Cortico-cortical evoked potential by single-pulse electrical stimulation is a generally safe procedure

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Title: Cortico-cortical evoked potential by single-pulse electrical stimulation is a generally safe procedure

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Highlights

1) Although rare, ADs and clinical seizures were more frequently triggered within SOZ.

2) Stimulation intensity did not seem to be a risk factor of ADs and clinical seizures.

3) Cortico-cortical evoked potential is a generally safe procedure.

Abstract (199/200 words)

Objective: Cortico-cortical evoked potential (CCEP) by single-pulse electrical stimulation (SPES) is useful to investigate effective connectivity and cortical excitability. We aimed to clarify the safety of CCEPs.

Methods: We retrospectively analyzed 29 consecutive patients with intractable partial epilepsy undergoing chronic subdural grid implantation and CCEP recording. Repetitive SPES (1 Hz) was systematically applied to a pair of adjacent electrodes over almost all electrodes. We evaluated the incidences of afterdischarges (ADs) and clinical seizures.

Results: Out of 1283 electrode pairs, ADs and clinical seizures were observed in 12 and 5 pairs (0.94% and 0.39%, per electrode pair) in 7 and 3 patients (23.3% and 10.0%, per patient), respectively. Of the 18-82 pairs per patient, ADs and clinical seizures were induced in 0-4 and 0-3 pairs, respectively. Stimulating 4 SOZ (2.5%) and 8 non-SOZ pairs (0.75%) resulted in ADs. We observed clinical seizures in stimulating 4 SOZ (2.5%) and 1 non-SOZ pair (0.09%). The incidence of clinical seizures varied significantly between SOZ and non-SOZ stimulations (p=0.001), while the difference in AD incidence tended towards significance (p=0.058).

Conclusion: Although caution should be taken in stimulating SOZ, CCEP is a safe procedure for presurgical evaluation.

Significance: CCEP is safe under the established protocol.

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Key words: cortico-cortical evoked potential, single-pulse electrical stimulation, afterdischarge, clinical seizure

Abbreviations: SPES = single-pulse electrical stimulation; CCEP = cortico-cortical evoked potential; SOZ = seizure-onset zone; AD = afterdischarge.

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1. Introduction

Neuronal networks, specifically cortico-cortical networks between functionally important areas, are necessary for various functional processing in the human brain. In patients with epilepsy, the normal functional networks can be partly altered, leading to epileptic seizures. Understanding normal functional and abnormal (epileptic) networks is necessary for the development of neuroscience and epilepsy therapy, especially for the patients who have epilepsy surgery.

Cortical responses to direct, single-pulse electrical stimulation (SPES) have been used to evaluate normal functional networks, abnormal networks, and cortical excitability. Since Buser and Bancaud et al. evaluated the direct cortical responses in patients undergoing neurosurgery (Buser et al., 1969; Buser and Bancaud, 1983), various groups have investigated the responses elicited by SPES since the advent of modern digital EEG technology around 2000. European groups have mainly focused on the late responses that were induced with delays of more than 100 ms after SPES (Valentin et al., 2002; Valentin et al., 2005). In our previous studies, we investigated the early responses by SPES, named cortico-cortical evoked potentials (CCEPs), to electrically trace cortico-cortical connections *in vivo* (Matsumoto et al., 2004; Matsumoto et al., 2007). Although CCEPs have only been investigated in patients with epilepsy or tumors who undergo invasive

presurgical evaluation, they have been extensively used to evaluate the cortico-cortical networks associated with various normal brain functions (Matsumoto et al., 2004; Matsumoto et al., 2007; Greenlee et al., 2007; Conner et al., 2011; Matsumoto et al., 2012; Terada et al., 2012; Matsuzaki et al., 2013; Entz et al., 2014; Matsumoto et al., 2017), as well as to evaluate cortical excitability associated with epileptogenicity (Matsumoto et al., 2005; Iwasaki et al., 2010; Enatsu et al., 2012; Usami et al., 2015; Kobayashi et al., 2017).

