

## Research paper

# Threshold variation of transcranial motor evoked potential with threshold criterion in frontotemporal craniotomy

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## ABSTRACT

**Objective:** Motor threshold usually varies in the intraoperative motor evoked potential (MEP) by transcranial evoked stimulation (TES). This study investigated the degree of change in the motor threshold before and after surgery in TES-MEP monitoring with threshold criterion. This study aimed to evaluate the threshold change and discuss the factors influencing the motor threshold.

**Methods:** We retrospectively analyzed TES-MEP monitoring during supratentorial surgery with frontotemporal craniotomy in 72 patients without pre- and postoperative motor weakness. We analyzed the percentage changes between the affected and the unaffected sides, correlating the changes on the two sides.

**Results:** The percentage change on the affected and the unaffected side was  $4.4 \pm 15.1\%$  and  $0.4 \pm 6.5\%$ , respectively. The percentage change on the affected side was significantly larger than that on the unaffected side. A significantly positive correlation between the percentage change on the affected and the unaffected sides was detected.

**Conclusion:** The threshold for the TES-MEP varied significantly more than that on the unaffected side.

**Significance:** It is important to understand the characteristics of threshold variation for the evaluation of TES-MEP.

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## 1. Introduction

Intraoperative motor evoked potential (MEP) monitoring can detect corticospinal tract damage and may improve neurological outcome (Szelényi et al., 2006; Sala et al., 2006; Macdonald et al., 2013). Methods of electrical stimulation for intraoperative MEP monitoring include transcranial electrical stimulation (TES), direct cortical stimulation (DCS), and subcortical stimulation (Szelényi et al., 2003; Szelényi et al., 2006; Szelényi et al., 2007; Szelényi et al., 2010; Seidel et al., 2013; Landazuri and Eccher, 2013; Shibani et al., 2015; Moiyadi et al., 2018). TES-MEP is popular in neurosurgery (Tomio et al., 2016) because subdermal stimulation electrodes can be placed easily and steadily; TES-MEP can be performed throughout surgery regardless of whether open or closed.

There are two kinds of warning criteria to evaluate the intraoperative TES-MEP examination (Abboud et al., 2018). One criterion is the amplitude criterion, which has been a major criterion in neurosurgery (MacDonald et al., 2013). Another criterion is the threshold criterion, which has been proposed by Calancie et al. in spinal

surgery (Calancie et al., 1998). The threshold criterion has a high sensitivity and multifactor influence on the threshold, such as general anesthesia and brain shift (Langeloo et al., 2007; Abboud et al., 2016). These intraoperative environmental changes cause threshold variation and make it difficult to evaluate how much threshold change could signal a warning sign during TES-MEP with threshold criterion. However, there are few clinical studies that describe the variation of motor threshold in TES-MEP with the threshold criterion. Here, we report our clinical experiences on how much the threshold varies in TES-MEP during procedures in supratentorial cases without pre- or postoperative motor weakness and discuss the reasons underlying this threshold change.

## 2. Methods

### 2.1. Patient selection

To compare the initial threshold, final threshold, and threshold change on the affected and unaffected sides, data were retrospectively collected from 299 cases of intraoperative MEP monitoring during surgeries at the Neurosurgical Department of Shinshu University Hospital from December 2007 to August 2017. TES-

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MEP monitoring for supratentorial surgery in 72 patients was included in this study. Direct cortical stimulation in 36 patients, spinal MEP in 45 patients, and infratentorial lesion in 123 patients were excluded. Preoperative motor weakness in 20 patients and postoperative motor weakness in 3 patients were also excluded (Fig. 1).

## 2.2. Intraoperative motor evoked potential technique

General anesthesia was induced by injecting a short-acting barbiturate or propofol and a neuromuscular blocking agent to intubate the subject. Inhalational agents and neuromuscular blocking agents were not administered after intubation. Anesthesia was maintained by constant infusion of propofol (100–300 mg/kg/min) with a bispectral index monitor (BIS). Narcosis was also induced either by constant infusion or as intermittent bolus of fentanyl or remifentanyl. In most cases, nitrous oxide (<50%) was also given.

