

Intraoperative cortico-cortical evoked potentials for the evaluation of language function during brain tumor resection: initial experience with 13 cases

Clinical article

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Object. The objective in the present study was to evaluate the usefulness of cortico-cortical evoked potentials (CCEP) monitoring for the intraoperative assessment of speech function during resection of brain tumors.

Methods. Intraoperative monitoring of CCEP was applied in 13 patients (mean age 34 ± 14 years) during the removal of neoplasms located within or close to language-related structures in the dominant cerebral hemisphere. For this purpose strip electrodes were positioned above the frontal language area (FLA) and temporal language area (TLA), which were identified with direct cortical stimulation and/or preliminary mapping with the use of implanted chronic subdural grid electrodes. The CCEP response was defined as the highest observed negative peak in either direction of stimulation. In 12 cases the tumor was resected during awake craniotomy.

Results. An intraoperative CCEP response was not obtained in one case because of technical problems. In the other patients it was identified from the FLA during stimulation of the TLA (7 cases) and from the TLA during stimulation of the FLA (5 cases), with a mean peak latency of 83 ± 15 msec. During tumor resection the CCEP response was unchanged in 5 cases, decreased in 4, and disappeared in 3. Postoperatively, all 7 patients with a decreased or absent CCEP response after lesion removal experienced deterioration in speech function. In contrast, in 5 cases with an unchanged intraoperative CCEP response, speaking abilities after surgery were preserved at the preoperative level, except in one patient who experienced not dysphasia, but dysarthria due to pyramidal tract injury. This difference was statistically significant ($p < 0.01$). The time required to recover speech function was also significantly associated with the type of intraoperative change in CCEP recordings ($p < 0.01$) and was, on average, 1.8 ± 1.0, 5.5 ± 1.0, and 11.0 ± 3.6 months, respectively, if the response was unchanged, was decreased, or had disappeared.

Conclusions. Monitoring CCEP is feasible during the resection of brain tumors affecting language-related cerebral structures. In the intraoperative evaluation of speech function, it can be a helpful adjunct or can be used in its direct assessment with cortical and subcortical mapping during awake craniotomy. It can also be used to predict the prognosis of language disorders after surgery and decide on the optimal resection of a neoplasm. (<http://thejns.org/doi/abs/10.3171/2014.4.JNS131195>)

KEY WORDS • awake craniotomy • cortico-cortical evoked potentials • surgery • brain tumor • oncology • language function • diagnostic and operative techniques

SURGICAL removal of intraaxial brain tumors located within or close to language-related cerebral structures represents a significant challenge. To minimize the risk of permanent postoperative speech dysfunction, detailed localization of the frontal language

area (FLA) and temporal language area (TLA), as well as their subcortical connections, is critical. At present it can be more or less precisely done with advanced neuroimaging techniques, such as functional MRI,^{2,5,12,13,22,29–31,33} diffusion tensor imaging,^{4–6,9,22,37} magnetoencephalography,⁴ and PET.^{4,29} However, the most effective and precise method is direct brain mapping using electrical stimulation, which can be accomplished either after implantation of chronic subdural grid electrodes^{4,5,20,21,36,37} or during awake craniotomy.^{1,5,6,13,16,22,27,29,31,34,35,37,40}

Abbreviations used in this paper: CCEP = cortico-cortical evoked potentials; ECoG = electrocorticography; FLA = frontal language area; TLA = temporal language area.

Nevertheless, despite its proven effectiveness and widespread acceptance, direct intraoperative brain mapping has some limitations. First, not all patients are suitable for awake craniotomy or can tolerate the procedure.^{27,31,37} Second, intraoperative evaluation of the verbal response is generally subjective and can be significantly influenced by the level of consciousness and cooperativeness of the patient, as well as by the parameters of cortical stimulation. Third, negative intraoperative cortical mapping does not fully prevent postoperative deterioration of speech function, which can be observed immediately after surgery in 4%–23% of such cases.^{16,34} Fourth, intraoperative evaluation of language can be difficult in patients with a preexisting speech deficit.²² Fifth, despite the high reliability of intraoperative cortical mapping for anatomical localization of language-related areas, the functional interconnections of these areas generally remain obscured. Sixth, intraoperative mapping of cortical and subcortical structures with electrical stimulation can be performed only at some time points before or between different stages of tumor removal, but is not suitable for constant monitoring during the whole procedure. Finally, while the appearance of durable speech disorders during surgery generally leads to reluctance to perform further tumor resection, the postoperative prognosis of such disorders is hardly predictable. For these reasons, further searches for novel methods of objectively assessing language during awake craniotomy seem reasonable.

The objective in the present study was to evaluate the recording of intraoperative cortico-cortical evoked potentials (CCEP) as an adjunctive method of assessing speech function during the resection of intraparenchymal brain neoplasms. To the best of our knowledge, there have been no previous reports on the application of this neurophysiological technique for brain tumor surgery.

Methods

Between February 2006 and July 2012, intraoperative monitoring of CCEP was applied in 13 patients (11 men and 2 women; mean age 34 ± 14 years) during removal of intraparenchymal brain neoplasms located within or close to language-related structures (FLA, TLA, arcuate fasciculus, and superior longitudinal fasciculus) in the dominant cerebral hemisphere. Detailed characteristics of the patients are shown in Table 1. The ethics committee of the Tokyo Women's Medical University approved the study protocol, and each patient provided informed consent before surgery.

Preoperative Evaluation

Preoperatively 11 of 13 patients had normal language function, whereas mild dysphasia was noted in 2. The neoplasms were predominantly located within the middle or inferior frontal gyrus (6 cases), inferior parietal lobule (4 cases), or insula (3 cases) of the left cerebral hemisphere. In all cases the diagnosis was based on multimodal MRI, which included pre- and postcontrast T1-weighted, T2-weighted, FLAIR, diffusion-weighted, diffusion tensor, and spectroscopic images. Additionally, PET scanning with ¹¹C-methionine, ¹¹C-choline, and ¹⁸F-FDG was per-

formed. In all patients the intracarotid amobarbital test revealed that the left cerebral hemisphere was language dominant.

