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Case Report

Multimodal approach leads to seizure-freedom in a case of highly refractory drug-resistant focal epilepsy

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ABSTRACT

Drug-resistant, nonlesional, extratemporal lobe focal epilepsy can be difficult to treat and may require a high degree of multidisciplinary teamwork to localize the seizure onset zone for resective surgery. Here, we describe a patient with longstanding drug-resistant, nonlesional, extratemporal focal epilepsy with a high seizure burden who became seizure-free after prolonged evaluation and eventual left frontal cortical resection. Prior evaluations included magnetoencephalography, invasive video-EEG monitoring, and implantation of a responsive neurostimulation (RNS) device for ongoing intracranial stimulation. Highly sophisticated techniques were utilized including stereotactic localization of prior evaluations to guide repeat stereo-EEG (SEEG), electrical stimulation mapping, SEEG-guided radiofrequency ablation, and awake resection with language and motor mapping using a cognitive testing platform. Incorporating a wide array of data from multiple centers and evaluation time periods was necessary to optimize seizure control and minimize the risk of neurological deficits from surgery.

Introduction

Approximately 30–35% of patients with epilepsy will have drug-resistance, where seizures persist despite treatment with at least two appropriately chosen anti-seizure medications (ASMs) at adequate doses [1]. Carefully selected patients with drug-resistant focal epilepsy may respond to resective epilepsy surgery. Patients who have nonlesional and extratemporal lobe epilepsy have lower rates of excellent outcomes than those with either a lesion on MRI or temporal lobe epilepsy [2,3]. Advanced techniques can be used to understand prior evaluations, plan epilepsy surgery to optimize seizure control and limit deficits from resective surgery. This includes the consideration of repeat stereo-EEG monitoring in patients who already have undergone this in the past to determine candidacy for resective surgery. Electrical stimulation mapping (ESM) through SEEG electrodes can be used to map eloquent cortex. This can be followed by radiofrequency ablation of the seizure onset zone (SOZ), which has the potential to lead to seizure reduction or transient seizure freedom that has prognostic implications for future resection [4]. The risk of permanent neurological deficits can be reduced with awake resections with language and motor mapping. We describe a case where these techniques were employed and resulted in seizure freedom in a patient with a complex epilepsy history.

Case presentation

A 50-year-old left-handed man presented to the epilepsy clinic for evaluation of longstanding drug-resistant focal epilepsy (Fig. 1A). Seizure onset was at 16 years of age with no risk factors for epilepsy. The patient reported one semiology which consisted of an aura of anxiety or euphoria; following this he would slump into the fetal position in either direction and make high-pitched vocalizations. There was occasional loss of awareness. Historically, with some seizures he would run around the room, scream, or jump on the bed; however, these behaviors were no longer present.

Abbreviations: ASMs, anti-seizure medications; EMU, epilepsy monitoring unit; ESM, electrical stimulation mapping; RNS, responsive neurostimulation; SEEG, stereo-EEG; SOZ, seizure onset zone; SMA, supplementary motor area.

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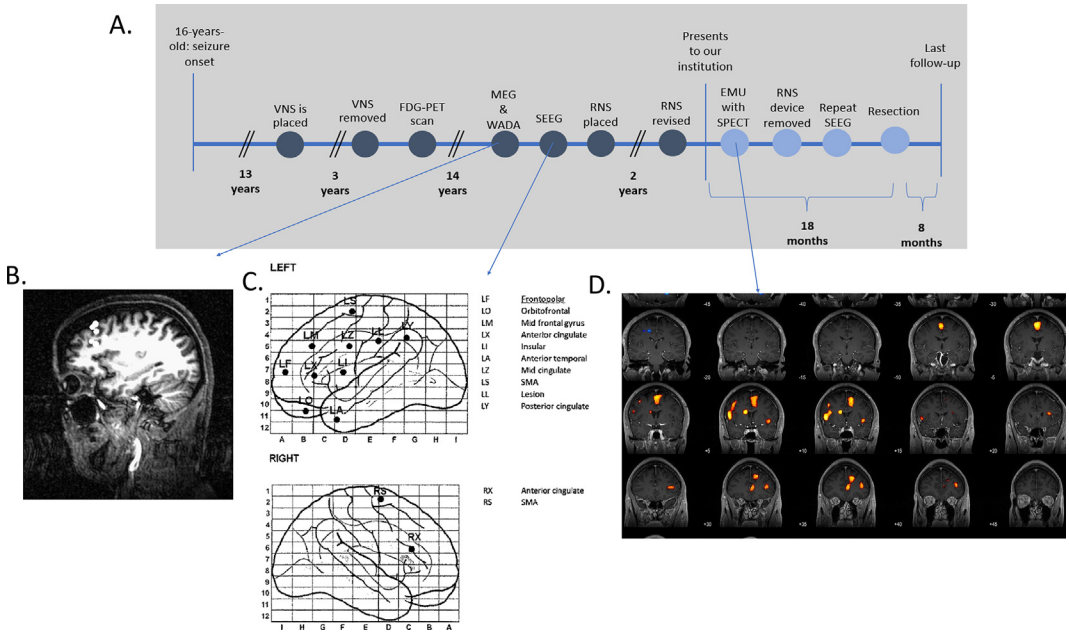


