Neurophysiological basis of direct cortical stimulation and applied neuroanatomy of the motor cortex: a review

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Intraoperative electrical stimulation of the motor cortex is a sensitive method for intraoperative mapping and monitoring of this region. Two different stimulation techniques have been established, the bipolar and monopolar techniques. Controversy exists regarding the most suitable method. Both methods have advantages and disadvantages and different electrophysiological backgrounds. The present study is a review of the electrophysiological basis of direct cortical electrical stimulation of the motor cortex. Both methods are discussed and their field of application is presented. (DOI: 10.3171/2009.8.FOCUS09141)

KEY WORDS • review • intraoperative monitoring • cortical stimulation

THE intraoperative use of neurophysiological techniques allows reliable identification of the sensorimotor region, and constitutes a prerequisite for its anatomical and functional preservation. The clinical impact of IOM has been demonstrated in various publications.^{6,7,21,22,25–29,31,33,64,76–78,89,98–100} Although the basic principle of cortical stimulation is the application of an electrical impulse on the cortex, two different methods have been established, the BCS and the MCS techniques. Recent literature shows a wide spectrum of application for both techniques, and a discussion is ongoing in which either method is favored. Therefore, controversy exists regarding the superiority of each method.

However, cortical electrical stimulation, especially in patients in whom general anesthesia has been induced, is a complex neurophysiological phenomenon. Both techniques are suitable to perform cortical stimulation; however, they differ in their electrophysiological parameters. The purpose of this manuscript was to present the basic mechanisms for both methods and to explain the differences in their effect on the motor cortical system.

Mapping Methods

Bipolar Cortical Stimulation

Fritsch and Hitzig⁴¹ first described the motor cortex as a functional unit in 1870, and since then many techniques have been developed for direct electrical stimulation of motor cortex areas.

Sir Victor Horsley^{52–54} triggered movements in the extremities of monkeys and later also of humans by electrically stimulating the cerebral cortex. Keen^{59–61} performed this procedure with the so-called double brain electrode, which consisted of a rubberized handpiece with two partially isolated end poles. A battery provided the current for stimulation.

Modifications of this technique and their application in patients undergoing awake surgery were described in subsequent decades by many authors,^{18,44,56,83} including Gruenbaum and Sherrington in 1903 as well as Cushing in 1909. However, it was the basic study published by Penfield and Boldrey⁸³ in 1937 that established intraoperative cortex stimulation as a routine method in conscious patients. It should be noted, though, that this stimulation technique could not be applied in patients under general anesthesia.

It was only in 1991 that LeRoux et al.⁷⁰ presented a modification of the stimulation method already applied by Penfield, which enabled direct cortex stimulation under general anesthesia. This bipolar stimulation technique has become a standard method in the meantime.^{5,36,37,62,72,73} A varying pulse sequence had been applied with a relatively low frequency of 50–60 Hz. Thus, King and Schell⁶² in 1987 reported on the application of a bipolar monophasic stimulation technique with a frequency of 50 Hz. It became evident, however, that a sequence of 250–500 pulses was necessary to trigger an MEP. Comparable results were published by Ebeling et al.^{36,37} in 1989, and by Berger et al.^{5,6} in 1990. The stimulation intensity needed to trigger an MEP, however, had a very high range (up to 40 mA). Yingling et al.¹⁰⁸ reported

Abbreviations used in this paper: BCS = bipolar cortical stimulation; EPSP = excitatory postsynaptic potential; IOM = intraoperative monitoring; MCS = monopolar cortical stimulation; MEP = motor evoked potential; PMC = primary motor cortex; SMC = secondary motor cortex.

FIG. 1. Schematic representation of current flow following electrical stimulation of a nerve.

on precise localization of the motor centers with the aid of bipolar stimulation.

Extensive experience with this technique constitutes its major advantage. However, BCS does not allow an objective analysis. Furthermore, the movements elicited by the stimulation cause interference during microneurosurgery, thus preventing continuous monitoring of motor function during tumor resection. This is the major disadvantage of the method as compared with continuous monopolar stimulation. The rare induction of an intraoperative seizure by low-frequency stimulation is a further disadvantage of this technique.

Bipolar cortical stimulation is a sensitive method for mapping the motor cortex, especially the premotor frontal cortex.⁶⁴ The effect of the bipolar stimulus is on the level of the cortex, making the method a standard technique for mapping cortical function. However, in several reports investigators used BCS for mapping of the subcortical pathways. As a mapping technique, this is the standard for cortical and subcortical mapping.^{25–28,30–34} Bipolar cortical stimulation is the only technique available today for the intraoperative mapping and monitoring of speech-related cortex.

