Chapter 3

Motor Evoked Potentials in Supratentorial Glioma Surgery

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70040

Abstract

Primary brain tumors, that is gliomas, are frequently located close to or within functional motor areas and motor tracts and therefore represent a major neurosurgical challenge. Preservation of the patients' motor functions, while achieving a maximum resection of tumor, can be only achieved by monitoring and locating motor areas and motor tracts intraoperatively. The intraoperative use of motor evoked potentials (MEPs) represents the current gold standard to do so. However, intraoperative MEP monitoring and mapping can be quite challenging and require a profound knowledge of the MEP technique, brain anatomy and physiology and anesthesia. In this chapter, a systematic review of PubMed listed literature on MEP monitoring and mapping in glioma surgery is presented. The benefits, limitations, technical pearls and pitfalls are discussed from the perspective of an experienced neurosurgical/neurophysiological team.

Keywords: intraoperative neurophysiological monitoring, glioma surgery, motor evoked potentials, intraoperative motor mapping

1. Introduction

Primary brain tumors, that is gliomas, which are frequently located close to or within functional motor areas and motor tracts of the brain [1] represent a major neurosurgical challenge [2]. Surgery-related neurological deficits often arise from direct damage to the cortical or subcortical structures or from ischemia [3, 4]. Preservation of the patients' motor functions, while achieving a maximum resection of tumor, can be only achieved by monitoring and locating motor areas and motor tracts intraoperatively [5, 6]. Therefore, it is nowadays agreed within

the neurosurgical community that the intraoperative use of motor evoked potentials (MEPs) represents the current gold standard to monitor and map the primary motor cortex and the corticospinal tract (CST).

As early as in the 1980s, Merton and Morton discovered that a high-voltage single electrical stimulus applied over the skull could activate the motor cortex and the subcortical motor pathways and consequently generate MEPs, which could be easily recorded from the limb muscles [7]. This finding was then exploited for the development of intraoperative neuromonitoring techniques that involve MEPs induced via both direct cortical and transcranial cortical electrical stimulation and direct subcortical white matter stimulation [7–9]. Since then, the intraoperative use of MEPs has substantially contributed to improved functional outcomes of glioma patients [10] as well as pushing the boundaries of surgery for lesions considered inoperable in the pre-MEP era [6].

However, intraoperative MEP monitoring and mapping can be quite challenging and require a profound knowledge of the MEP technique, brain anatomy and physiology and anesthesia.

Therefore, it is usually accomplished with the combined efforts of a multidisciplinary team of neurosurgeons, neuroradiologists, neuroanesthesiologists and intraoperative neurophysiologists, who together contribute to prevent neurological damage in glioma patients. Given that each tumor induces specific modifications in the brains' functional network, surgery must be tailored according to functional and anatomical boundaries of each patient individually [11].

2. Technique

The intraoperative use of MEPs encompasses both monitoring and mapping techniques. Whereas monitoring techniques continuously assess the functional integrity of the CST by repetitively testing MEPs frequently during surgery, MEP mapping instead is designed to identify the primary motor cortex and the subcortical CST within ambiguous neural tissue at appropriate surgical stages. For example, mapping the exposed cortex during the early stages of surgery enables to localize or, if not exposed, rules out the primary motor cortex in the surgical field before the cortex is incised and therefore harmed. In the later stages of surgery, it is often critical to localize the CST within the subcortical white matter during tumor resection, therefore it is localized using subcortical MEP mapping. Conversely, MEPs after transcranial and/or direct cortical stimulation are frequently elicited and recorded during all stages of surgery to proof the integrity of the CST and recognize impending damage to it when it is still potentially reversible. MEP monitoring therefore enables the surgeon to adjust the surgical manipulation early enough to prevent permanent damage to the cerebral motor system.

