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Intraoperative Language Area Mapping: Cortico-Cortical Evoked Potential

Tae-Min Cheon[1], Soo-Hyun Yoon[2], Myoung-Jeong Kim[2], Kyung-Min Kim[1]

[1]Department of Neurosurgery, Inha University Hospital, Inha University College of Medicine, Incheon, Korea
[2]Department of Neurology, Inha University Hospital, Incheon, Korea

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Correspondence
Kyung-Min Kim
Department of Neurosurgery,
Inha University College of Medicine,
Inha University Hospital,
100 Inhang-ro, Michuhol-gu,
Incheon, Korea
Tel: +82-32-890-2053
E-mail: nsdrkm84@gmail.com

Since the cortico-cortical evoked potential (CCEP) was first introduced in 2004, CCEP monitoring has been utilized in various types of brain surgery to achieve maximal safe resection (MSR). MSR is the primary goal in improving the prognosis of glioma; however, this is particularly challenging when the tumor is located around eloquent areas. Since the complexity of the language network system makes it more difficult to achieve MSR, language area mapping is essential when tumors are located around these areas. Awake surgery has been the gold standard for intraoperative language area mapping. However, awake craniotomy is not always feasible due to various clinical and patient-related factors. CCEP monitoring has emerged as a promising alternative for intraoperative language function assessment under general anesthesia to overcome the limitations of awake surgery. This review aims to summarize the current evidence on CCEP-guided surgery, focusing on its effectiveness in preserving language function.

Keywords Cortico-cortical evoked potential; Brain tumor; Language area; Mapping; Preservation.

HISTORY AND DEFINITION OF CORTICO-CORTICAL EVOKED POTENTIAL

Cortico-cortical evoked potential (CCEP) was first introduced by Matsumoto et al. [1] in 2004 as an extra-operative epilepsy surgical procedure based on the principle of neuronal connectivity. In language area mapping, CCEP detects electrical activity between Broca's and Wernicke's areas, which are functionally connected cortical regions. Through CCEP monitoring, the surgeon can localize the arcuate fasciculus (AF), a white matter fiber tract connecting the frontal language area and temporal language area, allowing for mapping and predicting functional language areas within these regions [2]. CCEP can be monitored using two techniques depending on the direction of stimulation: anterior CCEP and posterior CCEP. Anterior CCEP is a method that stimulates the frontal lobe, and the evoked electrical signals are detected in the temporal lobe along the AF. In contrast, the posterior CCEP method stimulates the temporal lobe, and the electrical signals are detected in the frontal lobe. Since the AF is more widely distributed in the temporal lobe, the anterior CCEP method can define CCEP signals more clearly than the posterior CCEP method, making it the preferred method in clinical fields [1,2]. CCEP typically consists of four consecutive voltage peaks called P1, N1, P2, and N2. The N1 and N2 peaks are first and late negative voltage peaks, distinguishable from stimulus artifacts. N1 is usually more pronounced in the recorded signal than the other peaks because it is attributed to the excitation of pyramidal cells. P1 and P2 refer to positive voltage peaks preceding and following N1, respectively [3,4].

CLINICAL SIGNIFICANCE OF CCEP MONITORING

Maximal safe resection (MSR) is an essential treatment concept for improving the prognosis of patients with glioma [5-7].

However, when the tumor is located near an eloquent area, especially language areas, preserving these areas becomes particularly challenging because of the complexity of the language network system [8,9]. Awake surgery has been the gold standard for monitoring language areas during brain tumor surgery. This approach allows surgeons to directly localize the language area while stimulating different brain regions. However, awake surgery is not always feasible due to a variety of clinical factors, such as the extensiveness of the tumor, the presence of high-grade features that elevate the risk of increased intracranial pressure, the patient's age and psychological state, and an approximately 5.4% risk of intraoperative seizures during surgery [10,11]. In situations where awake surgery is not feasible, CCEP, which monitors and localizes language areas under general anesthesia, could be a highly valuable alternative. Additionally, CCEP monitoring is considered a highly practical method due to its very low intraoperative seizure incidence rate of 0.39% [12].