Fig. 1. Timeline and prior SEEG. A. Timeline showing the prior epilepsy evaluation and treatment in addition to the management at our institution. B. MEG (sagittal view) showing left frontal interictal activity. C. Schematic showing the prior SEEG primarily targeting the left frontal region which was completed at an outside institution. D. SPECT result from the epilepsy monitoring unit at our institution showing multiple areas of hyperperfusion, including in the left frontal region.

Seizures lasted for 2–8 min and occurred multiple times daily, with around 100 seizures per month. Despite a high seizure burden, the patient was able to maintain full-time employment and functioned at a high level.

He had previous triala of numerous ASMs, and at presentation to our institution was on a combination of three ASMs. A vagus nerve stimulator had been previously placed, was deemed ineffective, and subsequently removed. He had undergone extensive evaluations at outside institutions (Fig. 1), including magnetoencephalography (Fig. 1B), a Wada test which showed left language dominance, and stereo-EEG (SEEG) monitoring targeting the left frontal region 2 years prior (Fig. 1C) which recorded numerous seizures of left frontal onset (in the mesial portion of the left superior frontal gyrus; contacts LM2-4, and LS 1–2). Due to concerns related to disruption of language function and insufficient seizure onset localization, a resection was not performed and a responsive neurostimulator (RNS) was implanted to target the area of presumed SOZ including a left frontal depth electrode and two cortical strip electrodes targeting the lateral frontal cortex and the supplementary motor area (SMA) (Fig. 2A and 2B). The depth electrode and the lateral cortical strip were initially connected to the RNS device. Due to lack of efficacy, two years later during RNS battery replacement, the lateral cortical strip was disconnected and the cortical strip targeting the SMA region was connected.

Two months after initial presentation, the patient was admitted to our epilepsy monitoring unit (EMU) and was noted to have left frontal spikes and sharp waves during sleep. Sixteen seizures with the typical semiology of grimacing followed by suddenly falling in one direction, curling into the fetal position, and making high-pitched vocalizations were captured with onset maximal over the left frontocentral region (Fig. 2C). In addition, the patient had multiple subtle clinical seizures during sleep lasting 5–10 s occurring up to 10 times an hour with varying clinical manifestations, including arousal, turning to the side, fidgeting, oral automatism, or grimacing with a similar EEG onset to the more typical clinical seizures. Subtraction ictal single-photon emission computed tomography (SPECT) coregistered to MRI (SISCOM) performed during a clinical seizure showed multiple small nonspecific areas of hyperperfusion including the left medial frontal region (Fig. 1D).

Despite efforts at optimizing RNS stimulation parameters and ASMs, the patient's seizure burden remained fairly constant. Eight months following his inpatient scalp monitoring his RNS device was removed in preparation for a second SEEG evaluation. Due to adhesions and significant scarring, the two cortical strips and depth electrode were left in place. One year following initial presentation, the patient underwent repeat SEEG evaluation (Fig. 3A).

A combination of the prior work-up, including magnetoencephalography (showing left frontal interictal activity) and previous SEEG, in addition to the recent scalp EEG and SISCOM was used to plan repeat invasive monitoring with denser coverage over the left frontal region than the initial SEEG (Fig. 3A). As part of his presurgical evaluation, he also completed a neuropsychological evaluation, which revealed primarily deficits in learning and memory for both verbal and visual information as well as cognitive slowing and difficulty with executive function (i.e. set-shifting, problem-solving). Overall, his profile was compatible with involvement of frontal networks.