Figure 1 shows the stimulation and recording sites for MEPs as used at our and most other institutions during surgeries for supratentorial gliomas within or near to the primary motor cortex and/or CST. It also illustrates the differences in technique for the different stimulation sites which are transcranial MEPs (t-MEPs), direct cortical MEPs (dc-MEPs) and subcortical MEPs (sc-MEPs). **Tables 1** and **2** summarize the stimulation and recording parameters used at our institution.

http://dx.doi.org/10.5772/intechopen.70040

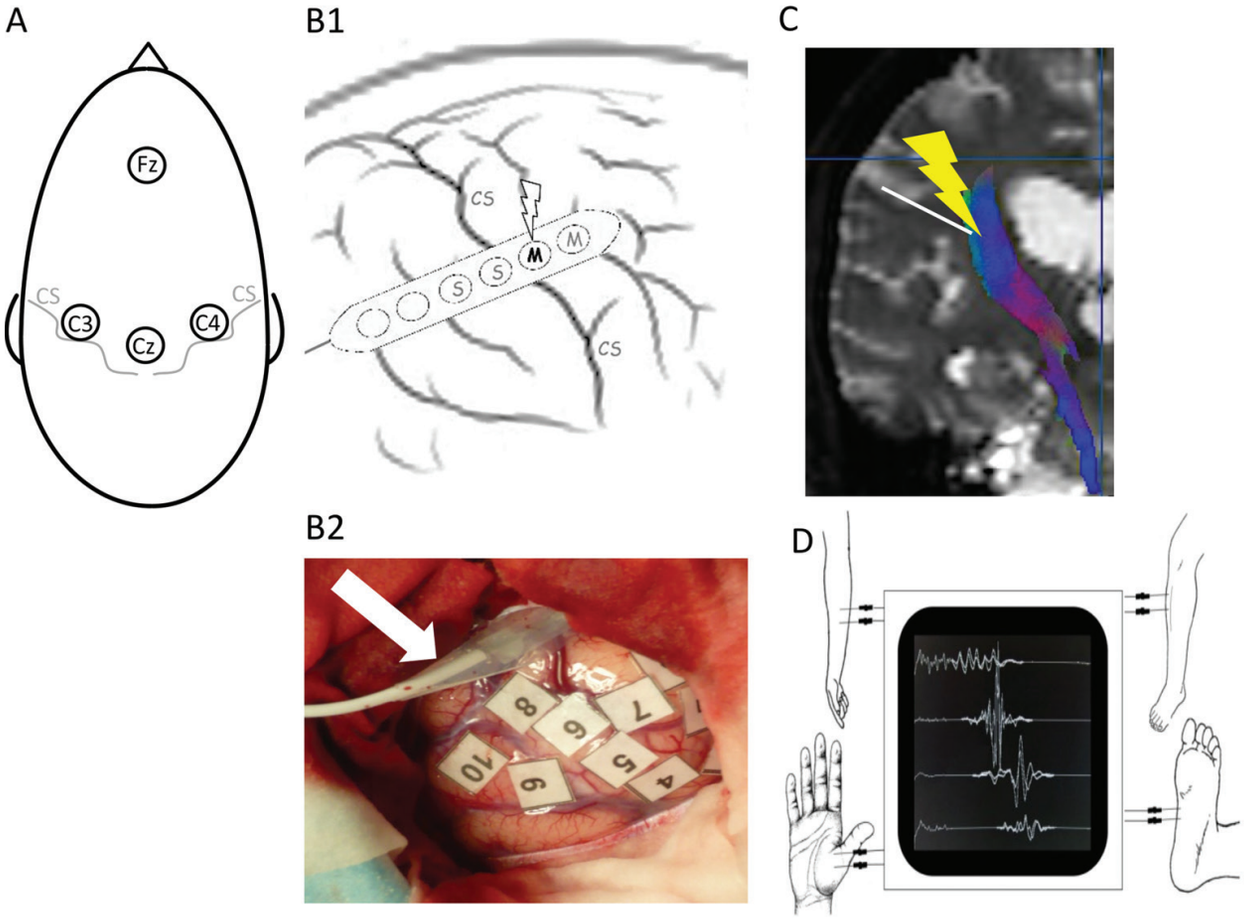

Figure 1. Stimulation and recording sites for motor evoked potentials (MEPs) used during surgeries for supratentorial gliomas. Usually, different stimulation sites are employed during surgery to elicit different types of MEPs that give distinct information intraoperatively. A shows the electrode montage for transcranial MEPs using corkscrew scalp electrodes in relation to the central sulcus (CS). The active electrodes (C3, C4, Cz) are located over the precentral gyrus using anatomical surface landmarks according to the international 10–20 EEG system (in black circles). B1 shows the stimulation site for direct cortical MEPs using a strip electrode with six contacts placed on the primary sensory cortex (S) and primary motor cortex (M). One contact over the primary motor cortex is chosen as active contact (bold M and flash) to deliver currents with comparably low intensity directly to the motor cortex. B2 shows the corresponding intraoperative photograph to scheme B1 taken after craniotomy, dura opening, placement of the strip electrode (white arrow) beneath the dura onto the cortex. The strip electrode is placed under the craniotomy margin away from the surgical field to avoid interference with surgery. Sterile numbers are placed on the cortex for the documentation of the functional mapping results. C shows a magnetic resonance imaging illustrating the corticospinal tract using diffusion tensor imaging technique. For subcortical MEP mapping, the subcortical white matter and the corticospinal tract are stimulated using a stimulation probe or a surgical suction tube with an electrode tip (white bar with yellow flash). D shows the upper and lower extremity target muscles used for MEP recorded during supratentorial glioma surgery. The MEPs are displayed on a screen and their amplitudes and latencies are analyzed continuously during surgery. CS=central sulcus, M=contact on the primary motor cortex, S=contact on the primary sensory cortex.

MEP monitoring is routinely performed by a dedicated team in all glioma cases of presumed tumor location close to the primary motor cortex or the corticospinal tract. This is achieved either by transcranial electrical stimulation with cork screw scalp electrodes (t-MEPs) (**Figure 1A**) or by direct cortical stimulation (dc-MEPs) via a cortical strip electrode placed on the precentral gyrus (**Figure 1B1**). In both cases, a constant current anodal stimulation, train-of-5 stimuli with an interstimulus interval of 4.0 ms and an impulse width of 500 μs are

Parameter	Value