The TES-MEP electrode was placed on C3' or C4', which was 7 cm lateral from the midline on the line between Cz' (2 cm posterior to Cz) and the midpoint of the zygomatic arch. The corkscrew electrode for the TES-MEP stimulation electrode was set on the scalp. The peg-screw electrode was placed directly on the skull where there was a skin flap, but the skull remained intact. The peg-screw electrode consisted of a peg-screw and a connecting cable. The diameter of the peg-screw was 3.5 mm, and the length was 20 mm. The peg-screw was made of stainless steel SUS-316. The connecting cable was made of an insulated alligator clip electrode that was connected to a peg-screw. The usage of peg-screw was approved by the Ethics Committee of Shinshu University School of Medicine.

MEB 2216 (Nihon Kohden Co. Ltd., Tokyo, Japan) was used as an electrophysiological device. Transcranial electrical stimulation was delivered by a train of 5-pulse anodal constant current stimulation (mA), where the duration of each stimulus was 0.3 ms with an initial interstimulus interval of 2.0 ms. Threshold was defined as stimulation intensity of evoked muscle response exceeding 20  $\mu$ V in peak-to-peak amplitude with appropriate response latency (e.g., latency to abductor pollicis brevis was 20–25 ms). Compound muscle potentials were recorded using a pair of staple electrodes placed on the bilateral abductor pollicis brevis (APB). Signals were amplified and filtered (20–2000 Hz) before display.

Initial threshold stimulation intensity was evaluated for each electrode to determine the baseline for MEP monitoring after craniotomy and before dural opening. Anodal stimulation was elicited from the contralateral extremities. The polarity was then changed to the opposite side. The threshold stimulation intensity was recorded at multiple intervals throughout the surgery, and the final

threshold stimulation intensity was evaluated after the procedure on both sides. Percentage change between the initial and final thresholds was expressed in percentage. Data of age, sex, disease, and approach were also collected.

## 2.3. Statistical analysis

Threshold data are presented as the mean  $\pm$  standard deviation (SD). The Mann-Whitney *U* test was used for comparison of the percentage change between the affected and the unaffected side. The correlation of percentage change on the affected and unaffected sides was assessed using Spearman's correlation. Probability values less than 0.05 were considered significant. XLSTAT<sup>®</sup> for Mac (Addinsoft SARL, Paris, France) was used for the statistical analysis.

## 3. Results

### 3.1. Patient characteristics

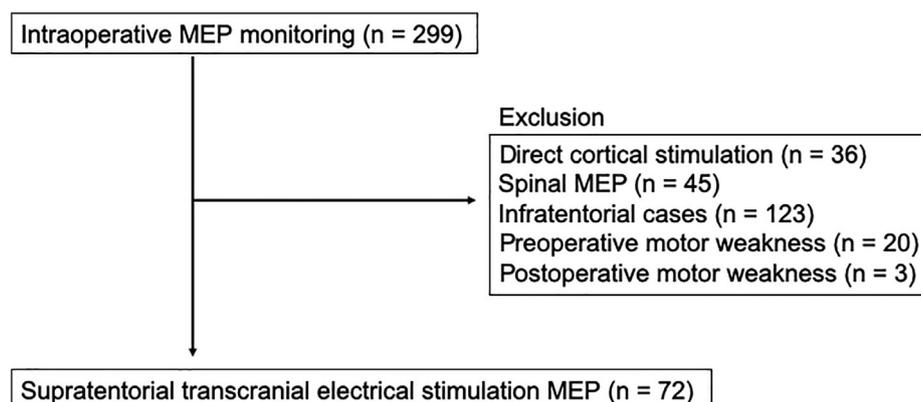
The characteristics of patients are presented in Table 1. There were 22 male patients and 50 female patients. The median age was 62 (range 10–77) years. Forty-seven patients had an aneurysm, and 25 patients had a tumor (15 meningiomas, 4 gliomas, and 6 other tumors). All patients were treated with frontotemporal craniotomy. There were no complications related to general anesthesia, surgery, or TES-MEP.

