery since 1930, first by Foerster [1], and then later, by Penfield [2–4]. In recent years, the technique of intraoperative cortical stimulation has been adopted for the identification and preservation of language function and motor pathways. Stimulation depolarizes a very focal area of cortex which, in turn, evokes certain responses. Although the mechanism of stimulation effects on language are poorly understood, the principle is based upon the depolarization of local neurons and also of passing pathways, inducing local excitation or inhibition, as well as possible diffusion to more distant areas by way of orthodromic or antidromic propagation [5]. Studies employing optical imaging of bipolar cortical stimulation in monkey and human cortex have shown precise local changes, within 2–3 mm, after the activation of cortical tissue [6, 7]. With the advent of the bipolar probe, avoidance of local diffusion and more precise mapping have been enabled with an accuracy estimated to be approximately 5 mm [6].

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## Rationale for Intraoperative Cortical and Subcortical Stimulation Mapping

Hemispheric gliomas are often located within or adjacent to functional areas (e.g., rolandic cortex, supplementary motor areas, corona radiata, internal capsule, and uncinate fasciculus). Because gliomas have a tendency to invade underlying white matter tracts, it is important to identify both cortical sites and their descending pathways for the motor and somatosensory systems. Although extensive resection of a tumor involving the nondominant temporal lobe may be achieved without functional consequences other than a quadrantanopia, surgical resections in the dominant temporal lobe are more challenging due to the variable localization of language. Thus, although traditional neurosurgical teaching restricts temporal lobe resections to within 4 cm of the temporal tip and limits the removal of the superior temporal gyrus, dominant temporal lobe resections can nevertheless be associated with permanent postoperative language deficits.

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Thus, prediction of cortical language sites through classic anatomical criteria is inadequate, as there is significant individual variability of cortical organization [8–11], distortion of cerebral topography from tumor mass effect, and functional reorganization through plasticity mechanisms [12–14]. A consistent finding of language stimulation studies has been the identification of significant individual variability among patients [9]. Speech arrest is variably located and can go well beyond the classic anatomical boundaries of Broca's area for motor speech. It typically involves an area contiguous with the face-motor cortex and, yet, in some cases is seen several centimeters from the sylvian fissure. This variability has also been suggested by studies designed to preoperatively predict the location of speech arrest based upon the type of frontal opercular anatomy [15] or using functional neuroimaging [16–22]. Similarly, for temporal lobe language sites, one study of temporal lobe resections assisted by subdural grids demonstrated that the distance from the temporal pole to the area of language function varied from 3 to 9 cm [23]. Functional imaging studies have also corroborated such variability [24]. Furthermore, because functional tissue can be located within the tumor nidus [25], the standard surgical principle of debulking tumor from within to avoid neurologic deficits is not always safe. Consequently, the use of intraoperative cortical and subcortical stimulation to accurately detect functional regions and pathways is essential for safely removing dominant hemisphere gliomas to the greatest extent possible.

It is recommended that, for any tumor involving the dominant temporal, mid- to posterior frontal, and mid- to anterior parietal lobes, an awake craniotomy should be employed to identify language sites before the tumor is removed. Functional magnetic resonance imaging (fMRI) may also provide preoperative assessment of sensory and motor pathways and has been shown to be valuable in determining the rolandic cortex. This method is not reliable, however, for identifying language sites and does not provide an adequate replacement for intraoperative stimulation mapping.

## Preoperative Assessment and Surgical Suitability

The patient's neurological status should be assessed preoperatively to determine the extent of motor or language function impairment, if any. If the patient has severe hemiparesis or hemiplegia, motor mapping will often not be useful. However, if antigravity movements are present preoperatively, it is usually possible to stimulate both cortical and subcortical motor pathways intraoperatively. In children younger than 5 or 6 years of age, due to cortical electrical inexcitability, somatosensory evoked potentials (SEPs) can be used to identify the central sulcus.

