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Functional Mapping for Glioma Surgery, Part 2: Intraoperative Mapping Tools

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Keywords

Intraoperative mapping; awake craniotomy; language mapping; direct cortical stimulation

1. Introduction

Surgical resection is a mainstay of treatment for patients who are diagnosed from a presumed glioma, even when involving areas of the brain with presumed functional significance (i.e. eloquent cortex). Care must be taken to preserve neurologic function while striving for maximal extent of resection as permanent postoperative neurological impairments, particularly involving language and motor function, are associated with worse overall survival and lower quality of life [1–4]. Intraoperative functional mapping of lesional and perilesional tissue is a well-established technique for avoiding permanent neurological deficits [5,6]. It involves the administration of short pulses of electrical stimulation to identify specific functions and is either activating (e.g. eliciting a motor response) or disruptive (e.g. speech arrest).

In this review, we describe techniques used for motor and language mapping, as well as less traditional intraoperative testing paradigms for cognition mapping. Finally, we discuss complications associated with mapping and insights into their management.

2. Sensorimotor Mapping

Accurate motor mapping is imperative to successful resect tumors within or near the sensorimotor cortex [7,8]. Classically, intraoperative sensory-motor function was identified with neurophysiological monitoring that utilized motor evoked potentials (MEPs) and motor

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stimulation in asleep patients to visualize motor contraction (i.e. stimulation producing a "positive" response) (Table 1) [9]. MEPs can be generated via transcranial stimulation, direct cortical, or subcortical stimulation, with the magnitude and latency of the responses impacted by factors such as the depth of anesthesia, recent muscle relaxant, and neuromuscular blockade [10].

After identifying the motor cortex and central sulcus with phase reversal, continuous direct cortical MEP monitoring allows for a real time confirmation of a functional pyramidal tract [11]. Transcranial monitoring on the other hand has the advantage of allowing both hemispheres to be tested simultaneously and compared against each other, and it does not require the placement of a cortical strip electrode which has the potential to injury the cortex or a bridging vein, although its sensitivity relative to direct cortical MEPs is debated [12]. Numerous studies have found that MEP recordings can be successfully obtained in nearly all patients, and the irreversible loss of > 50% amplitude in the MEPs is a strong predictor of a permanent postoperative paresis [13–16]. However, there are still a small percentage of false positive changes in MEP, possibly due to brain shift during tumor resection, hypotension, or changes to the anesthetic regimen.

Utilization of direct cortical and subcortical electrical stimulation to map the eloquent cortex and axonal pathways of the sensorimotor system has become a standard of care [17]. There are two major methods for stimulating cortical and subcortical fibers: 1) monopolar stimulation which delivers short trains of high frequency (250-500 Hz) square wave monophasic pulses and requires electromyography (EMG) to visualize firing; and 2) bipolar stimulation which uses low frequency (60 Hz) to deliver long biphasic pulses [18,19]. The amplitude intensity of stimulation must be adjusted for the type of anesthetic used, with higher amplitudes required for asleep patients. Monopolar stimulation is very useful for identifying the motor tracts at a safe distance and estimating their proximity with a reasonably linear relationship of 1 mA of current for every 1 mm of distance between the probe and the white matter tract (generally consistent up to 25 mA) [18,20]. Bipolar stimulation is more targeted, and detection of a motor response subcortically with the bipolar probe indicates a close proximity to the motor system (usually within 5mm) and an increased risk for a permanent post-operative deficit. Recent work suggests that combinatorial techniques involving transcranial MEPs with concurrent monopolar and bipolar stimulation of the subcortical pathways can improve detection of the corticospinal tract and largely avoid severe post-operative deficits [1,21].

Unlike language mapping, awake mapping of the motor system is not necessary to achieve excellent outcomes, even for tumors within the primary motor cortex itself [22,23]. Fundamentally, major differences in mapping technique exist between awake and asleep approaches; awake patients can voluntarily move muscle groups to confirm the presence or absence of a deficit if there is a change in the mapping signals. Multiple studies have shown that, infrequently, false positive changes in MEP can occur, with discrepancies existing between the post-operative clinical exam and the intraoperative MEP findings [16,24]. However, some studies have suggested there is an increased risk of seizures during awake motor mapping, although this is likely dependent on the stimulation parameters utilized [25,26]. Moreover, the ability to map MEPs may be limited in an awake patient, as transcranial MEPs are often painful for the patient. Finally, when resections involve regions such as the supplementary motor area which are critical for movement planning and initiation, awake patients may become slow and/or apraxic despite intact corticospinal tract signaling and inevitable functional recovery, potentially pushing surgeons to stop tumor resection prematurely [27,28].

3. Language Mapping

Intraoperative language mapping is a well-established technique for avoiding permanent language deficits [29]. Stimulation is thought to result in focal disruption of networks involved in speech and language processing as demonstrated by correct and incorrect patient responses to various testing paradigms. Intraoperatively, electrical cortical stimulation (ECS) can be performed using low frequency (60 Hz, 1.0 msec biphasic square wave) bipolar stimulation. Intraoperative electrocorticography is performed using a 16-channel electrode and holder assembly (Grass Model CE1, Natus Medical Inc.) and interpreted by an epileptologist. Stimulation begins at 2 mA and then increases until positive sites are identified, after-discharge potentials occur, or a maximum current of 5 mA is reached (although other groups have utilized higher currents) [30]. Current is applied for 3-4 seconds, with 4-10 seconds between tasks. If a site causes an error, then it is tested at least two more times, and in general any site with > 50% error rate is marked and persevered.

