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Effect of propofol on cortico-cortical evoked potentials: findings of intraoperative dorsal language pathway monitoring

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Abbreviations: AF = arcuate fasciculus, AL = anterior language area, BIS = bispectral index, CCEP = cortico-cortical evoked potential, ECoG = electrocorticogram, ES = electrical stimulation, GABA = γ-aminobutyric acid, MEP = motor evoked potential, MRI = magnetic resonance imaging, PL = posterior language area, SD = standard deviation, SEP = somatosensory evoked potential

Highlights:

- The distribution of larger CCEP responses was marginally affected by anesthesia.
- The CCEP N1 amplitude increased from general anesthesia to waking.
- The CCEP provides the efficiency to preserve language functions even under general anesthesia.

Abstract

Objective

In order to evaluate the clinical utility even under general anesthesia, the present study aimed to clarify the effect of anesthesia on the cortico–cortical evoked potentials (CCEPs).

Methods

We analyzed 14 patients' data in monitoring the integrity of the dorsal language pathway by using CCEPs both under general anesthesia with propofol and remifentanil and awake condition, with the main aim of clarifying the effect of anesthesia on the distribution and waveform of CCEPs.

Results

The distribution of larger CCEP response sites, including the locus of the maximum CCEP response site, was marginally affected by anesthesia. With regard to similarity of waveforms, the mean waveform correlation coefficient indicated a strong agreement. CCEP N1 amplitude increased by an average of 25.8% from general anesthesia to waking, except three patients. CCEP N1 latencies had no correlation in changes between the two conditions.

Conclusions

We demonstrated that the distribution of larger CCEP responses was marginally affected by anesthesia and that the CCEP N1 amplitude had tendency to increase from general anesthesia to the awake condition.

Significance

The CCEP method provides the efficiency of intraoperative monitoring for dorsal language white matter pathway even under general anesthesia.

1. Introduction

When brain lesions are located within or near the language center of the brain, it is necessary to preserve postoperative language functions while ensuring maximal lesion resection. High-frequency electrical stimulation (ES) during awake craniotomy has recently become the gold standard for mapping the brain function of the cortex and white matter, including language functions (Duffau et al., 2005; Duffau, 2008). However, these cortical- and subcortical high-frequency ES methods could map only the stimulus site (part of the language cortices or language fibers). As a result, even during awake craniotomy, no methods have yet been established to monitor the integrity of the language network during surgery.

We have recently developed electrophysiological methods using cortico-cortical evoked potentials (CCEPs) for intraoperative monitoring in the dorsal language pathway (the arcuate fasciculus; AF) in awake patients (Yamao et al., 2014; Yamao et al., 2017). Direct single-pulse ES was administered to the cortex, and CCEPs were recorded from the remote cortex through cortico-cortical connections in the extraoperative setting to probe functional and seizure networks, as well as to evaluate epileptogenicity (Matsumoto et al.,

2004; Matsumoto et al., 2007; Koubeissi et al., 2012; Enatsu et al., 2013; Matsuzaki et al., 2013; Keller et al., 2014; Enatsu et al., 2015; Matsumoto et al., 2017). In our previous studies (Yamao et al., 2014; Yamao et al., 2017), we demonstrated that the CCEP connectivity was able to map the anterior (AL) and posterior language area (PL) even in the intraoperative setting, and that intraoperative dorsal language network monitoring was feasible only under general anesthesia or without preoperative neuroimaging studies. The CCEP technique potentially has a clinical application of intraoperative mapping and monitoring of the language network.

Intraoperative monitoring is affected by multiple factors, such as anesthetic agents, and anesthetic depth. Motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) have been widely used and are clinically significant, since MEPs and SEPs can indicate the integrity of the brain function, in particular the motor and sensory pathways, even under general anesthesia (Macdonald, 2006; Saito et al., 2015; MacDonald et al., 2019). MEP and SEP amplitude and latency were closely correlated with depth of anesthesia using propofol (Liu et al., 2005; Ohtaki et al., 2017). Similarly, in a recent

intraoperative CCEP study (Suzuki et al., 2019), N1 amplitude of the maximum CCEP response site was closely correlated with depth of anesthesia, but N1 peak latencies were not correlated. However, the effect of anesthesia on the CCEP connectivity, especially the distribution of CCEP responses, remains unclear. The integrity of the dorsal language pathway was monitored with the maximum CCEP response site recorded mainly at the PL (Yamao et al., 2014; Yamao et al., 2017), but the consistency of the maximum CCEP response site between awake and anesthetized patients was not evaluated. In addition, our previous comparison of N1 latencies (Yamao et al., 2014) has indicated that N1 onset might represent the fastest monosynaptic impulse directly projecting into the middle or deep cortical layers. Thus, it is also necessary to evaluate the anesthetic effect on N1 onset latencies, not only N1 peak latencies.