Stimulation sites	C3/4; C4/3; Cz/Fz: C3/Cz; C4/Cz
Number and form of stimuli	Train of five
Stimulus lengths	500 μs
Stimulus intensity	30–220 mA
Interstimulus interval	4 ms
Recording sites	ABP contralateral, forearm flexor contralateral, TA contralateral, ABH contralateral
Stimulus frequency	0.5 Hz
Display sensitivity	200 μV–2 mV
Low pass filter	3000 Hz
High pass filter	30 Hz

Note: ABH, abductor hallucis muscle; ABP, abductor pollicis muscle; TA, tibialis anterior muscle.

Table 1. Stimulation and recording parameters used for intraoperative monitoring with transcranial motor evoked potentials (t-MEPs).

used at our institution. Cortical and subcortical mapping (**Figure 1C**) is performed with a probe or, even more comfortably, with a surgical suction tube with an electrode tip that delivers monopolar current. For detecting a muscle, MEPs 27-gauge disposable subdermal needle electrodes are placed in a bipolar way with a distance of approximately 10 mm over the target muscles of the contralateral side of the tumor. We use the abductor pollicis brevis, the flexor carpi radialis for the upper extremity and the anterior tibial muscle and the abductor hallucis for the lower extremity.

Parameter	Value
Stimulation sites	Primary motor cortex, subcortical white matter
Number and form of stimuli	Train of five
Stimulus lengths	500 μs
Stimulus intensity	3–20 mA
Interstimulus interval	4 ms
Recording sites	ABP contralateral, forearm flexor contralateral, TA contralateral, ABH contralateral
Stimulus frequency	0.5 Hz
Display sensitivity	200 μV–2 mV
Low pass filter	3000 Hz
High pass filter	30 Hz

Note: ABH, abductor hallucis muscle; ABP, abductor pollicis muscle; TA, tibialis anterior muscle.

Table 2. Stimulation and recording parameters used for intraoperative monitoring with direct cortical motor evoked potentials (dc-MEPs), as well as subcortical motor evoked potentials (sc-MEPs) used for subcortical mapping.

Transcranial electrical stimulation is applied using corkscrew electrodes which are screwed into the scalp and therefore guarantee low impedances. We routinely place initially four electrodes at C3, C4, Cz and Fz and try to elicit muscle MEPs starting with a low stimulus intensity of 30 mA from a C3/Cz montage for left-sided tumors or a C4/Cz montage for right-sided tumors. Stimulus intensity is then increased in 5 mA steps until stable recordings from all muscles can be obtained (see **Tables 1** and **2** for target muscles). In the case of high stimulus intensities (above 150 mA) or vigorous muscle twitching, cork screw electrodes are added at C1, C2 and Cz+6 and stimulation is repeated with a C1/2, C2/1 or a Cz/Cz+6 montage again starting with low intensities that are incrementally increased. Using different montages of stimulating electrodes provides flexibility to optimize elicitation of muscle MEPs and avoiding muscle twitching which can interfere with surgery. Extremely high stimulus intensities are generally avoided because this might activate the corticospinal tract (CST) deep in the brain distal to the tumor and may therefore produce false-negative results [7, 12].