Extraoperative Cortical Mapping

For detailed cortical mapping before tumor removal, 9 of 13 patients underwent subdural implantation of chronic grid electrodes over the cortical area of interest. This technique was usually applied in cases presenting with seizures for precise localization of the epileptic focus relative to the neoplasm and eloquent cortical areas. Each grid (60 × 40 mm) contained 24 electrodes with a diameter of 3 mm and a distance of 10 mm between the centers (Unique Medical Co.). Usually two grids were implanted in each individual to cover a sufficient area of the cortex. Three-dimensional localization of electrodes relative to the brain surface was achieved using Leksell GammaPlan (Elekta Instruments AB), whereas matching of the cortical sulci and gyri was done with BrainVISA software.^{38,39} Patients underwent continuous (2–3 weeks) electrocorticography (ECoG) videomonitoring for detection of seizure activity.

Additionally, extraoperative cortical mapping was performed. For this purpose repetitive square wave biphasic current of alternating polarity (pulse width 0.5 msec, frequency 20 or 50 Hz, duration 1–2 seconds) was applied in a bipolar fashion to adjacent pairs of electrodes so that all electrodes were used. Continuous digital ECoG activity was monitored through nonstimulated electrodes to detect seizures and afterdischarges. The stimulus intensity increased steadily from 2 mA using stepwise increments of 1 mA until the effect was attained or abnormalities on ECoG were noted. The maximum stimulus intensity was 6 mA, which corresponds to 12 mA if a monophasic pulse were used. Of note, the maximum stimulus intensity recommended by guidelines of The Japan Awake Surgery Conference¹⁵ for cortical stimulation with the use of subdural electrodes is 16 mA. Cortical stimulations were performed using an Ojemann cortical stimulator (OCS-1, Integra Radionics, Inc.), whereas all recordings were made with a dedicated multimodal neuromonitor (Neuro-master Mee-1000, Nihon Kohden Corp.).

Regions of cerebral cortex were defined as language related if their stimulation consistently interrupted, disturbed, or slowed the patient's ability to name a pictured object, to pronounce a written familiar Japanese word, and/or to generate an action verb during the picture-naming task in the absence of seizures, afterdischarges, and positive and negative motor responses of the tongue (defined as involuntary contraction and impairment of rapid alternating movements, respectively). For confirmation of reproducible results, each cortical area was stimulated at least twice, although never in succession. The testing was recorded on video for subsequent reanalysis.

In our experience, extraoperative cortical mapping significantly reduces the time required for intraoperative localization of eloquent cortical areas (particularly in cases of dominant parietal lobe tumors) and for the overall operation, but cannot substitute for awake craniotomy with direct electrical stimulation particularly aimed at the identification of functionally important subcortical struc-

TABLE 1: Summary of clinical characteristics in 13 patients*

| Case No. | Age (yrs), Sex | Tumor Location | Tumor Histology | Type of Anesthesia | Stimulus Intensity (mA)† | Peak Latency (msec) | Intraop CCEP | | | Language Function | | | Time to Recovery (mos) |
|----------|----------------|----------------------|-----------------|--------------------|--------------------------|---------------------|--------------------------|------------------------------|--------------------|-------------------|--|-----------------------------|------------------------|
| | | | | | | | Direction of Stimulation | Changes During Tumor Removal | % Lesion Resection | Preop | Intraop | Postop | |
| 1 | 35, M | lt middle frontal | AO | local (awake) | 6 | 70 | TLA→FLA | unchanged | 98 | normal | dysarthria | yes‡ | 1 |
| 2 | 27, M | lt insula | O | local (awake) | 8 | 91 | TLA→FLA | disappeared | 80 | normal | paraphasia, dysarthria | yes | 8 |
| 3 | 62, M | lt inferior frontal | AOA | local (awake) | 6 | 90 | TLA→FLA | unchanged | 30 | mild dysphasia | mild dysphasia, similar to preop level | yes, similar to preop level | 3 |
| 4 | 12, M | lt middle frontal | CM | general | 6 | 73 | TLA→FLA | unchanged | 100 | normal | NA | no | NA |
| 5 | 29, M | lt middle frontal | O | local (awake) | 6 | 94 | TLA→FLA | unchanged | 95 | normal | normal | no | NA |
| 6 | 31, M | lt middle frontal | GBM | local (awake) | 6 | 98 | TLA→FLA | unchanged | 75 | mild dysphasia | mild dysphasia, similar to preop level | yes, similar to preop level | 1.5 |
| 7 | 21, F | lt inferior parietal | OA | local (awake) | 6 | 94 | FLA→TLA | disappeared | 95 | normal | paraphasia, repetition failure | yes | 10 |
| 8 | 33, M | lt inferior parietal | O | local (awake) | 4 | 66 | TLA→FLA | disappeared | 95 | normal | paraphasia, repetition failure, dysarthria | yes | 15 |
| 9 | 26, M | lt insula | AOA | local (awake) | 4 | 94 | FLA→TLA | decreased (up to 20%) | 85 | normal | paraphasia, repetition failure | yes | 6 |
| 10 | 41, M | lt insula | O | local (awake) | 4 | 92 | FLA→TLA | decreased (up to 40%)§ | 60 | normal | paraphasia, repetition failure | yes | 6 |
| 11 | 32, F | lt inferior frontal | AO | local (awake) | 4 | no response | no response | NA | 95 | normal | normal | no | NA |
| 12 | 31, M | lt inferior parietal | AOA | local (awake) | 3 | 80 | FLA→TLA | decreased (up to 20%) | 95 | normal | naming failure, repetition failure | yes | 6 |
| 13 | 58, M | lt inferior parietal | AO | local (awake) | 6 | 48 | FLA→TLA | decreased (up to 20%)§ | 40 | normal | paraphasia, repetition failure | yes | 4 |

* AO = anaplastic oligodendroglioma; AOA = anaplastic oligoastrocytoma; CM = cavernous malformation; GBM = glioblastoma multiforme; NA = not applicable; O = oligodendroglioma; OA = oligoastrocytoma; Prod = production.

† Electrical stimulus was applied with biphasic current; therefore, actual stimulus intensities are 2 times greater.

‡ Caused by dysarthria due to pyramidal tract injury.