Our ultimate goal is to establish a method of intraoperative language monitoring that can indicate the integrity of the language network even under general anesthesia. The objective of the present study was to clarify the anesthetic effect on the CCEP distribution, especially the effect of propofol, in monitoring the functional integrity of the AF by using

continuous single-pulse ES (CCEPs).

2. Methods

2.1. Patients

Patients had brain tumors or epileptic foci located within or near the perisylvian language areas in the language-dominant left hemisphere between January 2011 and March 2015 from Kyoto University Hospital. Informed consent was obtained from all patients, and the present study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (IRB C573). Of the 42 CCEP investigations in 40 patients, we included the following criteria: 1) the investigation was performed both under general anesthesia and awake and 2) the locations or types of subdural electrodes, which were used for electrical stimulation and recording, were not replaced during the surgical procedure. These inclusion criteria were employed because we analyzed waveforms of all recorded electrodes to evaluate CCEP connectivity in this study, whereas we compared the amplitude of the maximum CCEP response site in previous CCEP studies (Yamao et al.,

2014; Yamao et al., 2017). Therefore, we analyzed 14 CCEP investigations in 14 patients (mean age 43.6 years, ranging from ages 16 to 72; 9 males and 5 females). Language function was evaluated before and after surgery using the Japanese version of the Western Aphasia Battery (WAB). Postoperative evaluations [WAB and magnetic resonance imaging (MRI) scans including tractography] were performed between two and six weeks after surgery. For those who showed language impairment during the immediate postoperative evaluation, follow-up evaluation was performed within six months of surgery (Yamao et al., 2017).

Since we did not perform intraoperative magnetic resonance imaging with subdural electrode implantation, the location of subdural electrodes was identified based on operative visual inspection and neuronavigation data. The demographics are summarized in Table 1. Patients 1–11 are reported elsewhere (Yamao et al., 2014; Yamao et al., 2017).

2.2. General anesthesia and awake craniotomy

All surgical procedures were performed using an asleep-awake technique with direct electrical cortical stimulation, as described previously (Yamao et al., 2014; Yamao et al., 2017). A wide craniotomy exposing the distal end of the Sylvian fissure, the frontal operculum of the inferior frontal gyrus, and the posterior part of the superior and middle temporal gyri was performed under general anesthesia (Maldonado et al., 2011; Rolland et al., 2018). Propofol boluses were used only at the induction of general anesthesia. General anesthesia was maintained with propofol and remifentanil to achieve a target bispectral index (BIS) under 60, and the rate of propofol infusion was almost fixed at the beginning of CCEP monitoring after craniotomy. In all patients, to avoid seizure, phenytoin was administered just before or after the anesthetic was stopped. We diagnosed waking, or "the awake condition," as the state just after extubation, or BIS >70. After patients were awaken, the pain was controlled with the decreased dose of remifentanil (0–0.03 μg/kg/min).

2.3. Intraoperative single-pulse electrical stimulation

As reported previously (Yamao et al., 2014; Yamao et al., 2017), we used single-pulse ES, in the following order:

1) After craniotomy, under general anesthesia, grid-type (4 x 5 or 2 x 8) subdural electrodes were placed on the ventrolateral frontal and lateral temporoparietal cortices. The electrodes were made of platinum with a recording diameter of 3 mm and an inter-electrode distance of 1 cm (Unique Medical Co., Ltd., Tokyo, Japan).
2) Under general anesthesia, we applied single-pulse ES (1 Hz, square-wave pulse of alternating polarity, 0.3 ms duration, 10–15 mA, two sets of 30 stimuli) to cortices around the AL. Based on the CCEP distribution in the PL, namely, CCEP connectivity, we determined the stimulus site (i.e. the putative AL).
3) To evaluate the integrity of the dorsal language pathway, online sequential $CCEP_{AL \rightarrow PL}$ monitoring (stimulating the AL and recording CCEPs from the PL) was performed under general anesthesia and in the awake condition (the same stimulation conditions that we used to identify the CCEP connectivity, as mentioned above).