### 3.2. Initial threshold stimulation intensity on the affected and unaffected sides

The initial and final mean threshold stimulation intensities were  $45.3 \pm 17.9$  mA (mean  $\pm$  SD) and  $47.5 \pm 21.2$  mA, respectively, on the affected side and  $55.6 \pm 16.7$  mA (mean  $\pm$  SD) and  $56.1 \pm 17.9$  mA, respectively, on the unaffected side (Table 2).

**Table 1**  
Clinical characteristics of patients.

Characteristics	
Number (men/women)	72 (22/50)
Age, median (range) (years)	62 (10–77)
Disease	
Aneurysm	47
Tumor	
Meningioma	15
Glioma	4
Others	6



**Fig. 1.** Flowchart for patient selection.

**Table 2**  
Threshold stimulation intensity on the affected and unaffected sides.

	Affected side	Unaffected side
Initial threshold (mean ± SD) (mA)	45.3 ± 17.9	55.6 ± 16.7
Final threshold (mean ± SD) (mA)	47.5 ± 21.2	56.1 ± 17.9
Range of change (%)	-41.3–38.8	-16.0–17.1
Percentage change (mean ± SD) (%)	4.4 ± 15.1	0.4 ± 6.5

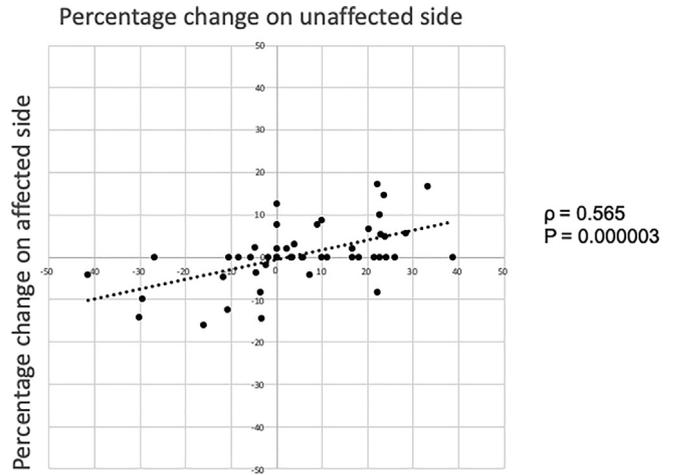
SD: standard deviation.

3.3. Percentage change on the affected and unaffected sides

The percentage change (final – initial threshold/initial threshold) on the affected and unaffected sides was 4.4 ± 15.1% and 0.4 ± 6.5%, respectively (Table 2). The percentage change on the affected side was significantly greater than that on the unaffected side (P = 0.04) (Fig. 2). The proportion of the percentage change, more than or equal to 20%, was 20.9% on the affected side and 0% on the unaffected side.

3.4. Correlation of the percentage change between the affected and unaffected sides

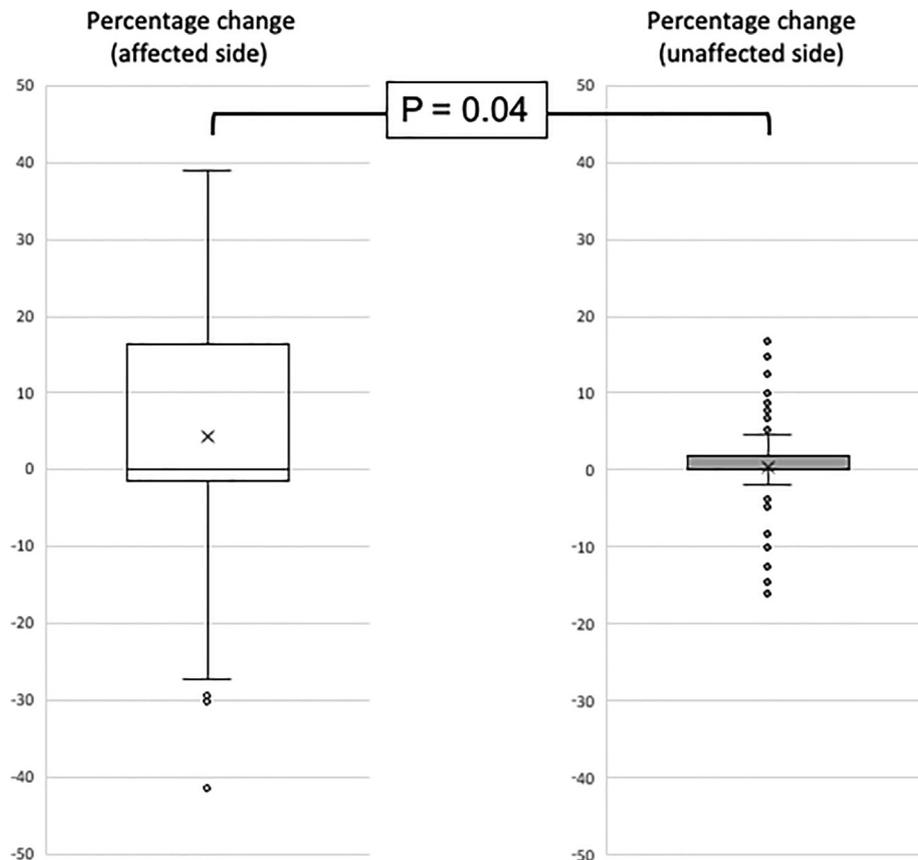
The increasing or decreasing tendency of the threshold was correlated with both hemispheres. A scatter plot analysis demonstrated a significantly positive correlation ( $\rho = 0.565$ ,  $P = 0.000003$ ) between the percentage change on the affected and unaffected sides (Fig. 3).