Because the intensity needed for dc-MEPs (**Table 2**) is 10 times lower than for t-MEPs (**Table 1**), dc-MEPs are preferred over t-MEPs in all cases, where the surgical approach allows access to the primary motor cortex. Even if the motor cortex itself is not exposed, a six to eight contact strip electrode for direct cortical stimulation is slid underneath the dura and oriented perpendicularly to the assumed central sulcus (**Figure 1B1/2**). Somatosensory evoked potentials (SEP) phase reversal can be used as a help to identify the central sulcus.

Then the first electrode in front of the sulcus is usually used as the stimulating anodal contact and the strip electrode is kept in place by a compress and by clamping it subdurally [7]. Usually, the cork screw electrode mounted at Fz serves as the cathodal pole.

Stimulation intensity begins with 5 mA and is increased continuously in steps of 2 mA until stable MEPs can repeatedly be obtained from all target muscles. Amplitudes are then evaluated by a trained intraoperative neurophysiologist measuring peak-to-peak differences as well as the latencies defined as the time span from start of the stimulation to the first assessable amplitude [13]. After this, a baseline is set and continuous monitoring is performed throughout the whole operation with an interval of at least 120 s. In stages of surgery where the CST is particularly endangered, the intervals are shortened to 10 s.

Monopolar subcortical stimulation to elicit sc-MEPs represents the gold standard for functional localization of the CST [14]. Its technique is described in **Figure 1**. It is used during resection of gliomas when closely approaching the CST in the deep white matter or to identify the primary motor cortex. When employed to evaluate the distance of the stimulation site to the CST, an initial stimulus intensity of 15 mA is used initially. When MEPs can be obtained at 15 mA after stimulating the wall of the resection cavity, stimulation intensities are gradually decreased in 5 mA steps until MEP responses can be obtained with a stimulus intensity as low as 5 mA. Given that this indicates a close proximity of around 5 mm to the CST, resection is usually stopped there.

3. Warning criteria and functional outcome

Warning criteria for MEP monitoring and mapping during glioma surgery must be carefully defined to be able to warn the surgeon early enough to prevent permanent damage to the

patients' motor system, while not impeding tumor removal to early. This requires a well-balanced approach between the two rivaling goals, that is tumor removal and functional integrity. This means that if the warning criteria are too cautiously defined, it would lead to many false-positive test results with negative impact on the extent of tumor resection in functionally intact patients. On the other hand, less restrictive warning criteria would lead to more false-negative test results putting more patients at risk of impaired motor functions while enhancing the extent of tumor resection.

Whereas there is rather high proportion of false-positive results, false-negative results are rarely reported and can typically be explained on the basis of basic errors in technique or interpretation [15].

The optimal MEP technique and warning criteria would lead to true test results only, while avoiding false-negative results with patients sustaining new motor deficits and also avoiding false-positive results indicating motor deficits that these patients will actually not exhibit postoperatively.

The most employed criterion for MEP monitoring is the amplitude criterion. This means that the stimulus intensity which is able to elicit stable MEPs in all target muscles is set at the beginning of surgery and kept the same throughout the whole operation. From there on, a drop of MEP amplitude of 50% or more compared with the baseline amplitude results in a warning. To a lesser extent, the threshold criterion is also used by some groups in addition to the amplitude criterion. This means that, in cases where an increase in stimulus intensity of 20% or more is needed to elicit MEPs, the surgeon is warned.

Concerning the stimulation site, most groups rely on dc-MEP monitoring; in all cases the surgical approach enables them to do so rather than on t-MEPs, for the reasons mentioned above.

However, a report by Lee et al. [16] shows that relying on t-MEP monitoring for supratentorial lesion surgery leads to similar results concerning test-accuracy and functional outcomes compared with reports from groups heavily relying on dc-MEP monitoring.

Table 3 summarizes the warning criteria and functional outcomes of surgical series reported in the literature. The list also includes a series of 95 patients from the authors of this chapter who underwent surgery for perirolandic gliomas with the aid of MEP neuromonitoring and mapping.

