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Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice

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There is increasing evidence that the extent of tumor removal in low-grade glioma surgery is related to patient survival time. Thus, the goal of resecting the largest amount of tumor possible without leading to permanent neurological sequelae is a challenge for the neurosurgeon. Electrical stimulation of the brain to detect cortical and axonal areas involved in motor, language, and cognitive function and located within the tumor or along its boundaries has become an essential tool in combination with awake craniotomy. Based on a literature review, discussions within the European Low-Grade Glioma Group, and illustrative clinical experience, the authors of this paper provide an overview for neurosurgeons, neurophysiologists, linguists, and anesthesiologists as well as those new to the field about the stimulation techniques currently being used for mapping sensorimotor, language, and cognitive function in awake surgery for low-grade glioma. The paper is intended to help the understanding of these techniques and facilitate a comparison of results between users. *(DOI: 10.3171/2009.12.FOCUS09237)*

Key Words • awake craniotomy • direct cortical stimulation • low-grade glioma surgery • brain mapping

The direct intraoperative application of electric current onto the human cortex for localizing and activating function dates back to the 1930s.[10,20,37] Its definite impact on preserving function in the resection of low-grade gliomas has been reported.[6–8,13,18,36] Nevertheless, methodological rigor and the meticulous performance of mapping procedures are indispensable to avoid any false-positive or false-negative stimulation results, which could lead to inadequate tumor resection or cause permanent neurological deficits. If all the technical rules are not respected faithfully, inaccurate results will create a false sense of security, which could lead to undesired surgical results and permanent neurological sequelae. Based on published material, personal experience, and discussions with members of the European Low-Grade Glioma Group who are dedicated to the intraoperative stimulation procedure, the most important aspects of brain mapping during surgeries in awake patients are presented and reviewed.

The purpose of the mapping procedure is to reliably identify cortical areas and subcortical pathways involved in motor, sensory, language, and cognitive function. Although similar techniques are utilized, the application of mapping at different centers involves a diversity of approaches.

Electrical Stimulation

The technical aspects of electrical stimulation include the stimulator device; the stimulation parameters consisting of the individual pulse type, pulse width, frequency of stimulation, and applied intensity; and the stimulation probe being used to deliver the electric current.

Stimulator Device

For brain mapping purposes, constant-current stimulators are considered safer and more reliable because they deliver the preset current independently from the imped-

Abbreviations used in this paper: CUSA = Cavitron ultrasonic aspirator; DT = diffusion tensor; ECoG = electrocorticography; EMG = electromyography; MEP = motor evoked potential.

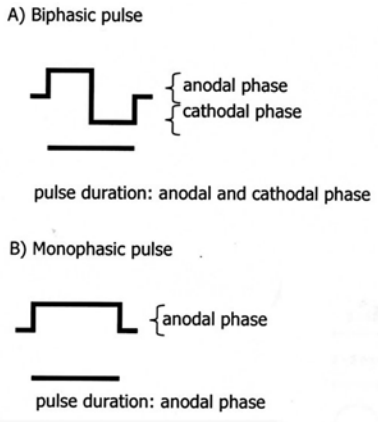

Fig. 1. Schematic of monophasic and biphasic pulse forms.

ance of the cortical or subcortical surface. Conversely, in constant-voltage stimulators, the delivered current also depends on the impedance. Hence, if impedance decreases, the amount of current delivered can dramatically increase and compromise the safety of the procedures. An extensive discussion of the differences between constant-current and constant-voltage stimulators is beyond the scope of this review.

Stimulation Parameters

For brain mapping, a low frequency paradigm has been established, consisting of the application of short pulse trains with frequencies of 25–60 Hz. The most commonly applied frequencies are 50 Hz (Europe) or 60 Hz (North America).