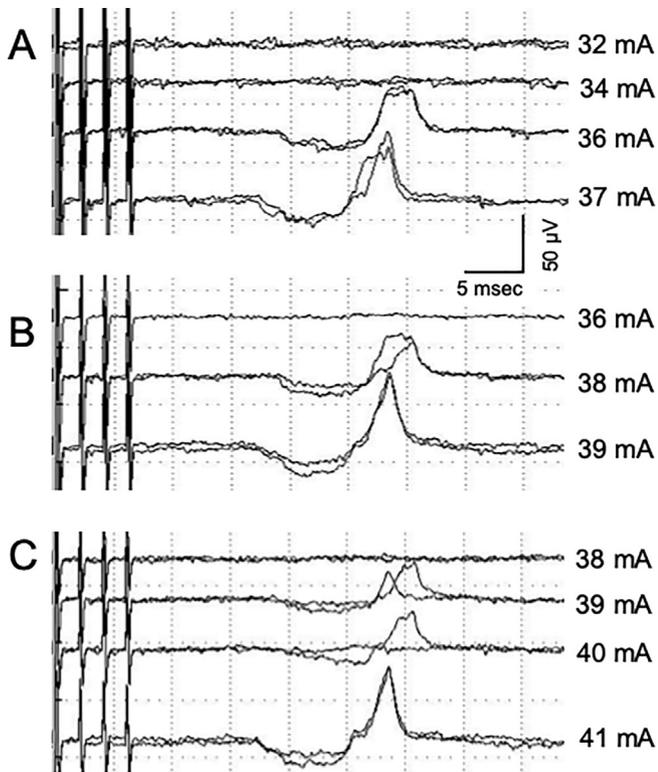
**Fig. 3.** Scatter plot analysis showing a significantly positive correlation ( $\rho = 0.565$ ,  $P = 0.000003$ ) between the percentage change on the affected and unaffected sides.

3.5. Representative MEP case about threshold changes on the affected side

A 61-year-old woman who had an unruptured middle cerebral artery aneurysm underwent clipping surgery during the right frontotemporal craniotomy. The initial threshold stimulation intensity of the left APB was 36 mA before opening the dura (Fig. 4A). The threshold gradually increased to 38 mA and 39 mA during the dissection of the Sylvian fissure (Fig. 4B) and the exposure of the



**Fig. 2.** Percentage change (final – initial threshold/initial threshold) on the affected and unaffected sides. The percentage change on the affected side is significantly greater than that on the unaffected side (P = 0.04).



**Fig. 4.** Representative MEP case showing threshold elevation during surgery without the injury of the motor pathway. One division: 5 ms/50  $\mu$ V.

aneurysm, respectively (Fig. 4C). The threshold stimulation intensity remained unchanged during surgery on the unaffected side. These data show a gradual increase in the motor threshold due to CSF evacuation or brain shift.

