# Intraoperative neurophysiological monitoring under general anesthesia

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## Introduction

The early steps in determining cortical functional organization during neurosurgical procedures were performed in awake patients and date back into the early 1930s [12, 30]. At that time, the identification and assessment of cortical functional organization within the vicinity of a brain pathology (e.g., tumor, epileptic foci) was possible only by direct electrical stimulation of the cerebral cortex. The observation of the elicited interference with the awake patient's behavior, movement, and language performance served as guidance for the surgical tumor resection. Only in the late 1970s monitoring of somatosensory evoked potentials (SEP) and in the early 1990s monitoring of motor evoked potentials (MEPs) were introduced into the operating room. It was utilized in spine and spinal cord surgery and then for neurovascular procedures, before it was finally implemented into brain tumor surgery.

Overall, the development of reliable application of anesthetics, microsurgical tools and commercially available neuromonitoring equipment did allow for routine and standardized intraoperative neurophysiological monitoring in the anesthetized patient. The intraoperative methods should help to achieve the aim of a maximal tumor resection and a minimal – if any – permanent morbidity. The neurophysiological methods should be sensitive and specific towards the neuronal pathways assessed and easy and safe to perform and should provide real-time information and online analysis. An essential prerequisite for successful neurophysiological monitoring is the potential to reverse changes indicating neurological injury and thereby to prevent injury to the nervous tissue, as well as high re-test reliability.

## Methods

In the anesthetized patient, intraoperative neurophysiological monitoring for brain tumor surgery combines localizing and monitoring methods. For localization, the phenomenon of phase-reversed SEP – recorded across the central sulcus – and direct cortical stimulation (DCS) with low-intensity electrical pulses to elicit MEPs are being used. Monitoring methods are SEPs and MEPs, as well as – for brainstem surgery – auditory evoked potentials . The complementary use of the quoted potentials allows for safe tumor surgery in the vicinity of the central and insular region.

### *Somatosensory evoked potentials*

Somatosensory evoked potentials were first described in 1947 [6], but it took about 30 years of further technical development before successful intraoperative utilization was reported [26].

H. Duffau (ed.), *Brain Mapping*

To elicit SEPs, a peripheral nerve, commonly the median nerve at the wrist and the posterior tibial nerve at the medial malleolus are stimulated at a frequency of 3.1 to 5.8 Hz. The response is recorded either directly at exposed cortex or at the scalp of the primary somatosensory cortex at C3', Cz', and C4' (according to the international 10-20 EEG system). The simultaneous recording of the responses generated at the upper cervical level allows for excluding general effects to the SEPs such as temperature, peripheral nerve conduction block due to malpositioning of a limb, or anesthesia.

Because of the near linear correlation between the cortical SEP amplitudes and the cerebral perfusion when decreased below 15 ml per 100 g of brain parenchyma, SEPs are used in neurovascular procedures. The loss of SEP amplitude correlates to cortical infarcts in the territories of the middle cerebral artery and the internal carotid artery [17]. In contrast, the relative insensitivity of SEPs to subcortical ischemia gave rise to concerns and might limit the use of SEPs in indicating ischemia resulting from injury of perforating arteries supplying the internal capsule. The lack of publications about pure SEP losses in intracranial surgery should be seen in the light of the introduction of MEPs.

As the SEPs reflect the activity of the leminscal pathways and somatosensory cortex, reports of false-negative SEPs – i.e., not predicting motor deficit – have been driven by the expectation to monitor the motor pathways alike. As neurosurgical outcome assessment tends to focus on postoperative motor status, even studies analyzing the predictive value of SEPs relate postoperative motor deficits instead of sensory deficits with intraoperative SEP alterations. In intracranial neurosurgical procedures, the sensitivity of SEPs to predict minor postoperative deficits was 64% and the negative predictive value was 95%; regarding severe postoperative deficits, the sensitivity was 81% and the negative predictive value 98% [39].

