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Steady-State Cortico-cortical Evoked Potential

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Purpose: The present study evaluated the utility of the steady-state responses of cortico-cortical evoked potentials (SSCCEPs) and compared them with the responses of conventional CCEPs.

Methods: Eleven patients with medically intractable focal epilepsy who underwent the implantation of subdural electrodes or stereoelectroencephalography were enrolled. Conventional CCEPs were obtained by averaging responses to alternating 1-Hz electrical stimuli, and 5-Hz stimuli were delivered for recording SSCCEPs. The distribution of SSCCEPs was assessed by a frequency analysis of fast Fourier transform and compared with conventional CCEPs.

Results: Steady-state responses of cortico-cortical evoked potentials were successfully recorded in areas consistent with conventional CCEPs in all patients. However, SSCCEPs were more easily disturbed by the 5-Hz stimulation, and small responses had difficulty generating SSCCEPs.

Conclusions: Steady-state responses of cortico-cortical evoked potentials may be a useful alternative to conventional CCEPs.

Key Words: Steady-state, Cortico-cortical evoked potential, Evoked potential, Brain network.

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Evoked potentials have become an important tool not only for understanding human brain functions but also for intraoperative monitoring in brain surgery. The conventional form is a transient evoked potential recorded in response to an isolated discrete stimulation. To achieve this isolation, the interstimulus interval needs to be sufficiently long to separate stimuli from each other and delivered at the independent baseline. This evoked potential is generally identified by averaging responses. In contrast to transient evoked potentials, harmonic changes in amplitude and phase may also be induced in response to a fixed-rate train of stimuli.[1–4] At a high frequency of stimulation in which the interstimulus interval is shorter than the duration of the response, responses to individual stimuli overlap and become oscillatory activities.[4] Because the responses to these periodic stimuli have a stable amplitude and phase over time, they are termed steady-state evoked potentials. Steady-state evoked potentials have been used in visual evoked potentials,[4–9] auditory evoked potentials,[3,10–13] and sensory evoked potentials.[14,15]

"Cortico-cortical evoked potential" (CCEP) is a technique for tracing *in vivo* brain tracts.[16] In this procedure, electrical stimuli are applied directly to the cortex, and evoked potentials generated via cortico-cortical fibers are recorded. This method has been applied to delineate various brain networks and may be used for the intraoperative monitoring of language function.[17,18]

The aim of the present study was to evaluate the utility of steady-state responses of CCEPs (SSCCEPs) and compare them with the responses of conventional averaged CCEPs.

The authors have no conflicts of interest to disclose.

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METHODS

Patients

Eleven patients (4 female patients, 6–43 years old) with medically intractable focal epilepsy who underwent the implantation of subdural electrodes (9 patients) or stereoelectroencephalography (SEEG) (2 patients) at Sapporo Medical University between February 2018 and August 2019 were enrolled in the present study (Table 1). Seizure onset zones and the sites of implantation are shown in Table 1. The present study was approved by the Ethical Committee of the Sapporo Medical University Graduate School of Medicine (No. 23-161), and written informed consent was obtained from all patients.

Implantation of Electrodes

Subdural electrodes were implanted in the lateral, mesial, and basal aspects of each hemisphere in all patients. Grids consisted of 2 or 4 rows, with each row containing 5 to 8 platinum electrodes and a 10-mm center-to-center interelectrode distance (Unique Medical Co, Ltd, Tokyo, Japan). Electrodes were made of platinum with a recording diameter of 3 mm and interelectrode distance of 1 cm.

The strip consisted of a single row of six electrodes in the same configuration as that used for the grids.

Regarding SEEG implantation, targets and trajectories were planned with iPlan 3.0 (BrainLAB, Feldkirchen, Germany). Electrodes consisted of 10 cylindrical 2.3-mm-long platinum contacts with a diameter of 0.89 mm (Ad-tech, Racine, WI). The locations of the implanted electrodes were assessed using presurgical three-dimensional reconstructed MRI coordinated with postoperative high-resolution volumetric computed tomography (slice thickness of 1 mm) to provide a visual correlation between each electrode position and the corresponding cortical area or deep structure.

TABLE 1. Characteristics, Seizure Onset Zone, and Stimulation Area in Each Case

Case	Age	Sex	Diagnosis	Procedure	Implantation Side	Seizure Onset Zone	Anatomic Area of Stimulation	Functional Area of Stimulation
1	29	M	Lt TLE	SDE	Left	Mesial temporal area	Posterior superior temporal gyrus	Language
2	13	F	Lt FLE	SEEG	Left	Frontal operculum	Posterior temporal operculum	Nonfunctional
3	16	M	Rt PLE	SEEG	Right	Supramarginal gyrus	Supramarginal gyrus	Seizure onset zone
4	20	M	Lt TLE	SDE	Left	Mesial temporal area	Superior temporal gyrus	Language
5	43	M	Lt TLE	SDE	Left	Mesial temporal area	Inferior frontal gyrus	Language
6	17	F	Lt TLE	SDE	Left	Mesial temporal area	Superior parietal lobule	Language
7	36	F	Lt TLE	SDE	Left	Mesial temporal area	Mesial temporal area	Seizure onset zone
8	25	M	Rt PLE	SDE	Right	Superior parietal lobule	Superior parietal lobule	Seizure onset zone
9	8	M	Rt OLE	SDE	Bilateral	Rt lingual gyrus, rt cuneus	Rt lingual gyrus	Seizure onset zone
10	6	F	Rt OLE	SDE	Bilateral	Rt occipital lobe	Lt superior occipital gyrus	Not available
11	18	M	Lt PLE	SDE	Bilateral	Lt superior parietal lobule	Rt posterior middle temporal gyrus	Not available