In general, direct electrical stimulation of the cerebral cortex can induce electroencephalographic seizure patterns termed afterdischarges (ADs), as well as clinical seizures (Adrian, 1936). The safety of high-frequency (~50 Hz) stimulation for functional brain mapping has been investigated (Cherlow et al., 1977; Bernier et al., 1990; Lesser et al., 1984; Blume et al., 2004; Kalamangalam et al., 2014; Suzuki et al., 2018), whereas that of SPES (usually 1 or <1 Hz of stimulus frequency) for CCEP has not, even though CCEPs are widely used in both research and clinical practice. In the present study, we aimed to clarify the safety of CCEPs in the human cerebral cortex by evaluating the occurrences of stimulus-induced ADs and clinical seizures as indices of safety. It is important to confirm its safety, particularly because the seizure-onset zones (SOZs) are stimulated to evaluate the epileptogenicity.

2. Materials and methods

2.1. Patient profiles

We retrospectively recruited 29 consecutive patients (12 women, 17 men; age range: 16-61 years) with medically intractable partial epilepsy who underwent presurgical chronic subdural grid (SDG) implantation and CCEP recordings between April 2010 and March 2017. The patient profiles are summarized in Table 1. Because the noninvasive evaluations showed unclear ictal onset in the scalp EEG and normal brain MRI, Patient 1 underwent the SDG implantation twice; the first implantation was bilateral and aimed to lateralize the seizure onset (Patient 1, 1st SDG implantation) and the second was to localize the seizure onset (Patient 1, 2nd SDG implantation). In total, CCEP recordings were performed 30 times in 29 patients.

The intracranial subdural electrodes were made of platinum and had a recording diameter of either 2.3 mm (Ad-Tech, Rachine, WI, USA) or 3.0 mm (Unique Medicall Co. Ltd, Tokyo, Japan). The center-to-center electrode distance was 1.0 cm, except for 4 patients with a 0.5 cm distance for clinical needs (Patients 11, 18, 19, and 20). In 7 patients (Patients 11, 13, 14, 15, 16, 17, and 23), depth electrodes were implanted in addition to the SDG; however, we only focused on the stimuli on and recordings by SDG electrodes.

The precise electrode locations were confirmed by co-registration of the subdural electrodes to three-dimensional, volume-rendered MRIs, reconstructed from MPRAGE (magnetization prepared rapid acquisition with gradient echo), which were examined after electrode implantation. Using the 2D-MRI, we identified the electrode locations in relation to the major cortical sulci by using its signal void due to the property of platinum electrodes. The details of this methodology for identifying the electrode location have been described elsewhere (Matsumoto et al., 2003; Matsumoto et al., 2004).

This study was approved by the ethical board of our institute (institutional review board numbers: 443 and C1212). Written informed consent was obtained from all participants and their families before the CCEP examinations.

2.2. CCEP recording

CCEP recordings were performed after the clinical seizure had been recorded and the dosages of antiepileptic drugs (AEDs) had been returned to normal levels in all patients except for 2 patients (Patients 17 and 25) in whom spontaneous clinical seizures were not recorded during the period of SDG implantation, despite a drastic decrement of AEDs. The methodological details of CCEP have been reported elsewhere (Matsumoto et al., 2004; Matsumoto et al., 2007). Repetitive SPES (a square wave pulse 0.3 ms in duration) of 1 Hz was systematically applied to a pair of two adjacent