## *Motor evoked potentials*

Transcranial electric stimulation (TES) and transcranial magnetic stimulation (TMS) became routinely used clinically in the 1980s. Those devices generated single-pulse outputs and did not reliably elicit MEPs intraoperatively. The breakthrough was the technical modification towards a short train of stimuli in 1993 [38]. The applied train contains a short series of pulses at high frequency (mostly five pulses with a duration of 0.5 ms each, 250–500 Hz). The pulses activate preferentially fast-conducting axons of the corticospinal tract. Those fast-conducting neurons are essential for executing voluntary movements. Studies of monkeys with direct recordings from the corticospinal tract demonstrated that the direct activation of the corticospinal tract (D-wave) occurred after a single pulse was applied to the motor cortex. Those results were later confirmed with human patients during intramedullary tumor surgery [4, 8, 9, 29]. The multipulse stimulation activates a series of descending volleys which activate spinal alpha-motoneurons and thus evoke muscle responses. When the stimulation is applied transcranially, the site of neuronal activation within the white matter is critical (Fig. 1). With increasing stimulation intensity a shorter latency of the D-wave is recorded, indicating an activation of fibers with increasing depth within the white matter. Only when high-voltage stimulation (1000 V) is used, current penetrates as deep as to the level of the foramen magnum [18, 31]. On the other hand, there is evidence that moderate anodal suprathreshold TES, as well as anodal direct cortial stimulation, activates the corticospinal tract close to the axon hillock [10]. Thus, MEPs are elicited within the white matter, in contrast to the cortical SEPs, which are generated within the grey matter.

This knowledge and the distribution of the vascular territories are of importance for the intraoperative interpretation of SEP and MEP data. In the absence of a preexisting motor deficit and after establishing the reliable MEP technique, monitorability is achieved in 95–

99% of the patients. In insular glioma and central-region tumor surgery, MEP alteration might occur in up to 44% of the patients [27, 28]. Unaltered MEPs with regard to MEP configuration, amplitude, and stimulation threshold correlated with no new motor deficit. This has to be distinguished from lesions of the supplementary motor area, for which the intraoperative preservation of MEPs predicts the full or nearly complete recovery of a patient's voluntary-movement abilities [32, 42]. The irreversible loss of MEPs is always followed by a severe motor deficit, disabling 42% of the patients severely and permanently (Fig. 2 shows an exemplary MEP loss). MEP alterations ranging from reversible deterioration over reversible loss to irreversible deterioration are followed by a range of unchanged, transiently deteriorated to moderate permanent motor deficits [27, 28, 32]. A critical approach to the value of MEPs might therefore conclude that intraoperative MEP alteration is not sensitive enough to predict postoperative motor outcome. Whereas for spine surgery, the presence or disappearance of MEP amplitude criteria is commonly accepted, it became evident soon