Lt, left; OLE, occipital lobe epilepsy; PLE, parietal lobe epilepsy; Rt, right; SDE, subdural electrodes; SEEG, stereoelectroencephalography; TLE, temporal lobe epilepsy.

ECoG Recording and Evaluation of Nonepileptic Epileptiform Activity

Recordings from intracranial electrodes were obtained with Neurofax EEG-1200 (Nihon Kohden, Tokyo, Japan) using the following settings: a sampling rate of 2,000 Hz, low-filter setting of 0.016 Hz, and high-filter setting of 600 Hz. These intracranial recordings were retrospectively analyzed with bandpass filtering between 5 and 600 Hz.

Functional Brain Mapping

A cortical electrical stimulation was performed in a bipolar manner followed by a monopolar manner for functional mapping as part of the routine presurgical evaluation. Repetitive square-wave electrical currents of alternating polarity, with a pulse width of 0.3 ms, were delivered at a frequency of 50 Hz for 5 seconds. The current was increased from 0 to 15 mA for the subdural electrodes and from 0 to 12 mA for SEEG electrodes in steps of 1 to 2 mA until a behavioral response was observed. In all trials, the stimulation was performed at least twice to confirm reproducibility.

CCEP Recording

Neurofax EEG-1200 with a JE-120 amplifier, MS-120-EEG cortical stimulator, and Nihon Kohden PE-210 software stimulator switch box (Nihon Kohden, Tokyo, Japan) were used for the stimulations and recording. Electrical stimuli were delivered to two adjacent contacts in a bipolar manner. The anatomic and functional areas of the stimulation are shown in Table 1. Square-wave electrical pulses of alternating polarity with a pulse width of 0.3 ms were delivered through a pair of electrodes for 40 seconds at a fixed frequency of 1 Hz. Current intensity started at 2 mA and was increased by 2 mA in stepwise increments to 15 mA for the subdural electrodes and 8 to 10 mA for SEEG electrodes. To confirm reproducibility, the 8- to 10-mA sessions were performed twice. Thereafter, 5-Hz electrical stimuli were delivered to the same contacts for 10 seconds at 5 and 10 mA for recording SSCCEPs (4 and 8 mA in patients 2 and 3, respectively). Conventional CCEPs were obtained using the off-line averaging time locked to the stimulus onset. The averaging time window was 400 msec with a 100-msec prestimulus period. The baseline was set between −100 and −1 ms. After averaging, the epoch distorted by the definite artifact was discarded from the analysis. Forty responses were averaged in each session. A frequency analysis of SSCCEPs was performed by fast Fourier transform over a range of 0 to 10 Hz. Hanning windows and a 50% overlap ratio were used for fast Fourier transform computations. These off-line analyses were performed using Matlab R2008a (MathWorks, Inc, Natick, MA).

Data Analysis

Statistical analyses were performed using JMP Pro 15.0.0 (SAS, Cary, NC, 2019). To investigate the relationship between conventional CCEPs and SSCCEPs, Fisher exact test was performed to test the null hypothesis that SSCCEP results were independent of conventional CCEP results. At each electrode site examined, we obtained one of four possible outcomes using the two methods (conventional CCEP, SSCCEP): (+, +), (+, −),

(−, +), or (−, −). Given the paired nature of conventional CCEP and SSCCEP testing at each electrode site, a 2×2 table was constructed in which each cell contained the number of observed pairs of (conventional CCEP, SSCCEP) results. The corresponding 2×2 table was then used in Fisher exact test of the independence of conventional CCEPs versus SSCCEPs. Amplitude of conventional CCEP was measured with electrodes where (conventional CCEP, SSCCEP) was (+, −). Cortico-cortical evoked potentials typically consists of an early negative surface deflection termed N1 and a later slow wave called N2. The amplitude of N1 was measured as the height of a vertical line drawn from the negative peak of an early component. The amplitude of N2 was measured as the maximum deflection through the measurement. As a correlation coefficient, the phi coefficient was calculated. Disturbed electrodes were excluded from all calculations.

RESULTS

Steady-state responses of cortico-cortical evoked potentials were safely and successfully recorded in all patients. No patients had afterdischarges or clinical seizures because of the 5-Hz electrical stimuli. Raw ECoG data revealed that the 5-Hz electrical stimulation induced stable responses time-locked to the stimulation pulses in both the subdural electrodes (Fig. 1C) and the SEEG electrodes (Fig. 2C).

The fast Fourier transform analysis detected SSCCEPs after a power increase to 5 Hz. Steady-state responses of CCEPs were detected in the areas consistent with conventional CCEPs, revealing intralobar and interlobar connections in lateral convexity and basal temporal areas (patients 1–7).