electrodes over almost all electrodes on both the SOZ and non-SOZ using constant-current stimulation devices (MEE-1232 or PE-210A, Nihon Kohden, Tokyo, Japan). We selected the electrode pairs for stimulation, ensuring that 1) the 2 electrodes did not cross the sulcus and that 2) the electrodes to be stimulated would not be duplicated. Adjacent electrode pairs were stimulated without arbitrary selections, except when recording from a particular electrode was technically compromised. The total numbers of implanted SDG electrodes and SPES pairs per patient are shown in Table 1. The SOZs were defined by the earliest ictal ECoG changes (at least within 5 s of the initial changes), the resection area, and clinical outcome. Although Patient 25 had no spontaneous seizure, she did present a stimulus-induced habitual seizure. After surgical removal of the areas including the pair that induced seizure and showing earliest ECoG changes during the stimulus-induced seizure, she has been seizure free for more than 2 years. For this reason, we defined the resected areas as the SOZ in this patient. The total numbers of SPESs on the SOZ and non-SOZ in each patient are listed in Table 1. Each pair of electrodes was stimulated 60-100 times per session, with an intensity of 4-15 mA. Typically, the CCEP response consists of early N1 (first negative component with a peak latency of 10-50 ms) and late N2 (second negative component with a peak latency of 100-200 ms) (Matsumoto et al., 2004; Matsumoto et al., 2017; Matsumoto and Kunieda, 2018). In this safety study, we did not focus on the waveforms of CCEP responses (N1 and N2), but on

whether the SPES for CCEP evoked an AD or a clinical seizure. CCEP was recorded by setting the sampling rate of ECoG at 1000 or 2000 Hz (EEG-1100 or -1200, Nihon Kohden, Tokyo, Japan) and a band-pass filter at 0.08-300 or 600 Hz. The reference electrode was placed on the skin of the mastoid, contralateral to the SDG electrodes. During the CCEP recording, the patients were awake and remained still.

2.3. Identification of ADs and clinical seizures as indices of safety

We used ADs and stimulus-induced clinical seizures as indices of safety in CCEP recording. ADs were defined as rhythmic activities and/or repetitive spikes that lasted at least 5 s. Clinical seizures were defined as ADs that showed evolution in distribution, frequency, amplitude, and morphology with clinical symptoms. At our institute, at least 2 board-certified neurologists and EEGers always carefully observe the patient and monitor the ECoG when recording the CCEP to check for ADs and clinical seizures. Therefore, all ADs and clinical seizures induced by SPES in this study were detected during the CCEP recordings. We did not intervene with medications for ADs or clinical seizures unless the seizures evolved into focal to bilateral tonic-clonic seizure. We only intervened by administering intravenous diazepam to one patient (Patient 25) whose induced seizure evolved into a focal to bilateral tonic-clonic seizure. Brief bursts of pulse electrical stimulation were not performed during CCEP recordings.

We examined the stimulus site, the duration of the EEG changes, and the location and distribution of the EEG changes in relation to the stimulus site and SOZ. In addition, we evaluated whether the EEG changes were consistent with the spontaneous seizure in all cases of clinical seizures and ADs. We evaluated the location and distribution of the EEG changes by reviewing whether they involved the adjacent (<2 cm from the stimulus site), near (2-5 cm from the stimulus site), and remote (>5 cm from the stimulus site or in a different lobe from the stimulus site) electrodes.

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 25.0 software (IBM Japan, Tokyo, Japan). Fisher's exact test (two-tailed) was used to assess the differences between the SOZ and non-SOZ for both ADs and clinical seizures. As non-parametric tests, Mann-Whitney U test and Kruskal-Wallis test were used to evaluate differences between the groups. In all tests, we considered $p<0.05$ to be statistically significant.

3. Results

3.1. Profiles of stimulus electrode pairs

In total, 1283 electrode pairs were stimulated (mean: 42.8 ± 13.9, range: 18-82 pairs per CCEP recording). In 28 patients with an identified SOZ (all except for Patient 17), SPES was delivered to 162 pairs on the SOZ, and to 1067 pairs in the non-SOZ (Table 1).