CCEP MONITORING PROCEDURE UNDER GENERAL ANESTHESIA

General anesthesia is started with the administration of intravenous propofol and remifentanil to induce sedation. The muscle relaxant rocuronium (0.6 mg/kg) is administered intravenously only for intubation. During anesthesia maintenance, the target concentrations of propofol and remifentanil are 4 μg/mL and 4 ng/mL, respectively. Mean arterial blood pressure is maintained within 20% of the baseline levels, and the bispectral index (BIS) value is maintained between 40 and 60, which is the optimal range for CCEP monitoring under general anesthesia [13]. A craniotomy is performed to expose the frontal and temporal lobes, including the tumor. After opening the dura, the brain surface of the frontal and temporal lobes is exposed, and a grid-type subdural electrode (4×5) is placed on the temporal lobe surface, covering the region expected to be Wernicke's area. A strip electrode (1×4) or bipolar stimulator is used to stimulate the cortical language areas around the frontal lobe to localize the AF connecting Broca's and Wernicke's areas. CCEP signals are detected in the temporal lobe with the serial repositioning of the frontal electrode. The stimulation intensity typically begins at 10 mA with a frequency of 1 Hz and a pulse duration of 0.3 ms. If an evoked potential is not detected, the stimulation intensity can be sequentially increased by 1 mA up to 15 mA. In cases where artifact signals are frequent and it becomes difficult to distinguish them from positive response signals, the stimulation intensity can be decreased by 1 mA. It is important to distinguish between positive response signals and artifact signals. The positive response signal shows distinct amplitude peaks called the P1 and N1 peaks, whereas artifact signals produce a continuous waveform without a clear N1 peak. Additionally, if evoked potentials are detected in electrodes adjacent to the strip electrode, these are likely artifact signals. Through this process, the stimulation point that evokes positive response signals at the temporal lobes is identified and marked with aseptic surgical stickers, completing the language area mapping. The tumor is resected while preserving the mapped language areas. If the tumor is considered to invade the AF, continuous CCEP monitoring can be applied. Schematic illustrations for the CCEP monitoring procedure are depicted in Fig. 1.

CLINICAL OUTCOMES OF CCEP-GUIDED SURGERY

Several published studies revealed the outcomes of the CCEP monitoring technique for language area mapping. Saito et al. [2] applied the CCEP monitoring technique to brain tumor surgery in 2014 and demonstrated the feasibility of CCEP monitoring in resecting gliomas affecting language areas. Among the 13 patients included in the study, 12 underwent CCEP monitoring with awake surgery, and one patient received general anesthesia. In the early postoperative period, 10 patients exhibited speech impairments, but all of the patients recovered their speech function within an average of 6.1 months. Notably, the time of language function recovery differed according to intraoperative changes in CCEP signals ($p<0.01$). Although the patients presented with deteriorated language function after surgery, they all recovered from postoperative speech impairments within 3 months if no changes in intraoperative CCEP signals were detected. Tamura et al. [14] and Ookawa et al. [15] performed CCEP monitoring during awake surgeries on five and seven patients, respectively. In Tamura's study, two out of five patients experienced transient naming difficulty for 2 weeks but fully recovered. In Ookawa's study, three of the seven patients exhibited transient speech impairment, and one developed mild verbal aphasia; however, all patients recovered language function within 8 weeks. In 2017, Yamao et al. [16] reported a CCEP monitoring study involving 20 patients, four of whom underwent general anesthesia. Their findings demonstrated an association between positive language sites using intraoperative CCEP monitoring and preoperative neuroimaging findings from functional MRI (62.5%–90.9%). However, this correlation was not statistically significant ($p=0.17$). In this study, successful CCEP signals were obtained in all four general anesthesia cases. An increase in N1 amplitude was observed in 16 patients, supporting the notion that CCEP signals serve as a dynamic marker of neuronal connectivity and the functional integrity of the AF. The key significance of this study is the exploration of CCEP signal reversibility and