A 32-channel intraoperative monitoring system (MEE 1232 Neuromaster,

equipped with MS 120B electrical stimulator; NIHON KOHDEN CORPORATION, Tokyo, Japan) was used to deliver electric currents and to record CCEPs and raw electrocorticograms (ECoGs). The reference electrodes were placed on the skin over the contralateral mastoid process. The bandpass filter for data acquisition was set at 0.5 or 1–1,500 Hz with a sampling rate of 5,000 Hz.

In the operating theater, the intraoperative integrity of the dorsal language pathway can be evaluated in real time by observing the largest CCEP N1 amplitude recorded at the posterior language area (see Video 1; the video recording of the on-line monitoring). In this study, in order to exclude the influence of intraoperative artifacts for the precise analysis of CCEP waveforms, CCEPs were also analyzed offline in MATLAB (Mathworks, Inc., Natick, MA) by averaging ECoGs time-locked to the stimulus onset (analysis window: -100 to +500 ms, baseline: –100 to –5 ms).

2.4. Analysis of CCEP waveform

The N1 peak was identified as a first negative deflection from the stimulus artifact. The onset, peak latency, and amplitude of N1 were measured as reported previously (Figure 1) (Matsumoto et al., 2004; Yamao et al., 2014). We only took those negative deflections (N1) as significant when the amplitude was larger than six times the standard deviation (SD) of the baseline fluctuation (between 100 and 5 ms before the stimulus onset) in each CCEP investigation (Usami et al., 2015).

To examine an anesthetic effect, we compared CCEP distribution, using the correlation ratio of CCEP responses and the similarity of waveforms, and CCEP amplitudes and latencies, between the two conditions: just before the anesthetic ceased (i.e. “general anesthesia”), and immediately after the patients became fully awake (i.e. “awake condition”), in the following manner.

1) To compare the correlation ratio of CCEP responses, first, we checked for the locus of maximum CCEP response site between the two conditions. We also evaluated the number of electrodes with the amplitude showing >6 standard deviation (SD) from the baseline fluctuation, ≥20% (20-100%), and ≥60% (60-100%) of the maximum CCEP

response between the two conditions, respectively. The correlation ratio of CCEP responses (the numbers of electrodes showing ≥20% and ≥60% CCEP responses of the maximum CCEP response) were performed using the following equations, respectively:

$$\text{Correlation ratio } (\geq X\%) = (A \cap B)/(A \cup B),$$

where A= the number of electrodes showing ≥X% of the maximum CCEP response under general anesthesia and B= the number of electrodes showing ≥X% of the maximum CCEP response in the awake condition (X = 20 or 60).

2) In addition to the correlation ratio, we evaluated the similarity of CCEP waveforms. For the intraoperative dorsal language pathway monitoring (Yamao et al., 2014; Yamao et al., 2017), we compared the N1 amplitude of the maximum CCEP response sites, and N1 peak latency ranged from 10 to 50 ms (Matsumoto et al., 2017). Therefore, a waveform correlation coefficient was calculated at large CCEP response sites; sites showing ≥60% of the maximum CCEP response, (analysis window: -5 and +100 ms from the stimulus) in each investigation. The waveform correlation coefficient was defined as the covariance of two CCEP waveforms (under general anesthesia and in the

awake condition) divided by the product of their standard deviations. The waveform correlation was calculated using the N1 part of the CCEP waveforms (i.e., from the preceding trough to the following trough of the N1 activity). We defined ≥0.7 of a correlation coefficient as a strong agreement.

3) The N1 onset and peak latency, and N1 amplitude of the maximum CCEP response site between the two conditions were calculated.

2.5. Statistical analysis

The t-test was used to compare N1 onset latencies and the distribution correlation ratio between the two conditions. *P* values <0.05 indicate statistical significance. Statistical analyses were performed with JMP software (version 14, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. The correlation ratio and similarity of CCEP responses between awake patients and patients under general anesthesia

In all investigations, single-pulse ES was delivered to the frontal stimulus site, and CCEPs were successfully recorded from the lateral temporoparietal area both under general anesthesia and in the awake condition, without provoking clinical seizures or seizure patterns on ECoG. In all investigations, the locus of the maximum CCEP response site was not changed between the two conditions.