§ In these cases some recovery of CCEP was noted after termination of tumor removal.

tures, such as the arcuate fasciculus and superior longitudinal fasciculus.

Surgery

Surgery was performed according to the previously described concept of the information-guided brain tumor removal, presuming maximum possible resection of the neoplasm with minimal risk of permanent postoperative neurological complications.^{23–26} Intraoperative MRI (AIRIS II, Hitachi Medical Corp.), updated neuronavigation, comprehensive neurophysiological monitoring, and detailed histopathological characterization of resected tissue obtained at various stages of the procedure were used routinely. In cases of malignancy, neurochemical guidance of lesion resection with 5-aminolevulinic acid was applied as well. In cases of high-grade gliomas, surgery was generally directed at the maximum possible removal of the contrast-enhanced area visualized on T1-weighted MRI; for low-grade gliomas, surgery was focused on maximum removal of the hyperintense area demonstrated on T2-weighted MRI. Histopathological diagnosis of tumors was based on the current criteria of the WHO.¹⁹

Intraoperative Brain Mapping

In all but one patient, tumor removal was done during awake craniotomy and was guided by positive mapping of cortical language areas and subcortical structures. These procedures followed dedicated guidelines of The Japan Awake Surgery Conference.¹⁵ Before surgery, patients were familiarized with the tasks used during intraoperative language mapping.^{15,37}

For intraoperative brain mapping, electrical stimulation of the cortex was applied with repetitive square wave biphasic current of alternating polarity (pulse width 0.5 msec, frequency 50 Hz, duration 1–2 seconds) using a bipolar electrode probe with an interpolar distance of 5 mm and tip diameters of 1 mm. Stimulation was performed in a systematic manner every 8–10 mm of the cortical surface. Continuous digital ECoG activity was monitored to detect seizures and afterdischarges. The stimulus intensity increased steadily from 2 mA using stepwise increments of 1 mA until the effect was obtained or abnormalities on ECoG were noted. The maximum stimulus intensity was 6 mA, which is in concert with the experience and recommendations of others.^{1,5,16,22,34,40} The maximum stimulus intensity in this study corresponded to 12 mA if a monophasic pulse were used, which is in concordance with guidelines of The Japan Awake Surgery Conference.¹⁵ Cortical stimulations were performed using an Ojemann cortical stimulator, and all recordings were done with a dedicated multimodal Neuromaster Mee-1000 neuromonitor.

To demonstrate language assessment tasks to the patient, the dedicated intraoperative examination monitor for awake craniotomy^{23,24} was used, which allows real-time visualization, integration and recording of a wide spectrum of data, including a view of the patient's face during response, the type of test provided, the position of the cortical stimulator in the surgical field, and so forth.

Cortical stimulation immediately preceded task presentation for the patient and continued for 1–2 seconds.¹⁵ As in extraoperative brain mapping, regions of the cerebral cortex were defined as language-related areas if their stimulation consistently interrupted, disturbed, or slowed the patient's ability to name a pictured object, to pronounce a written familiar Japanese word, and/or to generate an action verb during the picture-naming task in the absence of seizures, afterdischarges, and positive and negative motor responses of the tongue. For confirmation of the reproducible results, each cortical area was stimulated at least 3 times, although never twice in succession. The stimulated sites were initially marked with sterile tags, whereas eloquent cortical areas were delineated with the surgical pen upon the completion of mapping. One centimeter of brain tissue close to the defined borders was preserved during tumor resection. Removal of the neoplasm was accompanied by subcortical stimulation through the resection cavity directed at identifying the language pathways. The devices used for this purpose and the parameters of stimulation, including intensity, were similar to those used for cortical mapping.¹⁵

During the entire procedure under awake conditions, the patient's ability to speak freely was constantly monitored through continuous conversation with a member of the treatment team who was specialized in assessing language function and provided specific tasks to evaluate recalling, counting, fluency, and comprehension.³⁷

Intraoperative CCEP Monitoring

Intraoperative CCEP monitoring was performed continuously before, during, and after tumor resection, with special attention on assessing response during removal of the deep part of the neoplasm adjacent to the arcuate fasciculus and superior longitudinal fasciculus. For this purpose the strip electrodes (diameter 3 mm, distance between centers 10 mm, Unique Medical Co.) were positioned above the FLA and TLA, which were identified with cortical stimulation (Fig. 1). Additionally, recordings through the resection cavity were tried occasionally. Two adjacent electrodes were stimulated in a bipolar fashion with a constant-current square wave of alternating polarity (pulse width 0.3 msec, frequency 1 Hz). Continuous digital ECoG activity was recorded to detect seizures and afterdischarges. The stimulus intensity increased steadily from 2 mA using stepwise increments of 1 mA until the response was attained or abnormalities on ECoG were noted. Actual stimulus intensities in the present study varied from 3 to 8 mA, which is lower than the 10–15 mA used in previous studies of extraoperative CCEP recordings in patients with epilepsy.^{4,7,8,21} The reference electrode was placed in the area of the contralateral mastoid process. The bandpass filter for data acquisition was set at 5–1500 Hz with a sampling rate of 5000 Hz for each channel.

In each case the stimulus was applied to the FLA with recordings from the TLA and vice versa, and the CCEP response was defined as the highest observed negative peak in either direction. During each stimulation session two or more trials of 100 responses were averaged using the stimulus onset as the trigger and a delay of 10 msec to

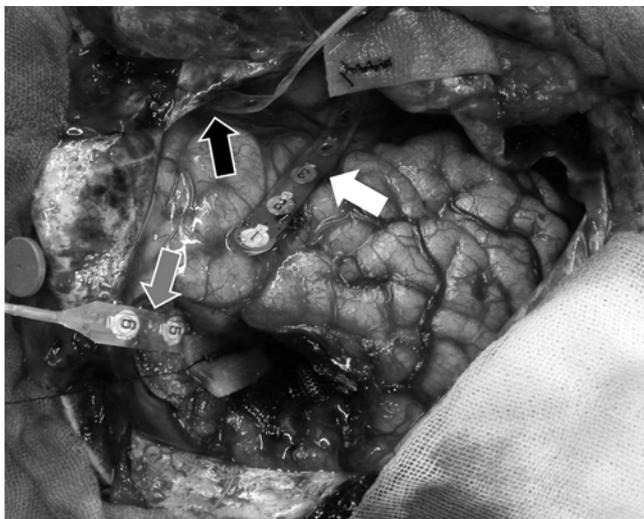


Fig. 1. Case 5. Intraoperative photograph showing strip electrodes for CCEP monitoring, located above the TLA (black arrow) and FLA (white arrow) and within the resection cavity (gray arrow) during removal of the left frontal glioma.