During SEEG monitoring, 16 typical clinical seizures and numerous subtle clinical seizures (similar to the ones seen in the EMU) were recorded. On SEEG, onset involved polyspikes primarily at contacts within in the superior frontal gyrus in the pre-SMA and SMA region including LE 6–8, LP 12–17, and LV 12–17 with early involvement of LEN 9–10, LN 8–9, LY 14–15, LF 4–5 and 9–10 (Fig. 3B). The ictal pattern was similar to what was seen on the first SEEG (Fig. 3D). There were also frequent synchronous polyspike discharges seen at the same contacts interictally. The patient underwent extra-operative ESM for motor and language mapping purposes (pulse rate 50 Hz, pulse duration 0.2 ms, train duration 3 s, current intensity 1–5 mA). With stimulation of LP 12–13 and LP 14–15, there was speech arrest and eye deviation to the right. No neurological deficits were present with stimulation of the other areas of SOZ. Stimulation produced brief afterdischarges at LN 4–5 and LF 3–4 but no seizures. Just prior to explantation, radiofrequency ablation of LE 5–8, LV 12–17, LEN 8–10 was performed [5]. After ablation, the patient had 14 days of seizure freedom,

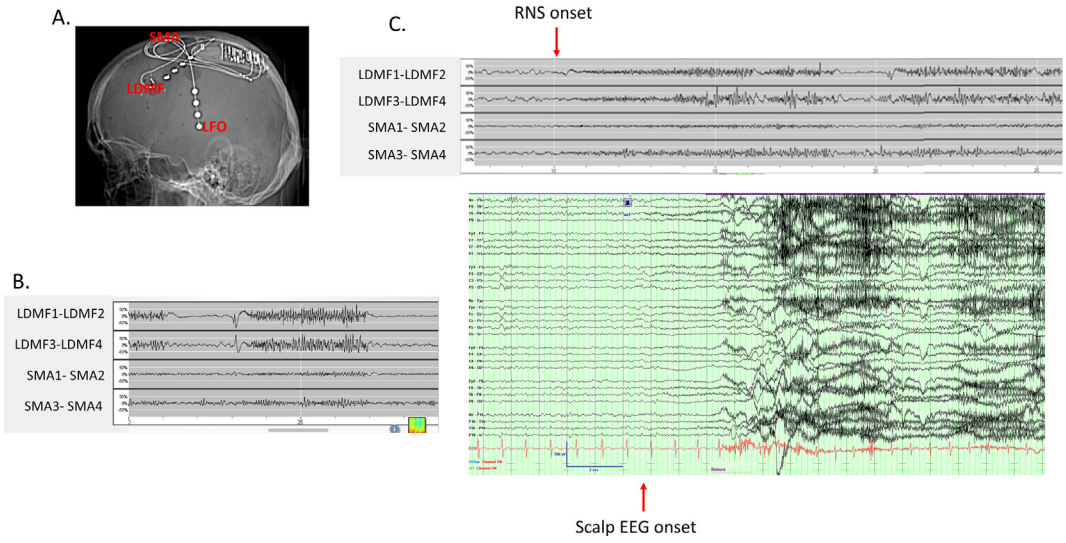


Fig. 2. RNS data. A. CT showing the configuration of the previously placed RNS leads. Initially the left frontal depth (LDMF) and the lateral frontal cortical strip (LFO) were placed. However, due to lack of efficacy, LFO was disconnected and a strip over the supplementary motor area (SMA) was placed. There was an attempt at lead removal, but due to adhesions, this was not possible. B. RNS EEG data showing presumed seizure activity (or robust interictal activity) in the LDMF leads, consisting of a spike-wave complex followed by a high frequency discharge. C. Simultaneously acquired RNS ECoG (top) and scalp EEG (longitudinal bipolar montage) from EMU admission (bottom). Seizure onset in RNS occurs in LDMF electrode and precedes scalp onset by around 1 s. Ictal activity resembles that observed at other times in the RNS data (as in panel B).