Intraoperative language testing can involve assessment of several components of language and include picture naming, counting, repetition, reading, writing, sentence completion, and assessing language syntax. The most common intraoperative language mapping task employed is picture naming, which is used for its speed, simplicity, and ability to detect gross language disruption. Errors during picture naming have been aggregated into 6 categories: semantic paraphasias (king -> “queen”), circumlocutions (pen -> “thing used to write”), phonological paraphasias (deletions or substitutions of syllables), neologisms (made-up words), performance errors (slurred or stuttered responses), and “no response” errors [31]. Counting is another commonly used task to identify speech arrest sites. The patient is asked to slowly count to either 5 or 10 while stimulation is applied to different cortical and subcortical sites. If the patient can continue to move their arm and tongue but counting is interrupted, this is consistent with speech arrest. Alternatively, if arm movement or tongue movement are also impaired, the response is more consistent with either motor arrest or anarthria, respectively.

Word repetition is not as frequently employed as picture naming and counting in the operating room but is still a useful adjunct for assessing language. Patients with conduction aphasia generally have fluent natural speech and preserved perception capabilities, but an inability to repeat words verbatim. To test word repetition, patients are first familiarized with a list of words usually between two to four syllables long and containing simple and difficult words (i.e. words with consonant clusters and pseudo-words that are derived from scrambled real words (e.g.“delight” → “ledite”). Patients are then instructed to repeat individual words while ECS is applied to the cortex.

Reading tasks involve having the patient read short, unrelated sentences that have not been previously rehearsed. While the patient is reading, stimulation is applied to assess for interference in function. Writing tasks involve hand-writing dictated text by using the dominant hand. Patients should be able to see what they are writing, and a writing pad is often held up to them at a visible distance by other operating room staff. While writing, direct cortical stimulation is applied, and writing deficits may include letter omissions, writing arrest, or illegible script [32]. To date, language syntax is the least commonly tested language domain with intraoperative mapping. Given the need to test more than a single word to investigate syntax, the tasks are more complex, take more time, and are harder to perform in the operating room setting.

4. Non-language Cognitive Mapping

While language mapping remains the predominant eloquent function mapped in awake patients, many other cognitive domains, such as memory, attention, motivation, and emotion are affected in patient with intrinsic brain tumors [33]. Moreover, deficits in these domains undeniably impact quality of life, and efforts should be made to preserve these higher order cognitive functions when possible in patients. While a minority of patients have an improvement in their cognitive function after tumor resection, cognitive decline is common after surgery, with attention and processing speed being the most impacted [34].

Complex executive functions like selective attention, working memory, inhibitory control, and mental flexibility, are challenging to measure and test intraoperatively. An intraoperative version of the Stroop task, which measures the patient's ability to resist interference, has been developed to assess some of these executive functions. Puglisi et al. found positive stimulation sites in the right inferior frontal gyrus and frontostriatal white matter pathways, and showed that preserving positive sites identified with this task reduced early and late deficits in post-operative executive function [35,36].

A calculation task has been utilized during resections of the dominant angular gyrus and nondominant parietal lobe in an attempt to preserve this cognitive ability, and the positive subcortical sites have been identified and preserved intraoperatively with good patient outcomes [37,38]. Also, a working memory task, called the double task, has been used in Perisylvian resections near the superior longitudinal fasciculus [39]. During this task, the patient completes a movement while simultaneously performing a picture naming task. Should patients develop an ideational apraxia, they can perform the movements spontaneously but not upon request. Finally, ECM has been used to try to identify regions critical for memory storage and retrieval during resection of lesions in the left anterior temporal lobe, frontal lobe, and fornix [40,41]. The selection of which executive functions to map should be tailored to individual patients' goals. Additionally, given there are numerous cognitive domains, future work is needed to address which tasks are best suited to preserve cognitive function possible within the time constraints of a surgical resection.

5. Management of Intraoperative Complications Associated with Mapping

There are several issues that can arise when performing intraoperative mapping including stimulation-induced seizures, loss of airway, and patient non-compliance. As with any surgical procedure, patient selection and preoperative optimization of risk factors are critical to avoid intraoperative complications. A full assessment of a patient's medical comorbidities, neurological deficits, seizure frequency, body habitus, and level of anxiety should be taken into consideration when formulating the operative plan.

Stimulation-induced intraoperative seizures are the biggest contributor to awake craniotomy failure [5,42,43]. Historically, intraoperative stimulation-induced seizures were controlled with intravenous lorazepam, but this often-necessitated cessation of intraoperative testing due to patient sedation. More recent methods for seizure abortion include first irrigating with iced Lactated Ringer's solution applied locally to the cortical surface followed by intravenous Propofol if seizures do not abate. Intraoperative electrocorticography may help as a preventative measure as it allows not only for the identification of after-discharge potentials, but also for identifying an appropriate stimulation current for intraoperative testing. Patients should always be continued on their prior antiepileptics leading up to a craniotomy or should receive an intraoperative agent before starting the craniotomy. Using these interventions, awake mapping failure rates can be as low as 0.5% [5].