A new approach to the threshold criterion was recently described in a publication by Abboud et al. [17]. The authors evaluated the accuracy of changes in threshold level involving contra- and ipsilateral MEPs, contrary to the usual approach to compare the changes of ipsilateral MEPs to the baseline recording. Ninety-three patients underwent t-MEP monitoring during resection of gliomas located close to central motor pathways but not involving the primary motor cortex. An increase in the threshold level on the contralateral side of more than 20% beyond the percentage increase on the ipsilateral side was considered a significant alteration.

Interestingly none of their patients without a significant threshold increase exhibited a new motor deficit postoperatively, whereas all 13 patients with a significant MEP alteration

Author/year	MEP techniques	Warning criteria	New motor deficits	New motor deficits undetected by MEP monitoring (transient and permanent)
Authors of this chapter/2017	t-MEPs, dc-MEPs	Amplitude<50% and/or threshold increase of 20%	23% transient 6% permanent	2.1%
Abboud/2016 [17]	t-MEPs bilateral	Threshold increase >20%	14% (transient and permanent)	0%
Obermueller/2015 [18]	dc-MEPs	Amplitude<50%	19% transient 14% permanent	N/A
Lee/2014 [16]	t-MEPs	Amplitude<50%	10% transient 7% permanent	13%
Krieg/2013 [19]	dc-MEPs	Amplitude<50%	37% transient 11% permanent	N/A
Krammer/2009 [20]	t-MEPs	Amplitude<50% and/or threshold increase of 20%	15% (transient and permanent)	1.6%
Neuloh/2007 [21]	t-MEPs, dc-MEPs	Amplitude<50%	21% transient 10% permanent	2.7%
Sala/2003 [22]	t-MEPs, dc-MEPs	Amplitude<50%	24% transient	N/A

The list also includes a series of 95 patients from the authors of this chapter who underwent surgery for perirolandic gliomas with the aid of MEP neuromonitoring and mapping.
dc-MEP, direct cortical motor evoked potentials; N/A, data not available; t-MEPs, transcranial motor evoked potentials.

Table 3. MEP methods, the warning criteria and functional outcomes in neurosurgical series reported in the literature.

exhibited a new motor deficit. Hence, this method resulted in a 100% sensitivity and specificity. This is the first surgical series showing such a high accuracy of MEP monitoring. Although no new motor deficit was undetected with this method, 14% of their patients sustained new motor deficits, nevertheless. This signifies the importance of not just a high accuracy but also a timely warning to prevent neurological deficit.

4. Illustrative case

A 26-year-old male patient, who has undergone surgery for a left frontal low-grade astrocytoma 2 years earlier, exhibited a significant recurrent tumor on the latest magnetic resonance images (MRI) posteriorly to the old resection cavity as shown in **Figure 2A**. Preoperative functional imaging using MRI tractography (**Figure 2B**) and functional MRI (**Figure 2C**) proved the tumor's close relationship to the CST and the primary motor cortex. Therefore, it was decided to employ MEP monitoring and mapping for the planned resection of this astrocytoma.

