Disconnection of the pathological connectome for multifocal epilepsy surgery

Kyousuke Kamada, MD, PhD,¹ Hiroshi Ogawa, MD, PhD,¹ Christoph Kapeller, PhD,² Robert Prueckl, PhD,² Satoru Hiroshima, MD, PhD,¹ Yukie Tamura, MD,¹ Fumiya Takeuchi, PhD,³ and Christoph Guger, PhD²

¹Department of Neurosurgery and ³Center for Advanced Research and Education, School of Medicine, Asahikawa Medical University, Hokkaido, Japan; and ²g.tec Guger Technologies OG, Graz, Austria

OBJECTIVE Recent neuroimaging studies suggest that intractable epilepsy involves pathological functional networks as well as strong epileptogenic foci. Combining cortico-cortical evoked potential (CCEP) recording and tractography is a useful strategy for mapping functional connectivity in normal and pathological networks. In this study, the authors sought to demonstrate the efficacy of preoperative combined CCEP recording, high gamma activity (HGA) mapping, and tractography for surgical planning, and of intraoperative CCEP measures for confirmation of selective pathological network disconnection.

METHODS The authors treated 4 cases of intractable epilepsy. Diffusion tensor imaging–based tractography data were acquired before the first surgery for subdural grid implantation. HGA and CCEP investigations were done after the first surgery, before the second surgery was performed to resect epileptogenic foci, with continuous CCEP monitoring during resection.

RESULTS All 4 patients in this report had measurable pathological CCEPs. The mean negative peak-1 latency of normal CCEPs related to language functions was 22.2 ± 3.5 msec, whereas pathological CCEP latencies varied between 18.1 and 22.4 msec. Pathological CCEPs diminished after complete disconnection in all cases. At last follow-up, all of the patients were in long-term postoperative seizure-free status, although 1 patient still suffered from visual aura every other month.

CONCLUSIONS Combined CCEP measurement, HGA mapping, and tractography greatly facilitated targeted disconnection of pathological networks in this study. Although CCEP recording requires technical expertise, it allows for assessment of pathological network involvement in intractable epilepsy and may improve seizure outcome.

<https://thejns.org/doi/abs/10.3171/2017.6.JNS17452>

KEY WORDS cortico-cortical evoked potential; connectivity; connectome; diffusion tensor imaging; epileptogenic foci; functional network; high gamma activity; epilepsy

A SUBSTANTIAL minority of patients with epilepsy continues to experience frequent seizure activity despite treatment with multiple antiepileptic drugs (AEDs). This intractable epilepsy may arise from multiple foci or low seizure threshold (high epileptogenicity). In addition, there is growing evidence from neuroimaging studies that intractable epilepsy involves pathological functional networks that allow rapid spread of focal seizure activity.^{3,11} Combined electroencephalography (EEG) and functional MRI (fMRI) has revealed that focal interictal epileptic dis-

charges propagate through specific networks and induce widespread metabolic changes in the whole brain.⁷ It has also been suggested that abnormal neuronal activity in epileptic networks may be activated during interictal periods as well as during ictal states to promote neuroplastic changes that further strengthen pathological network connectivity. Therefore, identification of pathological epileptic networks distinct from normal resting-state functional networks could reveal the pathogenic mechanisms for seizure initiation and propagation and thereby provide guidance

ABBREVIATIONS AED = antiepileptic drug; AF = arcuate fasciculus; CCEP = cortico-cortical evoked potential; CPS = complex partial seizure; DTI = diffusion tensor imaging; ECoG = electrocorticography; ECS = electrocortical stimulation; EEG = electroencephalography; FC = functional connectivity; fMRI = functional MRI; GCS = generalized convulsive seizure; HGA = high gamma activity.

SUBMITTED February 20, 2017. **ACCEPTED** June 2, 2017.

INCLUDE WHEN CITING Published online December 22, 2017; DOI: 10.3171/2017.6.JNS17452.

TABLE 1. Demographic characteristics of individual patients

Case No.	Age (yrs), Sex	Focus	Pathology	Symptoms
1	29, F	Lt frontotemporal	FCD I	CPS, GCS
2	28, M	Bilat frontal	None	CPS, GCS
3	32, F	Rt temporal	FCD I	CPS, GCS
4	31, M	Rt temporal	FCD I	CPS, GCS

FCD I = focal cortical dysplasia type I.

for treatment. In addition to fMRI, functional networks can be mapped electrophysiologically using stimulus-response measures (electrocortical stimulation [ECS]) and by monitoring endogenous resting oscillatory activity. Among resting-state signals, high gamma activity (HGA) augmentation in the range of 60–170 Hz is assumed to reflect cortical center functioning.^{4,19,20} Sinai et al. reported a detailed comparison of ECS and HGA mapping in patients with subdural grid implantation²³ and suggested their combined utility for preliminary network mapping.