avoid artifacts caused by the stimulation itself. The complete CCEP response was obtained in 100 seconds, but it usually stabilized after the application of 30 stimuli; therefore, the changes, if presented, could be identified in 30–40 seconds. A decrease in the CCEP response was considered to occur when its amplitude reduced approximately 20% or more. All stimulations and recordings of CCEP were performed with a dedicated multimodal neuromonitor (Neuromaster Mee-1000). Patients in the awake condition were not specifically requested to perform any task during CCEP evaluation.

Postoperative Evaluation

Tumor resection rate was assessed with contrast-enhanced MRI performed within 48 hours after surgery. Speech function was evaluated initially after the patient awoke from anesthesia and subsequently on a daily basis until discharge from the hospital. Thereafter all patients were regularly followed up in the outpatient clinic by an attending neurosurgeon. In cases of high-grade gliomas, adjuvant radiochemotherapy was administered as appropriate.

Statistical Analysis

Nonparametric statistical tests were applied to evaluate factors associated with speech disturbances in the early postoperative period and with the time required to recover speech. For statistical analysis, in cases with normal postoperative speech function, the time to speech recovery was considered as 0. Statistical significance was defined at $p < 0.05$.

Results

Intraoperative brain mapping was successfully accomplished in all 12 patients who underwent awake craniotomy. In all cases the FLA and TLA were identified

within the posterior part of the inferior frontal gyrus and the posterior part of the superior temporal gyrus, respectively. Additionally, in one patient (Case 13) the middle part of the superior temporal gyrus also contained the TLA.

In 10 of these 12 patients, intraoperative speech dysfunction persisted to the end of surgery. However, in 2 (Cases 3 and 6) of the 10 patients mild dysphasia was present before surgery and was not aggravated during lesion resection, whereas in another patient (Case 1) dysarthria caused by pyramidal tract injury was observed, but dysphasia was not. Among 7 other patients paraphasias and repetition failures were mainly encountered.

An intraoperative CCEP response was not obtained in one patient (Case 11), presumably because of technical problems. In 4 patients (Cases 4 and 6–8) a clear bidirectional response was evident, whereas in 8 others (Cases 1–3, 5, 9, 10, 12, and 13) a definite CCEP response was observed in only one direction. Overall, the best response was identified from the FLA during stimulation of the TLA (7 cases) and from the TLA during stimulation of the FLA (5 cases) with a mean latency of 83 ± 15 msec (range 48–98 msec, median 91 msec). Attempts to detect the CCEP response with strip electrodes located within the resection cavity were not successful in any case.

During removal of the neoplasm the CCEP response was unchanged in 5 cases, decreased (up to 20%–40%) in 4, and disappeared in 3. In all cases changes in the CCEP response abruptly appeared during removal of the deep part of the tumor in the presence of speech dysfunction, but the occurrence of the latter was not always accompanied by alterations in response. In 2 patients (Cases 10 and 13) some recovery of CCEP was noted within 20–30 minutes and was not accompanied by improvement in speech.

Limits for tumor removal were identified through subcortical stimulation of language or motor pathways (Cases 1, 3, 5, 6, and 11), decrease or disappearance of the CCEP response (Cases 7, 8, and 12), or both of these factors (Cases 2, 9, 10, and 13). The median resection rate was 95% (range 30%–100%). Histopathological examination revealed 7 high-grade gliomas, 5 low-grade gliomas, and 1 cavernous malformation. The mean duration of surgery, including two intraoperative MRI sessions, was 8.2 ± 1.7 hours (range 5–10 hours).

Postoperative Course

During the early postoperative period, impairment of speech was noted in 10 of 13 patients. However, as mentioned above, in 2 patients (Cases 3 and 6) the mild dysphasia had been present before surgery and was not aggravated during lesion resection; in another patient (Case 1) dysarthria caused by pyramidal tract injury was observed, but dysphasia was not.

All 7 patients with a decreased or absent CCEP response after tumor removal experienced deterioration in speech function compared with its preoperative level. In contrast, in 5 cases with an unchanged intraoperative CCEP response, including 2 with preexisting mild dysphasia, speaking abilities were preserved at the preoperative level, except in the patient in Case 1, who experienced dysarthria due to pyramidal tract injury. The difference

was statistically significant ($p < 0.01$, chi-square test with continuity correction).

Speech function recovered in all patients within, on average, 6.1 ± 4.2 months after surgery (range 1–15 months, median 6 months). The time to speech recovery was significantly associated with the type of intraoperative change in CCEP recordings ($p < 0.01$, Kruskal-Wallis test) and was, on average, 1.8 ± 1.0 , 5.5 ± 1.0 , and 11.0 ± 3.6 months, respectively, if the response was unchanged, was decreased, or had disappeared. In this way, the absence of intraoperative CCEP changes had 100% sensitivity, specificity, and positive predictive value for the recovery of language function within 3 months after surgery. Additionally, the time to speech recovery was significantly associated with lesion location, taking, on average, 1.8 ± 1.0 , 6.7 ± 1.2 , and 8.8 ± 4.9 months, respectively, in cases of frontal, insular, and parietal neoplasms ($p < 0.02$, Kruskal-Wallis test).

Other evaluated factors, namely patient age, sex, tumor histopathological grade, lesion resection rate, maximum stimulus intensity, peak latency, and direction of stimulation during CCEP recording, did not demonstrate a statistically significant association with postoperative impairment of speech function and the time to its recovery.

Illustrative Cases

Case 8

History and Examination. A 33-year-old man experienced several episodes of generalized seizures. He had no other neurological symptoms or signs, and his speech function was normal. Magnetic resonance imaging demonstrated a nonenhancing intraaxial brain tumor centered in the left inferior parietal lobule, which had a hypointense signal on T1-weighted images and a slightly heterogeneous hyperintense signal on FLAIR images. Intracarotid amobarbital test revealed that the left cerebral hemisphere was language dominant.