In patients 1 and 4, conventional CCEPs and SSCCEPs were observed in the frontotemporal lateral cortices and basal temporal areas after the stimulation of the posterior superior temporal gyrus (Figs. 1D, 1E, 2J, and 2K). Conventional CCEPs and SSCCEPs were both detected with SEEG electrodes in the insula, frontal/temporal operculum, hippocampus, and lateral temporoparietal cortices with the stimulation of the posterior temporal operculum (patient 2: Figs. 2D and 2E) and supramarginal gyrus (patient 3: Figs. 3G and H).

Conventional CCEPs revealed intralobar and interlobar connections of the fronto-temporo-parietal lobes with the stimulation of the posterior inferior frontal gyrus (patient 5: Fig. 3B), superior parietal lobule (patient 6: Fig. 3E), and mesial temporal area (patient 7: Fig. 3H). In these patients, SSCCEPs were observed in a distribution that was consistent with conventional CCEPs (Figs. 3C, 3F, and 3I).

Furthermore, conventional CCEPs and SSCCEPs revealed the lateral–mesial intrahemispheric connections of the parietal (patient 8: Figs. 4B and 4C) and occipital lobes (patient 9: Figs. 4E and 4F), and interhemispheric connections from the lateral occipital areas (patients 10, 11: Figs. 5B, 5C, 5E and F).

Steady-state responses of cortico-cortical evoked potentials were recorded in areas in which conventional CCEPs were induced regardless of intralobar or interlobar connections or medial–lateral intrahemispheric and interhemispheric connections. The distribution of SSCCEPs was consistent with conventional CCEPs in all patients. The null hypothesis of independence between conventional CCEPs and SSCCEPs was rejected for all cases ($P < 0.001$). However, in several electrodes, SSCCEPs were detected in fewer contacts than conventional CCEPs (C and D electrodes in patient 1; J electrode in patient 2; A electrode in patient 3; and B and C electrodes in patient 5). In these contacts, conventional CCEP waveforms were small. In addition, recordings around the stimulation sites of SSCCEPs were more easily disturbed than those of conventional CCEPs. Phi, the correlation coefficient between conventional CCEPs and SSCCEPs, was 0.787 ± 0.118 (mean ± SD). At electrodes at which (conventional CCEP, SSCCEP) was (+, −), the N1 amplitude was 83.6 ± 41.0 μV (mean ± SD) and the N2 amplitude of conventional CCEPs was 108.0 ± 76.6 μV (mean ± SD).

DISCUSSION

In the present study, SSCCEPs were successfully recorded in all patients. The distribution of SSCCEPs was consistent with conventional CCEPs. However, SSCCEPs were more easily disturbed by the 5-Hz stimulation, and small responses with less than 108 μV had difficulty generating SSCCEPs.

Steady-state responses have several advantages over conventional transient evoked potentials, including a high signal-to-noise ratio, shorter recording time, and the capacity to tag cortical activity with a specific frequency of stimuli.[15] Furthermore, SSCCEPs are easier to visually detect and may be obtained without off-line averaging. Previous studies reported the utility of auditory steady-state responses for intraoperative monitoring.[12,13] Cortico-cortical evoked potentials have also been applied for intraoperative monitoring to preserve language function.[16,17] The present results indicate that SSCCEPs may replace conventional CCEPs for more convenient intraoperative monitoring; however, further studies are needed. Furthermore, the physiologic brain commonly exhibits oscillatory activities, and we speculate that SSCCEPs more closely simulate intracerebral signal transfer than single-pulse CCEPs. Future studies are warranted to establish whether SSCCEPs reflect an information transfer system in the brain.

In CCEPs, distribution and amplitude are important evaluation components. The consistency of distribution between CCEPs and SSCCEPs suggests that SSCEPs are an alternative to conventional CCEPs. However, the present study had several limitations. Small-amplitude responses had difficulty generating SSCCEPs. Steady-state responses are susceptible to the stimulus frequency. At a sufficiently high stimulus frequency stimulation, steady-state responses become sinusoidal; however, below this stimulation rate, responses to individual stimuli retain some of the features of the responses.[4] The wide spatial variety of CCEP waveforms may cause spatial differences in SSCCEP responses. Each contact may have a specific stimulus frequency appropriate to SSCCEPs. Therefore, further studies are needed to establish whether the 5-Hz stimulation is suitable for generating SSCCEPs. Another limitation is the stimulus artifact. A high-frequency stimulation makes stimulus artifact removal difficult.[19] The present study revealed that SSCCEP recordings around