In addition to testing motor and sensory function, it is also imperative to assess the patient's language function intraoperatively to determine if the baseline naming error rate is <25 %. Similarly, those patients who will undergo intraoperative mapping for language sites should be preoperatively tested for language errors by being presented a series of slides with common objects to be named. After confirming that the face-motor cortex and Broca's area are functional by asking the patient to protrude the tongue and count to 10, slides of common objects are shown. Each slide will start with a phrase such as "this is a … " or "these are … " to test reading and speech output. Patients must be able to name common objects with less than a 25 % baseline error rate, based on presenting each slide three times.

In patients who have moderate to severe dysphasia in either comprehension or expression, successful language mapping will not be possible. Therefore, this group of patients may either be operated on asleep, without any attempt to do more than an internal decompression, or challenged with steroids for 7–10 days and reevaluated regarding their baseline error rate in naming. An alternative approach may be to biopsy the tumor, confirm histopathology, and then treat the lesion with chemotherapy to reduce its size and induce functional improvement that will subsequently allow for intraoperative mapping.

In 85 % of the population, the left hemisphere is dominant for language, whereas language representation is bilateral in 9 %, and right-side

dominance is present in only 6 %. The dominant hemisphere is on the left for 98–99 % of right-handed individuals. When in doubt, cerebral dominance may be verified using Wada's (intracarotid amytal) test or estimated using functional MRI or magnetic source imaging (MSI). On preoperative MRI, the central sulcus, and the motor strip that is located within the gyrus directly in front of it, is identified using the most cranial (rostral, superior) cuts of axial T2-weighted MR images. This landmark is a reliable marker for the motor cortex, regardless of mass effect, and allows one to predict where the functional motor region will be before surgery. On mid-sagittal and near mid-sagittal MR images, the rolandic (i.e., somatosensory-motor) cortex is identified by following the cingulate sulcus posteriorly and superiorly to its termination point. These MRI landmarks serve as useful guides to preoperatively determine the proximity of the lesion to the motor cortex.

## Intraoperative Preparation

The patient is brought to the operating room and placed in the position appropriate for the area to be exposed. Special care is given to padding and protecting all extremities. A Foley catheter is inserted regardless of the need for osmotic diuretics. The head is fixed in position using a Mayfield clamp and local analgesia. The area of the scalp around the incision is infiltrated with a local anesthetic consisting of a 1:1 ratio of lidocaine (0.5 %) to Marcaine (0.25 %), combined with bicarbonate. A heating blanket is used to keep the core temperature above 36.5 °C. If the patient's temperature drifts too low, especially under general anesthesia, cortical stimulation mapping will be difficult due to cortical inhibition. An intravenous propofol drip maintains the sedative hypnotic anesthesia to keep the patient asleep. An alternative is dexmedetomidine, which lowers the risk of respiratory depression and therefore is advantageous for patients with potentially high intracranial pressure; although emergence from this agent is less rapid than propofal. In case of a decrease in the arterial oxygen saturation, oxygen is administered through a nasal cannula. Prophylactic antibiotics are routinely used and given during the induction phase of anesthesia. Preoperative antieplieptics (e.g., 1 g fosphenytoin) are administered to minimize the risk of intraoperative seizures.

## Intraoperative Stimulation of Cortical and Subcortical Pathways

In general, a limited craniotomy should expose the tumor and up to 2 cm of surrounding brain. Because the dura is pain-sensitive, the area around the middle meningeal artery should be infiltrated with the lidocaine-marcaine mixture to alleviate discomfort while awake. Prior to dural opening, the patient should be awakened and encouraged to hyperventilate briefly in order to relax the brain. Using bipolar electrodes, cortical mapping is started at a low stimulus (1 mA per channel) and increased to a maximum of 6 mA, if necessary. A constant-current generator delivers biphasic square wave pulses (each phase, 1.25 ms) in 4-s trains at 60 Hz across 1-mm bipolar electrodes separated by 5 mm. Stimulation sites (approximately 10–20 per subject) can be marked with sterile numbered tickets. Throughout motor and language mapping, continuous electrocorticography should be used to monitor afterdischarge potentials and, therefore, eliminate the chance that speech or naming errors are caused by subclinical seizure activity. The best management of intraoperative stimulation-induced focal motor seizures or stimulation-induced afterdischarge potentials is rapid cortical irrigation at the stimulation site with ice-cold Ringer's solution. This will abruptly stop the seizure activity originating from the irritated cortex without using short-acting barbiturates. The current necessary to evoke motor movement will vary depending on the anesthetic condition of the patient, with lower currents used under awake conditions. The motor strip is stimulated in the asleep patient with a starting current of 2 mA per