Several groups have demonstrated pathological functional connectivity (FC) within resting-state functional networks in patients with generalized epilepsy,^{12,13} including aberrant networks connected to the hippocampus in patients with temporal lobe epilepsy.^{21,22} It is thus becoming clear that functional networks involving epileptogenic foci facilitate seizure initiation and propagation. Detailed investigations of the FC patterns would, therefore, help in revealing patient-specific pathological networks, which might be targets for surgical disconnection.¹⁸

Physiological and pathological networks in patients with epilepsy can also be mapped by implanting subdural electrode grids and measuring cortico-cortical evoked potentials (CCEPs) in response to stimulation of a distant site, such as an epileptic focus. CCEP mapping has garnered favorable attention as a direct method to identify normal connections mediating motor- and language-related functions.¹⁶ Alarcon et al. were the first to use single-pulse electrical stimulation to probe epileptogenicity.¹ They found that delayed responses, which usually occur 100 msec to 1.5 seconds after the electrical stimuli, appear to be specific to the epileptogenic zone and could be considered as surrogate markers of epileptogenicity. These authors suggested that removal of areas involved in generating delayed responses was associated with good seizure control. On the other hand, Enatsu et al.⁵ found that stimulation of the ictal onset zones evoked larger CCEPs in the ictal propagation area than out of the propagation area and suggested that the epileptogenic pathology might be more closely associ-

ated with impairment of cortical inhibition over the broad cortical area rather than normal cortices. Matsumoto et al. elucidated the pathophysiology of ictal motor semiology and rapid spread of epileptic discharges within the motor system. It has been speculated that spread of epileptic activity within such networks is predictive of relatively poor outcome following epilepsy surgery.¹⁴ Therefore, CCEP mapping may be a powerful tool to identify both normal connections to preserve, and aberrant connections targeted for disconnection.

In this study, we used subdural electrode grids to measure CCEPs to identify pathological networks in patients with intractable epilepsy. Furthermore, combined CCEP, HGA distribution, and diffusion tensor imaging (DTI)-based tractography allowed us to map patient-specific networks for surgical planning.^{9,10} Based on these networks, our initial strategy was to disconnect functional connectomes with epileptogenic foci, continuously monitoring pathological CCEPs. If the contiguous areas showed pathological CCEPs, we additionally resected the epileptogenic lesions. Detailed bedside CCEP mapping and intraoperative CCEP monitoring with DTI tractography enabled us to make ratiocinative surgical strategies.

Methods

Study Cohort

Four patients suffering from intractable epilepsy underwent surgical treatment between April 2013 and December 2016. The diagnosis was made according to the criteria published by the International League Against Epilepsy.⁶ All patients were without gross structural brain abnormalities, such as mesial temporal sclerosis, tumors, or cortical dysplasia, on anatomical MRI and exhibited no substantial brain metabolic abnormalities. Monitoring of seizure and epileptic activity by using 24-hour video-electrocorticography (ECoG) revealed relationships between semiology and pathological electrophysiology. Demographic data of all patients is shown in Table 1.

The research ethics board of Asahikawa Medical University approved the study. Written informed consent was obtained from all patients and their families.

HGA Mapping

We routinely implant pairs of 20-channel ECoG grids with a 3-mm electrode diameter and 10-mm interelectrode distance (Unique Medical), 4-channel strip electrodes, and 8-channel grids to cover the bilateral temporal lobe bases, including the parahippocampal gyrus. In addition,

TABLE 2. Stimulus-response latencies in 4 cases with pathological CCEPs

CCEP	Stimulus Point	No. of Electrodes	Mean Latency ± SD (msec)	Location of CCEP
Normal*	Temporal language	3.1 ± 1.2	22.2 ± 3.5	Frontal language
Pathological				
Case 1	Lt frontal lobe	3	22.2 ± 1.5	Lt temporal cortex
Case 2	Lt frontal lobe	6	24.4 ± 1.2	Rt frontal cortex
Case 3	Rt hippocampus	4	18.1 ± 0.8	Rt temporal cortex
Case 4	Rt hippocampus	4	20.2 ± 0.7	Rt posterior temporal area/base

* Cases 1 and 2. Number of electrodes for these cases presented as mean ± SD.

FIG. 1. Case 1. **A:** Electrocorticogram showing 2 seizure-onset zones in anterior frontal (red circles) and middle temporal (blue circles) regions. In most seizure events, the frontal activity frequently spread to the lateral temporal cortex. **B:** Axial MR image demonstrating no pathological findings. **C:** Frontal (red) and temporal (blue) foci marked on the electrode templates. Figure is available in color online only.

we insert a high-resolution 60-channel grid (1.5-mm-diameter electrodes with 5-mm interelectrode distance) on the primary sensorimotor area and a 4-channel strip facing the dura matter adjacent to the parietal vertex for reference and ground channels. After video-ECoG monitoring to identify epileptogenic foci, all patients underwent HGA and CCEP recording with the subdural grids.