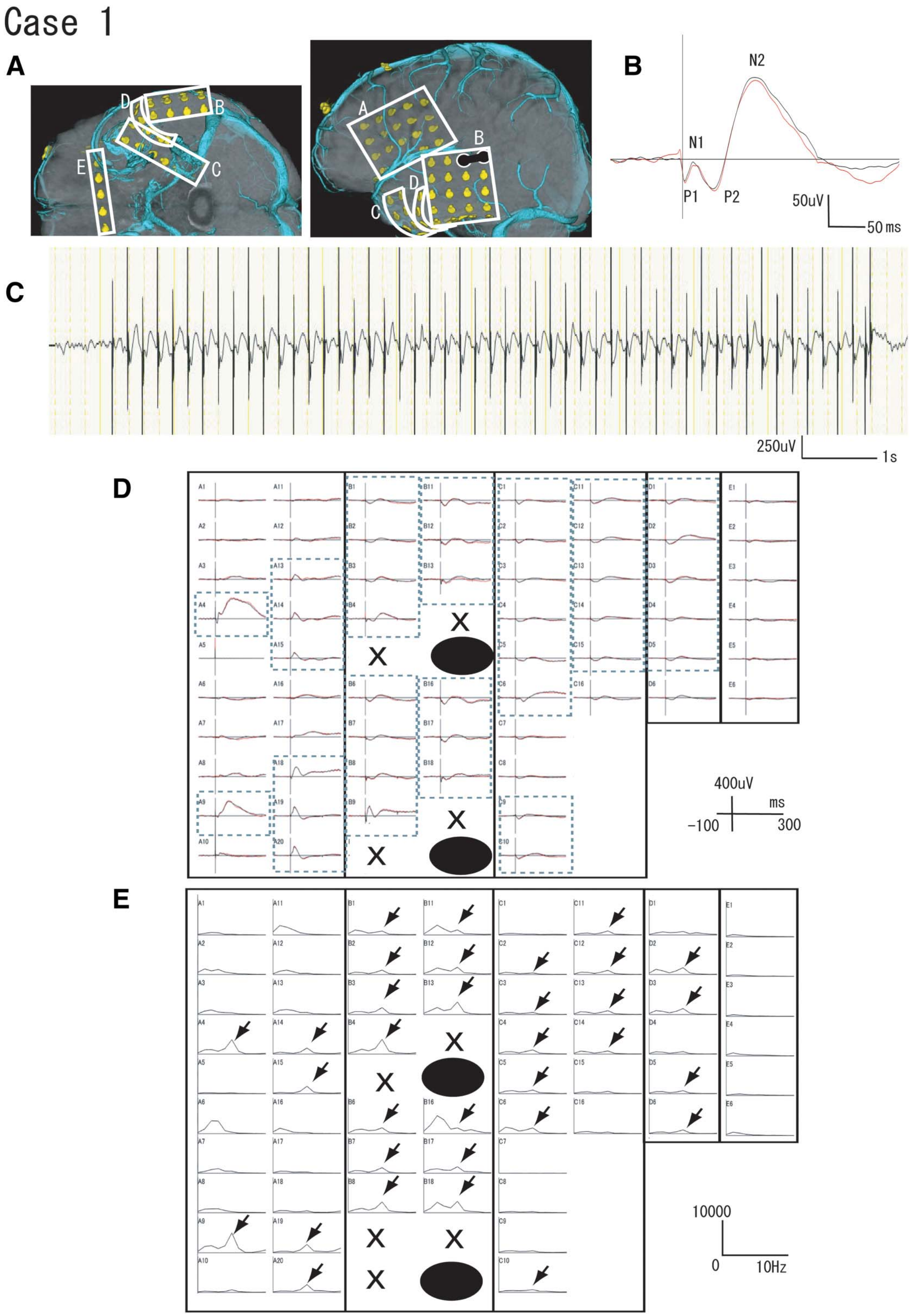

FIG. 1. Results in patient 1. **A**, Location of subdural electrodes and stimulation sites (black circles). **B**, Representative waveform of conventional cortico-cortical evoked potentials. **C**, Raw ECoG data in the 5-Hz electrical stimulation at a single electrode. **D**, Waveforms of conventional cortico-cortical evoked potentials. **E**, Frequency analysis of steady-state responses of conventional cortico-cortical evoked potentials. The distribution of conventional cortico-cortical evoked potentials and steady-state responses of conventional cortico-cortical evoked potentials is shown by dashed squares and arrows, respectively. Black circles and crosses indicate the stimulus sites and noisy channels, respectively.