channel, and reduced to 1 mA when stimulating the awake patient. The amplitude of the per-channel current is adjusted in 1–2 mA increments until motor movements are identified. A total current above 16 mA (8 mA per channel) has never been necessary to evoke sensory or motor response. Most commonly, the inferior aspect of the rolandic cortex is first identified by eliciting responses in the face and hand. As the leg motor cortex is tucked away against the falx, a strip electrode may be inserted along the falx, and stimulation using the same current applied to the lateral cortical surface may be delivered through it to evoke leg motor movements. This maneuver is safe due to lack of bridging veins between the falx and the leg motor cortex. Similarly, if the craniotomy is near but not overlying the rolandic cortex, a subdural strip electrode may be inserted under the dural edge and stimulated to evoke the desired response.

Once the motor cortex is defined, the descending tracts may be found using similar stimulation parameters. Descending motor and sensory pathways may be followed into the internal capsule and inferiorly to the brainstem and spinal cord. This is especially recommended during resection of infiltrative glial tumors because functioning motor, sensory, or language tissue can be located within a grossly obvious tumor or surrounding infiltrated brain. The current spread associated with bipolar stimulation is limited to 2 or 3 mm. If the motor cortex is not identified under any circumstance by using a functional stimulator, an attempt to identify the subcortical pathway is made using a current between 5 and 10 mA. One of the potential reasons for failure to find functional cortical sites is inability to open the dura overlying the cortex because of scar tissue. Another explanation could be the anesthetic regimen. A peripheral nerve stimulator is used to confirm a train of four muscle contractions before stimulating the cortex or subcortical white matter. If cortical sites of motor function are found and subcortical pathways cannot be identified, then repetitive stimulation of the cortical site is performed to ensure that the cortex and its descending pathways are intact. Tumor resection should be followed by a final stimulation of cortical sites to confirm that the pathways are intact. Even if the patient's neurological status is worse postoperatively, the presence of intact cortical and subcortical motor pathways implies that the deficit will be transient and resolve in days to weeks. Although somatosensory evoked potentials (SSEPs) may be helpful in identifying the central sulcus, they do not help in localizing descending subcortical motor and sensory white matter tracts. Determination of the subcortical pathways is important while removing a deeply located tumor within or adjacent to the corona radiata, internal capsule, insula, supplementary motor area, and thalamus. Because the current spread from the electrode contacts is minimal during bipolar stimulation, resection should be stopped when movement or paresthesia is evoked.

## Identification of Cortical and Subcortical Language Sites

Speech arrest is based upon blocking number counting without simultaneous motor response in the mouth or pharynx. Dysarthria can be distinguished from speech arrest by the absence of perceived or visible involuntary muscle contraction affecting speech. For naming or reading sites, cortical stimulation is applied for 3 s at sequential cortical sites during a slide presentation of line drawings or words, respectively. All tested language sites should be repeatedly stimulated at least three times. A positive essential site can be defined as an inability to name objects or read words in 66 % or greater of the testing per site. In all cases, a 1 cm margin of tissue should be measured and preserved around each positive language site in order to protect functional tissue from the resection [26]. The extent of resection is directed by targeting contrast-enhancing regions for high-grade lesions and T2-hyperintense areas for low-grade lesions. Some groups advocate the use of language mapping along subcortical white matter pathways, as well [27, 28].

Despite the considerable evidence supporting the use of intraoperative cortical stimulation mapping of language function, the efficacy of this technique in preserving functional outcome following aggressive glioma resection remains poorly under-

stood. Nevertheless, the long-term neurological effects after using this technique for large, dominant-hemisphere gliomas are important to define in order to accurately advocate its use [29].