3.2. ADs

ADs were induced by stimulating 12 electrode pairs (0.94%) in 7 patients (23.3% of all the 30 recordings) (Table 1). Out of the 18-82 electrode pairs per patient, ADs were induced in 0-4 pairs (0-14.8%). Among the 12 ADs, 4 were induced by SPES on the SOZ (4/162; 2.5%) and 8 were induced by SPES on the non-SOZ (8/1067; 0.75%), indicating that ADs tended to appear on the SOZ than on the non-SOZ, although the difference was not significant (p=0.058). Regarding the sites of SPES that induced ADs, 7 pairs were located in the mesial temporal lobe (MTL), 2 in the lateral temporal lobe, 2 in the lateral frontal lobe (outside the perirolandic area), and 1 in the perirolandic area.

The EEG characteristics of all ADs and clinical seizures are summarized in Table 2. The duration of EEG changes ranged from 9 to 519 seconds (median: 44.5 seconds) across the 12 ADs. The EEG changes

involved only the adjacent electrodes in 3 ADs (2 in SOZ stimulation and 1 in non-SOZ stimulation), the adjacent and near electrodes in 6 ADs (2 in SOZ stimulation and 4 in non-SOZ stimulation), adjacent, near, and remote electrodes in 2 ADs (2 in non-SOZ stimulation), and only the remote electrodes within the SOZ in 1 AD (non-SOZ stimulation). All 4 ADs induced by SOZ stimulation involved the SOZ, while 5 out of the 8 ADs induced by non-SOZ stimulation involved the SOZ. Only 1 AD was consistent with the EEG changes seen in the spontaneous seizure; all others were inconsistent in the following ways: narrower distribution was observed in 6 ADs, partial overlap with the changes in the spontaneous seizure occurred in 2 ADs, and different locations with no overlap was seen in 3 ADs.

3.3. Stimulus-induced clinical seizures

Clinical seizures were induced by stimulation of 5 electrode pairs (0.39%) in 3 patients (10.0% of all the 30 recordings) (Table 1). Of the 18-82 pairs per patient, stimulus-induced clinical seizures occurred in 0-3 pairs (0-13.6%). A representative ECoG of stimulus-induced clinical seizure is shown in Figure 1 (Patient 3). Of the 5 clinical seizures, 4 were induced by the SPES on the SOZ (4/162; 2.5%) and 1 was induced by the SPES on the non-SOZ (1/1067; 0.09%). This difference was significant between SOZ and non-SOZ stimulation ($p=0.001$). The only non-SOZ stimulus site that induced a clinical seizure was adjacent to the SOZ. Another representative ECoG of

stimulus-induced clinical seizure (Patient 25) is presented in Figure 2. We administered intravenous diazepam to this patient when her seizure progressed into focal to bilateral tonic-clonic seizure. She recovered to baseline within 10-15 minutes and presented with no permanent adverse events in either neurological examination or ECoG findings after the stimulus-induced seizure. All 5 stimulus-induced seizures were habitual in terms of both clinical and EEG aspects in each patient. Among the 5 sites of SPES that induced clinical seizures, 4 were in the perirolandic area and the other 1 was in the MTL.

The duration of EEG changes ranged from 51-241 seconds (median: 142 seconds) in the 5 clinical seizures. As such, the changes lasted significantly longer than those of ADs ($p=0.019$). In all stimulus-induced clinical seizures, the EEG changes involved the adjacent, near, and remote electrodes, including the SOZ. These EEG changes were consistent with those in the spontaneous seizures except in Patient 25, whose spontaneous seizures were not recorded.

3.4. Stimulus intensities

The mean stimulus intensities for the SOZ and non-SOZ were 9.5 ± 1.7 mA and 9.5 ± 1.4 mA (mean ± S.D.), respectively, indicating no significant difference between SOZ and non-SOZ stimulation ($p=0.84$ by Mann-Whitney U test).

Among the 1283 SPES electrode pairs, 5 presented clinical seizures and 12 presented ADs; the remaining 1266 showed neither. To investigate whether stimulus intensity influenced the induction of ADs and stimulus-induced clinical seizures, we compared the stimulus intensity among the 3 groups. The mean stimulus intensity was 9.3 ± 1.3 mA (mean ± S.D.) in the pairs presenting AD, 11.0 ± 3.3 mA in the pairs presenting stimulus-induced clinical seizure, and 9.5 ± 1.4 mA in the pairs that showed neither. There were no significant differences in stimulus intensity between any of the 3 groups (p=0.153 by Kruskal-Wallis test).