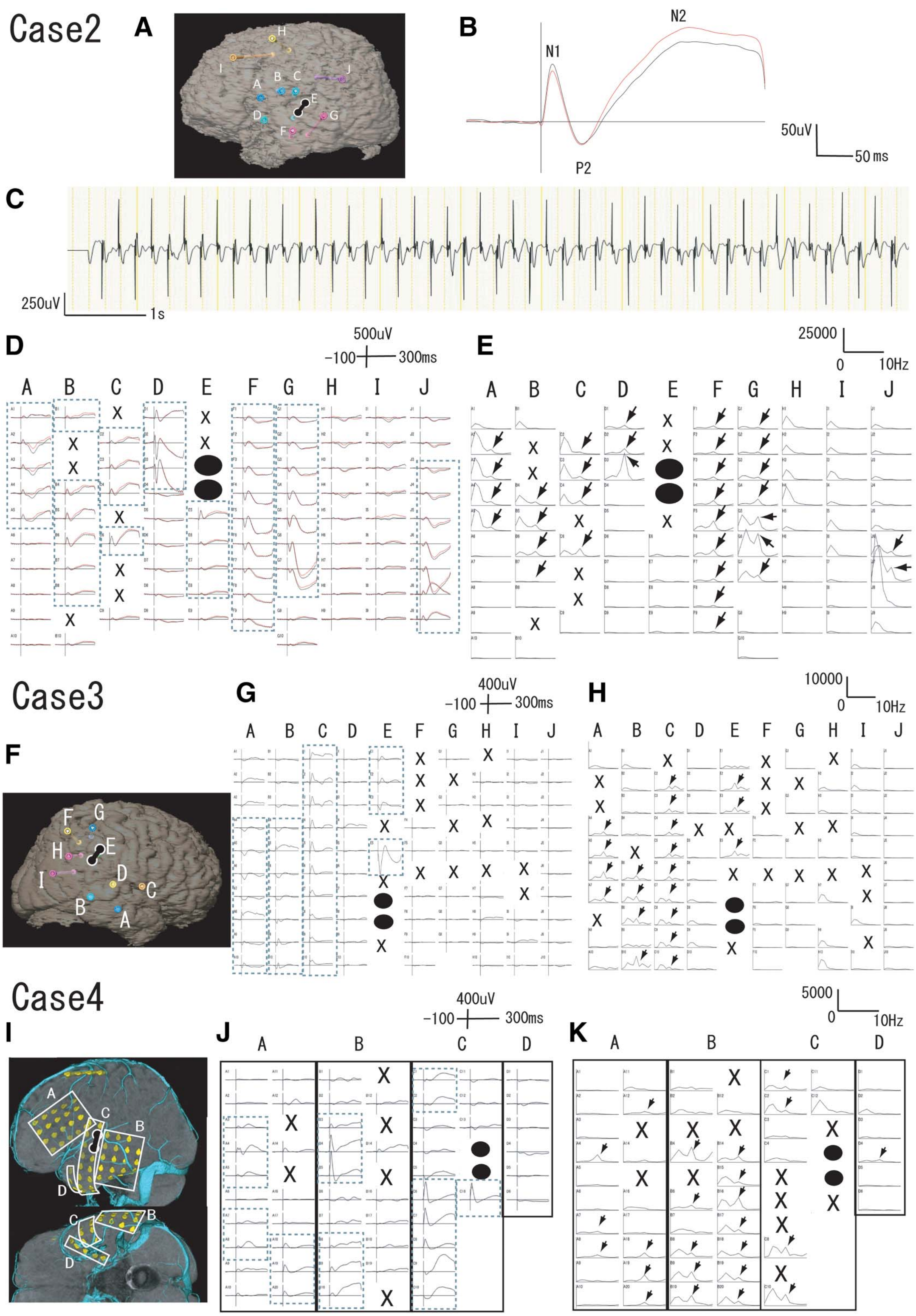

FIG. 2. Location of stereoelectroencephalography in patient 2 (**A**) and patient 3 (**F**) and subdural electrodes in patient 4 (**I**). **B**, A representative cortico-cortical evoked potential waveform and (**C**) raw ECoG data in the 5-Hz electrical stimulation recorded by a single stereoelectroencephalography electrode in patient 2. The waveforms of cortico-cortical evoked potential in patient 2 (**D**), patient 3 (**G**), and patient 4 (**J**). Frequency analyses of steady-state responses of cortico-cortical evoked potentials in patient 2 (**E**), patient 3 (**H**), and patient 4 (**K**).