The ECoG was recorded at a 1200-Hz sampling rate with 24-bit resolution and high oversampling to increase the signal-to-noise ratio using a 256-channel g.HIamp biosignal amplifier (g.tec medical engineering GmbH). For ECoG functional mapping, patients were first asked to relax for 15 seconds (rest phase) and then perform a task (such as hand grasping, word reading, etc.) for 15 seconds (active phase). Signals during rest and active phases were recorded 3 times. Electrophysiological recording was triggered by stimulus presentation using a real-time processing system driven by Matlab and Simlink. Every task was repeated twice to confirm the reproducibility of the real-time HGA mapping.^{8,19} Task-related HGA changes at 60–170 Hz were determined by extracting the coefficient of

determination (r^2) based on the band power values for the rest and active phases. Finally, HGA electrodes showing significantly increased signals by t-test (active channels) were identified in real time (red circles overlapping ECoG channels on the active electrode).

CCEP Recording for Functional Connectivity

Based on seizure monitoring and functional mapping with ECS and HGA, we measured CCEPs in response to stimulation of identified epileptogenic foci and eloquent areas for identification of functionally connected areas. The electrical stimulus was a constant current square-wave pulse of 0.3-msec duration delivered at 1 Hz. Two adjacent channels were used as bipolar stimulating electrodes to apply localized current to the targeted cortical area. Stimulus polarity was alternated to reduce stimulus artifacts. Current amplitude was set at 80% of the ECS intensity that induced muscle cramp. CCEPs were synchronized to stimulus onset for averaging using a transistor-transistor-logic trigger. In each session, we recorded CCEPs twice to con-

FIG. 2. Case 1. Normal and pathological CCEP results. **A:** Blue and red electrode pairs indicate stimulus points and blue and red squares show recording locations of pathological and normal CCEPs, respectively. Note that each first component (N1) waveform is approximately 24 msec after the stimuli. **B:** Pathological CCEPs peaking at 24 msec (arrow). **C:** Normal CCEPs appearing at 24 msec poststimulus (arrow). **D:** Tractography revealing fiber connections between the frontal and temporal regions via uncinate fascicles. Figure is available in color online only.

firm reproducibility and set the poststimulus recording period as -100 msec to 800 msec. The Welch test, a derived t -test for populations with different variances, was used to check for significant differences between the averaged baseline and CCEP waveforms. The significance threshold was set to $p < 0.05$ for a 2-tailed t -distribution. We then validated the HGA-CCEP mapping results by ECS.²⁵

Magnetic Resonance Protocols

All 4 patients underwent preoperative DTI-MRI using a 3.0-T whole-body MRI machine with echo-planar capabilities and a 32-channel surface coil (Discovery 750 W; General Electric) to investigate structural associations with electrophysiological measures. We used a single-shot spin echo echo-planar sequence with TR 13,000 msec and TE 66.4 msec to acquire 55 interleaved contiguous 3-mm axial images. A data matrix of 128×128 over a 240×240 -mm field of view was obtained by acquiring 128 echoes per excitation. DTI data were acquired along 30 noncollinear gradient directions with a b value of 1000 sec/mm^2 follow by additional $b = 0$ imaging (T2-weighted images). After interpolation of DTI data, spatial resolution was $0.9375 \times 0.9375 \text{ mm}^2$. For each patient, a high-resolution anatomical data set was also acquired by a 3D spoiled gradient recalled echo sequence (3D-MRI).

Probabilistic tractography was performed using the FMRIB diffusion toolbox (FDT version 2.0; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT>). BEDPOSTX was used to model 5000 iterations within each voxel at a curvature threshold of 0.2, step length of 0.5, and maximum step number of 2000. Target masks were used (cerebral peduncle, the motor and language areas, epileptogenic foci) and distribution of fiber orientations was calculated between pairs of masks (functionally connected areas). The connection probability was calculated by the number of tracts that reached a target voxel from a given seed voxel. The seeds for fiber tracking were placed on voxels overlapping subdural grid channels that induced normal or pathological CCEPs. We tested 50%, 25%, and 15% of maximum connectivity as thresholds to determine the optimum threshold to identify the voxel with maximum connectivity within the connectivity distribution map for each patient.¹⁷

Intraoperative CCEP Monitoring

We continuously monitored CCEPs evoked by stimulation of epileptogenic foci and language-related centers during resection under general anesthesia. The surgical procedure was designed to avoid moving the grids and strips during continuous CCEP recording. Alteration of CCEP profiles and tractography-based neuronavigation

FIG. 3. Case 1. **A:** Dissection of the sylvian fissure to expose the limen insulae while keeping the electrode position stable to monitor CCEPs. **B:** Removal of the anterior roof of the inferior temporal horn, preserving the ependymal layer (arrow). **C:** Operation sketch showing electrode grids, the shifted sylvian vein, and exposed ependymal layer (arrow). Copyright Kyousuke Kamada. Published with permission. **D:** Postoperative tractography showing complete disconnection of the uncinate fascicles. Figure is available in color online only.

enabled us to confirm successful disconnection of pathological networks in real time.

Results

Video-ECOG Monitoring

More than 3 seizures were captured from each patient to identify epileptogenic foci. Case 1 showed multiple foci on the left frontotemporal region and Case 2 exhibited multiple foci in bilateral frontal lobes. The other 2 cases (Cases 3 and 4) demonstrated foci between the right hippocampus and lateral aspect of the right temporal lobe.