No Level I randomized trial exists for language mapping. Our experience with 250 consecutive dominant hemisphere glioma patients (WHO grades II–IV) suggests that functional language outcome following awake mapping can be favorable, even in the setting of an aggressive resection [30]. Overall, 159 of these 250 patients (63.6 %) had intact speech preoperatively. At 1 week postoperatively, 194 (77.6 %) remained at their baseline language function while 21 (8.4 %) worsened and 35 (14.0 %) had new speech deficits. However, by 6 months, 52 (92.8 %) of 56 patients with new or worsened language deficits returned to baseline or better, and the remaining 4 (7.1 %) were left with a permanent deficit. Interestingly, among these patients, any additional language deficit incurred as a result of the surgery improved by 3 months or not all. Thus, using language mapping, only 1.6 % (4 of 243 surviving patients) of all glioma patients develop a permanent postoperative language deficit. One explanation for this favorable postoperative language profile may be our strict adherence to the "one-centimeter rule," first described by Haglund et al. which demonstrated that, for temporal lobe tumors, a resection margin of one centimeter or more from a language site significantly reduces postoperative language deficits [31].

## Identification of Cortical and Subcortical Motor Sites

For patients with gliomas that are located within or adjacent to the rolandic cortex and, thus, the descending motor tracts, awake or asleep stimulation mapping of cortical and subcortical motor pathways enables the surgeon to identify these descending motor pathways during tumor removal and achieve an acceptable rate of permanent morbidity in these high-risk functional areas [32–34]. Akin to speech mapping techniques, no Level I trial exists for motor mapping. The best evidence published comes from several level III studies over the last 15 years; all studies lack long-term survival data. In one recent study, new immediate postoperative motor deficits were documented in 59.3 % of patients in whom a subcortical motor tract was identified intraoperatively and in 14.5 % of those in whom subcortical tracts were not observed; permanent deficits were observed in 6.5 and 3.5 % of patients (a non-significant difference), respectively [32]. Another study of subcortical motor pathways in 294 patients who underwent surgery for hemispheric gliomas, 14 patients (4.8 %) had a persistent motor deficit after 3 months. Interestingly, in this study patients whose subcortical pathways were identified intraoperatively were statistically significantly more prone to develop an additional transient or permanent motor deficit (27.5 % vs. 13.1 %) [34]. In another study consisting of 60 patients (44 with glioma) with an 87 % gross total or subtotal (<10 cm [35] residual) resection rate, the overall neurological morbidity was 5 % after using cortical motor mapping [33]. Thus, collectively the recent literature suggests that intraoperative cortical and subcortical motor mapping can safely identify corridors for resection, as well as define the limits of tumor resection.

## The Value of Negative Mapping

In contrast to the classic mapping principles practiced in epilepsy surgery, where 95–100 % of operative fields contain a positive language site, a paradigm shift is emerging in brain tumor language mapping, where positive language sites are not always found prior to resection. In our practice, because of our use of tailored cortical exposures, less than 58 % of patients have essential language sites localized within the operative field (Fig. 1). Our experience suggests that it is safe to employ a minimal exposure of the tumor and resect based upon a negative language map, rather than rely upon a wide craniotomy to find positive language sites well beyond the lesion. However, language mapping techniques such as this are generally more successful and safer at high-volume neurosurgical centers.

Negative language mapping, however, does not necessarily guarantee the absence of eloquent