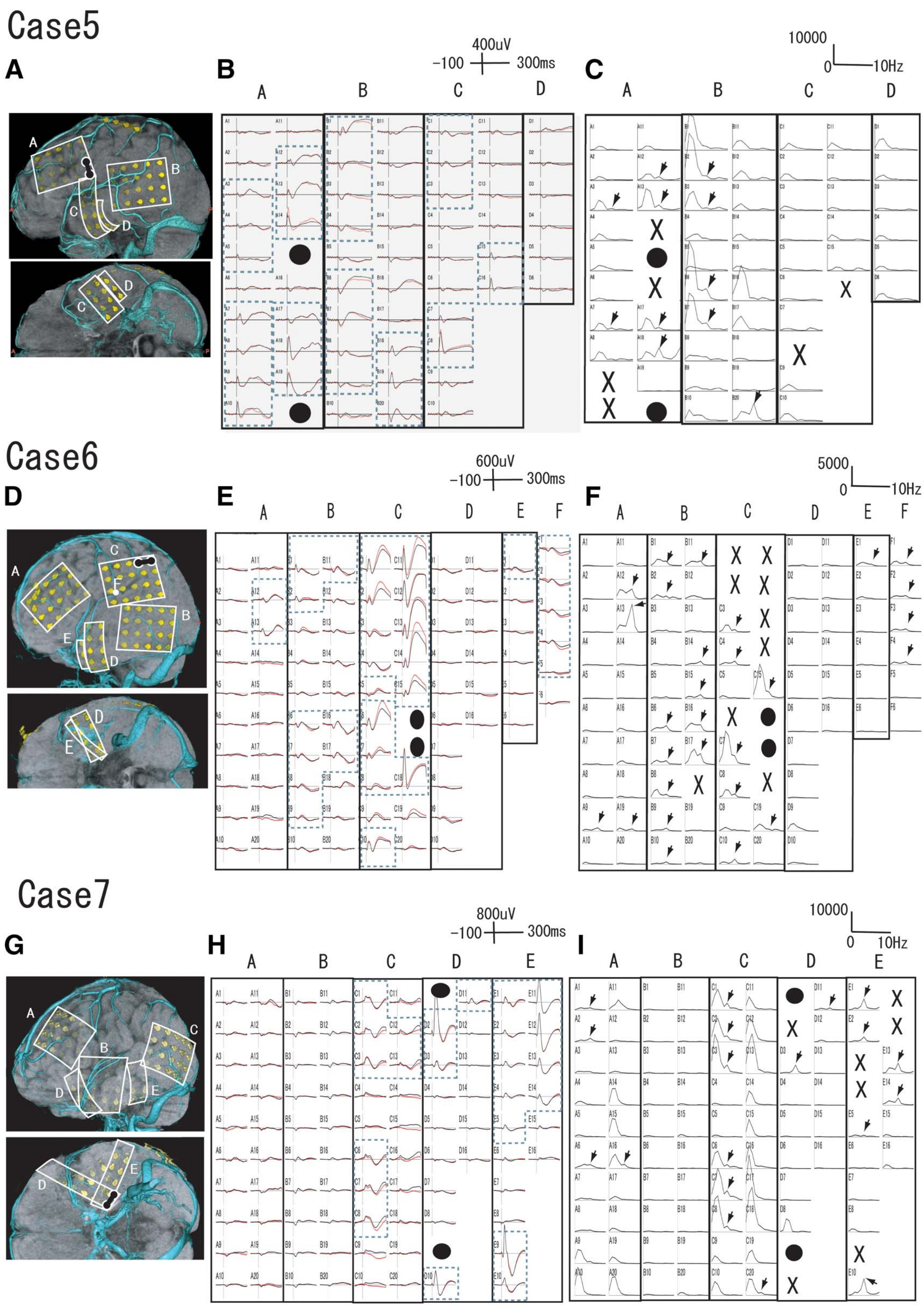

FIG. 3. Location of subdural electrodes in patient 5 (**A**), patient 6 (**D**), and patient 7 (**G**). Waveforms of cortico-cortical evoked potentials in patient 5 (**B**), patient 6 (**E**), and patient 7 (**H**). Frequency analyses of steady-state responses of cortico-cortical evoked potentials in patient 5 (**C**), patient 6 (**F**), and patient 7 (**I**).