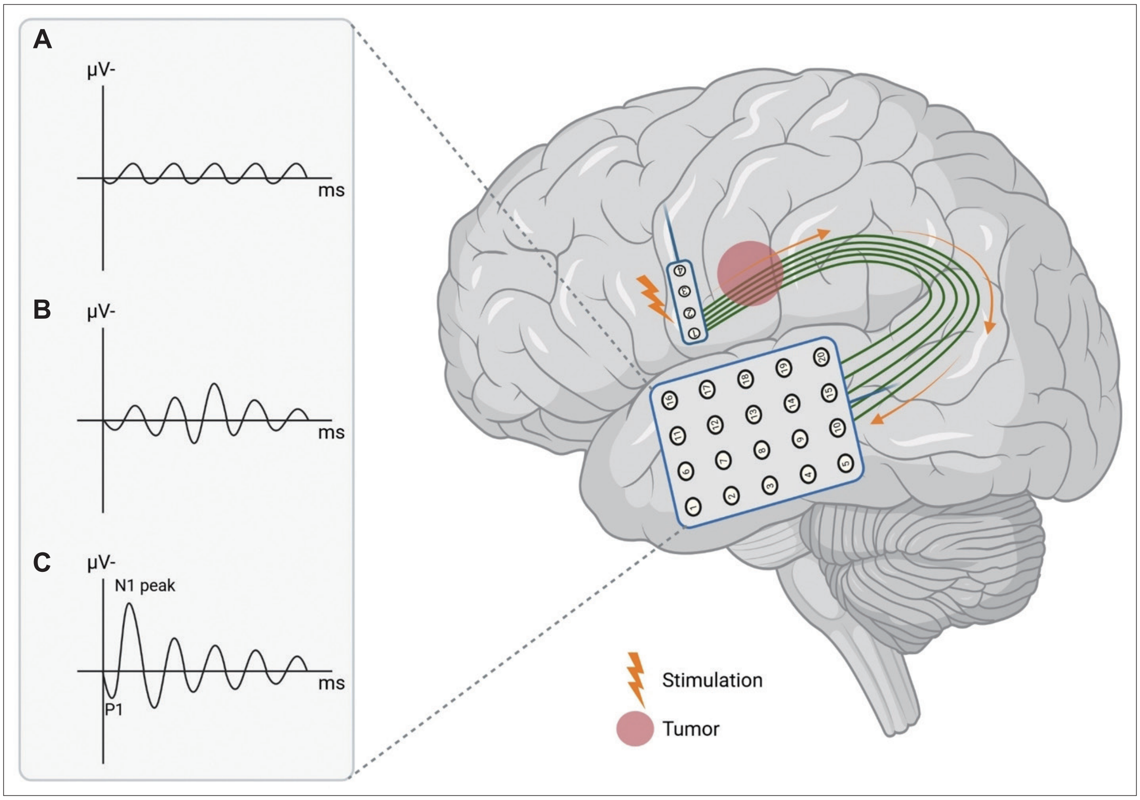

Fig. 1. Schematic illustrations depicting intraoperative CCEP monitoring. Following craniotomy and dura incision, a grid-type subdural electrode (4×5) was positioned on the surface of the temporal lobe, while a strip-type electrode (1×4) was used to stimulate the frontal lobe in a bipolar fashion. The green line represents the arcuate fasciculus. A: No peak amplitude was detected, indicating a negative result. B: Evoked potential without distinct N1 peaks, implying artifact signals. C: A clear N1 peak, indicating a positive result.

the identification of cut-off values for predicting language function outcomes. The reversibility of CCEP signals was observed after tumor resection by alleviating brain edema. Patients who exhibited less than a 50% reduction in N1 amplitude experienced only temporary speech impairment and full recovery. Notably, only one patient, who showed a 51.5% decline in N1 amplitude, developed persistent speech impairment. These findings suggest that a 50% reduction in N1 amplitude may serve as a critical threshold for preserving the dorsal language pathway. In a 2019 study by Suzuki et al. [13], CCEP-guided surgeries were performed for 13 patients with tumors in the language-dominant hemisphere. In this study, CCEP monitoring was executed under both general anesthesia and awake conditions. A key aspect of this study is the demonstration of anesthesia effects on CCEP signals. CCEP signal amplitudes were increased as the elevation of BIS level. Under general anesthesia with a BIS level below 65, decreases in CCEP signal amplitudes ranged from 11.3% to 75.2% (median 31.3%), with these differences being statistically significant ($p<0.01$). However, no significant difference in CCEP latencies between awake and general anesthesia was found. The findings indicate that CCEP amplitudes are influenced by anesthesia depth, whereas latencies remain unaffected. Saito et al. [17] published a study in 2022 involving seven patients who underwent awake craniotomy with both direct stimulation and CCEP monitoring. In this study, intraoperative CCEP changes were observed in two patients, both of whom revealed postoperative language deficits. While one patient who showed a 60% reduction in CCEP signal amplitude during surgery required 24 months for recovery, another patient with a 20% decrease in CCEP amplitude recovered language function within 1 month.