4. Discussion

The present study evaluated the safety of SPES in the CCEP study by evaluating the occurrence rates of ADs and stimulus-induced clinical seizures. Among the 1283 electrode pairs of SPESs from the 29 epilepsy patients with chronic SDG implantation, ADs were induced in 7 patients (23.3% of the examined patients) by stimulating 12 electrode pairs (0.94% of the pairs stimulated); clinical seizures were induced in 3 (10.0%) by stimulating 5 electrode pairs (0.39%). We revealed significant differences between SOZ and non-SOZ stimulation with regards to the incidence of ADs and stimulus-induced clinical seizures per electrode pair stimulated. There were no differences in stimulus intensity between the SOZ and non-SOZ, nor were there any differences in intensity among stimuli that caused ADs, clinical seizures, and neither.

4.1. ADs and clinical seizures by SPES

No studies have verified the correlation between SPES and ADs or stimulus-induced clinical seizures. On the other hand, several studies have investigated the relationship between high-frequency electrical stimuli (~50 Hz) and ADs. Blume et al. reported that ADs were elicited by 12% of high-frequency electrical stimuli in each of their examined patients, and that these ADs evolved to clinical seizures in 48.3% of the patients (Blume et al., 2004).

Suzuki et al. recently reported that the rate of AD induction was 72% in all examined patients (Suzuki et al., 2018). In our patients, the occurrence rates of both ADs and stimulus-induced clinical seizures per electrode pair were 2.5% during SPES, even upon stimulating the SOZ, and the occurrence rates of ADs and clinical seizures per patient by SPESs were 23.3% and 10.0%, respectively. The occurrence rates of ADs and the details of electrical stimuli (stimulus sites, stimulus intensity, etc.) vary among studies. However, with regards to the occurrence rates, high-frequency stimuli for functional brain mapping can induce ADs and clinical seizures more frequently than SPES, most likely because the total electric charge is higher. In other words, SPES/CCEP is safe for presurgical and even intraoperative evaluations of normal functional connectivity and cortical excitability.

By reviewing EEG characteristics, we found that stimulus-induced seizures showed relatively longer EEG changes than ADs. All adjacent (including the SOZ), near, and remote electrodes were involved in all the induced clinical seizures. However, although the adjacent electrodes were involved in 11 and the near electrodes in 8 out of 12 ADs, the remote electrodes were in only involved in 3 of the ADs. All of the stimulus-induced seizures showed EEG changes consistent with those of spontaneous seizures. However, only 1 AD showed consistent EEG changes, while the others showed inconsistent EEG changes, including narrower distributions, partial overlaps, and different locations.

It has been reported that the CCEPs by SPES on or around the SOZ presented greater increment of the amplitude in the stimulus intensity versus CCEP N1 amplitude curve than those induced by SPES on the non-SOZ, probably because the epileptic focus has enhanced cortical excitability (Iwasaki et al., 2010). We previously reported the case of one patient with focal cortical dysplasia at the primary somatosensory area of the foot who showed unexpected induction of a habitual seizure during SPES on the SOZ to record CCEP (Matsumoto et al., 2005). Both SPES and paired-pulse stimulation revealed an enhancement of interictal intracortical inhibition and an increase in ictal cortical excitability at the focus. We revealed that SPES (0.9 Hz) decreased both epileptic seizures and interictal epileptiform discharges (Yamamoto et al., 2002; Yamamoto et al., 2006). These lines of evidence suggest that SPES on the SOZ can modulate the underlying cortical excitability.