Operation. Tumor removal was performed during awake craniotomy and continuous CCEP monitoring with stimulation of the TLA and recordings from the FLA. In total 95% resection of the lesion was attained under the guidance of cortical and subcortical mapping of language-related structures. During removal of the neoplasm, paraphasia, repetition failure, and dysarthria were noted, whereas an initially normal CCEP response demonstrated an abrupt decrease in amplitude and occasionally disappeared (Fig. 2). The histopathological diagnosis was oligodendroglioma.

Postoperative Course. After surgery the patient experienced the same speech disorders as intraoperatively, which recovered very slowly but became normal 15 months later. He did not have epileptic seizures during follow-up.

Case 13

History and Examination. A 58-year-old generally healthy man experienced generalized seizures. Magnetic resonance imaging revealed nonenhancing intraaxial

brain tumor in the left parietal lobe. There were no other neurological symptoms, and the patient was initially followed up with anticonvulsants and regular neuroimaging at another hospital. Two years later, however, the appearance and gradual enlargement of a contrast-enhanced area at the peripheral part of the lesion was noted. Malignant transformation was suspected, and the patient was sent to our clinic for surgical treatment. On admission the patient was neurologically intact, and his speech function was normal. Magnetic resonance imaging revealed a tumor centered in the left inferior parietal lobule, which had hypointense signal on T1-weighted images and heterogeneous hyperintense signal on FLAIR images. The contrast-enhanced lesion was located within the left insula. Intracarotid amobarbital test revealed that the left cerebral hemisphere was language dominant.

First Operation. Two-stage surgical removal of the tumor was planned. Initially, the contrast-enhanced insular tumor was totally resected with the patient under general anesthesia. Histopathological examination revealed anaplastic oligodendroglioma. At the end of surgery chronic grid electrodes were implanted subdurally for detailed cortical mapping before resection of the residual neoplasm.

First Postoperative Course. The postoperative course was uneventful. The patient's speech function remained normal. Cortical mapping using grid electrodes identified the FLA in the posterior part of the inferior frontal gyrus and the inferior part of the precentral gyrus. The TLA was located in the middle and posterior parts of the superior temporal gyrus and in the inferior parietal lobule.

Second Operation. Three weeks later the second-stage awake craniotomy was performed. Intraoperative brain mapping revealed the same location of the FLA as was defined with cortical stimulation using chronic grid electrodes; however, the TLA was identified only in the middle and posterior parts of the superior temporal gyrus. Continuous CCEP monitoring was performed with stimulation of the FLA and recordings from the TLA. During resection of the deep part of the neoplasm, paraphasia and repetition failure were noted, whereas subcortical electrical stimulation resulted in short-term speech arrest. It was accompanied by a decrease in the CCEP response in the posterior part of the superior temporal gyrus up to 20% and an increase in peak latency, although these parameters were stable in the middle part of the gyrus (Fig. 3). Approximately 30 minutes later partial recovery of the CCEP response was noted. Nevertheless, to avoid an irreversible deterioration in language function, further resection of the neoplasm was abandoned. In total 40% tumor removal was attained.

Second Postoperative Course. The postoperative course was uneventful. Despite the presence of speech production disorders in the early postoperative period, language function gradually recovered and became normal by 4 months after surgery. The patient received a course of fractionated radiotherapy (60 Gy) with concomitant and adjuvant chemotherapy (nimustine hydrochloride), which resulted in stabilization of the residual tumor.