Normal Network CCEPs

In 2 of the 4 cases (Cases 1 and 2), we performed language mapping by ECS and then stimulated the frontal and temporal language areas to record CCEPs. We found a mean ($\pm$ SD) of 3.1 ± 1.2 channels in the left temporal lobe that were responsive to left frontal lobe stimulation. Mean latency between the language centers was 22.2 ± 2.1 msec. Conversely, a mean of 4.2 ± 2.4 channels in the left frontal lobe area were responsive to temporal stimulation with a mean delay of 26.2 ± 1.5 msec. In contrast, CCEPs between frontotemporal regions were barely detectable in

the nondominant hemisphere in the other 2 cases (Cases 3 and 4).

Pathological Network CCEPs

Pathological CCEPs showed different profiles from normal network CCEPs. We used alternating square pulses to evoke pathological CCEPs in functionally connected areas. Pathological CCEPs suggesting aberrant functional connectivity related to the epileptogenic foci were found in all 4 cases. The first 2 cases (Cases 1 and 2) demonstrated distant epileptogenic foci and the last 2 cases (Cases 3 and 4) showed contiguous foci within the temporal lobe. Table 2 summarizes the number of CCEP-detecting electrodes and the response latencies. Cases 1 and 2 with distant foci showed that pathological CCEPs had longer latencies than normal CCEPs. In contrast, contiguous foci showed shorter latencies (Table 2).

Treatment Strategy Concept

The first 2 cases (Cases 1 and 2) had epileptogenic foci in the left frontotemporal and bilateral frontal lobes. Pathological CCEPs during resection were stable without electrical artifacts. In contrast, Cases 3 and 4 had patho-

FIG. 4. Case 1. **A:** Intraoperative normal (blue squares) and pathological (red squares) CCEP results. **B:** Obvious pathological CCEP (red lines) before resection. **C:** CCEPs, which diminished after disconnection. **D:** Normal CCEPs appearing on the temporal regions. **E:** Normal CCEPs were preserved after disconnection of the pathological network. **F and G:** Postoperative MR images showing removal of the left frontal area (F, arrow) and a small incision in the left temporal tip (G, arrow). Figure is available in color online only.

logical CCEPs within the temporal lobe, which was close to the hippocampus.

During the operation in Cases 3 and 4, we gave the most attention to getting rid of electrical noise to monitor pathological CCEPs. These patients underwent complete resection of the pathological CCEP-positive area. We also implanted grids over the bilateral frontal and temporal areas, including the temporal bases. Both patients exhibited spikes and CCEP propagation from the hippocampus to the ipsilateral anterolateral aspect of the temporal lobe.

In all 4 cases, patients had a favorable prognosis following treatment. The pathological connections and surgical strategies for epilepsy treatment are briefly explained below.

Illustrative Cases

Case 1

A 29-year-old right-handed woman experienced her first epileptic episode 12 years prior to treatment and since then had suffered several generalized convulsive seizures (GCSs) and complex partial seizures (CPSs) every month while receiving multiple AEDs. Her seizures proceeded

autonomic and acoustic auras, frequently became generalized, and were associated with autism. Radiological examinations demonstrated no gross structural abnormalities. Video-EECoG monitoring demonstrated frequent left-dominant frontotemporal spike propagation, and ECoG monitoring revealed 2 foci, one in the left frontal region and the other in the anterolateral aspect of the left temporal lobe (Fig. 1).

Picture-naming and word-reading HGA mapping revealed language-related functions at the left inferior frontal gyrus and temporal base, and these functional regions were confirmed by ECS. CCEPs with stimuli to the language-related regions and epileptogenic focus on the temporal lobe were recorded from the upper and anterior parts of the inferior frontal gyrus, respectively (Fig. 2). Reciprocally, stimulation of the frontal language area evoked physiological CCEPs in the temporal language area, whereas stimulation of the focus on the frontal lobe evoked pathological CCEPs at the lateral aspect of the temporal area. Mean latencies of both normal and pathological CCEPs were approximately 22 msec (Fig. 2). Normal and pathological CCEPs were similar in latency despite differ-

FIG. 5. Case 2. **A:** Axial MR image demonstrating no abnormal structures. **B:** Ictal EEG showing 3-Hz spikes and waves and multiple spikes. **C:** ECoG from the bifrontal region that did not indicate the lesional hemisphere of onset. Channels of right (blue) and left (red) hemispheres showed frequent spikes and waves. Figure is available in color online only.

ent distances between stimulus points and CCEP-positive electrodes. Based on latency analysis, we speculated that pathological CCEPs spread via the uncinate fascicles, in contrast to normal CCEPs that spread through the superior longitudinal fascicles (arcuate fasciculus [AF]).