The individual pulse is rectangular and either monophasic or biphasic (Fig. 1). As described in the first experiments, cortical stimulation is more effective with anodal current; that is, a lower stimulation intensity is needed to see a stimulation effect.[21,23] Thus, the first phase of the pulse should be anodal. If a monophasic pulse is used, it should be anodal (or positive); if a biphasic pulse is used, it should be in an anodal/cathodal mode. The anodal phase duration can vary between 0.2 and 0.5 msec. In applying a biphasic current, the duration of the pulse includes both the positive and negative phases. Therefore, only half of the pulse duration is anodal and effective for stimulation—meaning that a monophasic pulse of 0.5 msec delivers the same anodal current as a biphasic pulse of 1 msec. However, as the charge is dependent on pulse duration (charge [Asec] = pulse duration [sec] × intensity [A]), the charge applied to the brain using a biphasic pulse is twice that applied using the same current but with a monophasic pulse. For safety considerations, the maximum stimulation intensity should not exceed 40 $\mu C/cm^2$/phase and is commonly limited to 20 mA.[1] For a detailed physical background regarding monopolar versus bipolar stimulation techniques see the study by Kombos and Süss.[28]

Historically, at times when only uncoupled stimulators were available, a biphasic pulse was seen to be less neurotoxic as the reversed pulse could minimize those effects.[40] With the utilization of coupled stimulators and limited application times during surgical procedures, neurotoxic effects have not been described.[2,22,31,40,41]

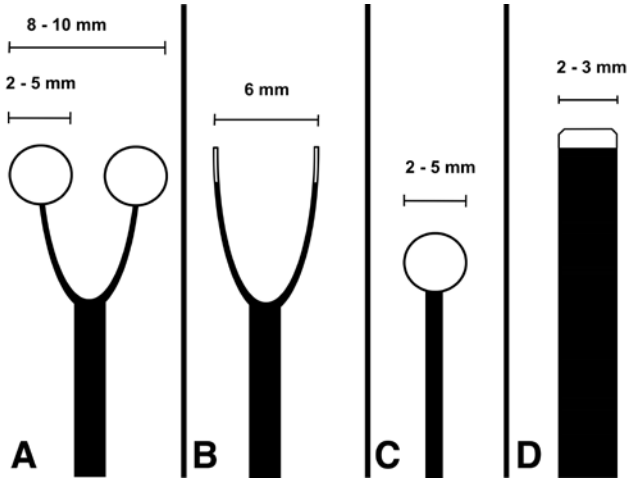

Fig. 2. Schematic of probes used for bipolar stimulation with ball tips **(A)** or straight tips **(B)** and for monopolar stimulations with a ball tip **(C)** or straight tip **(D)**.

Stimulation Probe

The use of a bipolar probe with 2 tips separated by 6–10 mm has become standard (Fig. 2). An interelectrode distance > 10 mm seems to favor the elicitation of large pyramidal tract neurons.[25] Alternatively, a monopolar probe with a frontal reference electrode can be used. The distribution of the electric field differs between monopolar and bipolar probes. Given the same stimulation intensities, a monopolar probe provides a homogeneous radiant spreading electric field, which leads to lower current densities in the area surrounding the reference electrode but has the benefit of more spacious stimulation effects. With this probe the probability of stimulating nervous tissue at a more distant site increases. In contrast, stimulation with a bipolar probe creates an electric field in which the current density is more homogeneous and the electric field lines between both poles are close to parallel (Fig. 3).[32,38] If monopolar and bipolar electrodes have the same shape, the current density close to the stimulating electrodes is the same and the greatest.

Documentation of Stimulation's Effect

Observation of the Patient

The most simple and most complex task for the examiner is observing the patient's reaction to stimulation. Movement can be observed and categorized by its complexity. Clonic movement relates to stimulation of the primary motor area, whereas tonic movement is more related to stimulation of the premotor area (Area 6). Furthermore, the absence of any induced movement should be tested for negative motor phenomena (see *Mapping of Motor Function*).

Recording Electrodes

Small movements or movements at distant sites can go unrecognized. Simultaneous brain mapping and monitoring of muscle activity by continuous EMG recording (either surface electrodes or needle electrodes) can be

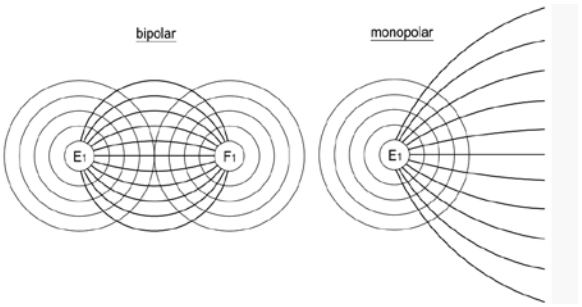

Fig. 3. Schematic of electric field distribution in bipolar **(left)** and monopolar **(right)** stimulations.

helpful.[50] Electromyography—complementary to ECoG—also allows for early detection of the spreading of muscle activation over a limb as a sign of seizure. These data can be stored and used for offline analysis and for the purpose of documentation. To record EMG activity, subdermal needle electrodes are used and are surprisingly well tolerated even during awake procedures. Alternatively, surface EMG electrodes placed in the belly-tendon fashion can be used.