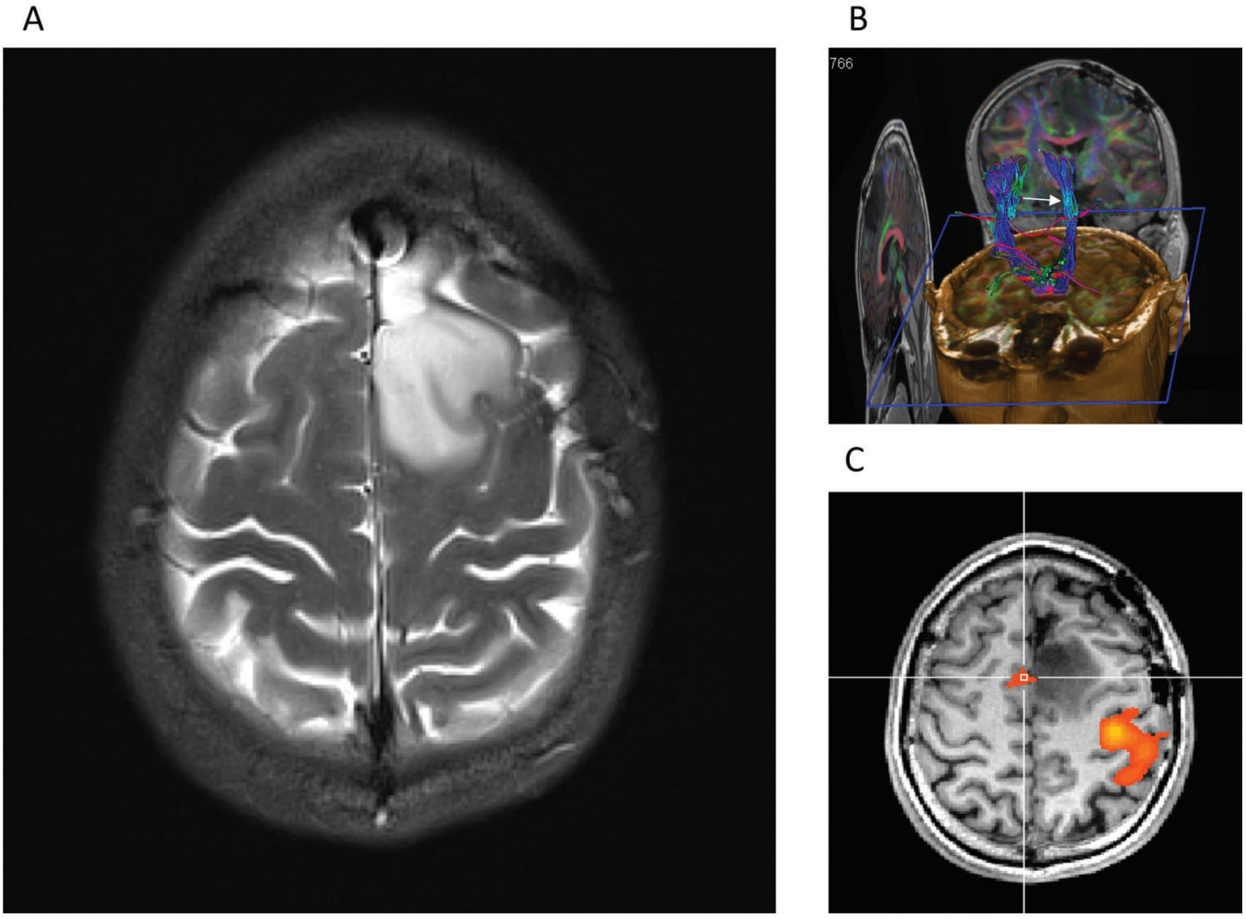

Figure 2. Preoperative images from a patient harboring a recurrent left frontal low-grade astrocytoma. Preoperative work up included T2-weighted magnetic resonance imaging (MRI) (A) showing the close relationship of the posterior tumor margin to the precentral gyrus, as well as MRI tractography and (B) showing the left-sided corticospinal tract displaced posteriorly (white arrow) by the tumor and a functional MRI of a right-sided finger-tapping paradigm showing activation in the area of the precentral gyrus' hand knob.

After positioning the patient in total intravenous general anesthesia, subcutaneous needle electrodes were placed over the target muscles of the right upper and lower extremity. Given that a surgical approach was planned that would allow the placement of a strip electrode over the primary motor cortex to obtain dc-MEPs, cork screw electrodes were only placed as a back-up in case t-MEPs have to be recorded. All electrodes were then connected to the neuromonitoring device and the electrode impedances were checked. Then the surgical approach was established by performing a left frontal paramedian craniotomy that also exposed the medial part of the left precentral gyrus. The dura was opened and the precentral gyrus was identified using monopolar direct cortical stimulation with an intensity of 10 mA. The strip electrode was placed subdurally perpendicular to the central sulcus in a direction away from the surgical field to avoid interference with the surgical procedure. Direct cortical stimulation for dc-MEPs was started with an intensity of 5 mA and incrementally increased up to the supramaximal intensity of 13mA. Stable MEPs could be obtained from all contralateral target muscles. Further increase of the stimulus intensity at this point did not further increase the MEP amplitudes so that the baseline was set and measurements were taken. Monopolar subcortical stimulation

http://dx.doi.org/10.5772/intechopen.70040

was set up then using the surgical suction tip for anodal subcortical stimulation throughout the whole operation, starting at an initial intensity of 15 mA. Corticotomy was performed and the anterior part of the tumor-harboring left superior frontal gyrus was resected without any significant changes of MEP amplitudes or latencies. As approaching the subcortical white matter just anterior to the precentral gyrus, MEPs in all upper extremity muscles could be elicited with the suction tip stimulation. The surgeon was alerted and the stimulus intensity was lowered to 10 mA which did not elicit any potentials. Cautious further resection of tumor at its posterior aspect suddenly led to a significant amplitude decline of the MEPs recorded from the abductor pollicis (ABP) of more than 50% compared with the baseline (**Figure 3**). The surgeon was alerted, surgery was stopped, the spatula was removed and the resection cavity was irrigated with warm Ringers' solution. After 12 min when the MEPs have recovered, a small remnant tumor was removed. Just before wound closure, the last intraoperative recordings showed no significant change compared to the baseline recording, indicating normal postoperative motor functions. Surgery was completed uneventfully.