We performed transvenous administration of propofol and maintained a level of > 80 on the bispectral index. During epilepsy surgery, we used two 20-channel grids to stimulate the frontal foci with continuous monitoring of pathological CCEPs on the temporal lobe (Fig. 3). We exposed the limen insulae to dissect the sylvian fissure. The key procedure was to widely expose the upper and anterior roof of the temporal horn after removal of the anterior part of the insular cortex. We finally exposed a 25-mm section of the left ventricle roof, indicating anatomical disconnection of the uncinate fascicles (Fig. 3B–D). After disconnection, pathological CCEPs disappeared (Fig. 4A–C), whereas normal CCEPs between the frontal and temporal

language areas were preserved (Fig. 4D and E). Postoperative DTI-based tractography demonstrated that the uncinate fiber was completely disconnected (Fig. 3D). Two years after the operation, the patient was seizure-free with no language impairment.

Case 2

A 28-year-old right-handed man began experiencing CPSs and GCSs with frequent absence seizures 10 years prior to surgery. Although multiple AED trials were administered, including valproic acid, phenobarbital, clonazepam, gabapentin, carbamazepine, levetiracetam, and lamotrigine, he continued to experience more than 5 seizures daily. Neuroimaging using MRI demonstrated no structural pathology (Fig. 5A). Twenty-four-hour video EEG monitoring demonstrated frequent 3-Hz spikes and waves from bilateral frontal lobes but did not clearly distinguish the epileptogenic hemisphere (Fig. 5B). The ECoG electrodes

FIG. 6. Case 2. **A:** Pathological CCEPs recorded from the left frontal lobe (red square) in response to stimulation of the right epileptogenic foci (red channels 8, 9, 10, 13, 14, 15, 18, 19, and 20). **B:** CCEP deflections (red square) over the right frontal channels. The CCEPs in this case consisted of 2 obvious deflections. Figure is available in color online only.

covering bifrontal, bitemporal, and orbitofrontal cortices revealed frequent spikes and waves from bilateral frontal lobes (Fig. 5C). It was thus difficult to determine the seizure-onset hemisphere, even on ECoG. Interictal bilateral spikes and waves and ictal spikes were randomly observed from both frontal lobes. Language HGA mapping showed active electrodes at the left middle and inferior frontal gyri, normal functional areas and left pathological foci partly overlapped by HGA mapping, ECS for language functions, and ECoG monitoring for epileptic foci.

Stimuli from electrodes 74, 75, and 76 on the right side evoked obvious pathological CCEPs from 9 channels (8, 9, 10, 13, 14, 15, 18, 19, and 20) of the contralateral hemisphere (Fig. 6). The first (N1) and second negative (N2) peaks were 24.4 and 55 msec after stimulation and approximately 100 μ V in amplitude (Fig. 6B). We stimulated the nonfunctional frontal channels for reference, and CCEPs were not induced anywhere. Combining tractography with the locations of positive ECoG channels and pathological CCEPs revealed a pathological network including the anterior corpus callosum (Fig. 7). Based on these results,

the patient and his family accepted partial anterior corpus callosotomy under continuous monitoring of pathological CCEPs. In the operating room, tractography-integrated neuronavigation and monitoring of bifrontal pathological CCEPs identified seizure-propagating projections through the anterior corpus callosum (Fig. 7).

We exposed the posterior border of the corpus callosum and started resection toward the anterior part with continuous CCEP monitoring. When we completed resection of the posterior border, CCEPs remained, but when we proceeded with anterior callosotomy, CCEP waveforms gradually decreased in amplitude with little latency change. When the resection reached the genu, CCEPs immediately disappeared (Fig. 7A). After resection, we recorded ECoG on the interhemispheric fissure and found no pathological activities. Real-time CCEP monitoring confirmed complete resection.

Thirty-six months after the operation, the patient was seizure free with administration of 800 mg/day of valproic acid, and he had started to work.

FIG. 7. Case 2. **A:** Dynamic changes in CCEP according to callosotomy. The resection procedure was performed from points 1 to 5 (arrows, left to right). Pathological CCEPs immediately diminished upon resection of point 3 and disappeared completely upon resection of point 5. **B:** Operation sketch showing the marked posterior border of the corpus callosum (blue dot and arrow) by neuronavigation. The callosotomy started from the posterior border to the anterior tip, exposing the cavity of the septum pellucidum (arrow). Copyright Kyouusuke Kamada. Published with permission. **C:** Tractography between CCEP responsive areas in bilateral hemispheres. **D and E:** Postoperative MR images demonstrating anterior corpus callosotomy (D) and biopsy on the left frontal lobe (E). Figure is available in color online only.

Case 3

A 32-year-old right-handed woman had suffered from intractable CPS for the last 12 years. Although radiological examinations demonstrated no structural abnormalities, video-EECoG monitoring demonstrated frequent right-dominant temporal spikes. ECoG monitoring revealed widespread epileptogenic activity on mesial and lateral temporal regions despite no radiological abnormality (Fig. 8A and B).