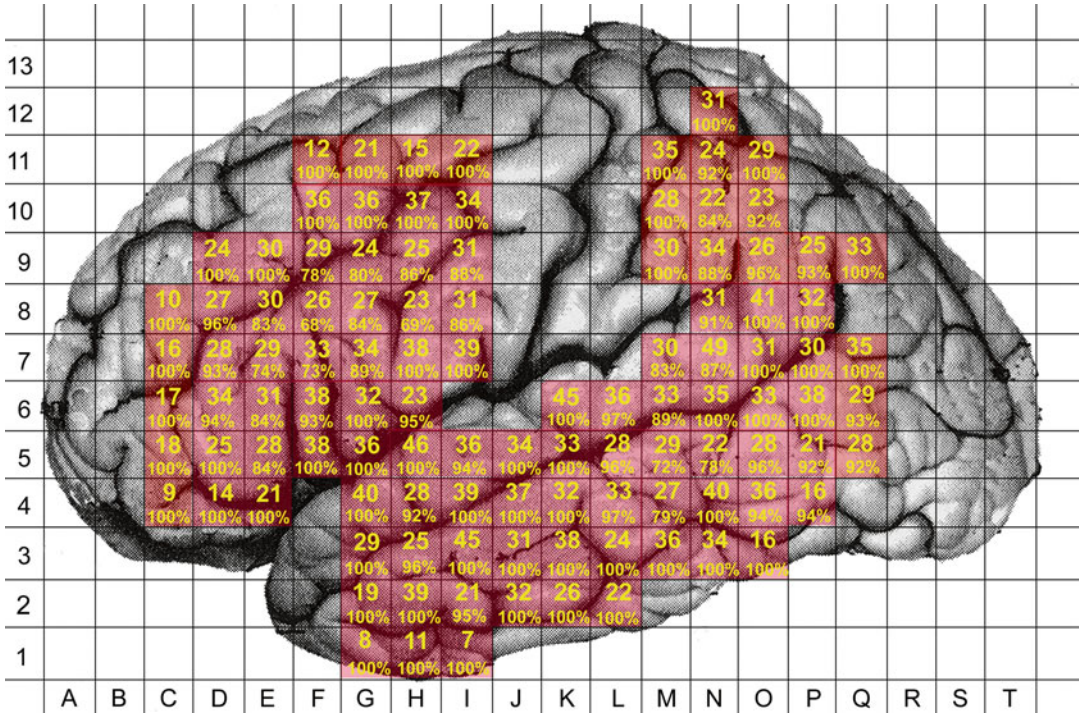


**Fig. 1** Negative language sites within the dominant hemisphere. A lateral view of the dominant hemisphere cortex specifying the location of all negative language sites per square centimeter. At each site, the upper value denotes the total number of patients stimulated and the lower value represents the percentage of these patients with no detectable language function at that site. (Adapted from Sanai et al. The New England Journal of Medicine, 358:18–27, 2008)

sites. Despite negative brain mapping, permanent postoperative neurologic deficits have been reported [36]. In our experience with 250 consecutive dominant hemisphere glioma patients, all four of our patients with permanent postoperative neurologic deficits had no positive sites detected prior to their resections. Other cases of unexpected postoperative deficits have also been attributed to progressive tumor infiltration into functional areas [37]. Furthermore, both intraoperative stimulation and functional imaging techniques have provided evidence for redistribution of functional neural networks in cases of stroke [13, 35, 38], congenital malformations [39, 40], brain injury [41], and tumor progression [13, 14, 42]. Not surprisingly, it has been hypothesized that brain infiltration by gliomas leads to reshaping or local reorganization of functional networks as well as neosynaptogenesis [43, 44]. This would explain the frequent lack of clinical deficit despite glioma growth into eloquent brain areas [13, 42, 45], as well as the transient nature of many postoperative deficits. In the case of language function located in the dominant insula, the brain's capacity for compensation of functional loss has also been associated with recruitment of the left superior temporal gyrus and left putamen [45].

## Postoperative Patient Management

Following surgery, patients are managed in the intensive care unit for up to 48 h. Antiepileptic levels are maintained above the upper limit for 3–5 days postoperatively, and then gradually lowered to the therapeutic range. A postoperative scan is obtained within 48 h of surgery to avoid postoperative enhancement representing surgical trauma. Dexamethasone is maintained at the dose of 16 mg/day and tapered slowly depending on the remaining mass effect on the postoperative scan. Patients with a transient and resolving pare-