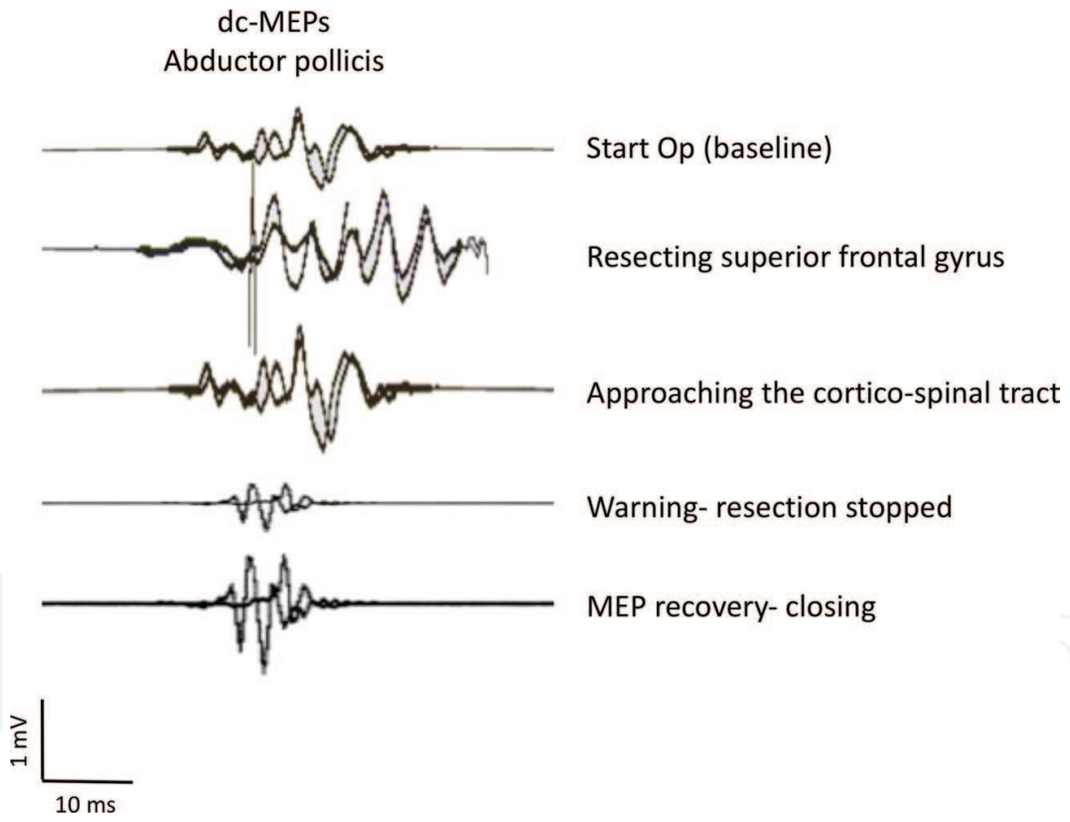

Figure 3. Intraoperative direct cortical motor evoked potentials (dc-MEPs) taken from the right abductor pollicis of a patient undergoing surgery for a left frontal recurrent astrocytoma. Baseline MEPs were obtained just after the placement of the strip electrode over the precentral gyrus. There were no significant changes of MEP amplitudes or latencies until subcortical resection was carried out in close proximity to the corticospinal tract at the posterior aspect of the tumor. Warning was given by the intraoperative neurophysiologist when a drop of MEP amplitude of more than 50% compared with the baseline recording was noted. Surgery was stopped, the spatula was removed from the resection cavity and the operating field was irrigated with warm Ringers' solution. After 12 min, the MEPs were recovered and a small remnant tumor was removed. Just before wound closure, the last intraoperative recordings showed no significant change compared to the baseline recording indicating normal postoperative motor functions.

In the immediate postoperative course, the patient exhibited a right-sided hemiplegia which recovered fully within 2 weeks and therefore proved to represent a supplemental motor area syndrome rather than a damage of the CST.

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