Although previous studies presented the feasibility and clinical outcomes of CCEP monitoring under general anesthesia [18-20], a study by Kim et al. [21] in 2022 statistically addressed language preservation outcomes. The study showed the effectiveness of CCEP monitoring through an objective evaluation of language function outcomes. In this research, CCEP monitoring was performed under general anesthesia in 29 patients, and valid CCEP signals were identified in 25. Among them, 20 patients underwent pre- and postoperative language assessments using the controlled oral word association test. The results indicated that the language function preservation rate for CCEP-guided surgery under general anesthesia was 65% during a 6-month follow-up period. In a study by Vega-Zelaya et al. [22] published in 2023, seven patients underwent brain tumor surgery under general anesthesia. Within 24 hours after surgery, three patients exhibited deteriorated dysarthria or aphasia symptoms; however, after 1 year, only one patient showed dysarthria symptoms similar to those before surgery. In a study by Seidal et al. [4] published in 2024, awake surgery was performed on 20 patients with tumors, and reliable CCEP signals were observed in 19 of them. In one patient, where the tumor predominantly involved the parietal cortex, reliable CCEP signals were not obtained. Among the 20 patients, aphasia symptoms improved in three during the immediate postoperative period, while 11 patients showed worsening symptoms. Only three patients continued to show worse aphasia symptoms after surgery. Detailed language function outcomes and clinical information on the reviewed studies are summarized in Table 1.

LIMITATIONS AND FUTURE DIRECTIONS OF THE CCEP MONITORING TECHNIQUE

CCEP monitoring under general anesthesia has proven to be a promising technique for preserving language function during glioma surgery [21]. Although awake surgery is still the standard method of resecting brain tumors around eloquent areas [10,11,23], CCEP can serve as an alternative to awake surgery in cases when awake surgery is not feasible. Considering that the language preservation rate for awake surgery is over 95%, CCEP-guided surgery under general anesthesia is not superior to awake surgery. However, in situations where awake surgery cannot be performed, it is clinically important to preserve language function through CCEP monitoring under general anesthesia [24]. Although the assessment criteria for language function and follow-up periods vary across studies, awake surgery remains superior in terms of preserving language function. Since research on CCEP monitoring under general anesthesia is still in the early stages, with a limited number of cases and short-term follow-up periods, additional studies are needed to validate the efficacy of CCEP-guided surgery.

Motor-evoked potentials and somatosensory-evoked potentials are techniques that can be used to map motor and sensory areas, as well as their associated pathways, under general anesthesia [25,26]. However, no intraoperative electrophysiological method has been established for the real-time monitoring of language function during surgery. Nevertheless, intraoperative CCEP monitoring has shown that changes in N1 amplitude during surgery correlate with postoperative language functional outcomes, suggesting that CCEP monitoring could be a useful tool for mapping language function areas [2,13,16,17]. Despite its potential, intraoperative CCEP monitoring has certain limitations. First, valid CCEP signals were achieved in 92.3% of patients undergoing awake surgery, whereas the success rate under general anesthesia was lower, ranging from 55.5% to 86.2% [2,18,21]. Additionally, no standardized protocols have been established for the CCEP monitoring technique, and technical variations remain a challenge. The brain is composed of sulci and gyri, and since CCEP signals are available only within the electrode coverage area, undetected functional connections may exist. Furthermore, the language network system is highly complex, involving not only the AF but also other tracts, such as the frontal aslant tract, which are not yet fully understood [27,28]. Therefore, monitoring only the AF may be insufficient for accurately predicting language function. Furthermore, CCEP monitoring requires a craniotomy larger than that needed for tumor resection

Table 1. Summarized clinical results of language area mapping utilizing CCEP monitoring

Study	Year	Patients No.	Type of anesthesia	Surgery	Language function preservation rate (%)	Follow-up periods
Saito et al. [2]	2014	13	Awake: 12 GA: 1	Tumor :13	100	15 months
Tamura et al. [14]	2016	5	Awake: 5	Tumor: 5	100	2 weeks
Ookawa et al. [15]	2017	8	Awake: 5	Tumor: 7 Epilepsy: 1	100	8 weeks
Yamao et al. [16]	2017	20	Awake: 16 GA: 4	Tumor: 20	75	6 months
Suzuki et al. [13]	2019	15	Awake: 15	Tumor: 13 Epilepsy: 2	80	-
Saito et al. [17]	2022	7	Awake: 7	Tumor: 7	85.7	24 months
Kim et al. [21]	2022	20	GA: 20	Tumor: 20	65	6 months
Vega-Zelaya et al. [22]	2023	7	Awake: 1 GA: 6	Tumor: 7	100	12 months
Seidal et al. [4]	2024	20	Awake: 20	Tumor: 20	85	-

GA, general anesthesia

alone, potentially increasing surgical time, infection risk, and intraoperative blood loss.