Mapping in Awake Patients

As stimulation-induced movements are easy to observe, it is typically recommended to start with the mapping of motor function. The presence of a speech therapist, neuropsychologist, or neurologist is very important for observation and judgment, especially for language and cognitive function. It is highly recommended to introduce members of the surgical team to the patient and to explain the intraoperative procedure as well as the testing to the patient at least a day prior to surgery. The patient might feel uncomfortable experiencing involuntary movement or the inhibition of voluntary movement and language, which could lead to feelings of fear and angst and might be accompanied by an alteration of vital and vegetative signs such as nausea, hypertonia, and tachycardia. Moreover, patients might conclude from positive testing that the tumor has invaded important cortical structures and thus that the tumor surgery might not be successful. Some patients experience overwhelming fear, which could interfere with further testing and even the whole surgical procedure. In such patients, ECoG is helpful for ruling out nonconvulsive but focal temporal seizures. The patient's guidance is very important, and therefore each step of the testing and stimulation procedure should be announced. Patients should be carefully examined and asked about any sensation, feelings, or movements, especially the contraction of pharyngeal muscles, which might not be observed by the examiner.

Mapping of Motor Function

While performing direct cortical stimulation, the stimulation intensity should be increased stepwise by 1 mA until a movement or EMG response is observed. This stimulation intensity should be used for further mapping of sensorimotor, language, and cognitive function. One to 2 msec duration of stimulation is sufficient to induce

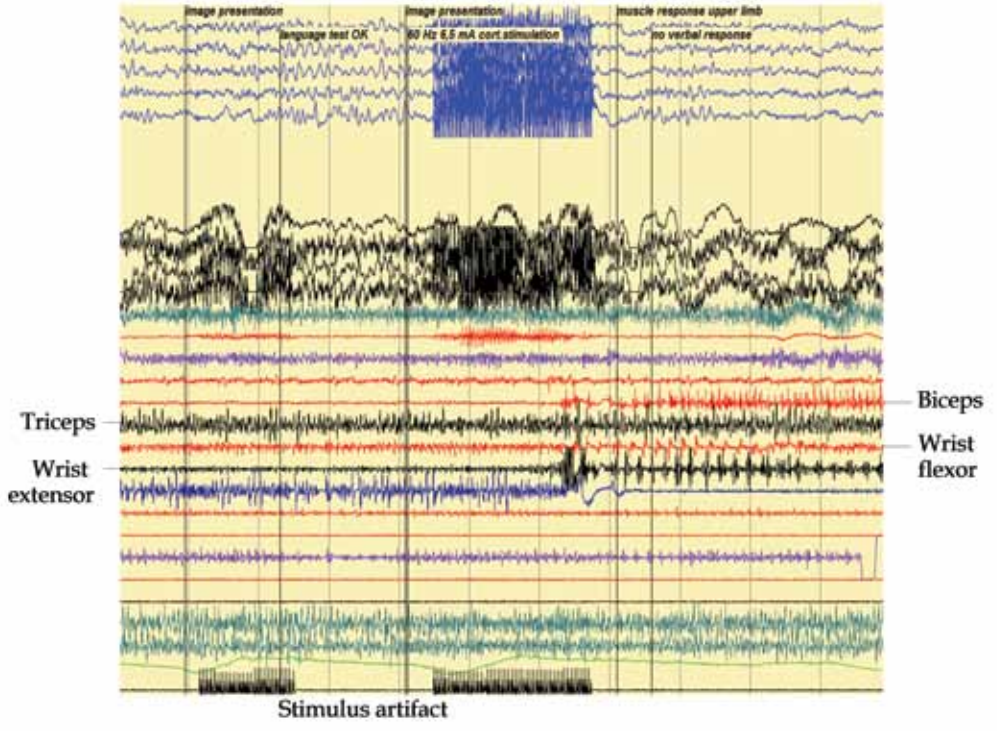

Fig. 4. Awake surgery ECoG (Traces 1–4), surface electroencephalography (Traces 6–9), and EMG traces (remaining traces) showing 60-Hz stimulations (6.5 mA) of the premotor cortex. During stimulation for language testing, a speech arrest was induced, followed by clonic jerks in the right upper limb muscles.