#### 4. Discussion

The intraoperative environmental changes influence motor threshold during TES-MEP. The intraoperative environmental changes can be divided into two types of factors – those influencing both hemispheres and those influencing only the affected hemisphere.

The intraoperative environmental changes influencing both hemispheres are considered as pharmacological factors and physiological factors. Pharmacological factors include halogenated inhalational anesthetic agents, nitrous oxide, opioid agents, ketamine, dexmedetomidine, barbiturates, benzodiazepines, etomidate, propofol, droperidol, muscle relaxants, etc. (Bithal, 2014; Sloan and Jantti, 2008; Soghomonyan et al., 2014; MacDonald et al., 2013). Physiological factors include blood flow, blood pressure, oxygenation, intracranial pressure, blood rheology, carbon dioxide, temperature, etc. (Bithal, 2014; Sloan and Jantti, 2008; Soghomonyan et al., 2014; MacDonald et al., 2013). Our results showed that there was a significant positive correlation in the percentage of threshold change between the affected and unaffected sides. Therefore, measuring the threshold of the unaffected side becomes an aid to evaluate TES-MEP monitoring with threshold criterion when measuring the threshold changes on the affected side. We can speculate the factors that cause the threshold change by understanding which hemispheres are involved in the threshold change. In addition, the attenuation of MEP on both hemispheres related to the depth and length of anesthesia during surgery was reported. Some authors reported that the reason for the gradual attenuation of MEP amplitude was not related to the dose of anesthetics and was proportional to the length of anesthesia

(Yang et al., 2012; Macdonald et al., 2013). However, other authors reported that MEP amplitude and latency closely correlated with the depth of anesthesia, and the deviation in MEP amplitude also correlated with the depth of anesthesia, which was smaller during awake surgery (high BIS level) than during surgery under deep anesthesia (Ohtaki et al., 2017). It is important to maintain a stable anesthetic environment and not to alter the anesthetic technique throughout the procedures for preventing unexpected threshold changes, as Bithal reported (Bithal, 2014).

Next, the intraoperative environmental changes influencing only the affected hemisphere include brain shift, cerebrospinal fluid (CSF) surface, and surgical manipulation (e.g., injury or compression of the motor pathway, regional blood flow, etc.). First, brain shift threshold changes are usually larger, but sometimes smaller, than the initial threshold. When the distance between the stimulation electrode and primary motor area becomes longer by brain shift, the threshold changes become larger because the electric fields are at the maximum level just below the electrodes (Tomio et al., 2016). Conversely, the threshold decreases when the distance between the stimulation electrode and the primary motor area decreases. Second, CSF surface seems to be an important factor to elicit MEP because the electrical currents can pass more easily from the stimulation electrode through the scalp and CSF, rather than through the skull, owing to tissue conductivity during TES-MEP (Szelényi et al., 2013). If there is air space between the stimulation electrode and primary motor area, the electrical current may pass to the brain through CSF and elicit MEPs because air has high resistance for conducting currents. Third, the threshold increases due to surgical manipulation, such as injury or compression of the motor pathway and decrease in regional blood flow due to vasospasm or retractor pressure (Rosenørn and Diemer, 1982). The threshold elevation caused by surgical manipulation must be investigated throughout the procedure, and a warning sign should be adequately issued by MEP with threshold criterion. Our results showed that the threshold change on the affected side was significantly larger than that on the unaffected side; there were no cases with motor deficit. The reasons for a larger threshold change on the affected side might be related to brain shift and the alteration of the CSF surface. Further, there was no significant difference in the threshold change between the corkscrew and peg-screw electrodes on the affected side.

The amplitude criterion has been standard for evaluating TES-MEP monitoring (Abboud et al., 2018). The stimulus intensity with the amplitude criterion varies in the literature: near-threshold intensity (MacDonald, et al., 2013), slightly suprathreshold level (Kombos and Süss, 2009), and 5%, 10%, and up to 20% above the motor threshold (Szelényi et al., 2010; Szelényi et al., 2007). With regard to the warning sign of the amplitude criterion, disappearance or a consistent amplitude reduction of >50% is reported to be a major criterion in brain and brainstem surgeries (MacDonald et al., 2013); however, there is some literature defining the amplitude reduction from >50% to >80% as significant (van Dongen et al., 2001; Jacobs et al., 2002; Langeloo et al., 2003, 2007; Dong et al., 2005; Schwartz et al., 2007; Szelényi et al., 2010). TES-MEP with amplitude criterion has the advantage to obtain stable MEPs because higher stimulus intensities do not tend to be influenced by the slight intraoperative environmental changes. However, the stimulus intensity and warning signs with amplitude criterion can vary depending on institutes and neurophysiologists.