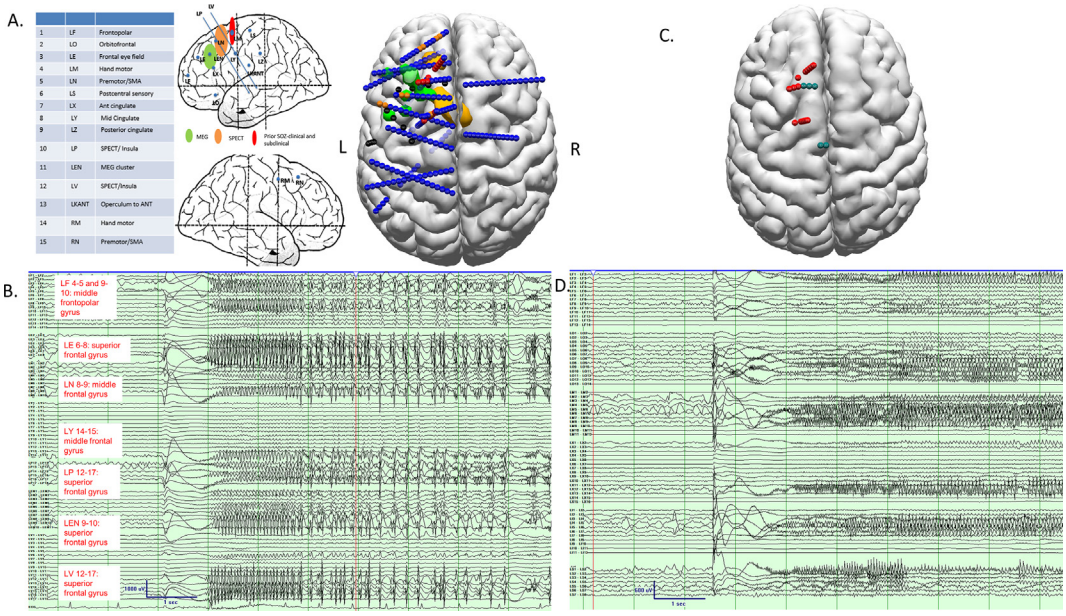
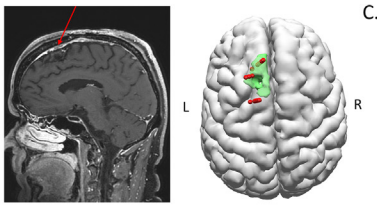


Fig. 3. SEEG implantation and ictal SEEG pattern. A. Schematic of the SEEG plan at our institution. The target of each electrode is seen in the table next to the figure showing the relationship of SEEG trajectories to the MEG, SPECT, and prior SEEG results. The image demonstrates that there was much denser left frontal coverage with the second SEEG targeting the supplementary motor area than with the first SEEG. An axial view of the schematic of SEEG implantation is also shown. With the axial view, the region highlighted in orange shows the area of the SPECT abnormality and green the area of the MEG cluster. The SEEG leads highlighted in red were associated with seizure onset and those in orange with early seizure spread. The leads in black display the location of the RNS. B.SEEG from the second implantation in bipolar montage showing a typical seizure, with many leads omitted to focus on the most active leads. C. Brain schematic comparing the presumed seizure onset from the first SEEG (green dots) to the seizure onset determined by the SEEG at our institution (red dots). D. SEEG from the first implantation done at an outside institution showing the similar pattern of ictal onset. SEEG parameters: low frequency filter: 1 Hz, high frequency filter: 70 Hz, notch: 60 Hz, sensitivity: 10 uV/mm, time base: 30 mm/*sec*. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

which was the longest period of seizure freedom since the onset of his seizures. However, seizures then recurred with a frequency up to 2 or more per day.

The patient subsequently underwent an awake focal cortical resection of the SOZ (Fig. 4A) with language and motor mapping using the tablet-based cognitive testing platform know as the "NeuroMapper" developed by David Sabsevitz, Ph.D.; Mayo Clinic, Jacksonville, FL and Medical College of Wisconsin) [6]. Language tasks included a verb generation task, non-word repetition, and picture naming. Motor function was monitored by assessing praxis and motor sequencing and planning tasks (e.g. Luria Motor Sequence). When the patient demonstrated motor sequencing and planning errors near the posterior border of the resection cavity along the superior frontal gyrus (near the location of LP contacts), it was deemed that the maximal safe resection had been reached. Post-operatively it was noted that the patient had tran-

A.



B.

	Presurgical	Postsurgical
Seizure frequency	100/month	0/month (seizure free)
Seizure severity (1/least severe - 10/most severe)	8	N/a
Quality of life (1/least satisfied - 10/most satisfied)	6	10
Sleep (1/worst - 10/best)	9	10

C.