Picture-naming and word-reading HGA mapping revealed no activation on the right hemisphere. Face-recognition HGA mapping, however, showed strong responses on the strip posterior to the 8-channel grid, which covered epileptogenic foci (Fig. 8C). ECS with pairs of the strip induced prosopagnosia. The pathological CCEPs on the lateral aspect and mesial temporal lobe were evoked by stimulating the mesial and lateral parts of the temporal lobe, respectively; we found the bidirectional pathological CCEPs between them (Fig. 9).

The strategy was to resect the lesion with epileptogenic activity and pathological CCEPs, preserving the face-rec-

ognition area. We first performed selective hippocampectomy using a transsylvian approach with stimulation to the lateral aspect of the temporal lobe. After the hippocampectomy we continued to observe the pathological CCEPs on the temporal base. Therefore, we performed further resection, including the temporal base and anterolateral temporal lobe, with preservation of the face-recognition area (Fig. 9C and D).

Thirty months after operation, this patient had experienced only a simple partial seizure for a few seconds twice a year with administration of 1000 mg/day levetiracetam.

Case 4

A 31-year-old right-handed man had suffered from intractable CPS for the last 14 years. Although he has taken medication involving multiple AEDs for more than 10 years, he has suffered from CPSs twice a week and GCSs once a month. After graduation from barber's school, he was not able to complete training to become a barber because of epilepsy. Because his radiological examinations were all normal, he was introduced to our institute in 2015.

FIG. 8. Case 3. **A:** Electroencephalogram showing seizure-onset zones (channels 125–132) in the temporal base. **B:** Coronal MR image demonstrating no abnormality. **C:** Posterior 4-channel grid (green circle) detected strong face-recognition responses. Figure is available in color online only.

Video-EECoG monitoring demonstrated ictal right-dominant temporoparietal spikes. ECoG monitoring revealed ictal spikes on mesial and lateral temporal regions and was spread posteriorly. The pathological CCEPs on the lateral aspect and mesial temporal lobe were evoked by stimulating the mesial and lateral parts of the temporal lobe (channels 155, 156, 163, and 164), respectively. We found the bidirectional pathological CCEPs between them (channels 145, 148, 149, and 140 on the lateral temporal lobe; Fig. 10).

The strategy was to resect the lesion with epileptogenic activity and pathological CCEPs, similar to the procedure in Case 3. On the basis of pathological CCEP distribution we achieved complete resection of the lesion and the pathological CCEP cortices (Fig. 10D and E). Twenty-eight months after the operation, the patient had been seizure free with administration of 1000 mg/day levetiracetam and had begun his barber training.

Discussion

In this report, we describe CCEP measurement procedures to identify normal and aberrant functional con-

nectivity within the brains of patients with intractable epilepsy. CCEPs have become popular for confirming normal functional networks identified by other methods, and recent studies have demonstrated bedside CCEP-based mapping with ECS validation.^{5,16} In contrast, few studies have used CCEPs to identify pathological functional networks.^{3,5,11} To make surgical plans, we collated the results of video-EECoG monitoring and CCEPs. If we saw multi-foci on ECoG monitoring, we performed CCEP recording by stimulating the epileptogenic foci and searching the pathological CCEPs. If consistent CCEPs appeared between 2 foci, suggesting abnormal functional connections, we used DTI tractography to identify the anatomical connectome extraoperatively. We then started disconnection of the connectome with continuous monitoring of pathological CCEPs by intraoperatively stimulating one epileptogenic focus. We discussed each surgical strategy before the operation.

Two patients (Cases 1 and 2) showed rapid decreases in pathological CCEP amplitudes upon disconnection of the target area with the epileptic foci, which resulted in favorable seizure outcome. In particular, these patients

FIG. 9. Case 3. **A:** Electrocorticogram showing electrode configurations. Electrical stimulation (red circle pair) evoked pathological CCEPs on the superior temporal region (channels 97 and 98). **B:** The stimulation (red circle pair) on the temporal lobe widely evoked pathological CCEPs (channels 128–132). **C:** Postoperative axial MR image showing the minimum resection of the temporal lobe on the basis of the mapping results. **D:** Postoperative coronal MR image showing complete resection of the mesial and lateral part of the right temporal region. Figure is available in color online only.

demonstrated immediate diminishing of obvious pathological CCEPs after disconnection. Intraoperative CCEP monitoring during disconnection of pathological networks may reveal the underlying pathology and provide prognostic information on epilepsy outcome and functional preservation, such as language-related functions. Furthermore, combining CCEP monitoring with DTI-based tractography may guide surgical procedures for disruption of aberrant networks, aiding seizure propagation with the greatest possible preservation of normal function.

CCEP recording is widely used to visualize functional networks with no patient cooperation and tasks. Matsumoto et al. first reported that CCEP recording at the bedside is a valuable technique for detection of functional connectivity among various brain regions.¹⁵ Although CCEP investigation has shown great potential for clinical practice, electrical artifacts from single-pulse stimuli can interfere with interpretation of CCEP profiles and network analysis. We, therefore, accepted only responses from electrodes well separated from the stimulus electrode and used a ground electrode made of the same material (e.g., platinum) to minimize direct-current artifacts.²⁴ As a result,

we succeeded in recording CCEPs with little artifact both before and during surgery to identify normal and pathological networks and changes concomitant with resection.