We calculated the similarity of CCEP between the two conditions at electrodes showing 1) >6 SD of the baseline fluctuation, 2) ≥20%, and 3) ≥60% of the maximum CCEP response in each patient. The mean numbers of electrodes showing ≥20% of the CCEP N1 maximum responses under general anesthesia and in the awake condition were 7.1 (ranging from 1 to 12) and 6.8 (ranging from 1 to 15), respectively. The mean numbers of electrodes showing ≥60% of the CCEP N1 maximum responses under general anesthesia and in the awake condition were 2.0 (ranging from 1 to 6) and 2.1 (ranging from 1 to 6), respectively. The mean correlation ratio of CCEP responses (≥20%) and (≥60%) was 0.72 ± 0.06 (ranging from 0.33 to 1.0; mean ± SD), and 0.86 ± 0.06 (ranging from 0.50 to 1.0; mean ± SD), respectively. The mean correlation ratio of CCEP responses (≥60%) was larger

than that (≥20%), but there was no statistical significance ($P = 0.08$).

With regards to the similarity of CCEP waveforms, a waveform correlation coefficient between two conditions was calculated at electrodes showing ≥60% of the maximum CCEP response. In all 14 CCEP investigations across all patients, the 14 electrode sites showed the maximum CCEP response, and other 11 electrode sites showed 60-99% of the maximum CCEP responses both under general anesthesia and in the awake condition. Thus, the 25 electrode sites showed ≥60% (60-100%) of the maximum CCEP responses across all patients. In the 14 maximum CCEP response sites, the mean waveform correlation coefficient was 0.95 (ranging from 0.86 to 0.99). In the 11 electrodes showed 60-99% of the maximum CCEP responses, the mean waveform correlation coefficient was 0.95 (ranging from 0.91 to 0.97). Therefore, in the 25 electrodes showing 60-100% of the maximum CCEP response across all patients, the mean waveform correlation coefficient was 0.95, indicating a strong agreement. Waveforms obtained from a representative case (Patient 10) are shown in Figure 2, and the results in all patients are summarized in Tables 2 and 3.

3.2. N1 latency and amplitude of the maximum CCEP response site between awake patients and those under general anesthesia

The average N1 amplitude at the maximum CCEP response site under general anesthesia was 324.9 μV (ranging from 74.6 to 997.0 μV), while the average N1 amplitude in the awake condition was 344.0 μV (ranging from 86.8 to 742.2 μV). N1 amplitude increased by an average of 25.8% (ranging from 0.5 to 76.8%) from general anesthesia to the awake condition in eight patients, while N1 amplitude decreased by an average of 16.4% (ranging from 4.5 to 25.6%) in three patients. In all three patients with N1 amplitude decreases (≤30%), the partial resection of the tumor started during general anesthesia (Supplementary figure 1). In these three patients (Patient 2, 7, and 11), postoperative tractography revealed the preservation of the AF (Supplementary figure 2), and they did not demonstrate even a transient decline in language function, including repetition, in the postoperative phase (Table 1).

An average N1 onset latency at the maximum CCEP response site in patients

under general anesthesia and in the awake condition was 10.0 ms (ranging from 3.0 to 13.6 ms) and 9.9 ms (ranging from 3.0 to 13.6 ms), respectively. N1 onset latency was equal in 6 patients from general anesthesia to the awake condition, decreased in 5, and increased in 3. The absolute value of the difference in N1 onset latency between the two conditions was 0.6 ± 0.4 ms (mean ± SD). An average of N1 peak latency at the maximum CCEP response site under general anesthesia and in the awake condition was 28.1 ms (ranging from 8 to 38.4 ms) and 27.4 ms (ranging from 8.4 to 33.4 ms), respectively. N1 peak latency was equal in 1 patient from general anesthesia to the awake condition, decreased in 7, and increased in 6. The absolute value of the difference in N1 peak latency between the two conditions was 1.9 ± 0.4 ms (mean ± SD). As for N1 onset and peak latency, there was no correlation in changes between the two conditions, but the absolute value of the difference in N1 onset latency, i.e., the variability of N1 onset latency, between the two conditions was significantly smaller than that of the N1 peak latency ($P = 0.04$). The results of the N1 amplitude and latency are summarized in Table 4.

