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Characteristics and clinical impact of stimulation-evoked seizures during extra-operative cortical mapping

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Abstract

Extra-operative electrocortical stimulation mapping (ESM) is used to identify functional cortex prior to epilepsy surgery, with the goal of preserving function postoperatively. Although attempts are made to avoid stimulation-evoked seizure activity, the clinical impact of these events with regard to safety, clinical utility, functional outcome and even disruption to the procedure itself is unknown. We conducted a retrospective review of 57 patients with pharmacoresistant focal epilepsy who underwent intracranial electrode implantation and ESM. Stimulation-evoked seizures (afterdischarges associated with clinical signs or symptoms) occurred in 19 patients (33%). Mapping sessions were disrupted for 11 of these patients (i.e., 19% of the full sample and 58% of the subgroup of patients with stimulation-evoked seizures). Patients who had ESM disruption were no less likely than patients without ESM disruption to be seizure-free at one year ($p = 0.63$) and two years ($p = 0.57$) postoperatively. Among 23 patients who underwent language assessment pre- and postoperatively, 4 (17%) had evoked seizures that disrupted language mapping; these patients were no more likely to show postoperative language declines relative to those had no ESM disruption ($p = 0.26$). Results suggest that evoked seizures occur frequently during ESM and can disrupt the procedure; however, these events do not appear to adversely affect postoperative outcomes. Nevertheless, attempts should be made to limit stimulation-evoked seizures in order to reduce patient discomfort, increase efficiency, and maximize the utility of ESM.

Keywords

cortical stimulation; functional brain mapping; epilepsy surgery; language; epilepsy; neuropsychology

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Disclosures

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1. Introduction

Surgical resection, an effective treatment for pharmacoresistant focal epilepsy, carries a risk of functional loss¹. When subdural electrodes are implanted to identify the area of seizure onset, extra-operative electrocortical stimulation mapping (ESM) is often conducted to identify critical language, motor, and sensory areas prior to resection.² These areas are typically spared with the goal of preserving function postoperatively.³

During ESM, a current applied to a functional cortical area either elicits a positive response or disables a specific function. Electrical stimulation can elicit afterdischarges (ADs)⁴, i.e., electrographic activity that resembles trains of spontaneous epileptiform discharges, and at times, ADs evolve into actual seizures associated with clinical signs and symptoms. Despite their regular occurrence, little is known about the effects of stimulation-evoked seizures on the procedure and clinical context. It would be useful for clinicians to know how often this potential consequence of ESM occurs, and moreover, the extent to which it may delay electrode explantation or affect surgical outcome. Researchers utilizing ESM or related procedures may also benefit from having this information which may be necessary for regulatory approvals. We sought to characterize stimulation-evoked seizures and determine the extent to which these events disrupt the procedure, and potentially, influence postoperative outcomes.

2. Methods

2.1 Subjects

We conducted a retrospective review of 57 patients with pharmacoresistant focal epilepsy who underwent long-term intracranial electrode implantation and extra-operative ESM at the Columbia Comprehensive Epilepsy Center between 1997 and 2012 (see Table 1). Patients were included if their records included documentation of the number of electrodes tested and sites at which seizures were evoked. On admission, patients were taking an average of 2.4 ± 0.8 anti-epileptic drugs (AEDs).

2.2 Data Collection

Subdural electrodes were stimulated with a constant current stimulator (Grass S12 prior to 2009, Ojemann after 2009). All subdural arrays used in this study had 1 cm center-to-center spacing. Non-overlapping adjacent electrode pairs were tested first (e.g. 1–2, then 3–4). If a functional pair was identified, each electrode was re-tested by pairing with a nearby electrode that was cleared for function. Pulse trains lasted up to 5 seconds with a pulse width of 200, 250, or 500 microseconds and frequency of 10, 20, or 50 Hz. Current was set initially at 1–5 mA and increased by 1–2 mA per stimulation until the target maximum (8–15 mA depending on the type of mapping) or until ADs were evoked. Seizures were defined as trains of ADs that evolved and spread, and were associated with clinical symptoms such as (but not limited to) sensations typical of a seizure aura or behavioral arrest.

During ESM, an EEG technologist reviewed the live EEG recording. When ADs occurred, the epileptologist attempted to stop them from developing into seizures by applying brief

bursts of stimulation at varying frequencies. Notes from the mapping sessions were used to determine whether sessions were discontinued prematurely.

2.3 Data Analysis

Sites at which evoked seizures occurred were quantified for each patient. Seizures were classified as focal or secondarily generalized based on descriptions recorded by the treating epileptologists at the time of mapping⁵. Also at the time of mapping, the treating epileptologists reviewed the video EEG record and determined whether stimulation-evoked seizures resembled the patient's habitual events.

Eleven patients (19%) had standard temporal lobe resections, 39 patients (68%) had tailored resections, two patients (4%) had subpial transections, and five patients (9%) did not have any surgical intervention. Seizure outcome was documented by an epileptologist at one and two years postoperatively. Patients were classified as seizure-free (Engel Class I) or not seizure-free (Engel Class II, III, or IV)⁶.

Language was assessed via three naming tests (Boston Naming Test (BNT)⁷, Auditory Naming Test (ANT)⁸, and Visual Naming Test (VNT)⁸, pre- and postoperatively, for a subset of patients. Reliable change indices (RCI) for each test were used to determine whether the change in each patient's score from pre- to postoperative testing was clinically meaningful. The RCI provides an upper bound estimate of score variation due to normal fluctuations and practice effects⁹. Language decline was defined as greater than or equal to an RCI value of change on at least one of the three naming tests.

