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Is Spontaneity Overrated? The Value of Cortical Stimulation–Induced Seizures

Association of Cortical Stimulation-Induced Seziure With Surgical Outcome in Patients With Focal Drug-Resistant Epilepsy

Cuello Oderiz C, von Ellenrieder N, Dubeau F, et al. *JAMA Neurol*. 2019.

Importance: Cortical stimulation is used during presurgical epilepsy evaluation for functional mapping and for defining the cortical area responsible for seizure generation. Despite wide use of cortical stimulation, the association between cortical stimulation–induced seizures and surgical outcome remains unknown. Objective: To assess whether the removal of the seizure-onset zone resulting from cortical stimulation is associated with a good surgical outcome. Design, Setting, and Participants: This cohort study used data from 2 tertiary epilepsy centers: Montreal Neurological Institute in Montreal, Quebec, Canada, and Grenoble Alpes University Hospital in Grenoble, France. Participants included consecutive patients (n = 103) with focal drug-resistant epilepsy who underwent stereoelectroencephalography between January 1, 2007, and January 1, 2017. Participant selection criteria were cortical stimulation during implantation, subsequent open surgical procedure with a follow-up of 1 or more years, and complete neuroimaging data sets for superimposition between intracranial electrodes and the resection. Main Outcomes and Measures: Cortical stimulation–induced typical electroclinical seizures, the volume of the surgical resection, and the percentage of resected electrode contacts inducing a seizure or encompassing the cortical stimulation–informed and spontaneous seizure-onset zones were identified. These measures were correlated with good (Engel class I) and poor (Engel classes II-IV) surgical outcomes. Electroclinical characteristics associated with cortical stimulation–induced seizures were analyzed. Results: In total, 103 patients were included, of whom 54 (52.4%) were female, and the mean (standard deviation) age was 31 (11) years. Fifty-nine (57.3%) patients had cortical stimulation–induced seizures. The percentage of patients with cortical stimulation–induced electroclinical seizures was higher in the good outcome group than in the poor outcome group (31 [70.5%] of 44 vs 28 [47.5%] of 59; $P = .02$). The percentage of the resected contacts encompassing the cortical stimulation–informed seizure-onset zone correlated with surgical outcome (median [range] percentage in good vs poor outcome: 63.2% [0%-100%] vs 33.3% [0%-84.6%]; Spearman $\rho = 0.38$; $P = .003$). A similar result was observed for spontaneous seizures (median [range] percentage in good vs poor outcome: 57.1% [0%-100%] vs 32.7% [0%-100%]; Spearman $\rho = 0.32$; $P = .002$). Longer elapsed time since the most recent seizure was associated with a higher likelihood of inducing seizures (>24 hours: 64.7% vs <24 hours: 27.3%; $P = .04$). Conclusions and Relevance: Seizure induction by cortical stimulation appears to identify the epileptic generator as reliably as spontaneous seizures do; this finding might lead to a more time-efficient intracranial presurgical investigation of focal epilepsy as the need to record spontaneous seizures is reduced.

Commentary

Cortical stimulation (CS)–induced seizures were first reported during the early days of neurosurgery when intraoperative electrical CS elicited patient's habitual auras.[1,2] Since then CS has been used to delineate the epileptogenic zone (EZ) in patients undergoing invasive presurgical investigations for pharmacoresistant epilepsy. The EZ has been defined as the region that produces the complete ictal electroclinical pattern.[3] Most of the data published on CS-induced seizures are restricted to anecdotal reports, and what is available relates mostly to stimulation studies using stereoelectroencephalography (SEEG). Until now the clinical utility of CS-elicited seizures to delineate the EZ was not well established because it had not been methodically investigated.

Two main schools of thought have been recognized: One born in France where CS-induced seizures have been routinely used as part of the invasive surgical workup and have helped define the EZ since the work of Bancaud and Talairach,[3,4] and another born in North America where epileptologists, influenced by Penfield's work, do not traditionally rely on the use of CS-induced seizures in the invasive surgical workup. In the North American approach, CS-induced seizures have largely been considered the by-product of CS procedures aimed at defining eloquent cortex, and many centers do not systematically perform CS to elicit seizures due to concern that symptoms may arise from areas remote to the stimulated site.