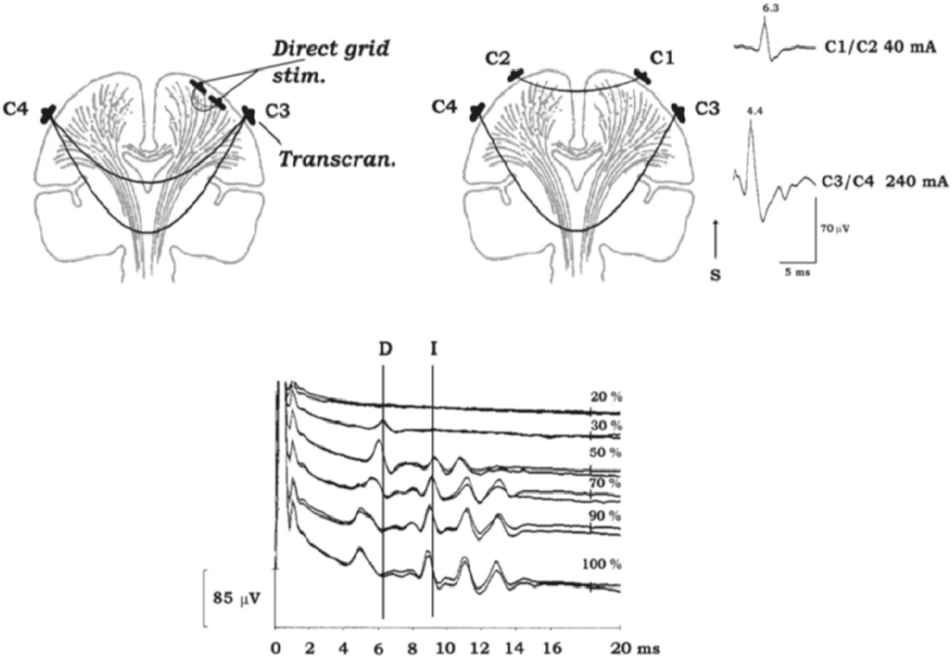

**Fig. 1.** *Top left*: Current flow during TES and direct brain stimulation via grid electrode are presented schematically. During strong TES, current penetrates deep in the brain, activating both corticospinal tracts. During direct brain stimulation, using a grid electrode current flow is restricted to a single corticospinal tract if one uses low current intensity and activates only restricted motoneuron pools from selective cortical areas (upper or lower extremities depending on the position of the stimulating electrode). *Top right*: Difference in amplitude and latencies of the D-waves record epidurally over the upper thoracic spinal cord in a patient undergoing surgery for a spinal cord tumor. Note the 1.9 ms difference between latencies of the D-waves when elicited with low intensity of current and stimulating montage C1/C2 versus high intensity of current and montage C3/C4. Note the higher amplitude of the D-wave when more axons of the corticospinal tract are recruited and current penetrates deep in the brain (C3/C4 montage and 240 mA stimulating current). *Bottom*: D- and I-waves recorded after single electrical stimulus delivered transcranially (anode at Cz, cathode 6 cm anterior) in a 14-year-old patient with idiopathic scoliosis. As a result of increasing the intensity of the stimulus, the electrical current activates the corticospinal tract deeper within the brain and the latency of the D-wave becomes shorter. As current becomes stronger, more I-waves are induced (100% corresponds to 750 V of stimulator output). Note that at the bottom, the three traces of D-waves have a double peak as a result of corticospinal tract activation at different depths within the brain. (Reproduced from [7] with permission, © Elsevier)

after the first experiences that this has to be refined for supratentorial surgery [25]. Even amplitude deterioration and prolonged transient losses were related with postoperative motor deficit. This empirical experience has led to a 50% amplitude decrement criterion, also being used for SEPs. This is supported by a data analysis of 29 patients experiencing only MEP alteration during the course of intracranial tumor resection. Irreversible MEP alteration was significantly more often correlated with postoperative motor deficit than was reversible MEP alteration ($p < 0.0001$) [35]. In those patients, irreversible MEP alteration was more often associated with postoperative new signal alteration in MRI than was reversible MEP alteration ($p = 0.018$). Further, MEP loss was significantly more often associated with subcortically located new signal alteration ($p = 0.006$). MEP deterioration was significantly more often followed by new signal alterations located in the precentral gyrus ($p = 0.036$). This supports the findings of previous studies by Neuloh et al [27].