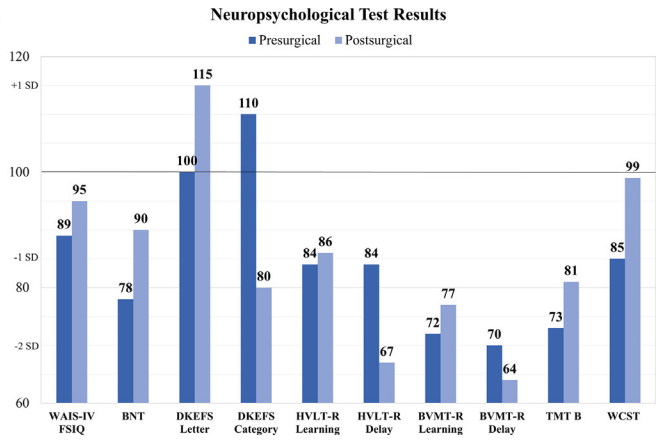


Fig. 4. Outcome information. A. Post-operative MRI showing expected postoperative changes from left frontal lobe corticectomy (arrow). In addition, a brain schematic shows the area of seizure onset determined by SEEG in relationship to the area of resection (green). B. Difference in seizure frequency and severity, quality of life and sleep from prior to and after surgery. C. Results of both presurgical and postsurgical neuropsychological testing showing mild differences in postsurgical testing compared to presurgical testing, with slightly more difficulty with verbal learning and memory and decline in semantic fluency. However, there was also mild improvement on measures of naming, lexical fluency, and executive function. Abbreviations: BNT = Boston Naming Test; BVMT-R = Brief Visuospatial Memory Test – Revised; DKEFS = Delis-Kaplan; Executive Function System; HVLT-R = Hopkins Verbal Learning Test – Revised; N/a = not applicable; TMT B = Trail Making Test Part B; WAIS-IV FSIQ = Wechsler Adult Intelligence Scale 4th Edition, Full Scale IQ; WCST = Wisconsin Card Sorting Test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sient difficulty with expressive language and fine motor coordination of the right hand which resolved within 2 weeks. Pathology showed severe gliosis.

Post-operative neuropsychological testing showed mild differences compared to the pre-operative testing (Fig. 4C). There was slightly more difficulty with verbal learning and memory and decline in semantic fluency. However, there was also mild improvement on measures of naming, lexical fluency, and executive function. The patient denied any significant cognitive concerns or functional impairment in his daily life. The patient has remained seizure free (Engel IA/ILAE Class 1 outcome) throughout last follow-up (8 months after surgery) and showed subjective improvements related to seizure severity, quality of life, and sleep (Fig. 4B).

Discussion

We describe a patient with longstanding nonlesional epilepsy and a high seizure burden who eventually became seizure free with resection and no long-term functional deficits. Prior SEEG monitoring did not result in resective surgery due to concern for disruption of language function and insufficient localization. The current approach included stereotactic localization of results obtained at other centers, repeat SEEG monitoring following RNS explantation, ESM, SEEG-guided radiofrequency ablation, and awake resection with language mapping using NeuroMapper [6]. This case highlights that reoperation may yield favorable results in carefully selected and planned cases.

Seizure semiology and results of prior evaluations were consistent with a left frontal SOZ. Frontal lobe semiology can be complex [7]. However, prior work has identified four different anatomical groups along the rostrocaudal axis based on semiology: (1) elementary motor signs that localize to the precentral and premotor areas, (2) a combination of elementary and nonintegrated gestural motor behavior that localize to the premotor and prefrontal regions, (3) integrated gestural motor behaviors and distal stereotypies that localize to the anterior lateral and medial prefrontal regions, and (4) fearful behaviors that localize to the paralimbic regions [8]. In addition, turning along the horizontal axis is associated with mesial frontal onset [9]. Our patient's semiology was most consistent with group 2 and included turning along the horizontal axis localizing to pre-motor areas including the pre-SMA and SMA [8].

In addition to the localization supported by semiology, the RNS recordings supported the possibility of a single left frontal lobe focus despite the lack of efficacy. RNS electrodes can be helpful diagnostically. Some studies have found network reorganization, network synchronizability, and interictal spike rate to be predictors of response [10–12]. In our case, the RNS appeared to be in close proximity to the SOZ given the pattern seen on recordings and correlation with seizures recorded in the EMU.