4. Discussion

In the present study, we demonstrated the anesthetic effects of propofol on the CCEP responses: 1) the CCEP distribution of larger CCEP responses, including the locus of the maximum CCEP response site, was marginally affected by anesthesia, and 2) the CCEP N1 amplitude had tendency to increase from general anesthesia to the awake condition.

There is no consensus concerning the effect of propofol on intraoperative ECoG (San-juan et al., 2010). Propofol infusions can effectively terminate refractory status epilepticus (Stecker et al., 1998), while propofol can cause epileptic activation of the ECoG (Smith et al., 1996; Hewitt et al., 1999). Remifentanil is an ultra-short-acting opioid, increasingly used today in neurosurgical anesthesia. In previous ECoG studies in temporal lobe epilepsy (McGuire et al., 2003; Kjaer et al., 2017), remifentanil activated epileptiform activity in the epileptogenic foci, such as the hippocampus and amygdala, while not in non-epileptic brain tissue, such as the frontal lobe. In this study, CCEP responses were recorded successfully under general anesthesia by propofol and remifentanil in all patients without provoking clinical seizures or seizure patterns on ECoG.

In a previous intraoperative MEP study (Ohtaki et al., 2017), MEP amplitude was significantly higher in the awake state as compared to deep anesthesia, and latency was shorter in the awake state. The same finding has been observed in SEP studies (Liu et al., 2005). Propofol directly activates the γ-aminobutyric acid $(GABA)_A$ receptor, resulting in anesthesia. $GABA_A$ is the major inhibitory system in the central nervous system, and is involved in the down-regulation of neuronal activity (Orser et al., 1994). Therefore, propofol induces a reduction in amplitude and a delay in the latency of SEPs. Propofol also increases the threshold of α-motor neurons in the anterior horn of the spinal cord, which induces a reduction of the MEP amplitude and a delay in the latency (Ohtaki et al., 2017). In this study, as reported in another intraoperative CCEP study (Suzuki et al., 2019), CCEP N1 amplitude also increased from general anesthesia to the awake condition, except in three patients (Patients 2, 7, and 11). In those three patients with N1 amplitude decreases (≤30%), the partial resection of the tumor had already started during general anesthesia, and especially in Patients 2 and 11 in whom N1 amplitude decreased during the general anesthesia (Supplementary figure 1), temporal lobectomy was also performed under the

general anesthesia. From previous studies (Yamao et al., 2014; Yamao et al., 2017), only more than 50% reductions in CCEP amplitude during the awake state would impact language function, in particular, permanent repetition related impairment due to damage to the AF, which was endorsed by inability to tract the AF tract postoperatively. In the three patients in our study with ≤30% N1 amplitude, the postoperative AF by diffusion tractography was preserved (Supplementary figure 2), and those three patients did not show even a transient decline including repetition during the postoperative period (Table 1). This suggests that 1) CCEP <50% amplitude decrease might neither influence the language function or tractography as reported in MEP studies (Mikuni et al., 2007; Saito et al., 2020), 2) CCEP recorded in our study might include responses of other language-related tracts, especially ventral language pathways (Ellmore et al., 2009; Nakae et al., 2020), considering the CCEP change under general anesthesia in Patients 2 and 11. High frequency subcortical ES will be required in order to detect the tracts beneath the sulci of the cortex or the floor of removal cavity, but subcortical ES could not be performed in those three patients due to clinical limitations. Combined 50 Hz and single-pulse subcortical ES would complement

diffusion tractography and help clarify the function and anatomy of the stimulated tracts.

As for latencies, neither N1 onset nor peak latencies were correlated with anesthesia, as reported elsewhere (Suzuki et al., 2019). However, the absolute value of the difference in N1 onset latency, i.e., the variability of N1 onset latency, between the two conditions was significantly smaller than that of the N1 peak latency, which implied that N1 onset latency is less affected by anesthetics. The precise generator mechanism of CCEPs still remains unclear, but different mechanisms are probably associated with the effect of anesthesia on the CCEP N1 potential, unlike MEPs and SEPs. From our previous studies (Matsumoto et al., 2007; Yamao et al., 2014), the N1 potential likely represents the summation of direct corticocortical impulses conveyed both by small fibers with slower conduction velocities and by large myelinated fibers that are activated through indirect oligo-synaptic corticocortical projections. N1 onset might represent the direct fastest monosynaptic impulse projecting into the middle or deep cortical layers, whereas the N1 peak might represent indirect oligo- or multi-synaptic responses, i.e., local jitter of synaptic activity at the site of stimulation and at the target cortex. Therefore, because propofol

affects synaptic transmission, N1 onset which represents direct monosynaptic connection is less affected; however, further prospective studies are needed to clarify the mechanisms of CCEP, and the anesthetic effect, on N1 latencies.