Szelényi et al. reported that the false-negative MEP is mainly caused by the increase in MEP stimulus to the deepening of activation to levels below an ischemic level. The authors suggested that there is a possibility to increase false-negative MEP results at higher stimulation intensities (Szelényi et al., 2005). Theoretically, TES-MEP monitoring with threshold criterion has an advantage to prevent false-negative MEP results because minimum stimulation

intensity has fewer possibilities of activating the deep brain region below the manipulating area. However, the motor threshold easily varies due to multiple factors, as we described, and this variation makes it difficult to evaluate the threshold change. In addition, there are few TES-MEP monitoring data with the threshold criterion to define which percentage is significant (MacDonald et al., 2013). Abboud proposed that an increase in the threshold level of more than 20% on the affected side beyond the increase on the unaffected side was considered a significant alteration in TES-MEP for the patients with supratentorial glioma (Abboud et al., 2016). However, our data showed that the threshold on the affected side can change widely. An increase in the threshold level of more than 20% on the affected side in 11.9% was shown in our data, even when the motor function was intact. The factor influencing the brain shift and CSF level can change in each patient and due to surgical characteristics such as position, craniotomy, brain atrophy, and length of surgery. These factors make it difficult to define the cutoff value because false-negative results increase with increase in the cutoff value but false-positive results increase with decrease in the cutoff value. When we use TES-MEP with threshold criterion, we have to consider what factors make the threshold change and judge whether the threshold change is a warning sign. Furthermore, a warning sign cannot be considered significant according to not only the increase in the threshold but also the acute threshold elevation on the affected side related to surgical manipulation. The threshold criterion might be suspected to produce more false-positive MEP results because of high sensitivity (MacDonald et al., 2013); however, we can avoid false-positive results by understanding the surgical field, surgical procedure, and intraoperative environmental changes as much as possible.

We typically use TES-MEP to prevent motor dysfunction in brain surgery when the primary motor area is not exposed by craniotomy. Corkscrew electrodes are most often used as the TES-MEP stimulation electrode (Legatt et al., 2016), but the peg-screw electrode placed directly on the skull is also used when there is a skin flap, but the skull remains intact as reported in this study. The threshold to elicit MEP was significantly lower with the peg-screw electrode than with the corkscrew electrode (Kanaya et al., 2019).

We believe the most important issue in MEP is to avoid false-negative results (detect patients' motor deterioration as soon as possible) and then decrease false-positive results (not to stop surgery inadequately). Therefore, we aim to maintain MEP monitoring with high sensitivity throughout surgery with threshold criterion to detect motor injury earlier and prevent false-negative MEP results as much as possible. False-negative results can be reduced by minimal stimulus intensity to the adequate brain region and false-positive results can be reduced to understand the intraoperative environmental change not only on the affected hemisphere but also on the unaffected hemisphere. The threshold can vary to even slight intraoperative environmental changes. If the neurosurgeons and neurophysiologists consider that motor threshold increases due to surgical manipulation, the neurosurgeons stop and change the surgical procedure and wait for recovering the MEP monitoring. It is important for neurophysiologists (the persons performing intraoperative monitoring) to judge the threshold change accurately by understanding the factors that influence the threshold in TES-MEP with threshold criterion. Of course, neurosurgeons must also understand and seek the reasons for threshold change as necessary.

## 5. Conclusion

We reported the threshold change between the initial and final thresholds on the affected and unaffected sides in TES-MEP with

threshold criterion. The threshold change and proportion of the percentage change were higher on the affected side than on the unaffected side. It is important to know the characteristics that the motor threshold can change due to the intraoperative environmental changes during surgery when we evaluate TES-MEP monitoring with threshold criterion.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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