3. Results

1737 electrode pairs were tested (mean 30.5 ± 13.4 pairs per patient). A total of 56 clinical seizures were evoked at 57 electrode pairs in 19 patients (33%). Four patients (7%) had secondarily generalized seizures. Twelve of the patients with stimulation-evoked seizures (63%) had seizures with semiology resembling their habitual seizures, and three patients (16%) had atypical seizures. Video data was not accessible for the remaining four patients (21%).

Evoked focal seizures with or without loss of awareness, but without secondary generalization, disrupted mapping in seven patients (47% of patients with seizures, 12% of all patients). Secondarily generalized seizures disrupted mapping in four patients (100% of patients with secondarily generalized seizures, 7% of all patients). Patients with and without disruption did not differ significantly with respect to demographic, seizure, or ESM-related variables (see Table 1). Among the 11 patients whose mapping sessions were disrupted due to stimulation-evoked seizures, mapping was subsequently restarted in seven patients (63.6%). Twenty-four additional patients had multiple mapping sessions for reasons other than evoked seizures, including persistent ADs, over-sedation, fatigue, or scheduling issues.

There was no significant group difference in the proportion of seizure-free (Engel Class I) patients between those who had evoked seizures and those who did not at one year (chi-square test, $p = 0.35$) or two years (chi-square test, $p = 0.12$) postoperatively. Similarly,

there was no significant group difference in the proportion of seizure-free patients between those who had ESM disruption due to stimulation-evoked seizures and those who did not at one year (chi-square test, $p = 0.63$) or two years (chi-square test, $p = 0.57$) postoperatively.

Twenty-three patients completed pre- and post-operative naming assessment. Among these patients, 22 patients completed the BNT, 21 completed the ANT, and 20 completed the VNT. Nine patients (39%) had evoked seizures. Four of these patients (17%) had evoked seizures that disrupted mapping. Nine patients (39%) exhibited postoperative naming decline. There was no significant difference in the proportion of patients who declined between those who had an evoked seizure (4 of 9) and those who did not (5 of 14; Fisher's exact test, $p = 1.00$). Similarly, there was no difference in the proportion of patients who declined between those who had ESM disruption due to stimulation-evoked seizures (3 of 4) and those who did not decline (6 of 19; Fisher's exact test, $p = 0.26$).

4. Discussion and Conclusions

Seizures evoked by stimulation, defined as afterdischarges that evolved and were associated with clinical symptoms, are a frequent complication of the ESM procedure, occurring in a third of the current sample. Often, they resulted in premature discontinuation of the mapping session, which presumably delayed completion of the full procedure. Certainly, these disruptions are inconvenient in the context of patient care, and are likely unpleasant for the patient; however, we did not find evidence that stimulation-evoked seizures contributed to adverse outcomes.

In our retrospective review, there was no evidence of direct harm to the patients from the evoked seizures. In most cases, the seizures were typical of the patient's habitual events, and the majority of evoked seizures remained focal. Secondarily generalized seizures were uncommon, although when they did occur, they invariably ended the mapping session. None of the evoked seizures in this sample progressed to status epilepticus. While this would be considered a serious complication of ESM with the potential for persistent adverse effects¹⁰, it appears fortunately to be very rare.

In theory, evoked seizures could hamper the quality of the data obtained during ESM. Specifically, evoked seizures might disrupt mapping to the extent that either: 1) inadequate functional mapping might result in inadvertent removal of essential language cortex and postoperative language decline, or, 2) due to concerns of removing functional cortex, inability to complete functional mapping (i.e., failure to identify areas that are not essential for function) might limit the resection, resulting in poorer seizure outcome. We did not find evidence of either outcome in this small series. Patients who had mapping sessions discontinued were equally likely to be seizure-free at one and two years postoperatively, and patients who had language mapping discontinued were no more likely to exhibit postoperative language decline. These results might suggest that clinical management of ESM disruption can minimize the risk of adverse surgical outcomes.

We caution that our sample was relatively small, and therefore, this study may have lacked sufficient power to detect meaningful group differences. Nevertheless, it is hoped that the

current study will serve to motivate investigators to conduct a larger, more comprehensive, prospective studies aimed to reduce the risk of stimulation-evoked seizures, and overall, determine the techniques and procedures necessary to optimize the ESM procedure.

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Highlights

- Seizures were evoked in 1/3 of patients during extra-operative cortical mapping.
- Mapping was disrupted in 58% of patients who had stimulation-evoked seizures.
- Mapping disruption was not associated with adverse seizure or language outcomes.

Table 1
Demographic and clinical characteristics of patients with and without ESM disruption due to stimulation-evoked seizures

	All patients	Disruption	No Disruption	
Number of subjects	57	11	46	
Gender	30 female 27 male	8 female 3 male	22 female 24 male	p = 0.14
Age in years	30.5 ± 12.5	25.6 ± 7.6	31.6 ± 13.2	p = 0.06
Age at seizure onset in years	14.6 ± 8.3	16.6 ± 7.6	14.1 ± 8.5	p = 0.36
Education level in years	13.1 ± 3.3	13.5 ± 3.6	13.0 ± 3.3	p = 0.69
History of focal seizures	50 patients	9 patients	41 patients	p = 0.61
History of secondarily generalized seizures	40 patients	8 patients	32 patients	p = 1.00
Implant location	Left (42 patients) Right (12 patients) Bilateral (3 patients)	Left (8 patients) Right (3 patients) Bilateral (0 patients)	Left (34 patients) Right (9 patients) Bilateral (3 patients)	p = 0.62
Language mapping performed	45 patients	9 patients	36 patients	p = 1.00
Motor mapping performed	27 patients	5 patients	22 patients	p = 0.75
Sensory mapping performed	11 patients	1 patient	10 patients	p = 0.54
Standard temporal lobectomy	11 patients	3 patients	8 patients	p = 0.43