A previous extraoperative CCEP study across spontaneous sleep stages revealed that CCEP N1 amplitude significantly increased during sleep (non-rapid eye movement sleep), compared with the awake state, and that more intense neuronal activation occurred during non-rapid eye movement sleep than in the awake state (Usami et al., 2015). The mechanism of the unconscious state by anesthetics remains unclear, but the state under general anesthesia using propofol was quite different from the spontaneous sleep state in terms of cortical excitability studied by CCEP. Further studies are warranted to evaluate the ECoG activity between the general anesthesia and the spontaneous sleep state.

As for CCEP distribution, the locus of the maximum CCEP response site had not changed between general anesthesia and the awake condition. The mean correlation ratio of CCEP responses (0.82 ± 0.07; mean ± SD) in ≥60% CCEP responses of the maximum CCEP response was larger than that in ≥20% (0.73 ± 0.07; mean ± SD). In addition, in 22

electrodes showing 60-100% of the maximum CCEP response across all patients, the mean similarity of the waveform (waveform correlation coefficient) was 0.95, indicating a strong agreement. These results suggest that CCEP distribution of larger CCEP responses including the maximum response site has good correlation among the two conditions. Namely, CCEP distribution of larger CCEP response is marginally affected by propofol. Thus, CCEP monitoring at the maximum CCEP response site is clinically reasonable for the preservation of language functions even when the surgery is performed only under general anesthesia.

There are several limitations to be considered in our study. The first limitation is the reliability of anesthesia level measurements. BIS monitoring was not able to be recorded in all patients because of clinical limitations. BIS analysis is based on the electroencephalogram, but BIS value might not fully reflect the real-time depth of anesthesia because BIS can be affected by various factors including electromyography (Ohtaki et al., 2017; Suzuki et al., 2019). In our study, CCEP monitoring started after craniotomy, that is, after the injection rate of propofol was almost fixed. Thus, this study

cannot discuss whether bolus injection of propofol affect N1 amplitude or not. In order to evaluate the “real” anesthetic effect of propofol, the measurement of the blood concentration at the same time as CCEP investigation would be warranted. In addition, in previous small cases (Jones et al., 2014; Yamao et al., 2017), under general anesthesia by using volatile anesthetics (sevoflurane or isoflurane), CCEPs were also available. The future systematic study would be required in order to clarify the protocol of anesthetics and anesthetic effects on the CCEPs. Second, the patient backgrounds with regard to antiepileptic drugs, location of subdural electrodes, location and pathology of tumor, and stimulus intensity varied. The inconsistency of these backgrounds would bias the findings. The subdural electrodes with an inter-electrode distance of 1 cm had limitations in spatial resolution and exploration of the sulcal part of the cortices (Ookawa et al., 2017). Other types of electrodes, such as depth electrodes or high-density electrodes, would provide more detailed results. Third, recent studies suggest that high frequency activities (>100 Hz), i.e. high-gamma activity related to evoked potentials are proxies for neuronal activity (Ray et al., 2008a; Ray et al., 2008b). In this study, stimulus-induced high gamma activity could

not be analyzed because of a lot of noise in the intraoperative setting. Fourth, in this study, a wide craniotomy was performed to map the anterior and posterior language areas, as reported by Duffau and his group, a pioneer of brain stimulation (Maldonado et al., 2011; Rolland et al., 2018). There is a trend in the neurosurgical community towards performing smaller craniotomies in order to provide minimally invasive surgery and reduce the postoperative morbidity and length of hospital stay. However, subdural electrode placement in a blind fashion potentially risks complications through vascular injury (Tanriverdi et al., 2009; McGinity et al., 2017). In these circumstances, intraoperative neurophysiological evaluations with subdural electrode placement would be limited, and alternative non-invasive preoperative evaluations such as functional MRI and tractography would help address this.

