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Negative is Not Always Negative: Improving Outcomes in Scalp Negative Seizures Using Intracranial EEG

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Abstract

Background: Refractory seizures sometimes arise from deeper foci within the brain. When difficult to detect on scalp EEG, chances of successful epilepsy surgery are reduced. Two patients had scalp Electroencephalogram (EEG) negative seizures, got intracranial EEG and did well with responsive nerve stimulation (RNS). Patient consent was obtained to utilize these cases for educational purposes.

Cases: Patient I is a 29-year-old female, with prior right temporal lobectomy, s/p vagal nerve stimulation (VNS) and 5-year seizure freedom before recurrence. Magnetic resonance imaging (MRI) and positron emission tomography (PET) showed signs of prior surgery. Scalp EEG and Magnetoencephalogram (MEG) were unremarkable. Neuropsychological testing showed diminished core verbal function and memory. Intracarotid amobarbital procedure (IAP)/Wada testing revealed left dominance for language and memory. Stereotactic EEG (sEEG) captured focal impaired awareness seizures and focal aware seizures with early involvement of the right posterior cingulate (RPC) and right posterior insular (RPI) regions. Brain mapping/cortical stimulation revealed motor function in RPC and sensory in RPI regions precluding resection/ laser ablation. RNS implantation in the RPC and RPI regions achieved seizure freedom 4 months after implantation.

Patient II is a 33-year-old female, who would wake up, laugh/curse, vocalize and show left (focal) predominant hyper motor movements progressing to tonic-clonic convulsion. MRI brain showed a venous angioma. PET revealed decreased uptake in right posterior parasagittal frontal and right inferior parasagittal frontal regions. MEG was unremarkable. Neuropsychological testing showed weak bi-frontotemporal systems. Wada testing showed left dominance for language and memory. SEEG captured hyper motor seizures with early involvement of right orbito frontal (ROF) with spread to right hippocampal (RH) regions. RNS implantation in the ROF and RH regions achieved 30% seizure reduction 3 months post implantation.

Conclusion: Scalp EEG negative seizures remain challenging to treat. sEEG delineates seizure network and localizes the onset zone. This understanding will better help treat patients using neuromodulation or targeted therapies like ablation.

Keywords: Scalp negative seizures, Scalp EEG, Stereotactic EEG, Deep epileptic foci, Medically refractory epilepsy

Abbreviations: EEG: Electroencephalogram; RNS: Responsive Nerve Stimulation; VNS: Vagal Nerve Stimulation; IAP: Intracarotid Amobarbital Procedure; PET: Positron Emission Tomography; MEG: Magnetoencephalogram; SEEG: Stereotactic EEG; RPC: Right Posterior Cingulate; RPI: Right Posterior Insular; ROF: Right orbitofrontal; RH: Right Hippocampus; iEEG: intracranial EEG; ASM: Antiseizure medications; ROSA: Robotic Stereotactic Assistance; iEEG: Intracranial EEG; EMU: Epilepsy Monitoring Unit; ECoG: Electrocorticogram; TBI: Traumatic Brain Injury

Introduction

Since 1929, electroencephalography (EEG) has been the cornerstone of diagnosis, classification, and management for epilepsy patients. However, there are limitations with scalp EEG. Electrical activity recorded by scalp electrodes is a summation of excitatory and inhibitory postsynaptic potentials in neurons of the superficial cortex layers. Small square centimeters must be activated synchronously to generate enough potential for the EEG changes noted at the scalp, which can be difficult in delineating epileptic foci from deeper parts of the brain or ones coming from dimensions of only a few millimeters [1]. Scalp negative seizures are electrographic seizures from deeper parts of the brain without specific scalp EEG correlate.

When developed in 1948, intracranial EEG was observed to show signals with anatomically precise information about engagement of neurons within a millimeter and regarding their temporal dynamics [2].

Approximately one-third people with epilepsy suffer from medication refractory epilepsy [3]. In these patients, when there is enough evidence to support underlying seizures using ancillary studies, despite a scalp negative EEG, iEEG (intracranial EEG) may be indicated to precisely locate the seizure focus for potential surgical intervention or neurostimulation [4].

Here, we describe two patients with scalp negative seizures studied with iEEG who responded well with responsive neurostimulation.

Cases

Patient 1

The first patient was a 29-year-old left-handed woman who presented with medically and surgically refractive epilepsy. She began having seizures at age 4 years and was treated with multiple antiseizure medications (ASMs). Her workup was remarkable for right mesial temporal sclerosis, and she then underwent right temporal lobectomy at age 12 years. She subsequently achieved seizure freedom for 5 years until recurrence. After multiple ASM trials and VNS placement, she continued to have 10 seizures per month, during the day and more frequently in sleep. Seizure semiology was noted as ringing in the ears, nausea, metallic taste, left leg numbness followed by staring with impaired awareness and some aphasia.

Brain MRI with and without contrast showed prior right temporal partial resection with residual right temporo-parietal encephalomalacia. PET scan brain revealed metabolic deficits in the right mesial/lateral temporal region associated with prior surgeries. She underwent continuous video monitoring with scalp EEG at the epilepsy monitoring unit (EMU), during which she had multiple typical events captured but without significant EEG changes besides diffuse theta delta slowing. There were occasional right frontocentral sharp waves in the setting of breach artifact.