Airway compromise is another concern when performing awake procedures. Patients who are over-sedated or are obese can develop hypercapnia which can precipitate cerebral edema or hypoxia. Tools such as nasal trumpets and laryngeal mask airways (LMA) have significantly enhanced airway options for these patients. Selection of an appropriate anesthetic regimen is also important for maintaining a balance between patient sedation and wakefulness to allow for intraoperative mapping. The two major techniques for performing awake craniotomy are the "asleep-awake-asleep" approach utilizing a combination of propofol-remifentanil and the "conscious sedation" technique. In a randomized control trial comparing dexmedetomidine to propofol-remifentanyl, the dexmedetomidine group was associated with fewer respiratory adverse events and there was no difference in the degree of sedation or the ability of patients to perform mapping tasks [44]. In general, our group begins with propofol-remifentanil and adds dexmedetomidine (with or without continuing propofol) if required [5].

Managing patient expectations and experience during intraoperative mapping is also critical for a successful operation, especially for patients who already suffer from anxiety at baseline. Patients must be well informed about the procedure, steps involved, neurologic symptoms they may experience during mapping, and management of intraoperative pain and sedation. With sudden movements, patients are at risk of scalp lacerations due to pin slippage, contamination of the operation field, and other bodily injury. Patient's with a high degree of anxiety should be optimized preoperatively on anxiolytics; however, some patient's may not be awake mapping candidates due to anxiety or confusion and may need to be done under general anesthesia. Working with an experienced anesthesia team can help alleviate sudden erratic behavior due to changes in the level of sedation intraoperatively. Additionally, repeated communication between the surgeon and patient is essential for behavior management throughout the case.

6. Summary and Future Directions

As the neurosurgical armamentarium expands, future advances in intraoperative mapping will need to consider the optimal combination of functional mapping techniques to complement ECS. As the understanding of basic human neuroscience advances, particularly in aspects of cognition, emotion, and higher-order communication, more agnostic techniques such as functional MRI will be essential to guide intraoperative validation with ECS. Advances in intraoperative imaging will provide real-time feedback to help account for brain shifts that occur following craniotomy and tumor debulking. Even ECS is not immune to further technological advances, as evidence by the recently published train-of-five bipolar technique for mapping motor cortex [45].

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Key Points:

- Intraoperative motor mapping can involve direct bipolar or monopolar stimulation as well as MEP monitoring via a transcranial or direct cortical strip electrode approach
- Intraoperative language testing may assess several language domains including naming, repetition, reading, writing, and syntax
- Intraoperative cognitive mapping is less frequently used but has been increasingly recognized as important for maintaining quality of life
- Appropriate patient selection and preoperative optimization of risk factors including seizures and anxiety

Synopsis:

Intraoperative functional mapping of tumor and peri-tumor tissue is a well-established technique for avoiding permanent neurological deficits and maximizing extent of resection. Motor, language, and other cognitive domains may be assessed with intraoperative tasks. Here, we describe techniques used for both motor and language mapping including awake mapping considerations in addition to less traditional intraoperative testing paradigms for cognition. We also discuss complications associated with mapping and insights into complication avoidance.

Clinics Care Points

- For motor mapping, MEPs are generated with transcranial stimulation or a subdural strip electrode placed over the primary motor cortex. This can be performed in addition to direct bipolar and/or monopolar stimulation.
- Subcortical mapping techniques are important for both motor and language mapping
- Intraoperative language testing can involve assessment of picture naming, counting, repetition, reading, writing, and assessing language syntax.
- As with any surgical procedure, patient selection and preoperative optimization of risk factors are critical to avoid intraoperative complications.

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Table 1.

Advantages and disadvantages of different stimulation techniques

Modality	Advantages	Disadvantages
Motor Evoked Potentials (MEP)	• Direct cortical MEP allows for continuous stimulation and verification of tract continuity • Transcranial MEPs allow both hemispheres to be tested simultaneously and compared against each other	• Signal can be affected by anesthetic, muscle relaxant, neuromuscular blockade, patient temperature, brain shift, and hypotension • Cortical strip placement can lead to vein injury • Transcranial MEP often painful for awake patients
Bipolar stimulation	• Key component of cortical and subcortical mapping of language and motor cortex • More focused area of stimulation leads to accurate identification of eloquent tissue	• Positive response subcortically usually means that subcortical fibers usually already within 5 mm • Increased seizure frequency when compared to monopolar stimulation in some studies
Monopolar Stimulation	• Key component of cortical and subcortical mapping of language and motor cortex • Stimulation intensity correlates with distance to tracts (1mA ≈ 1mm)	• More diffuse area of stimulation that can lead to spatially inaccurate eloquent cortex identification • Theoretical increased risk of tissue damage when compared to bipolar stimulation