Although the precise effects of SPES on the cerebral cortex have not been elucidated, several studies have provided clues to the underlying mechanisms. For instance, Alarcon et al. reported that SPES induced excitation immediately after stimuli and that this was occasionally followed by inhibition (Alarcon et al., 2012). By evaluating the CCEPs and their counterparts in high-frequency activities in the areas adjacent to the stimulus sites, as well as in remotely connected areas, we recently showed the pathological and physiological changes of high gamma power induced by

SPESs (Usami et al., 2015; Kobayashi et al., 2017). These dynamic transitions of cortical excitability induced by SPES may partly influence the ADs and stimulus-induced clinical seizures, resulting in differences in their occurrence rates between SOZ and non-SOZ stimulation, as seen in the present study. The mechanisms by which direct cortical stimuli, including SPES and high-frequency stimuli, modulate cortical excitability needs to be clarified in future studies.

4.2. Clinical implications and limitations

We demonstrated that CCEP is a safe procedure to evaluate physiological and pathological brain connectivity and excitability, although the careful monitoring of clinical symptoms and ECoG is indispensable. In one patient (Patient 25), the SOZ was detected using a stimulus-induced seizure when no spontaneous seizures were captured after AED reduction. Only one out of 55 electrode pairs of SPESs induced a habitual seizure. As in this representative patient, stimulus-induced clinical seizures could be used to delineate the epileptogenic zone. Although even our 1-Hz SPES did cause the clinical seizures, high-frequency (50 Hz) electrical stimulation induced clinical seizures more frequently than SPES (Blume et al., 2004; Suzuki et al., 2018). Based on our experiences, we can evaluate the motor function of the perirolandic area even with SPES by observing the induced repetitive twitches at the frequency of SPES in awake patients. SPES is likely safer

than high-frequency (50 Hz) electrical stimulation to map the normal function of the primary motor area in patients whose the epileptogenic zone is in the perirolandic area.

The present study had some limitations. Firstly, although SPES was safe for the patients in that the overall occurrence rates of ADs (0.94%) and stimulus-induced clinical seizures (0.39%) were relatively low, we could not evaluate in detail the possible precipitating factors, such as the cortical architecture and the pathology at the stimulus site, because of the small incidence number. The threshold for ADs is reportedly lower in stimulation of the perirolandic area than that of the other areas in high-frequency stimulation for functional brain mapping (Lesser et al., 1984). Even though SPES on the perirolandic areas and MTL structures showed a slight tendency to induce ADs and clinical seizures in the present study, it was difficult to perform any statistical tests due to the small numbers of ADs and stimulus-induced seizures. Secondly, we only evaluated the ADs and stimulus-induced clinical seizures in patients with SDG because the number of the patients with depth electrodes was limited. Thirdly, the occurrence rates of ADs and stimulus-induced clinical seizures per patient (23.3% and 10.0%, respectively) were not as low as those per electrode pair stimulated (0.94% and 0.39%, respectively). However, of the 18-82 electrode pairs per patient, ADs and clinical seizures were induced in 0-4 pairs (0-14.8% of the stimulated pairs) and 0-3 pairs (0-13.6%), respectively, indicating the

relatively low occurrence rates within each patient. In addition, because high-frequency stimuli for functional mapping can induce ADs and clinical seizures much more frequently than SPES (Blume et al., 2004; Suzuki et al., 2018), CCEPs by SPES is a relatively safe procedure.

Despite these limitations, we consider the investigation clinically valuable. Further evaluations of ADs and stimulus-induced clinical seizures using SPES on both SDG and depth electrodes including stereoelectroencephalogram in a larger number of patients may further support the safety of CCEP and develop its clinical potential.

5. Conclusion

Although caution should be taken when stimulating the SOZ and its surroundings, CCEP by SPES is generally a safe procedure. Unexpected stimulus-induced seizures can help delineate the epileptogenic zone.