TABLE 1: Practical stimulation guide

stimulation	stimulate entire exposed cortical area every 5 mm^2 (according to probe spacing) stimulate every site at least 3 times never stimulate same cortical area twice successively always perform checking test w/o stimulation btwn 2 stimulations
mapping	start w/ motor mapping: movement is easy to observe for cognitive & language tasks, stimulation should be started before presentation of the item for subcortical mapping, imagine path of the white matter tract stimulated & raise the intensity by 2 mA, repeating the stimulation very regularly while mapping the path tract
documentation	mark positive areas w/ small paper tag document anatomical relations *special advice:* *1) do not stop mapping after identifying only 1 eloquent site, but search for possible redundancies; a negative mapping does not protect, but creates the problem of questionable stimulation reliability* *2) an area invaded by a tumor has an increased impedance, which could justify an increase in the intensity of stimulation parameters relative to neighboring healthy tissue, especially in cases in which gliomas infiltrate functional areas*
side effect: seizure	irrigate w/ cold Ringer solution or isotonic NaCl; do not restimulate immediately afterwards special advice: stimulation intensity should be decreased during control stimulations in areas of decompressed brain tissues to limit the risk of inducing a seizure; no-response sites at beginning of surgery should always be retested after decompression intraop ECoG can be useful in detecting afterdischarges

movement if the primary motor cortex is stimulated. Longer durations of stimulus (2–4 msec) are required to induce motor responses from secondary motor areas. Electromyography can be used to record motor phenomena, showing even low-amplitude muscle responses and the onset of clonic muscle activity (Fig. 4).[50] Mapping of motor function can be performed in both awake and anesthetized patients. In awake patients, both muscle activation and muscle inhibition should be investigated, following a protocol related to the site of surgery. The absence of movement might be explained by a stimulation-induced inhibition of movement. In such cases, the testing of negative motor phenomena is helpful for identifying associative motor areas;[30] that is, the patient is asked to perform a continuous movement—for example, alternating extension and flexion of the wrist—which is inhibited by the stimulation. Once a movement is observed, the whole of the exposed cortical area is systematically mapped every 5 mm^2 (according to the probe spacing). The placement of sterile tags with numbers or letters on stimulation-positive spots is helpful for visualizing the cortical areas involved in motor, cognitive, or language function.[14,37] A meticulous drawing of the anatomy or a photograph and notes describing the evoked phenomena document the testing as well as help with further surgical planning and intraoperative reference.

Mapping of Language and Cognitive Function

For the mapping of language and cognitive function, the patient's compliance is very important, as is the close cooperation among members of the participating medical team. For stimulation-induced interference with speech, language, and cognition, the duration of the stimulus must be longer than that for motor mapping. The duration of stimulation is commonly set to 3–4 seconds. To exclude occasional noncompliance or temporary impairment related to a nonconvulsive seizure, every stimulation should start after presentation of the material has started and the patient has said an introductory sentence.[24] As repetitive stimulation can trigger seizures (see *Side Effects*), one could use an alternating testing mode; that is, one in which the patient continuously performs tasks, and each task with stimulation is followed by a task with sham stimulation (Table 1).

During resection of the tumor, continuous assessment of function as well as the potential risk of injury is necessary to maximize the extent of resection and prevent iatrogenic injury. Continuous clinical assessment during the resection is alternated with cortical and subcortical mapping and specific testing of the function anatomically closest to the resection site. As subcortical pathways might be involved within the tumor and at risk during resection, intermittent subcortical stimulation and testing has been shown to be effective at successfully preventing iatrogenic injury.[5,13,15,16,26,29]

Motor Function

For continuous monitoring of motor function in addition to periodical cortical/subcortical mapping, intentional movement of the patient can be continuously assessed. However, because this process can be exhausting for the patient and fatigue can mimic paresis, the only way to truly continuously assess the functional integrity of the motor pathways is to perform MEP monitoring.