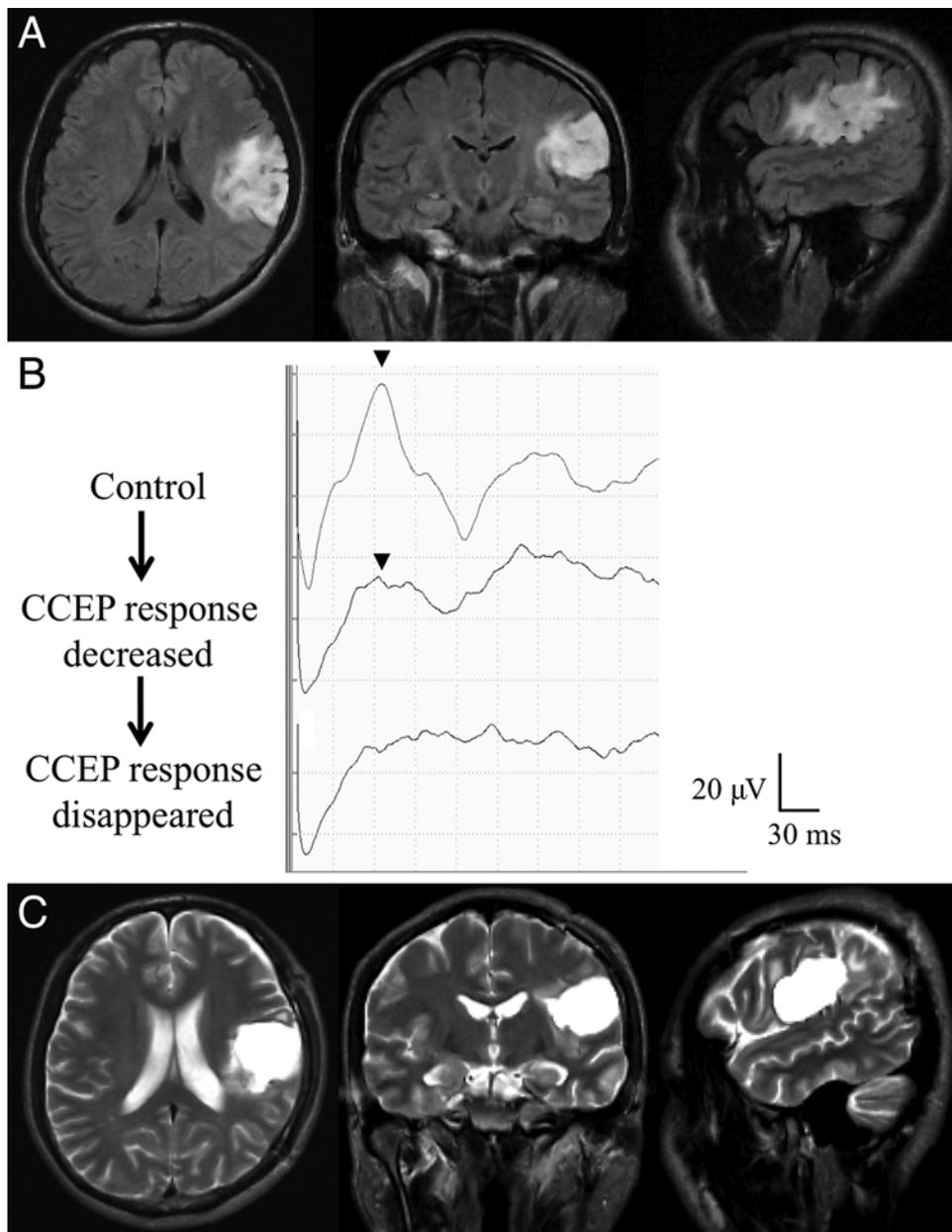


FIG. 2. Case 8. Oligodendroglioma in a 33-year-old man. Preoperative MR images (A) demonstrated tumor in the left inferior parietal lobe. The neoplasm was resected during awake craniotomy, and intraoperative CCEP monitoring was performed with stimulation of the TLA and recordings from the FLA. During surgery, paraphasia, repetition failure, and dysarthria were noted. An initially normal CCEP response demonstrated a decrease in amplitude and occasionally disappeared (B). The resection rate was 95% (C). After surgery, the patient experienced prolonged speech dysfunction with slow recovery within 15 months of follow-up.

Discussion

The technique of CCEP monitoring is based on electrical stimulation of one cortical area and recording the averaged response from another, which permits evaluation of their functional interconnections.^{4,7,8,17,20,21} Previous reports have demonstrated that this neurophysiological method can be useful for assessing the language network in patients with epilepsy and that the evolved response is well correlated with the location of the FLA and TLA.^{4,7,21} In the present study we showed for the first time that CCEP recordings can be effectively performed dur-

ing awake craniotomy for brain tumors and are feasible for the evaluation of language, since the evolved response was closely related to intraoperative and postoperative speech function, as well as to its prognosis after surgery.

Direct comparison of the results of CCEP monitoring presented herein with those previously reported by other groups is difficult. To the best of our knowledge, all previous studies have been based on recordings performed after subdural implantation of chronic grid electrodes in patients with seizures, whereas in the present study CCEP monitoring was applied during the resection of brain neoplasms. Moreover, the quantitative and qualitative differ-