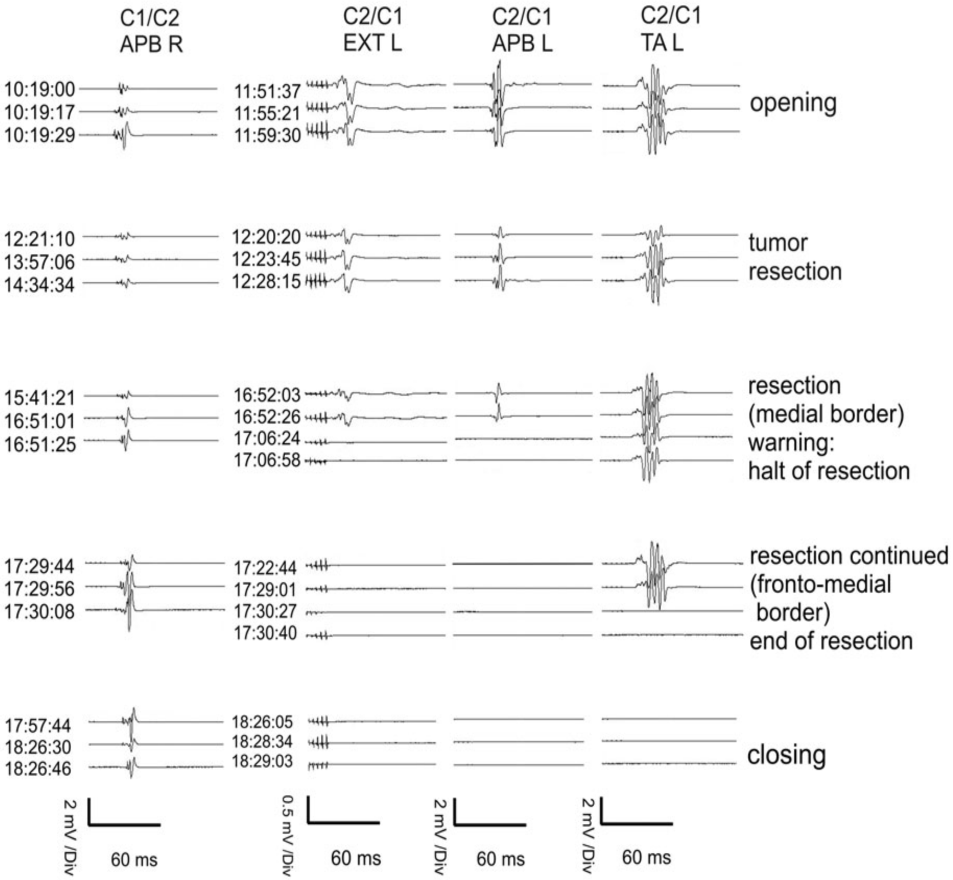

**Fig. 2.** In the course of a resection of an insular glioma, a subsequent MEP loss was observed, which was followed by a dense hemiplegia and a capsular infarct in this patient. The MEPs of the unaffected hemisphere remained unchanged, thus serving as control. (Reproduced from [35] with permission, © Lippincott Williams & Wilkins)

## *Visual evoked potentials*

Despite some enthusiastic reports about the intraoperative monitoring of VEPs and good correlation with postoperative visual function in surgery around the orbita, the method is not widely used [15, 34]. For surgeries adjacent to the visual pathways and occipital lobe, there is no strong evidence for a correlation between amplitude or latency changes and postoperative visual field defects. The flash stimulation method to elicit VEPs does not seem to be appropriate with regard to the functional organization of the visual pathways. This, in combination with the sensitivity of VEPs to anesthetics, remains a problem to be solved.

## *Intraoperative mapping in the anesthetized patient*

Due to tumor-related distorted anatomy, anatomical landmarks for the identification of the central sulcus are not always helpful. Imaging data such as 3 T MRI, special projection techniques (Mercator projection [16]), and fMRI enable the identification of the precentral gyrus. But studies of anatomy and function may demonstrate differing results [22]. This underlines that intraoperative DCS remains the gold standard for intraoperative verification of the motor cortex.

### *Phase reversal*

The phenomenon of a phase-reversed cortical SEP potential recorded over the precentral gyrus has been implemented in epilepsy surgery [13] and was transferred to brain tumor surgery. A strip or grid electrode consisting of plane or spherical electrodes is placed tangentially over the hand knob and presumably the central sulcus. The reliability to identify the central sulcus at the hand knob ranges from 90 to 94% [5, 20, 40]. In the absence of a somatosensory deficit, the method is reliable, but it may encounter problems in the presence of somatosensory deficits. It further might be difficult to obtain a phase-reversed potential from tibial nerve SEPs, which is of importance in parasagittally located tumors.

### *Direct cortical stimulation*

DCS subsumes two techniques. First, the 60 Hz technique was introduced to the broader neurosurgical community by Penfield in 1937 [30]. For this, a stimulation at 50 to 60 Hz is applied with a bipolar probe. The technique is commonly performed for mapping of cortical areas representing motor and language function in surgery of awake patients. In 1991, LeRoux et al [23] demonstrated its application in anesthetized patients. As minimal movement remains easily unrecognized in anesthetized patients, the additional recording of evoked muscle activity with a multichannel electromyogram proved advantageous [41].

Second, the technique with a train of five stimuli, a technical modification as described by Taniguchi et al in 1993 [38], can be applied for mapping and continuous monitoring of cortical and subcortical motor pathways. This method is predominantly applied with a monopolar anodal stimulation cortically and cathodal stimulation subcortically. Just recently the application for language testing was described, although the routine clinical application will need further development [2]. Performing DCS according to Taniguchi with a short series of high-frequency pulses, the stimulation parameters are the same as for TES except the limitation of the maximum stimulation intensity to 25 mA (see below for side effects).