Cuello Oderiz and colleagues addressed this CS dilemma in the article that is the subject of this commentary. Their main objective was to assess whether removal of the seizure-onset zone identified by CS is associated with a good surgical outcome. This in turn would prove the utility of CS-induced seizures in the identification of the EZ. They performed a retrospective analysis of a 10-year SEEG data set from the Montreal Neurological Institute and the Grenoble Alpes University Hospital. A total of 103 patients who underwent SEEG for presurgical evaluation with >1 year postsurgical follow-up were included in the study. Both their spontaneous seizures and the CS-induced seizures were analyzed. All patients underwent CS while receiving their home antiepileptic medications to decrease the likelihood of inducing atypical electroclinical seizures, and at least 24 to 48 hours after implant to avoid the effects of electrode insertion. Atypical seizures were rare in their sample, with only 7.8% (8/102) and 1.5% (1/66) of patients experiencing them at 50 Hz and 1 Hz stimulation, respectively. This is important because it is not clear whether nonhabitual CS-induced seizures have any diagnostic value.[5]

Both centers performed CS at 1 Hz and 50 Hz, and both used electrical currents of up to 5 mA in mesial temporal structures and 8 mA in the neocortex. They were able to induce electroclinical seizures in 57.3% (59/103) of patients, with a median response rate of 2 (range: 1-13) CS-induced seizures per patient. Curiously, 3 patients had CS-induced seizures exclusively at 1 Hz. The median current required to induce electroclinical seizures was 2 mA (range: 0.3-4). A significant difference in the median current was found between stimulating at 1 Hz and at 50 Hz, with higher current (3 [2-3] mA) needed when stimulating at lower frequency (vs 2 [0.3-4] mA; $P < .001$) in order to induce seizures. However, a potential benefit of stimulating at low frequency first is the lower occurrence of after-discharges if high-frequency stimulation is avoided. Previous reports suggested that not only high-frequency CS had a greater chance of eliciting habitual seizures but also produced more unexpected clinical responses.[6] The investigators also found a higher likelihood of CS-induced seizures in patients whose most recent seizure was more than 24 hours before stimulation (63.9% for patients with >24 hours vs 25.0% for patients with <24 hours; $P = .02$).

The investigators hypothesized that CS-induced seizures provide similar information regarding the EZ as spontaneous seizures. They evaluated the performance of the CS-informed seizure-onset zone for the delineation of the EZ by calculating the percentage of the induced seizure-onset zone contacts that were resected and correlating this information with postsurgical seizure outcomes. They analyzed coregistered magnetic resonance and computer tomography images of electrode contacts and resection cavities. On the basis of the superposition of the surgical cavity with the seizure-onset zone electrodes, they calculated the percentage of resected seizure-onset zone contacts for the spontaneous and CS-informed seizures and the percentage of resected channels inducing typical electroclinical seizures. The percentage of patients with a CS-induced seizure was higher in the good outcome group (Engel class I) compared to the poor outcome group (Engel classes II-IV) with 70.5% (31/44) vs 47.5% (28/59; $P = .02$), respectively. In addition, the median percentage of resected CS-informed seizure-onset contacts was higher in the good than in the poor outcome group (63.2% [0%-100%] vs 33.3% [0%-84.6%]; $P = .003$). A similar result was observed for spontaneous seizures with 57.1% (0%-100%) resected seizure-onset contacts in the good and 32.7% (0%-100%) in the poor outcome groups ($P = .002$). These data suggested that inducing a seizure was helpful in defining the EZ and also corroborated that the electrodes implanted covered the EZ appropriately.

This study provides solid evidence about the utility of CS-induced seizures in identifying the EZ and provides a guide for its CS mapping with SEEG. But there are some known limitations to this technique. In CS-induced seizures, ideally the symptoms are generated during the stimulation, and before significant propagation of the electrical discharge, which ensures close colocalization of the symptomatogenic area. However, sometimes spontaneous seizures arise in relatively silent areas of cortex and the initial symptom of the habitual seizures occurs during the propagation of the ictal activity, thus a CS-induced aura matching typical symptomatology can falsely localize the noneloquent EZ. In addition, after-discharges (epileptiform discharges elicited by and outlasting CS) may briefly propagate to areas functionally connected to the EZ and produce symptoms consistent with habitual auras by activating areas distant to the stimulated electrodes. In this case, the CS-induced habitual aura can falsely localize to the stimulated electrodes. Of note, a previous study on after-discharges did not find any consistent relationship between the site of stimulus eliciting after-discharges and that of spontaneously appearing seizures.[6] Although the reader is encouraged to use the aid of CS-induced seizures to define the EZ, this should always occur after developing a good understanding of the patient's habitual ictal symptomatology and in the context of previously captured spontaneous habitual seizures ideally with SEEG (or with scalp electroencephalography if the seizures cannot be spontaneously captured on SEEG). Epileptologists who are in need of capturing seizures within a short time frame due to the patient-driven factors, such as increased risk of complications, may consider CS with the purpose of inducing habitual seizures as long as they take into consideration the limitations of this technique.

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