sis or speech deficit may benefit from a short course of inpatient rehabilitation and speech therapy, although it is not necessary. Our current data indicate that for patients who started with no language deficit preoperatively, their new postoperative deficits resolve entirely by 3 months. For those with a preoperative language deficit, however, if they did not return to baseline by month 3, their deficit is likely permanent. When using stimulation mapping methods to identify subcortical pathways, the surgeon is able to achieve an acceptable risk of permanent motor deficits in a high-risk patient population, which consists of patients with gliomas that are within or adjacent to motor tracts. In this setting, if both cortical and subcortical sites are found with stimulation mapping, one can expect a 7.6 % rate of permanent motor deficits postoperatively, of which only 2.3 % of our patients had two-fifths strength or less. In cases in which subcortical pathways could not be identified but for whom the functionally intact status was confirmed by stimulation of the corresponding cortical sites, the incidence of permanent morbidity was 2.3 %, and no patient had two-fifths function or less. Our results indicate that subcortical stimulation methods can be applied in patients whose tumors are located within or adjacent to functional motor pathways and will result in an acceptable rate of postoperative morbidity that is mostly transient.

## Literature Review: Assessing the Value of Intraoperative Stimulation Mapping

In the recent literature, approximately 90 publications examine the utility of intraoperative stimulation mapping techniques in achieving greater extent of resection for gliomas while minimizing morbidity. Within these studies, cohorts varied between 20 and 648 patients, with a median of 50 patients per study. Nearly all these reports provide Level III evidence in support of this microsurgical adjunct, with the exception of two randomized studies [46, 47] that examined anesthetic or fluorescence-guided techniques to maximize extent of resection.

A recent meta-analysis of this growing literature included 8091 patients and identified intraoperative cortical stimulation mapping as predictive of a twofold reduction (3.4 % vs. 8.2 %) in late severe neurological deficits in adult patients with supratentorial infiltrative gliomas [48] (Fig. 2). Importantly, this additional benefit did not come at the expense of extent of resection (75 % GTR with mapping vs. 58 % without mapping), even though lesions were more often located in eloquent locations (99.9 % vs. 95.8 %). Typically, the observed transient neurologic deficits usually subsided within a few weeks to 3 months after resection and were due to the proximity of critical brain structures adjacent to the resection cavity. Ultimately, a randomized controlled trial to determine the impact of awake craniotomies and stimulation mappings will be necessary to control for all known and unknown confounders inherent to the existing observations studies.

## Conclusions

Glioma resections using awake craniotomy and intraoperative stimulation mapping techniques are associated with fewer neurological deficits and more extensive resection. Unlike motor function, speech and language are variably distributed and widely represented, thus emphasizing the utility of language mapping in this particular patient population. Using this approach, and in conjunction with standardized neuroanesthesia and neuromonitoring, the postoperative motor and language resolution profiles following glioma resection may be predictable. Specifically, any additional language deficit incurred as a result of the surgery will improve by 3 months or not all. Our experience also emphasizes the value of negative language mapping in the setting of a tailored cortical exposure. While the value of extent of resection remains less clear, the available literature for both low-grade and high-grade hemispheric gliomas demonstrates mounting evidence that a more extensive surgical resection is associated with a more favorable life expectancy for both low-grade and high-grade glioma patients. This objective should be cautiously pursued for all gliomas, even in the setting of eloquent location.