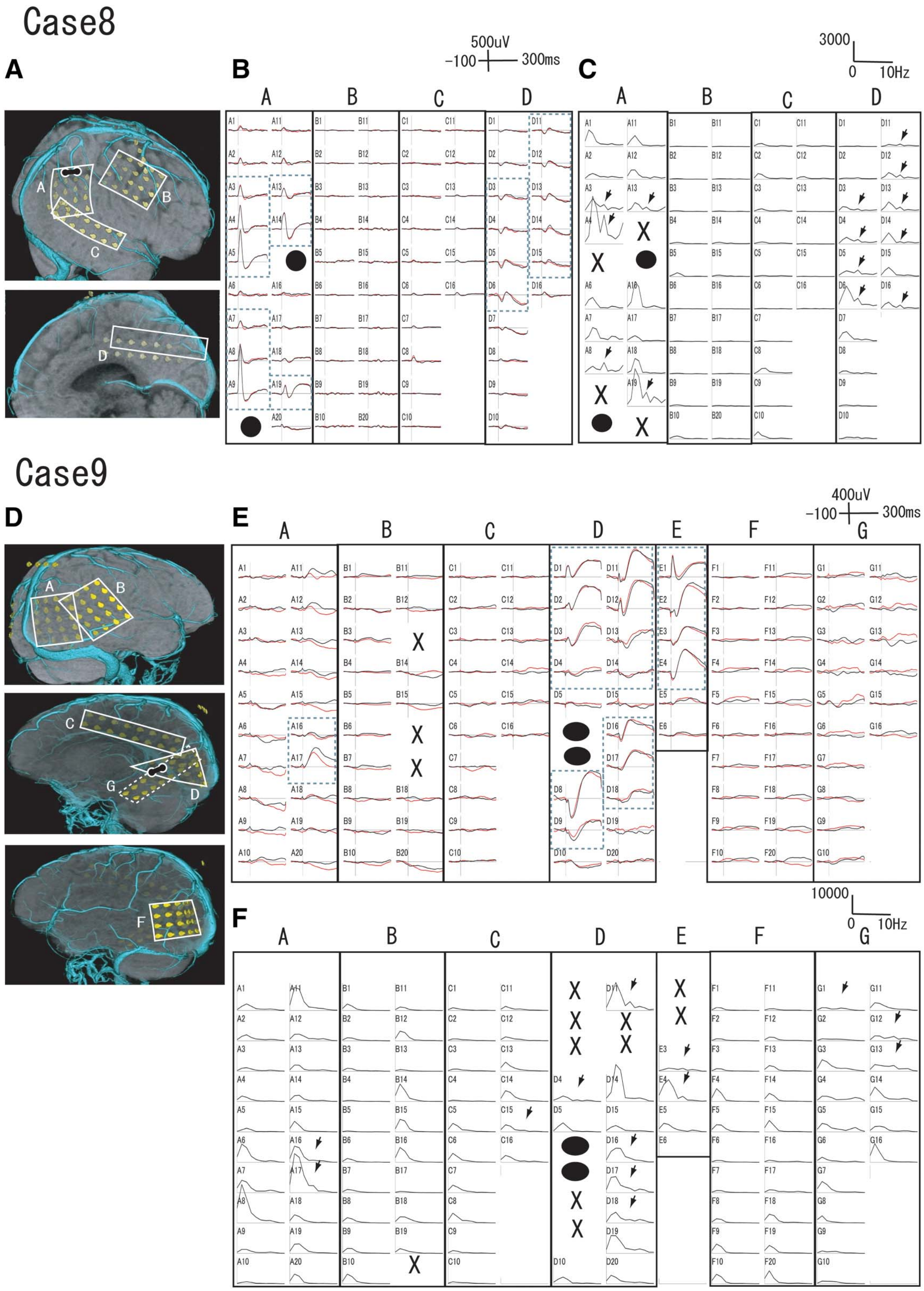

FIG. 4. Location of subdural electrodes in patients 8 and 9 (**A** and **D**). Waveforms of cortico-cortical evoked potentials and frequency analyses of steady-state responses of cortico-cortical evoked potentials in patient 8 (**B** and **C**) and patient 9 (**E** and **F**).

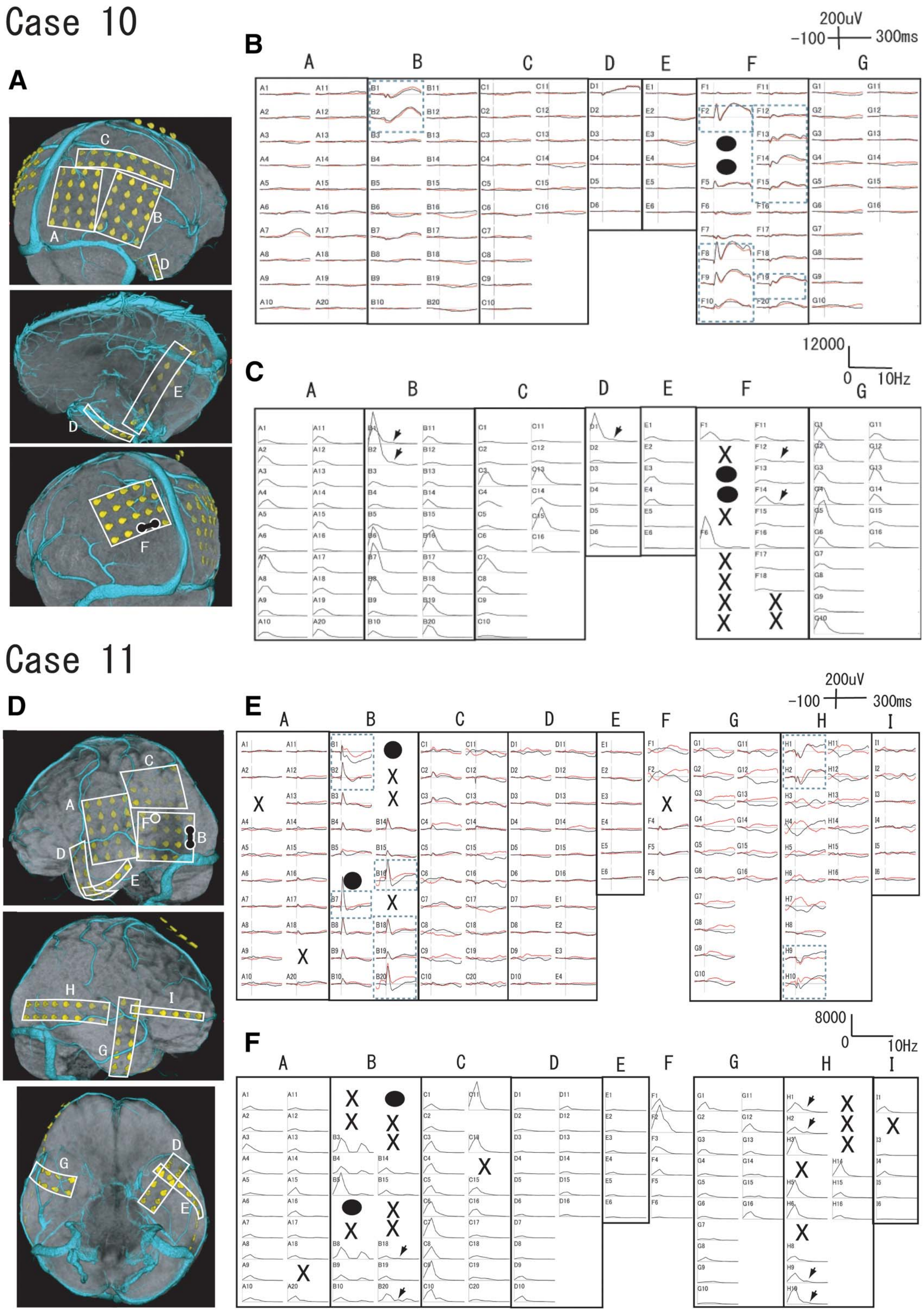

FIG. 5. Location of subdural electrodes in patients 10 and 11 (**A** and **D**). Waveforms of cortico-cortical evoked potentials and frequency analyses of steady-state responses of cortico-cortical evoked potentials in patient 10 (**B** and **C**) and patient 11 (**E** and **F**).