One of the major challenges of CCEP monitoring is inconsistent N1 and N2 waveform peaks. Unlike direct cortical stimulation during awake surgery, where functional responses, such as speech arrest, provide clear validation, CCEP signals rely on electrophysiological signals, which can differ between patients. Matsumoto et al. [1] reported an N1 peak and amplitude latency of 20−40 ms. However, reports regarding the N1 peak are inconsistent. Seidel et al. [4] applied electrical stimulation with a square-wave biphasic current, featuring a pulse width of 0.6 ms and a frequency of 50 Hz, at an average intensity of 3−6 mA during CCEP monitoring in 20 patients with awake surgery. In the awake state, N1 peak latency was measured at 21.32±7.59 ms with an N1 amplitude of 72.73±63.82 μV. In the asleep state, the N1 peak latency was 21.22±7.33 ms, with an N1 amplitude of 54.92±36.98 μV. Vega-Zelaya et al. [22] performed electrical stimulation in six patients under general anesthesia and one patient with awake surgery, starting at 5 mA and gradually increasing in increments of 5 mA up to a maximum of 20 mA. The average N1 latency was 37.7±0.8 ms (range 24.8−46.4 ms), and the amplitude was 184.1±17.0 μV (range 30.6−540.2 μV). In a study by Tamura et al. [14], awake surgery was performed on five patients, where biphasic electrical pulses (50 Hz frequency, 0.3 ms pulse duration) were applied with intensities ranging from 3 mA to 15 mA. The mean latency of the N1 peak was 55.4±21.4 ms, and the mean amplitude of the main peak was 58.02±30.6 μV. The amplitude and latency of CCEP waveforms may fluctuate due to differences in individual brain anatomy, variations in cortical excitability, and the effects of anesthesia. This inconsistency complicates the interpretation of results, as weak or absent waveforms do not necessarily indicate a lack of functional connectivity, while strong responses may not always correlate with essential language pathways. Another important limitation is the influence of anesthesia on CCEP signals. Since general anesthesia affects neuronal excitability and synaptic transmission, it can alter CCEP responses, potentially reducing the clarity of waveforms. Different anesthetic agents have varying effects on cortical activity, and while some studies have optimized anesthesia protocols for intraoperative electrophysiology, the degree to which these effects impact language network mapping remains an area of ongoing investigation. Thus, further research is needed to determine the best anesthetic strategies that maintain stable CCEP signals without compromising patient safety.

Further research should aim to develop standardized waveform interpretation protocols to enhance the clinical utility of CCEP monitoring and ensure greater consistency in identifying critical language pathways. Investigating the effects of different anesthetic agents and refining multimodal mapping techniques could also improve the accuracy of CCEP-guided functional assessments. Larger prospective studies are needed to establish stronger correlations between CCEP waveforms and long-term language outcomes. Despite these limitations, CCEP monitoring remains a valuable tool for glioma surgery, particularly in cases where awake craniotomy is not feasible. Although CCEP monitoring could not completely replace awake surgery, advancements in the CCEP monitoring technique and multimodal integration could solidify its role as a reliable alternative for preserving language function. Continued refinement of the monitoring technique will be essential to maximizing both oncological and functional outcomes in glioma patients.

CONCLUSION

Although awake surgery remains the gold standard for language area mapping, CCEP monitoring under general anesthesia could be a good alternative for situations where awake surgery is not feasible. Further clinical studies are essential to refine the technique, particularly in terms of waveform and interpretation consistency. As more data is gathered and protocols are standardized, we anticipate that CCEP monitoring will continue to evolve and become a more reliable tool in neurosurgical practice.

Ethics Statement

Not applicable

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

ORCID iDs

Tae-Min Cheon https://orcid.org/0009-0002-7596-9820
Soo-Hyun Yoon https://orcid.org/0009-0006-5093-3601
Myoung-Jeong Kim https://orcid.org/0009-0008-9811-3551
Kyung-Min Kim https://orcid.org/0000-0002-1150-3338

Author Contributions

Conceptualization: Kyung-Min Kim. Data curation: all authors. Funding acquisition: Kyung-Min Kim. Investigation: Kyung-Min Kim. Methodology: Kyung-Min Kim. Project administration: Kyung-Min Kim. Writing—original draft: Tae-Min Cheon, Kyung-Min Kim. Writing—review & editing: Kyung-Min Kim.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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