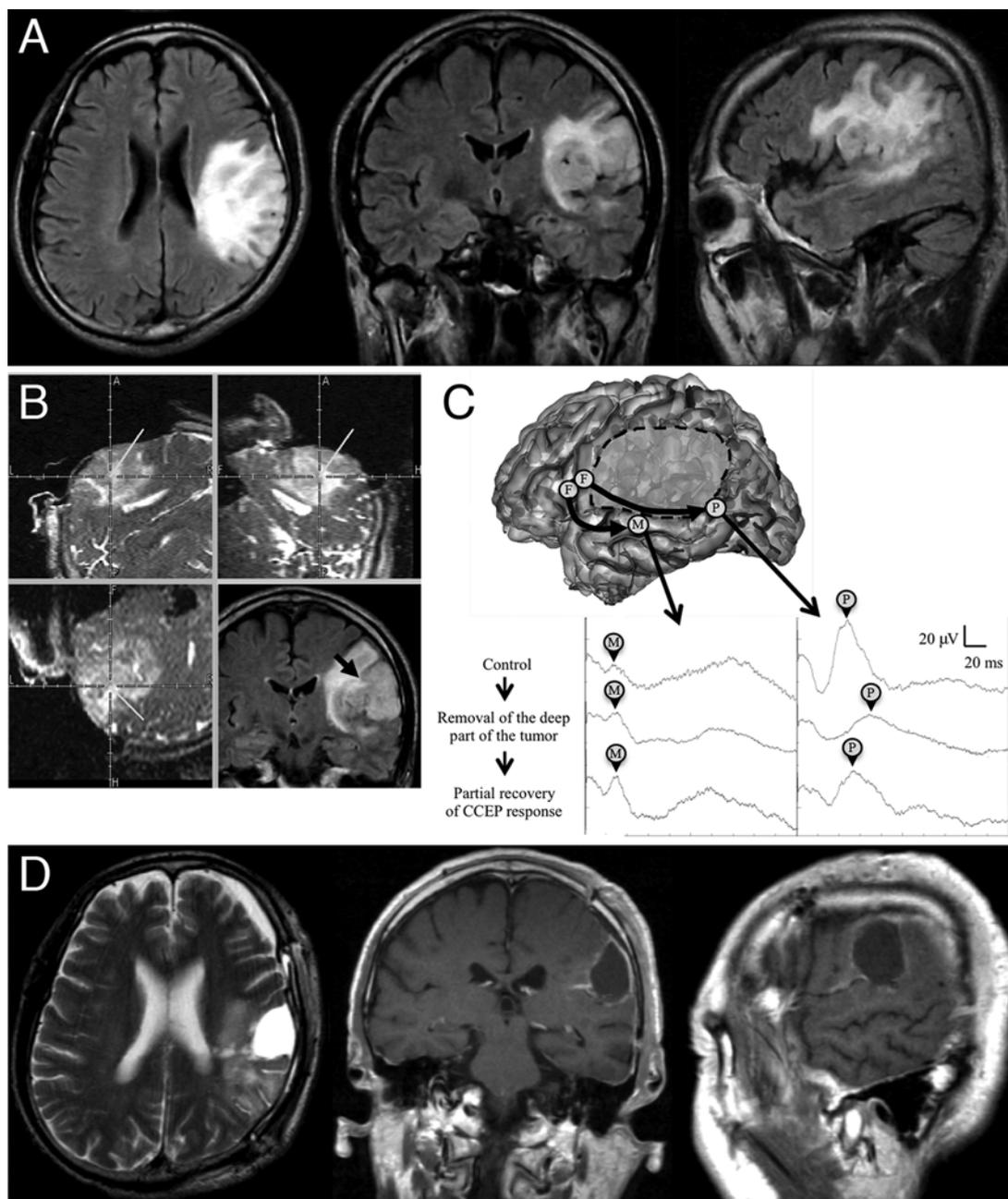


FIG. 3. Case 13. Anaplastic oligodendroglioma in a 58-year-old man. A neoplasm in the inferior parietal lobule (**A**) was resected during a second-stage awake craniotomy and intraoperative CCEP monitoring with stimulation of the FLA and recordings from the TLA. During removal of the deep part of the tumor, language function was impaired, whereas subcortical electrical stimulation resulted in short-term speech arrest (**B**, *black arrow*). It was accompanied by a decrease in CCEP response (**C**) in the posterior part of the superior temporal gyrus (P) up to 20% and an increase in peak latency, whereas these parameters recorded from the middle part of the gyrus (M) were stable. Approximately 30 minutes later some recovery of the CCEP response was noted. However, only partial resection of the tumor was attained (**D**) to avoid permanent postoperative speech dysfunction. After surgery the patient experienced paraphasias and repetition failures, with gradual recovery within 4 months of follow-up. *Curved arrows* (**C**) show the directions of stimulation, presumably along dorsal and ventral language pathways, and *arrowheads* (**C**) indicate peak corresponding to CCEP response. F = FLA.

ences in subcortical fibers interconnecting evaluated cortical areas, as well as the distance between stimulating and recording electrodes, are reflected in the intersubject variability of latency and amplitude of CCEP responses^{3,4} and may differ in cases of nonstructural brain pathology and tumors adjacent to the area of interest, particularly

because of the invasive and compressive effects of the latter. In their original study, Matsumoto et al.²¹ investigated language-related CCEP in 8 patients with epilepsy. The response typically consisted of an early (N1) and late (N2) negative peak with latencies of 22–36 msec and 113–164 msec, respectively, during stimulation of the FLA and

Cortico-cortical evoked potentials

recordings from the TLA, and 23–39 msec and 90–161 msec in the opposite direction. Recordings were successfully accomplished in the posterior language area after stimulation of the anterior language area in 7 of 8 patients, and in 3 of 4 patients when it was done in the opposite direction. Therefore, interconnections between anterior and posterior cortical language areas were considered bidirectional²¹ in contrast to the classic model of language.¹¹ In our cases CCEP response frequently consisted of two negative peaks, but only the highest one evoked in any direction was evaluated because it was considered to be more suitable for the purpose of intraoperative monitoring. Since the median peak latency was 91 msec, it probably corresponded to N2, which mainly reflects the direct arrival of slow multisynaptic volleys via the cortico-subcortico-cortical pathway.²¹ Moreover, in the present study the intraoperative CCEP response strongly depended on the direction of stimulation and was clearly bidirectional in only 4 patients. In Cases 9, 10, 12, and 13, responses could not be reliably observed in the FLA during stimulation of the TLA, while they were clearly identified in the opposite direction. It has been previously remarked that the CCEP response in the anterior language area during stimulation of the posterior language area is less well defined, because of the more scattered distribution of the projecting neurons within the latter and the subsequent activation of the smaller number of projecting neurons at one time with the stimulation technique applied.²¹ Additionally, the degree of evoked response may be related to the size of pyramidal neurons, which are smaller in the posterior language area and may require greater stimulation intensity.²¹ On the other hand, the strip electrodes for intraoperative CCEP recordings in our patients were positioned in the cortical areas, whose direct electrical stimulation resulted in speech abnormalities, while the best response in the TLA during stimulation of the FLA can be presented in spatially different areas.²¹ In some way it can explain the unidentified CCEP response in the TLA after stimulation of the FLA in our Cases 1–3 and 5. Finally, the absence of a noted response from white matter within the resection cavity may be particularly caused by a predetermined delay in recordings of 10 msec after trigger, since subcortical CCEP responses usually have short latencies.⁸

It is evident that the intraoperative evaluation of CCEP may provide new insights into the neurophysiological organization of speech function. For example, according to the traditional model, the FLA and TLA are interconnected via a single neuronal pathway involving the arcuate fasciculus and superior longitudinal fasciculus.¹¹ However, this model cannot explain the different CCEP responses observed during speech impairment accompanying the removal of the deep part of the left inferior parietal glioma in Case 13: deterioration of peak latency and amplitude was noted in the posterior part of the superior temporal gyrus but not in its middle part. On the other hand, such a finding may favor the recently described dorsal and ventral pathways of the language network.^{1,10,14,35} The former involves the arcuate fasciculus and superior longitudinal fasciculus and interconnects the FLA with the TLA and parietal cortex,⁹ whereas the

latter includes the uncinate fasciculus and inferior fronto-occipital fasciculus and interconnects the FLA with the TLA and occipital cortex.^{1,10,35} In such a way, in our patient isolated deterioration of the CCEP response in the posterior part of the superior temporal gyrus may have been caused by alterations of the dorsal pathway but preservation of the ventral one.

Moreover, the application of intraoperative CCEP monitoring may have definite clinical importance. During awake craniotomy the majority of patients in the present study demonstrated speech dysfunction, which usually appeared during removal of the deep part of the tumor that affected the subcortical language pathways. Trinh et al.⁴⁰ noted that the presence of language and/or motor abnormalities not resolved by the end of surgery is associated with an 88% probability of a neurological deficit in the immediate postoperative period and that patients in such cases are more than 6 times more likely to have dysfunction at the 3-month follow-up.⁴⁰ In our series the changes in CCEP were constantly observed in the presence of intraoperative speech abnormalities, but the appearance of the latter was not always accompanied by alterations in the CCEP response. Changes in CCEP were variable and ranged from complete disappearance to a more or less prominent decrease followed by some recovery, which was associated with the time interval to restore language function. Of note, the absence of any intraoperative CCEP change had 100% positive predictive value for the recovery of speech function within 3 months after surgery. Additionally, monitoring CCEP facilitated intraoperative evaluation of speech in patients with a pre-existing deficit (Cases 3 and 6) and was helpful in differentiating dysarthria caused by pyramidal tract injury from dysphasia (Case 1). Therefore, CCEP recording can be considered as a useful adjunct for assessing language during surgery and predicting its postoperative prognosis.