stimulus sites were more easily disturbed by stimulus artifacts. At a high-frequency stimulation, subsequent stimuli may be delivered before fluctuations or artifacts induced by the stimulation disappear, and, thus, the signal may be more strongly affected by baseline fluctuations. The appropriate stimulus intensity to prevent stimulus artifacts and record significant SSCCEP responses is a subject for future study. In addition, previous studies reported that steady-state responses may be affected by attentional focus[4,20] and mental illness.[20] The effects of the mental status on SSCCEPs also need to be clarified for clinical applications.

Despite these limitations, SSCCEPs may offer a useful alternative to conventional CCEPs. The further accumulation of cases is needed to establish appropriate stimulus parameters and indications for this method.

REFERENCES

1. Adrian ED, Matthews BH. The Berger rhythm: potential changes from the occipital lobes in man. Brain 1934;4:355–385.
2. Adrian ED, Matthews BH. The interpretation of potential waves in the cortex. J Physiol 1934;81:440–471.
3. Korczak P, Smart J, Delgado R, Strobel TM, Bradford C. Auditory steady-state responses. J Am Acad Audiol 2012;23:146–170.
4. Norcia AM, Appelbaum LG, Ales JM, Cottereau BR, Rossion B. The steady-state visual evoked potential in vision research: a review. J Vis 2015;15:4.
5. May JG, Cullen JK Jr, Moskowitz-Cook A, Siegfried JB. Effects of meridional variation on steady-state visual evoked potentials. Vis Res 1979;19:1395–1401.
6. Tobimatsu S, Kurita-Tashima S, Nakayama-Hiromatsu M, Kato M. Effect of spatial frequency on transient and steady-state VEPs: stimulation with checkerboard, square-wave grating and sinusoidal grating patterns. J Neurol Sci 1993;118:17–24.
7. Compston A. The Berger rhythm: potential changes from the occipital lobes in man. Brain 2010;133:3–6.
8. Victor JD, Mast J. A new statistic for steady-state evoked potentials. Electroencephalography Clin Neurophysiol 1991;78:378–388.
9. Tang Y, Norcia AM. An adaptive filter for steady-state evoked responses. Electroencephalogr Clin Neurophysiology 1995;96:268–277.
10. Emara AA, Gabr TA. Auditory steady state response in auditory neuropathy. J Laryngol Otol 2010;124:950–956.
11. O'Donnell BF, Vohs JL, Krishnan GP, Rass O, Hetrick WP, Morzorati SL. The auditory steady-state response (ASSR): a translational biomarker for schizophrenia. Suppl Clin Neurophysiol 2013;62:101–112.
12. Rampp S, Rensch L, Simmermacher S, Rahne T, Strauss C, Prell J. Viability of intraoperative auditory steady state responses during intracranial surgery. J Clin Neurophysiol 2014;31:344–351.
13. Rampp S, Rensch L, Simmermacher S, Rahne T, Strauss C, Prell J. Intraoperative auditory steady-state monitoring during surgery in the cerebellopontine angle for estimation of postoperative hearing classes. J Neurosurg 2017;127:559–568.
14. Brenner CA, Krishnan GP, Vohs JL, et al. Steady state responses: electrophysiological assessment of sensory function in schizophrenia. Schizophr Bull 2009;35:1065–1077.
15. Colon E, Legrain V, Mouraux A. Steady-state evoked potentials to study the processing of tactile and nociceptive somatosensory input in the human brain. Neurophysiol Clin 2012;42:315–323.
16. Kunieda T, Yamao Y, Kikuchi T, Matsumoto R. New approach for exploring cerebral functional connectivity: review of cortico-cortical evoked potential. Neurol Med Chir (Tokyo) 2015;55:374–382.
17. Yamao Y, Suzuki K, Kunieda T, et al. Clinical impact of intraoperative CCEP monitoring in evaluating the dorsal language white matter pathway. Hum Brain Mapp 2017;38:1977–1991.
18. Saito T, Tamura M, Muragaki Y, et al. Intraoperative cortico-cortical evoked potentials for the evaluation of language function during brain tumor resection: initial experience with 13 cases. J Neurosurg 2014;121:827–838.
19. Bach M, Meigen T. Do's and don'ts in Fourier analysis of steady-state potentials. Doc Ophthalmol 1999;99:69–82.
20. Varghese L, Bharadwaj HM, Shinn-Cunningham BG. Evidence against attentional state modulating scalp-recorded auditory brainstem steady-state responses. Brain Res 2015;1626:146–164.