In a comparison of the two methods, three major differences have to be highlighted: (1) the duration of stimulation, (2) the frequency of stimulation, and (3) the type of probe being used. The 50 Hz technique has to be applied for more than 0.5 s in order to observe an effect of the stimulation and thus it is commonly applied for 1–4 s. The resulting charge (stimulus) exceeds the one necessary to elicit MEPs by the train of five pulses. This might well explain the higher incidence of seizures compared to that with the train of five pulses [36]. The induced tonic movement and the high probability of seizures limit the use the 50 Hz technique as a continuous monitoring method and thus it is used only for mapping. Stimulation with a bipolar probe creates a more focal electric field compared to that with a monopolar probe. It is thought that the stimulation with the bipolar probe provides more precise results in localizing. With the monopolar probe 69% of all motor responses were elicited by DCS in the precentral gyrus and 23% in the premotor area compared to 54% and 38%, respectively, when stimulation was done with the bipolar probe. By stimulation of the motor cortex with the monopolar probe, 96% of all stimulation sites elicited MEPs compared to 95% with the bipolar probe; when the premotor cortex was stimulated with the monopolar probe, that rate was only 15%, whereas it was 27% when the bipolar probe was used [21].

## Side effects and safety

TES has a low incidence of side effects. For about 1% of patients, seizures are reported [37]. With the application of bite blocks and moderate stimulation techniques, serious tongue bite injuries and airway obstruction can easily be avoided [24].

When directly applying electric current to the brain, side effects and safety have to be addressed. The most likely side effect is the occurrence of a focal or secondary generalized seizure. This is usually self-terminating. As the bolus administration of sedatives reduces the excitability of the nervous system, this alters the further mapping and monitoring procedure. This is avoided by the administration of cold Ringer solution directly onto the cortex, which will terminate the seizure [33]. Long-term stimulation in animal experiments revealed that the application of a charge of 40 μC per phase is safe without introducing kindling or lesioning of brain tissue [1]. There are no reports for humans which relate intraoperative DCS with histopathological findings or kindling, although in daily practice the applied charge per phase exceeds 40 μC [14]. This might well be explained by the fact that intraoperatively the duration and frequency of stimulation is timely limited.

## Principles of clinical application

The intraoperative workflow in functional-monitoring-guided resection of central-region tumors utilizes intraoperative monitoring with transcranially elicited MEPs and recorded SEPs. The unaffected hemisphere serves as control and helps to judge intraoperative signal alteration. Comparable to testing in awake procedures, the first step after dura opening is the localization. The central sulcus is determined by the phase reversal, which is followed by a targeted mapping of the motor cortex. A strip electrode (disc electrodes embedded in silicone) is placed over the cortex for a stimulation at the intensity of the lowest motor threshold. The selection of muscles is determined by the tumor location and should cover the area with the greatest risk of damage. Electrodes not being used for stimulation might be used for electrocorticography or SEP. Alternatively, the exposed motor cortex is mapped first with a stimulating probe, and the strip electrode is being placed parallel over the precentral gyrus thereafter.

During tumor resection, SEPs and MEPs are recorded in an alternating fashion, providing real-time information in less than a minute about the functional integrity of the somatosensory and motor cortex and their related pathways. In the Frankfurt setting, for dissections close to the pyramidal tract any deterioration of MEPs is indicated. Comparable to those groups using only mapping methods, tumor resection is further guided by intermittent cortical and subcortical stimulation to delineate the extension of the resection. The decision when to stop resection in the presence of MEPs is highly dependent on the stimulation parameters being used, the aspect of the resection cavity, and the surgeon's experience. When clinical outcome and imaging results of experienced groups are compared, especially lesions resulting from subcortical ischemia due to perforator injury appear to contribute to permanent morbidity [3, 11, 19, 27, 28].

## Conclusion

The combined use of mapping and monitoring techniques in supratentorial surgery and especially in tumor surgery in the vicinity of the motor cortex, corticospinal tract, somatosensory cortex, and lemniscal pathway allows for tumor resection in brain areas previously being considered unresectable. Further studies analyzing not only functional outcome but also tumor recurrence and progression in comparison with their history in patients not being operated on will help for treatment decision.

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