Conflict of interest

Department of Epilepsy, Movement Disorders and Physiology (Kyoto University Graduate School of Medicine) is the Industry-Academic Collaboration Courses, supported by Eisai Co., Ltd., NIHON KOHDEN CORPORATION, Otsuka Pharmaceutical Co., and UCB Japan Co., Ltd.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure Legends

Figure 1: A representative ECoG of stimulus-induced clinical seizure (Patient 3)

A: Ictal ECoG induced by SPES on the pair of electrodes on the precentral gyrus (C19-C20). Repetitive spikes appeared on the B plate, followed by paroxysmal fast occurring on the C plate (shown in the magenta frames). The patient showed a habitual seizure characterized by right foot twitches. The recording band-pass filter was 0.08-600 Hz and the filter for display is 1.6-50 Hz.

B: Configuration of implanted SDG electrodes. SOZs defined by the initial ictal ECoG changes in the spontaneous seizure are shown as red circles.

Abbreviations: ECoG = electrocorticogram; SPES = single-pulse electrical stimulation; SDG = subdural grid; SOZ = seizure-onset zone.

Figure 2: A representative ECoG of stimulus-induced clinical seizure (Patient 25)

A: In this patient (Patient 25), SOZ was not conventionally identified because spontaneous seizure did not occur despite AED reduction. One electrode pair of SPESs (A12-A17) induced a habitual seizure that included hyperventilation and right face twitches. This finally evolved to focal to bilateral tonic-clonic seizure. Clear ictal ECoG changes are highlighted by the

frames in magenta. The surgical removal of the areas including the pair that induced the seizure and showed the earliest ECoG changes during the induced seizure led to seizure freedom for more than 2 years. The recording band-pass filter was 0.08-300 Hz and the filter for display is 1.6-50 Hz. B: Configuration of implanted SDG electrodes. Probable SOZs, defined by this stimulus-induced clinical seizure, are shown as orange circles. Abbreviations: SOZ = seizure-onset zone; SPES = single-pulse electrical stimulation; AC-PC line = anterior commissure – posterior commissure line; VAC line = line vertical to the AC-PC line through the AC; Rt = right; AED = antiepileptic drug; ECoG = electrocorticogram; SDG = subdural grid.

Table 1: Patient profile

Patient	Age and gender	Epilepsy	Etiology	Implanted SDG electrodes	Total SPES pairs	SPES pairs for SOZ stim (ADs and clinical seizures)	SPES pairs for non-SOZ stim (ADs and clinical seizures)
1 (1st SDG)	23F	Rt FLE	FCD IA	52	27	3	24
1 (2nd SDG)	23F	Rt FLE	FCD IA	44	24	3	21
2	23M	Rt OLE	FCD IIA	52	18	2	16
3	40M	Lt F-PLE	Mixed oligoastrocytoma	56	22	5 (3 clinical seizures)	17 (1 AD)
4	22M	Lt F-TLE	Gliosis (F), FCD IA (T)	66	36	7	29 (1 clinical seizure)
5	44M	Rt FLE	Mixed oligoastrocytoma, FCD IA	48	26	2	24
6	24M	Lt FLE	FCD IB	100	50	10	40
7	17F	Lt TLE	FCD IB	60	34	6	28
8	29M	Lt TLE	HS, FCD IA	102	51	4 (2 ADs)	47 (1 AD)
9	34M	Rt P-TLE	Posttraumatic change (P), HS (T), Scar (T)	82	55	9	46
10	38F	Lt TLE	FCD IIA	88	44	3	41
11	28F	Rt PLE	Low grade neuroepithelial tumor	48	28	3	25
12	55M	Lt TLE	Diffuse astrocytoma	56	27	4 (1 AD)	23 (3 ADs)
13	41F	Lt TLE	FCD IA	102	49	4	45
14	52M	Lt TLE	Arteriovenous malformation, Gliosis, Inflammatory infiltration	110	38	10	28 (1 AD)
15	27F	Rt TLE	FCD IA	76	40	2	38
16	27F	Rt PLE	FCD IIB	72	36	7	29
17	39M	Lt FLE	FCD IIB	108	54	n.a.	n.a.
18	45M	Lt FLE	FCD IA	104	50	3	47
19	61M	Lt PLE	Oligoastrocytoma	106	58	8	50 (1 AD)
20	30F	Rt TLE	FCD IIA, Mild gliosis	102	40	2	38
21	28F	Lt TLE	Non-neoplastic brain tissue	106	55	5 (1 AD)	50
22	39M	Rt TLE	HS, FCD IA	90	48	3	45
23	29M	Rt FLE	FCD IA	100	58	8	50
24	21M	Lt TLE	HS, FCD IA	82	53	12	41
25	16F	Lt FLE	Dysmorphic neuroepithelial tumor	92	55	6 (1 clinical seizure)	49
26	41M	Lt TLE	HS, FCD IA	92	47	12	35 (1 AD)
27	16M	Rt F-T-PLE	FCD IC	162	82	4	78
28	39F	Lt FLE	FCD IIB	68	36	9	27
29	23F	Lt PLE	FCD IIB	84	42	6	36
Total					1283		
Total except for Patient 17					1229	162 (4 ADs and 4 clinical seizures)	1067 (8 ADs and 1 clinical seizure)