Recently, several groups have used intraoperative CCEP recording for functional monitoring of language networks.^{25,26} Yamao et al.²⁶ reported that intraoperative CCEP recording enabled surgeons to monitor the dorsal language network in the operating room, even in anesthetized patients unsuitable for awake craniotomy. They stressed that CCEP is a dynamic marker of functional connectivity or integrity of the AF and that a 50% amplitude decline of early CCEP components (N1) may be a suitable cutoff value to prevent permanent language dysfunction due to AF impairment. Tamura et al. described a passive mapping procedure for intraoperative guidance consisting of 2 steps: linguistic HGA mapping with sounds and CCEP with paired electrical stimuli to the temporal receptive language area.^{20,25} Electric stimulation to the identified temporal receptive language area by linguistic HGA mapping evoked CCEPs in the frontal language area. ECS mapping of the areas with CCEP responses revealed deficits of language-related functions with high sensitivity. In

FIG. 10. Case 4. **A:** Axial MR image demonstrating no pathological findings on any sequences. **B:** Pathological CCEPs recorded from the right temporal base (red circles) by stimulation to the lateral temporal lobe (channels 145, 148, 149, and 150, which are marked by filled red ovals). **C:** Evoked CCEPs on 4 channels of the temporal base. **D and E:** Postoperative MR images revealing complete and extensive resection of the temporal lobe on the basis of pathological CCEP locations. Figure is available in color online only.

our previous study, we demonstrated that intraoperative CCEP recording is feasible and reliable. Ogawa et al.¹⁹ and several other groups proposed that HGA mapping reflects localized cortical processing,²⁰ while CCEPs can reflect bidirectional responses between widely dispersed language cortices.

In our previous study, we stressed the utility of “passive” mapping, combining HGA and CCEP recording during conscious resection of brain tumors.²⁵ In the present study, we concentrated on identifying pathological networks related to epilepsy by applying electrical stimuli to each focus at the bedside and in the operation room. Matsumoto et al. applied single-pulse stimuli to epileptic foci to probe focal excitability (epileptogenicity) and seizure networks for diagnosis.¹⁴ In addition, other reports using implanted subdural grids to identify epilepsy networks at the bedside have found abnormal connectivity between the bilateral hippocampus in patients with intractable epilepsy. However, the information gathered in these studies was not used to guide surgical strategy. In the present study, however, we achieved successful disconnection of the connectome among foci in 4 epilepsy cases using CCEPs, both at the bedside and during surgery, which led to good long-term seizure control and functional prognosis. Continuous CCEP monitoring confirmed completed resection of the connectome during surgery. Thus, we propose that

combined CCEP monitoring, HGA mapping, and tractography may be advantageous in some cases and so warrant larger-scale application and evaluation. Based on this small sample, we suggest our techniques are as effective as fMRI.^{2,7} However, interpretation of CCEP recordings can be technically challenging. Therefore, continuous monitoring during disconnection is recommended for confirmation.

Conclusions

HGA, CCEP, single-unit recording, and depth electrode recording are promising methods for epilepsy diagnosis, surgical planning, and intraoperative guidance. HGA and CCEP can be combined with tractography for network analysis at both structural and function levels. Such combined methodologies may provide treatment options to previously intractable epilepsy cases. It is incumbent upon clinicians to understand these methods and their potential as well as emerging experimental methodologies from physics and neuroscience.

Acknowledgments

This work was supported in part by Grant-in-Aid for Scientific Research (B) No. 16H05434 from 2016 to 2019, Grant-in-Aid for Exploratory Research No. 17K19708 from 2017 to 2018, and Grant-

in-Aid for Scientific Research on Innovative Areas JP 17H05900 from 2017 to 2018 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