Decision making in regard to the optimal resection rate for glioma, whose removal under awake conditions is accompanied by the appearance of speech disturbances, is always difficult. It is evident that complete elimination of the neoplasm can be beneficial to patient survival, but its attainment at the cost of permanent postoperative speech dysfunction is hardly acceptable.²² The majority of persistent neurological deficits after awake craniotomy for glioma removal is related to the dissection of eloquent subcortical structures,⁴⁰ which can be identified with diffusion tensor imaging or intraoperative electrical stimulation. The former imaging technique, however, is susceptible to known inaccuracies, even if performed intraoperatively,^{28,32,37} whereas positive subcortical mapping through the resection cavity is associated with the immediate postoperative appearance or aggravation of speech dysfunction in 67%–100% of patients.^{1,6} In the present study tumor removal was guided by intraoperative CCEP recording. Unless subcortical stimulation caused speech arrest, the resection continued even in the presence of language disturbances until a prominent decrease in or disappearance of the CCEP response was observed. This strategy can be criticized since, like any neurophysiological technique based on the evaluation of an averaged response, intraoperative CCEP monitoring

may be susceptible to the temporary gap between structural injury and its detection. However, it seems that the 100 seconds required for recording the complete CCEP response is comparable with the time required for intraoperative neurophysiological methods of proven efficacy such as somatosensory evoked potentials (56.2 seconds for averaging 500 stimuli at 8.9 Hz) and auditory brainstem response (99 seconds for averaging 1000 stimuli at 10.1 Hz). It should be noted that the median resection rate in the current series was 95%, and in no cases were permanent speech production disorders remarkable after surgery, although they are encountered in approximately 2% of patients undergoing awake craniotomy with direct intraoperative brain mapping.^{1,34} Therefore, intraoperative CCEP monitoring can facilitate decision making as regards the optimal resection of gliomas located in the vicinity of language-related structures, although further studies on this important issue are definitely needed.

As was pointed out by Matsumoto et al.,²¹ CCEP recordings are task free and do not require any cooperation from the patient, which facilitates its use in persons who are not candidates for awake craniotomy or who cannot tolerate this procedure. In fact, in one of our patients (Case 4), removal of the neoplasm was done under general anesthesia. During surgery CCEP monitoring did not reveal any changes in the evoked response, and no postoperative language disorders were noted. While before making any solid conclusions, any beneficial outcome should be reproduced in additional cases, this observation pointed out the possibility of speech function control during brain tumor removal under general anesthesia. In such a way, the FLA and TLA can be localized with cortical mapping in patients undergoing surgery according to an awake-asleep strategy, through cortical mapping after initial implantation of the chronic subdural grid electrodes (as it was done in our patient), or by means of advanced neuroimaging. In particular, functional MRI provides 59%–100% sensitivity and 0%–97% specificity for correct identification of language-related cortical areas^{12,33} and is generally considered to be fairly good for demonstrating the FLA but less effective for demonstrating the TLA.

Possible disadvantages of the proposed technique of intraoperative CCEP monitoring include an increase in operation time and the requirement of a large craniotomy to provide access to the tumor, FLA, and TLA. It has been suggested that glioma resection guided by positive cortical mapping can, by itself, be associated with a greater risk of postoperative neurological deterioration, and a “tailored” craniotomy without intentional exposure of the eloquent cortex has been advocated.^{16,34,40} However, the mentioned drawbacks should not be overemphasized. While a larger craniotomy and intraoperative brain mapping have certainly led to some increase in the duration of surgery (roughly 1.5 hours per patient), the mean operation time in the present study (8.2 hours) corresponds well with our general experience with surgery for gliomas using intraoperative MRI.^{23–26} Recently, Leuthardt et al.¹⁸ reported an average operating room time of 7.9 hours (range 5.9–9.7 hours) in 12 patients treated with the combined use of awake craniotomy, intraoperative

cortical mapping, and intraoperative MRI, which seems concordant with time in the present study. It should be noted that neither a more extensive surgical approach nor a relative prolongation of the surgical procedure resulted in additional morbidity in our patients.

There are several limitations to the present study. First, it was conducted at a single institution, includes a small number of highly selected cases, and does not contain a control group, which do not permit detailed statistical evaluation of the predictive value of the presented technique for postoperative speech dysfunction and its prognosis, particularly in comparison with direct intraoperative assessment of language during awake craniotomy. Second, the exact threshold of CCEP decrease, which can be used for the termination of tumor resection to avoid permanent postoperative language dysfunction, was not determined. Third, the location of stimulating and recording electrodes used for intraoperative CCEP monitoring corresponded to rather restricted sites within the cortical language-related areas, which (especially, the TLA) can be distributed rather widely.^{21,29,34} Fourth, only interconnections between the FLA and the TLA were evaluated, although it is known that other cortical areas, especially the inferior parietal lobule, and their subcortical pathways are playing very important roles in speaking abilities.^{1,3,6,21,22,34,35} Fifth, while diffusion tensor imaging and subcortical stimulation were routinely performed in our patients, the correspondence between identified language pathways and CCEP response was not specifically addressed. Finally, the detailed neurophysiology of the evolved response, especially as related to the direction of stimulation, should be clarified further. Therefore, despite the rather promising results presented herein, evaluation of CCEP recordings for the assessment of speech function during brain tumor surgery definitely needs additional investigation.

Conclusions

Results of the present study demonstrate the feasibility of CCEP monitoring during the resection of intracranial tumors affecting language-related cerebral structures. This neurophysiological method can be useful in the objective evaluation of speech function as well as its direct assessment during awake craniotomy. Moreover, it can be helpful in predicting the prognosis of intraoperative and postoperative deteriorations in language and for deciding on the optimal resection of a neoplasm. Further experience with intraoperative CCEP recordings may open the possibility of monitoring speech function during neurosurgical procedures performed under general anesthesia.

Disclosure

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