Monopolar Cortical Stimulation

The choice of a monopolar stimulus is based on investigations performed by Hern,⁵¹ who examined the direct electrical excitability of pyramidal cells of the motor cortex and was the first author to propagate an anodic stimulation technique. These findings were confirmed by Gorman,⁴² who compared various techniques for direct stimulation of the cortex. Gorman demonstrated that direct monopolar anodic stimulation of the cortex required the lowest stimulation intensity to trigger an MEP. Ranck⁹⁰ performed a series of electrophysiological investigations showing that anodic stimulation directly excites the axons of the pyramidal cells. The MEPs could be recorded in conscious patients by applying an anodic rectangular pulse with a duration of 0.2 msec and a stimulation intensity ranging between 1 and 10 mA.

In 1993, Taniguchi et al.¹⁰¹ described a further modification of the monopolar stimulation technique. A high-frequency (300–500 Hz) anodic rectangular pulse was used to record MEPs during surgery after induction of general anesthesia. The requisite stimulation intensity of 20 mA was markedly below that of low-frequency bipolar stimulation. Five pulses were needed to trigger an MEP. This count was lower by a factor of 50–100 than in the previously mentioned studies on bipolar stimulation.^{5,36,37,62}

The monopolar anodic stimulus leads to excitation

FIG. 2. Schematic representation of the effect of anodal monopolar stimulation on nerve cells.

of the pyramidal cell zone. The high-frequency pulse sequence leads to an accumulation of EPSPs. As demonstrated by Landgren et al.⁶⁶ as well as by Day et al.,¹⁹ a temporary accumulation of EPSPs is necessary to activate the resting motor neurons, even after induction of general anesthesia.¹⁰² When a stimulus has been transmitted via the synapse, so-called EPSPs are registered in the postsynaptic membrane.¹¹ The EPSPs indicate the depolarization of the postsynaptic cell, which can last for up to 20 msec. An action potential is produced as soon as the membrane potential exceeds the threshold value of -60 mV. Two temporally separate stimuli reaching the synapse produce 2 EPSPs; these can accumulate and thus increase the membrane potential. An action potential is the result of this accumulation.

A series of tests¹⁰¹ in 9 patients showed that MCS provides a simple technique for low-intensity stimulation of the motor cortex. Repetitive stimulation could be performed throughout the entire operation. The short repetition time enabled surgical maneuvers to be correlated with changes in the MEPs. In 1996, Cedzich et al.¹⁷ demonstrated the practicability of motor cortex mapping (in 33 patients) as well as intraoperative monitoring (in 25 patients). The intraoperative application of this neurophysiological examination technique has failed thus far due to lack of experience.

Monopolar cortical stimulation has been proven to be a reliable method for monitoring subcortical pathways. Changes in MEP latency and amplitude serve as warning criteria during surgery and are of prognostic value.^{64,97,98}

Neurophysiological Basis

The electrical resistance and capacity of the pia mater are not measurable after a few minutes of air exposure.⁴ Electrical resistance is 4–6 times higher in the gray than in the white matter.^{3,79,91} According to Ohm's law, these different resistances influence the flow of current. After electrical stimulation of a nerve fiber, the current flows inward at the positive electrode (anode) and outward at the negative one (cathode) (Fig. 1).⁸⁸

Review of intraoperative mapping methods

Fig. 3. Chart showing epidural recordings following monopolar stimulation.

The extracellular space becomes negative at the cathode, thus increasing the intra/extracellular electrical gradients. This potential difference at the membrane leads to depolarization.⁹⁰ The cell membrane is depolarized at the cathode by the outward flow of current but hyperpolarized at the anode by its inward flow.^{85,88} Because a hyperpolarized membrane is refractory, too high a hyperpolarization will block conduction. Therefore, a depolarization generated below the cathode can only be conducted when the hyperpolarization at the anode is not too high.⁹⁰ Hence, a monopolar cathodic stimulation is conducted at low but not at suprathreshold intensities.⁵⁷

Axons have a lower stimulation threshold than dendrites.^{40,90} Hern et al.⁵¹ demonstrated that anodic stimulation of the motor cortex leads to stimulation of the pyramidal cells. The anodic flow enters the dendrites, causes hyperpolarization, and exits the axon, where it produces depolarization (Fig. 2).