Radiofrequency ablation at the conclusion of the second SEEG monitoring session provided a key prognostic benefit. The 2 weeks of seizure freedom following ablation motivated the eventual resective surgery. Radiofrequency ablation is a minimally invasive technique that leads to small lesions, which can provide diagnostic and therapeutic benefit [13]. While the long-term seizure outcomes from radiofrequency ablation are less favorable than resective surgery, one study reported 41% of patients were responders at 12 months with some patients remaining seizure free [4]. Seizure outcome from SEEG radiofrequency ablation has been shown to be a predictor of outcome from resective epilepsy surgery [5].

Following the response to radiofrequency ablation, the patient underwent an awake cortical resection with language and motor mapping. Awake mapping is widely used in tumor resections and is safe and effective for resections in nonlesional epilepsy patients [14,15]. The "NeuroMapper" was used during intraoperative ESM [6]. It is an open-source, tablet-based cognitive testing application that can be used to administer a variety of cognitive paradigms while stimulation is applied to delineate eloquent cortex [16]. This tool allows for standardization of ESM, records accuracy and reaction time, and helped define the posterior resection border. Here, stimulation of the superior frontal gyrus led to apraxia. Intraoperatively it was felt that further resection would put the patient at risk of developing SMA syndrome, which typically consists of transient contralateral motor deficits with hemineglect, dyspraxia, or apraxia [17,18]. However, tumor resection in this anatomic region has sometimes led to minor but permanent deficits [19]. Overall, a larger resection may have been considered in our case with a relatively low risk of permanent deficits. Our patient was high functioning at baseline and had concerns about the possibility of a permanent language deficit, favoring a more conservative

resection. This case highlights that performing an awake craniotomy using the "NeuroMapper" in nonlesional epilepsy is not only feasible but may result in better functional outcomes by minimizing long term deficits. Following resection, the patient had transient expressive language impairment and dexterity difficulties with the right hand, which completely resolved within 2 weeks, consistent with a mild SMA syndrome.

This case demonstrates the potential benefits of a complex multimodal approach and provides support for re-evaluating complicated patients who experience ongoing high seizure burdens. Resection of the SOZ was planned utilizing available technology including SEEG, ESM, radiofrequency ablation, and awake resection with language and motor mapping. Radiofrequency ablation was a crucial diagnostic test in this case, as the transient seizure freedom suggested increased chance of seizure freedom with resective surgery. An awake resection for purposes of language mapping utilizing a tablet-based cognitive testing platform ("Neuromapper") helped to reduce the risk of permanent neurological deficits.

Disclosures

BNL declares intellectual property licensed to Cadence Neuroscience Inc (contractual rights waived) and Seer Medical Inc (contractual rights waived), site investigator (Medtronic EPAS, NeuroPace RESPONSE, Neuroelectrics tDCS for Epilepsy), and industry consultant (Epiminder, Medtronic, NeuroPace, Philips Neuro; funds to Mayo Clinic). BHB declares licensed IP to Cadence Neuroscience Inc. and Seer Medical Pty. NMG is a co-investigator for the Medtronic EPAS study.

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Ethical statement

This publication follows the ethical standards of the journal. Institutional review board approval was not necessary as this is a case report. There is no personal identifiable information in the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kelsey M. Smith reports a relationship with CURE Epilepsy that includes: funding grants. Brian N. Lundstrom reports a relationship with NIH NINDS K23NS112339 that includes: funding grants. Brian N. Lundstrom reports a relationship with Epiminder, Medtronic, NeuroPace, Philips Neuro (funds to Mayo Clinic) that includes: consulting or advisory. Benjamin H. Brinkmann reports a relationship with Epilepsy Foundation of America (My Seizure Gauge), NIH NS123066, and the Mayo Clinic Neurology AI program that includes: funding grants. Brian N. Lundstrom and Benjamin H. Brinkmann has patent licensed to Cadence Neuroscience Inc and Seer Medical Inc. site investigator (Medtronic EPAS, NeuroPace RESPONSE, Neuroelectrics tDCS for Epilepsy)- Brian N. Lundstrom; co-investigator for the Medtronic EPAS study- Nicholas M. Gregg. ECA, HDS, KJS have no declarations of interest.

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