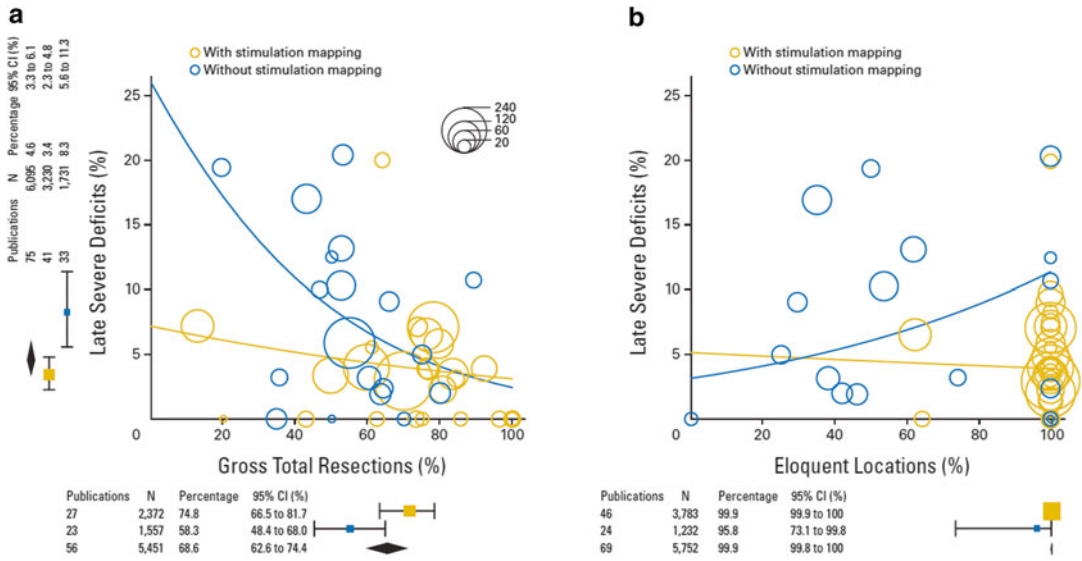


**Fig. 2** Meta-analysis of 8091 patients undergoing intraoperative cortical stimulation mapping. Glioma surgery outcome after resections with and without intraoperative stimulation mapping. (**a**) The relation between oncologic and neurologic outcome is plotted as a bubble chart with percentages of gross total resections (*x*-axis) and percentages of late severe neurologic deficits (*y*-axis) for patient populations after resection with (*gold circles*) and without (*blue circles*) intraoperative stimulation mapping. Sizes of circles are proportional to study cohort size. Summary estimates and 95 % Bayesian CIs for all glioma resections (*black diamonds*), resections with intraoperative stimulation mapping (*large gold squares*), and without intraoperative stimulation mapping (*small blue squares*) are plotted and listed in the axis margins. (**b**) The relation between eloquent localization and neurologic outcome is plotted with percentage of eloquent localizations (*x*-axis) and percentages of late severe neurologic deficits (*y*-axis). Color codes, sizes of circles, and logistic regression lines are similar to those in (**a**). (Adapted from De Witt et al. Journal of Clinical Oncology, 30(20):2559–65, 2012)

**Technical Nuances**

- Preoperative steroids and/or neoadjuvant chemotherapy may improve naming, reading, and motor speech significantly enough to allow a patient with difficulty in these functions to be successfully mapped.
- The best management of intraoperative stimulation-induced focal motor seizures is rapid cortical irrigation at the stimulation site with ice-cold Ringer's solution.
- Because the dura is pain sensitive, the area around the middle meningeal artery should be infiltrated with the lidocaine-marcaine mixture to alleviate discomfort while awake.
- It is important to remember that functional subcortical pathways may be located within grossly infiltrating tumor tissue.
- Limited cortical mapping without finding an essential functional site (i.e., negative mapping) can offer reliable data to proceed safely and efficiently with tumor removal. Negative mapping enables a tailored exposure of the tumor, rather than relying on a wider craniotomy to identify positive control sites.

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# Brain Mapping and Operating Safely in Eloquent Cortex

One of the greatest challenges in neurosurgery is safely removing lesions in and around eloquent cortex. Considerations starting with operative indications through preoperative functional mapping, intraoperative mapping, imaging, and functional monitoring, to decisions on when to stop surgery are intrinsic and essential to operating safely in eloquent cortex. Mastering the advantages and limitations of each of these steps can lead to a practical and safe application of the various tools available to the operating neurosurgeon in cases involving eloquent cortex.

This book provides the latest update of the most practical information available to neurosurgeons who encounter these cases. An outline of the advantages and the limitations of each tool as well as treatment algorithms for applications in specific clinical circumstances creates a clear guide to this most complex of neurosurgical problem. Clinical case examples are linked to intraoperative photos and videos showing hands on applications of cortical mapping in eloquent cortex in various pathologies. In this textbook, the practitioner will find a ready guide to navigating the practical decisions that are commonly faced when operating in eloquent cortex.

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