Electrical stimulation of the pyramidal cells results in a 2-stage conduction of the pulse through the tract.⁸⁰ First a wave (the so-called D wave) is registered directly after the stimulus. The D wave is caused by direct stimulation of the pyramidal tract. This is followed by a delayed series of waves (the so-called I waves). Apart from having a direct effect on the axons, the stimulus also leads to an indirect repetitive conduction in the pyramidal tract (I waves) (Fig. 3). Isolated destruction of the gray matter leads to extinction of the I waves, but the D wave remains unchanged.⁸¹

In humans, conduction is slow in 90% of the pyramidal fibers (thickness of 1–4 μm)⁶⁸ and rapid in only 1.7% (thickness 11–22 μm). Between 60 and 94% of the fibers are myelinated.^{23,68} The conduction rate of pyramidal fibers varies between 50 and 80 m/second.⁶⁸

Experimental studies in animals have shown that anodic stimulation of the motor cortex produces a D-wave response, whereas cathodic stimulation elicits a pure I-wave response (without D wave).⁵¹ Gorman⁴² observed that a cathodic stimulus leads to a measurable latency prolongation of 100–150 μsec in the medulla oblongata.

The EPSPs produced after an anodic stimulus are not only accumulated but also enhanced by the pulse sequence.⁸⁵ The high-frequency pulse sequence has the effect of generating not only D but also I waves, particularly after the third stimulus of the sequence. Intracortical connections conduct the stimulus into adjacent neurons, which in turn react with an I response. This results in the aforementioned enhancement of EPSPs following a monopolar anodic high-frequency stimulus and renders anodic more effective than cathodic MCS.

Fig. 4. A 3D reconstruction showing distribution of hand motor areas identified by BCS and MCS.

A bipolar stimulus is more effective with the stimulation electrodes aligned transversally, rather than longitudinally, to the axon.⁹² Nathan et al.⁷⁵ demonstrated that maximal focusing of the current density (A/cm^2) is achieved by spherical electrodes at a distance of 5 mm. The current density is at its maximum directly below the electrode ($0.05 \text{ A}/\text{cm}^2$) when applying bipolar stimulation with a current intensity of 10 mA ($0.05 \text{ A}/\text{cm}^2$). The current spreads in a laminar fashion and decreases with increasing distance from the stimulation electrode. With a monopolar stimulus, the flow of current decreases with increasing distance from the center of the electrode.

Experimental studies in animals¹⁰⁹ have shown that high levels of continuous electrical stimulation result in gliosis, with glycogen accumulation. Neuron destruction has even been observed in severe cases. On the cellular level, the increased intracellular Ca^{++} and lipid concentrations were found to result in destruction of the cell membrane and neurons.^{1,2,71,109}

The current flowing into the cortex via the electrode elicits an electrochemical reaction that alters tissue pH and leads to organic oxidation.⁷¹ In addition, the flow of current through the neurons causes neuronal hyperactivity, which impairs cellular homeostasis through a change in the intra- and extracellular concentration of K^+ and Ca^{++} . A destruction of the cell membrane may result from this reaction. Thus the current density should not exceed $40 \mu\text{C}/\text{cm}^2$ when applying continuous stimulation.^{2,74,86,87}

However, all these studies were performed during continuous stimulation (1.5–50 hours). There have not yet been any investigations describing the effects of intraoperative electrical stimulation on the human brain. Epileptic seizures must be attributed to electrical stimulation and not to neuronal damage.^{86,87,109}

Discussion

Contrary to the general view, there is considerable functional spreading of motor units throughout a much wider area than the classic narrow cortical strip along the central sulcus (Fig. 4). In a mapping study combining bipolar and monopolar stimulation of all motor responses elicited by BCS, 54.28% were located in the PMC, 37.85% outside the motor strip in the SMC, and 8% posterior to the central sulcus. Of all motor responses elicited by MCS, 68.57% were located in the PMC, 23.42% in the SMC, and 8% posterior to the central sulcus.⁶⁵

Humans and nonhuman primates are assumed to have at least 4 different motor areas: the PMC; the premotor cortex; the SMC; and the cingulate gyrus.^{8,9,20,43,55,58,67,69,80,84,93,94,96} Thus, anatomical orientation must, whenever possible, be complemented by intraoperative mapping of all these areas to prevent postoperative motor deficits.