For this purpose, continuous direct cortical stimulation of the precentral gyrus can be performed with a modified train-of-five technique. This technique, introduced for surgery in anesthetized patients, has been described as sensitive in detecting dysfunction of the motor cortex and the corticospinal tract.[33–35,46–48] A strip electrode containing 4–8 electrodes must be placed over the precentral gyrus. In awake patients a single stimulus or a short train consisting of 2–4 pulses (individual pulse width 0.3–0.5 msec, anodal constant-current stimulation; interstimulus interval 4 msec, stimulation close to motor threshold) is usually sufficient to elicit muscle

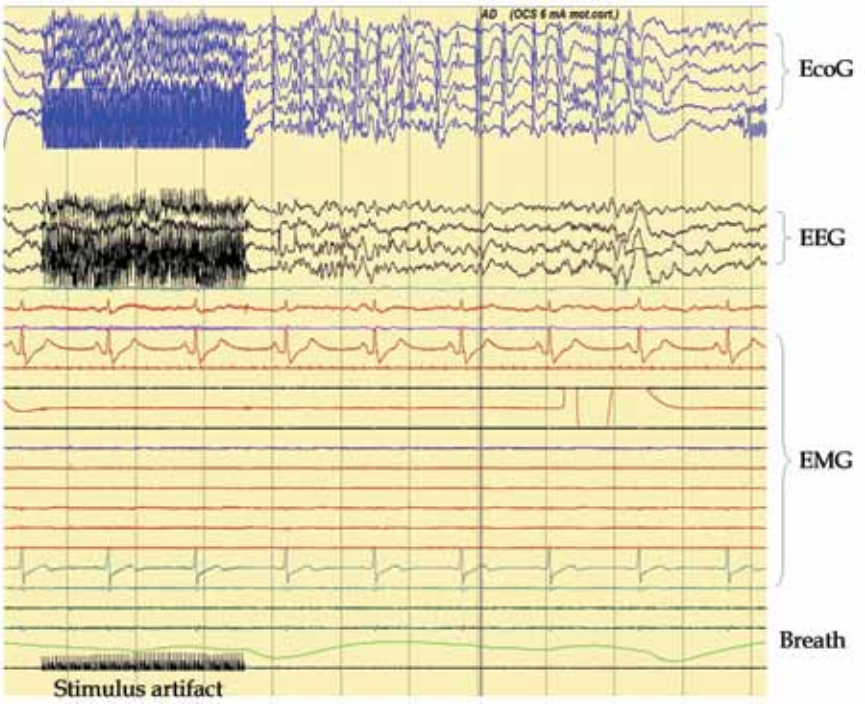

Fig. 5. Asleep surgery ECoG (Traces 1–6), surface electroencephalography (Traces 7–10), and EMG traces (remaining traces) obtained during 60-Hz stimulations (6 mA) of the primary motor cortex, showing nonconvulsive seizure activity.

MEPs. Motor evoked potentials must be recorded either with needle electrodes, preferably the same in use for continuous EMG assessment, or—if believed more convenient in awake patients—with surface EMG electrodes. The method's advantage lies in the independence of a patient's compliance and the ability to distinguish between lesions of the supplementary and those of the primary motor area.[51] Moreover, MEPs are useful for preventing vascular injury in insular and/or deep temporal regions, where critical arteries are at risk during tumor resection.[34] Test clamping can even be performed. The intraoperative use of direct cortical stimulation via a strip electrode to elicit MEPs can be performed repeatedly. As simultaneous cortical and subcortical stimulation can lead to false results, one must ensure that none of the methods is applied simultaneously.

Note that the same stimulation parameters (short-train technique with interstimulus interval of 4 msec) used for continuous MEP monitoring from a strip electrode can be used for cortical (anodal stimulation) and subcortical (cathodal stimulation) mapping from a hand-held monopolar probe. This option represents a valid alternative to the classic 60-Hz technique with the advantage of a lower risk of intraoperative seizures (see *Side Effects*). Nevertheless, the widespread use of the short-train technique during awake surgery is just starting and has recently been reported as a possibility for language testing in awake patients.[3]

Cognitive and Language Function

For cognitive and language tasks, either spontaneous speech or the continuous completion of standardized tasks can be performed. It is beyond the scope of this paper to provide a detailed description and philosophy of the tests being utilized at different centers.

Side Effects

Long-lasting side effects due to intraoperative brain stimulation have not been reported.[22] Seizures are the most common side effects and can be harmful to the patient, although there have been no reports of serious injury due to intraoperative seizures. Interestingly, seizures are easily terminated with the direct application of iced Ringer lactate onto the cortex.[44] Longer stimulus durations can induce seizures and are related to the occurrence of after-discharges at low stimulation intensities. Although preoperative epilepsy is expected to be related to an increased occurrence of intraoperative seizures, there are no data supporting this assumption.[45] Intraoperative seizures most frequently develop in patients with lesions involving the rolandic and prerolandic areas. Furthermore, they are more frequent with 50–60 Hz of stimulation than with the train-of-five technique.[45] The neurosurgeon should consider changing the stimulation modality in patients who are prone to have seizures during mapping.