SPES, single-pulse electrical stimulation; SOZ, seizure onset zone; stim, stimulation; AD, afterdischarge; SDG, subdural grid; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy; PLE, parietal lobe epilepsy; TLE, temporal lobe epilepsy; FCD, focal cortical dysplasia; HS, hippocampal sclerosis; n.a., not available

Table 2: EEG characteristics of stimulus-induced clinical seizures and ADs

Patient	Event	Stimulus site (anatomical location)	Stimulus intensity (mA)	Duration of EEG changes (sec)	Involvement of adjacent electrode (<2 cm)	Involvement of near electrode (2-5 cm)	Involvement of remote electrode (>5 cm or other lobes)	Involvement of SOZ	Consistency of propagation pattern with spontaneous seizure
3	Clinical seizure	SOZ (PCL)	12	180	+	+	+	+	Consistent
3	Clinical seizure	SOZ (PrCG)	6	51	+	+	+	+	Consistent
3	Clinical seizure	SOZ (PrCG)	15	241	+	+	+	+	Consistent
25	Clinical seizure	SOZ (PrCG)	10	142	+	+	+	+	(no spontaneous seizure)
4	Clinical seizure	non-SOZ (Ento)	12	104	+	+	+	+	Consistent
8	AD	SOZ (Ento)	10	50	+	-	-	+	Inconsistent: narrower distribution
8	AD	SOZ (Ento)	6	44	+	-	-	+	Inconsistent: narrower distribution
12	AD	SOZ (Ento)	8	14	+	+	-	+	Inconsistent: narrower distribution
21	AD	SOZ (Ento)	10	28	+	+	-	+	Inconsistent: narrower distribution
3	AD	non-SOZ (PrCG)	8	61	+	+	-	+	Inconsistent: narrower distribution
8	AD	non-SOZ (IFG)	10	34	-	-	+	+	Inconsistent: narrower distribution
12	AD	non-SOZ (IFG)	10	94	+	+	-	-	Inconsistent: different locations
12	AD	non-SOZ (FuG)	10	45	+	+	-	+	Consistent
12	AD	non-SOZ (ITG)	10	9	+	-	-	-	Inconsistent: different locations
14	AD	non-SOZ (Ento)	10	80	+	+	+	+	Inconsistent: partial overlap
19	AD	non-SOZ (FuG)	10	34	+	+	-	-	Inconsistent: different locations
26	AD	non-SOZ (ITG)	10	519	+	+	+	+	Inconsistent: partial overlap

AD, afterdischarge; SOZ, seizure onset zone; PCL, paracentral lobule; PrCG, precentral gyrus; Ento, entorhinal cortex; IFG, inferior frontal gyrus; FuG, fusiform gyrus; ITG, inferior temporal gyrus