The common histological denominator of the motor cortex in human and nonhuman primate brains is the agranular cytoarchitectonic pattern characterized by the Betz cells in the PMC and the rostrally adjoining frontal cortex. The agranular region is bordered rostrally by the prefrontal cortex and caudally by the granular somatosensory cortex. The cingulate gyrus marks the border of the agranular isocortex.^{104,105} In humans, parts of the cingulate cortex beneath the supplementary motor area are activated during various motor paradigms.^{82,96}

Neurologists and psychiatrists took an early interest in localizing cerebral functions. Clinicians thus made the first attempts at localization. Broca¹⁰ found a lesion at the foot of the third frontal gyrus while performing an autopsy in a patient who had suffered from a speech disorder. Wernicke¹⁰⁷ detected damage in the dorsal segment of the first parietal gyrus in a patient with a word comprehension disorder.

Stimulation experiments^{39,41} revealed a functional segmentation in the precentral gyrus. Dusser de Barenne³⁵ performed animal experiments in which the stimulant was not an electric current but strychnine applied to circumscribed regions of the postcentral gyrus. He found that after this procedure the animal scratched a certain body region. The postcentral gyrus could be functionally analyzed in this way.

Kleist, a student of Wernicke, drew up a “structural and functional map of the brain” based on his long-term experience, his observation of 300 World War I brain-injury victims, and his assessment of 106 circumscribed cerebral lesions examined in his own clinic.⁶³ Referring in this connection to the research results of Campbell,¹⁵ Smith,⁹⁵ Brodmann,^{12,13} Vogt,¹⁰⁶ Economo,³⁸ Cajal,¹⁴ and van Valkenburg,¹⁰³ he linked various regions with the cytoarchitectural fields of Brodmann.¹²

The knowledge gained by animal experiments was confirmed and even broadened during neurosurgical interventions.¹⁸ The introduction of stereotactic methods yielded new findings.^{45–50} Stereotactic surgery made it possible to stimulate or disconnect even deep structures and to record evoked potentials from particular brain centers by using implanted microelectrodes.

Rudin and Eisenman⁹² demonstrated that bipolar stimulation is more effective if the electrodes are transversely oriented rather than longitudinally to the surface of the cortex. Nathan et al.⁷⁵ found that current density (A/cm²) can be focused during bipolar stimulation by placing spherical electrodes 5 mm apart. This is why in our own series a bipolar stimulation probe with 2 spherical steel electrodes 5 mm apart was used. During BCS with 10 mA, the current peaks in the region directly below the bipolar electrodes (0.05 A/cm²).

When monopolar anodal stimulation is applied, current density decreases much less rapidly with depth.⁷⁵ Several studies have shown that an anode is more effective

for MCS than a cathode^{85,88}; anodal current enters and hyperpolarizes dendrites, and leaves and depolarizes the axon or cell body.⁸⁸ Hern et al.⁵¹ have demonstrated a direct action of monopolar anodal stimulation on pyramidal cells. This is due to the fact that the axon and regions adjacent to the cell body have a much lower threshold than the dendrites and the cell body.⁹⁰

Repetitive MCS induces repetitive excitation of the corticospinal tract.¹⁰¹ The high-frequency train achieves an accumulation of postsynaptic potentials, which activates the motor neurons even after induction of general anesthesia.

Intraoperative mapping requires frequent stimulation throughout the procedure. A bipolar stimulus lasts 2–4 seconds, as compared with the 1.4 msec needed for a monopolar stimulus. In addition to the difficulty in evaluating movement quantitatively, the increased stimulus duration prolongs the monitoring procedure.

The method of MCS requires a high-frequency electrical stimulus. No intraoperative seizures occur as a result of the stimulation.^{16,64,98} The major advantage of this new technique is that it allows objective analysis of the results. The motor responses recorded during surgery can be analyzed regarding latency, amplitude, and duration. Because MCS never causes movements, it may be used repeatedly.

Conclusions

Monopolar cortical stimulation has been proven to be a reliable method for monitoring subcortical pathways, and is just as sensitive as BCS for mapping the PMC. Changes in MEP latency and amplitude serve as warning criteria during surgery and are of prognostic value. The monopolar anodic stimulus leads to excitation of the pyramidal tract.

Bipolar cortical stimulation is a sensitive method for mapping the motor cortex, especially the premotor frontal cortex. The effect of the bipolar stimulus is on the level of the cortex, making the method a standard technique for mapping cortical and subcortical function. The only technique available today for the intraoperative mapping and monitoring of speech-related cortex is BCS. Surgery in the SMC requires a combination of bipolar stimulation for mapping and monopolar stimulation for monitoring the descending motor pathways.

Disclaimer

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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Review of intraoperative mapping methods

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Review of intraoperative mapping methods

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