Despite these limitations, many institutions, including our institution, have recently reported the usefulness of CCEPs for intraoperative mapping to preserve brain function (Kikuchi et al., 2012; Saito et al., 2014; Yamao et al., 2014; Tamura et al., 2016; Ookawa et al., 2017; Yamao et al., 2017). We previously demonstrated that: 1) a

combination of 50 Hz and single-pulse ES to the cortices and white matter delineated the cortical terminations of the dorsal language pathway electrophysiologically; and 2) when compared to 50 Hz mapping findings, the intraoperative CCEP connectivity pattern itself was able to delineate the dorsal language pathway. In the present study, that focuses on the effect of propofol, we demonstrated that the distribution of larger CCEP response sites, including the locus of the maximum CCEP response site, and the waveform were marginally affected by anesthesia. Therefore, although alternative preoperative neuroimaging studies, i.e., functional MRI or tractography, are still required, intraoperative CCEPs could be used to monitor the dorsal language network, even if CCEPs were only performed under general anesthesia.

5. Conclusions

Here, we report a correlation between CCEP responses and anesthesia. This single-pulse ES method provides the possibility of intraoperative monitoring to preserve language function only under general anesthesia. We hope that further multicenter collaborative studies will proceed to establish intraoperative language monitoring even under general anesthesia.

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Conflict of Interest Statement

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Figure legends

Figure 1.

Measurement of the N1 amplitude and latency of cortico-cortical evoked potentials. A line was drawn from the onset to the offset of the N1 peak, and the N1 amplitude was then measured as the height of a vertical line drawn from the negative peak of N1 to the intersection of the vertical line with the above-described line (Matsumoto et al., 2004). The latencies of N1 onset and N1 peak were measured from the time of stimulation to the N1 onset and N1 peak, respectively. The vertical bar represents the time of stimulation.

Figure 2.

Intraoperative CCEP distribution map (Patient 10). A: CCEP waveforms under general anesthesia and in the awake condition (before tumor removal). In each waveform, two trials are plotted in superimposition. CCEP distribution, including the maximum CCEP response site (Electrode B13), did not change between the two conditions. Each waveform was averaged and time-locked to the stimulus onset (analysis window: -100 to +500 ms,

baseline: –100 to –5 ms). To improve visualization, line has been lifted in each waveform. B: CCEP distribution map under general anesthesia. The diameter of the circle at each electrode represents the percentile to the amplitude at the maximum CCEP response site (Electrode B13). C: Change of the N1 amplitude during surgery at the maximum CCEP response site (Electrode B13). The waveform correlation coefficient was calculated at 0.95. The N1 amplitude increased from 188.6 to 232.6 μV. CCEP N1 latencies are shown only in the awake condition.

CCEP = cortico–cortical evoked potential

Video 1.

The illustrative case (Patient 10) of the on-line CCEP monitoring in the operation theater, using a 32-channel intraoperative evoked potential machine (MEE 1232 Neuromaster, equipped with MS 120B electrical stimulator; NIHON KOHDEN CORPORATION, Tokyo, Japan). The contents of the video are described below. (0-2 s); Left upper column; Preoperative MR images (left; fluid-attenuated inversion recovery image, right; T1-weighted

image with gadolinium enhancement). Right upper column; Electrode configuration in the intraoperative view (after tumor removal). Lower column; Electrode placement. A plate is placed on the frontal cortex, and B plate is placed on the temporoparietal cortex. (2-4 s); CCEPs were recorded by single-pulse electrical stimulation at the electrode pair A14-15 (anterior language area). Three consecutive sets (i.e., averaged CCEP waveforms) are shown at each electrode on the display. The upper two waveforms are the ones currently being recorded (two sets were obtained to confirm the reproducibility). The lower one is the one performed 5 min previously. The left 5 x 4 columns (red square) demonstrate waveforms on the B plate, and the right 3 x 4 columns (blue square) show waveforms on the A plate. Electrode B13 (red circle) shows the maximum CCEP response at the posterior language area. (4 s to the end of the video); Real-time CCEP acquisition. The blue waveform (the uppermost waveform) represents the ongoing averaged CCEP waveform. The other two waveforms (green) were already recorded previously. Note that the waveform being averaged on-line is very similar to the one recorded just previously (the second upper waveform in green) within several seconds (i.e., several trials), although 30 stimuli were delivered to obtain the averaged

CCEP in each set. The intraoperative integrity of the dorsal language pathway can be evaluated by the amplitude change in the maximum CCEP response site (Electrode B13).

CCEP = cortico–cortical evoked potential