References

- Alarcón G, Martínez J, Kerai SV, Lacruz ME, Quiroga RQ, Selway RP, et al: In vivo neuronal firing patterns during human epileptiform discharges replicated by electrical stimulation. **Clin Neurophysiol** **123**:1736–1744, 2012
- Benuzzi F, Ballotta D, Mirandola L, Ruggieri A, Vaudano AE, Zucchelli M, et al: An EEG-fMRI study on the termination of generalized spike-and-wave discharges in absence epilepsy. **PLoS One** **10**:e0130943, 2015
- Constable RT, Scheinost D, Finn ES, Shen X, Hampson M, Winstanley FS, et al: Potential use and challenges of functional connectivity mapping in intractable epilepsy. **Front Neurol** **4**:39, 2013
- Crone NE, Sinai A, Korzeniewska A: High-frequency gamma oscillations and human brain mapping with electrocorticography. **Prog Brain Res** **159**:275–295, 2006
- Enatsu R, Kubota Y, Kakisaka Y, Bulacio J, Piao Z, O'Connor T, et al: Reorganization of posterior language area in temporal lobe epilepsy: a cortico-cortical evoked potential study. **Epilepsy Res** **103**:73–82, 2013
- Engel J Jr: A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. **Epilepsia** **42**:796–803, 2001
- Fahoum F, Lopes R, Pittau F, Dubeau F, Gotman J: Widespread epileptic networks in focal epilepsies: EEG-fMRI study. **Epilepsia** **53**:1618–1627, 2012
- Kamada K, Ogawa H, Saito M, Tamura Y, Anei R, Kapeller C, et al: Novel techniques of real-time blood flow and functional mapping: technical note. **Neurol Med Chir (Tokyo)** **54**:775–785, 2014
- Kamada K, Todo T, Masutani Y, Aoki S, Ino K, Takano T, et al: Combined use of tractography-integrated functional neuronavigation and direct fiber stimulation. **J Neurosurg** **102**:664–672, 2005
- Kamada K, Todo T, Ota T, Ino K, Masutani Y, Aoki S, et al: The motor-evoked potential threshold evaluated by tractography and electrical stimulation. **J Neurosurg** **111**:785–795, 2009
- Kramer MA, Cash SS: Epilepsy as a disorder of cortical network organization. **Neuroscientist** **18**:360–372, 2012
- Luo C, Li Q, Lai Y, Xia Y, Qin Y, Liao W, et al: Altered functional connectivity in default mode network in absence epilepsy: a resting-state fMRI study. **Hum Brain Mapp** **32**:438–449, 2011
- Maneshi M, Moeller F, Fahoum F, Gotman J, Grova C: Resting-state connectivity of the sustained attention network correlates with disease duration in idiopathic generalized epilepsy. **PLoS One** **7**:e50359, 2012
- Matsumoto R, Kunieda T, Nair D: Single pulse electrical stimulation to probe functional and pathological connectivity in epilepsy. **Seizure** **44**:27–36, 2017
- Matsumoto R, Nair DR, LaPresto E, Bingaman W, Shibasaki H, Lüders HO: Functional connectivity in human cortical motor system: a cortico-cortical evoked potential study. **Brain** **130**:181–197, 2007
- Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibasaki H, et al: Functional connectivity in the human language system: a cortico-cortical evoked potential study. **Brain** **127**:2316–2330, 2004
- Morris JJ, Noll BC, Henderson KW: High-connectivity networks and hybrid inorganic rod materials built from potassium and rubidium p-halide-substituted aryloxides. **Inorg Chem** **47**:9583–9591, 2008
- Negishi M, Martuzzi R, Novotny EJ, Spencer DD, Constable RT: Functional MRI connectivity as a predictor of the surgical outcome of epilepsy. **Epilepsia** **52**:1733–1740, 2011
- Ogawa H, Kamada K, Kapeller C, Hiroshima S, Prueckl R, Guger C: Rapid and minimum invasive functional brain mapping by real-time visualization of high gamma activity during awake craniotomy. **World Neurosurg** **82**:912.e1–912.e10, 2014
- Ogawa H, Kamada K, Kapeller C, Prueckl R, Takeuchi F, Hiroshima S, et al: Clinical impact and implication of real-time oscillation analysis for language mapping. **World Neurosurg** **97**:123–131, 2017
- Pittau F, Dubeau F, Gotman J: Contribution of EEG/fMRI to the definition of the epileptic focus. **Neurology** **78**:1479–1487, 2012
- Pittau F, Grova C, Moeller F, Dubeau F, Gotman J: Patterns of altered functional connectivity in mesial temporal lobe epilepsy. **Epilepsia** **53**:1013–1023, 2012
- Sinai A, Bowers CW, Crainiceanu CM, Boatman D, Gordon B, Lesser RP, et al: Electrocorticographic high gamma activity versus electrical cortical stimulation mapping of naming. **Brain** **128**:1556–1570, 2005
- Tallgren P, Vanhatalo S, Kaila K, Voipio J: Evaluation of commercially available electrodes and gels for recording of slow EEG potentials. **Clin Neurophysiol** **116**:799–806, 2005
- Tamura Y, Ogawa H, Kapeller C, Prueckl R, Takeuchi F, Anei R, et al: Passive language mapping combining real-time oscillation analysis with cortico-cortical evoked potentials for awake craniotomy. **J Neurosurg** **125**:1580–1588, 2016
- Yamao Y, Suzuki K, Kunieda T, Matsumoto R, Arakawa Y, Nakae T, et al: Clinical impact of intraoperative CCEP monitoring in evaluating the dorsal language white matter pathway. **Hum Brain Mapp** **38**:1977–1991, 2017

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Kamada, Takeuchi, Guger. Acquisition of data: Ogawa, Prueckl, Hiroshima, Tamura. Analysis and interpretation of data: Prueckl, Takeuchi. Critically revising the article: Kapeller. Study supervision: Guger.

Correspondence

Kyousuke Kamada, Department of Neurosurgery, Asahikawa Medical University, 2-1, Midorigaoka-Higashi, Asahikawa, Hokkaido, 078-8510, Japan. email: kamady-k@umin.ac.jp.