The resection procedure and instruments, such as the bipolar coagulation probe or the CUSA, can mimic nonconvulsive seizure-related transient disturbance of a patient's performance. Reportedly, the use of the CUSA can interfere with motor and language mapping, inducing a transient masking of active sites.[9] Therefore, the simultaneous use of CUSA and bipolar coagulation and stimulation should be avoided.

Controversies in Mapping

Size of Craniotomy

A recent publication described a tailored craniotomy with sole exposure of the tumor region, language mapping of the exposed area, and guidance by positive and negative stimulation results,[42] with excellent effects. Note that this procedure has been established by a team with vast experience in cortical mapping and thus should only be relied on if the cortical stimulation technique is well established within the mapping team.

Electrocorticography Recording

The simultaneous recording of ECoG is used to determine spontaneous or stimulation-induced epileptic discharges, so-called afterdischarges that can occur after electrical stimulation of the cortical areas to detect nonconvulsive seizures (Fig. 5). As a rule, current used for cortical mapping should not exceed certain thresholds to avoid the possibility of misleading false-positive mapping results. Unfortunately, afterdischarge thresholds vary across the cortex.[49] For certain cortical sites, mapping may be successful only at currents above the afterdischarge thresholds.[39] Therefore, although ECoG is recommended by most to improve the reliability of mapping and to prevent intraoperative seizures, it also has some limitations that should be remembered during mapping. Still other authors have reported vast experience with successful mapping in a large group of patients without the use of ECoG.[17] To compromise between the efficacy of mapping and the afterdischarge thresholds, different stimulus durations and/or repetition rates may have to be used.

Focality of Stimulation

From studies of transcranial magnetic stimulation and direct cortical stimulation in tumor surgery, it is known that the excitation of cortical motor areas other than the primary motor cortex (M1) requires higher intensities.[27] Nevertheless, in intraoperative practice, the most practical and sufficient way is to determine the motor threshold and use this stimulation intensity for further mapping.[11,14]

Effectiveness of Monitoring and Mapping

A recent meta-analysis has underlined the growing evidence of the positive relation among the extent of tumor removal, the tumor progression–free interval, and the 5-year survival rate.[43] Despite the lack of Class 1 evidence, the effect of confounding factors, such as tumor histology and the intraoperative utilization of neurophysiological methods, has not been investigated in the studies included in the meta-analysis. Subcortical mapping has been proven useful in several studies;[4,12,13,17,19,26] thus, the deduction that it can help in maximizing the extent of tumor resection may be obvious.

Utilization of DT Imaging

As the extent of tumor removal seems to be important for a patient's overall survival, preoperative imaging for planning the resection becomes more and more important. Authors have analyzed relations between subcortical mapping and DT imaging.[5,29] A positive correlation has been found between a stimulation intensity of 8–12 mA and a < 6-mm distance between the stimulation site and visualized tracts. Nevertheless, the estimated distance between DT imaging and the location of stimulation is influenced by the inaccuracies of DT imaging, the invasiveness of the tumor, intraoperative brain shift affecting navigation accuracy, and the various stimulation parameters and probe types used. Up to now, only subcortical stimulation allows for the in situ real-time assessment of subcortical tracks.

Conclusions

The 50- or 60-Hz stimulation performed with a biphasic pulse and a bipolar stimulation probe is the most widely applied technique for mapping motor and cognitive function during awake surgery. The additional application of the MEP short-train technique broadens the stimulation strategies being used, especially in patients who are not fully compliant or those suffering preexisting partial neurological and developing partial deficits, which can impair intraoperative testing. The main advantage of this technique is the possibility of performing both mapping and continuous MEP monitoring while minimizing the risk of intraoperative seizures. The utilization of those short-train stimulation parameters for cognitive mapping is in its infancy. The relatively short duration of the stimulus has to be timely presented to interfere with the function being tested. Close clinical observation and guidance of the patient combined with recording of EMG activity allows for the best documentation of the mapping procedure.

Disclosure

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

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