During presurgical workup, MEG was performed to map eloquent cortex and showed no epileptiform discharges. Neuropsychological testing showed decline in core verbal function and memory function, suggestive of frontotemporal systems dysfunction in the language hemisphere. Wada test revealed left hemisphere dominance for language and significantly supporting memory along with right hemisphere. She underwent stereotactic EEG implantation (per the ROSA sEEG plan shown in **Figure I-1**) with extensive right hemispheric coverage that captured multiple typical focal seizures with onset and early involvement in the right posterior cingulate and right posterior insular regions as shown in sEEG in the **Figure I-2**. Brain mapping and cortical stimulation revealed motor function in right posterior cingulate regions and sensory functions in the insular regions precluding resection or laser ablation. She underwent responsive neurostimulator (RNS) implantation with two depth electrodes in the right posterior insular and right posterior cingulate regions. Since implantation, she reported significant improvement, with only 2 brief seizures over next 4 months (**Figure I-3**). She continues to be medically managed.

Patient 2

The second patient was a 33-year-old right-handed woman who presented with medically refractory epilepsy. Her seizures began at age 11 years and had the following reported semiologies of staring spells, nocturnal events described as violent thrashing movements with screaming and swearing followed by postictal lethargy and, cursing while turning to the left and running around. At the time of initial visit, she was taking carbamazepine 600 mg twice daily and lacosamide 200 mg every morning and 400 mg every night yet continued to report 2 or 3 seizures each month. Previous ASMs included phenytoin, valproic acid, and oxcarbazepine.

MRI brain with and without contrast showed a possible 6 mm venous angioma in the right posterior frontal lobe. PET scan brain revealed decreased uptake in the right posterior parasagittal frontal lobe and right inferior parasagittal frontal lobe. During EMU stay, she had multiple events overnight, during which she was observed to wake up, grimace, laugh, and then exhibit vigorous hyper motor movements of both legs, followed by cheerfulness and talking to her spouse. She was amnestic of these events. During these events, continuous video monitoring with scalp EEG showed stage 2 sleep with arousal without any obvious electrographic changes at onset or during the seizures, followed by postictal right frontocentral semirhythmic polymorphic slowing.

As part of her presurgical workup, MEG was normal. Neuropsychological testing reported lower scores on visual learning, memory, and object naming, likely reflecting weakness of bi-frontotemporal systems. Wada test revealed left hemisphere dominance for language and memory. She then underwent stereo EEG implantation with extensive bilateral coverage over frontal regions, which captured multiple typical hyper motor seizures with early involvement of the right orbitofrontal region and rapid spread to right hippocampal regions as seen in the **Figure I-4,5**.

She underwent RNS implantation with 2 depth electrodes in the right orbitofrontal and right hippocampal regions. Three

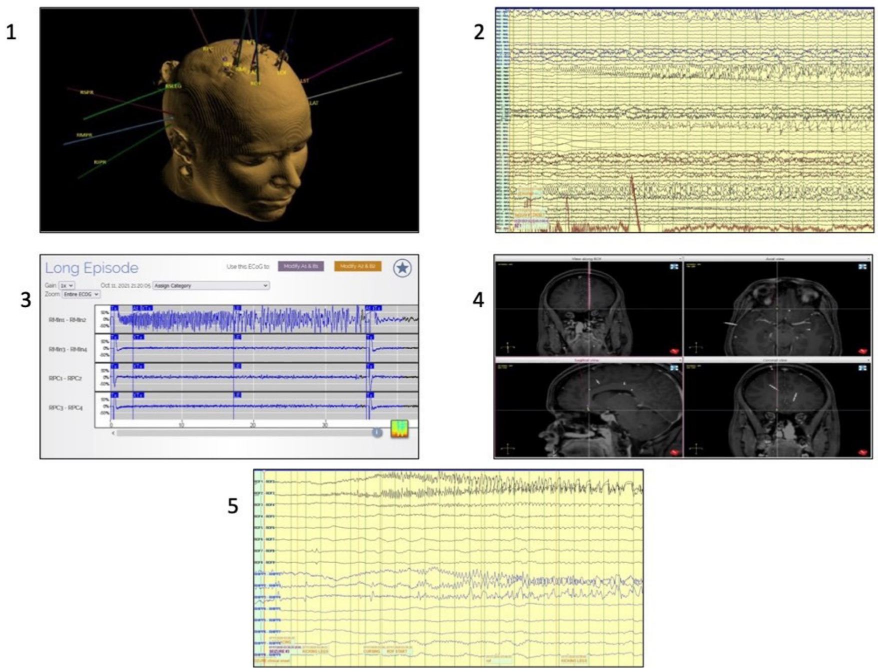

Figure I: (1) ROSA SEEG plan for patient 1. **(2)** ECoG showing seizure onset in right insular and posterior cingulate regions in patient 1 -limited montage only. **(3)** PDMS data showing seizure onset captured by RNS device in patient 1. **(4)** ROSA trajectory for electrode targeting right orbitofrontal region for the seizure onset zone for patient 2. **(5)** ECoG showing seizure onset in right orbitofrontal region with spread to right hippocampus in patient 2.

months later, she achieved 30% seizure reduction. One year after implantation, she reported seizure reduction of 75-100%, while on cenobamate 100 mg twice daily, lacosamide 200 mg twice daily, and levetiracetam 2000 mg twice daily.

Discussion

Scalp EEG negative seizures remain challenging conditions to treat. Casale et al. compared simultaneous recordings from patients with refractory seizures, revealing that scalp EEG is not sensitive in focal aware, and subclinical seizures but useful in focal impaired aware to focal to bilateral tonic clonic seizures [5]. Wazir et al. reported that post TBI patients had electrographic seizures captured on intracranial EEG but not on scalp EEG. Still, scalp EEGs are a great non-invasive tool for initial assessments.

Stereotactic EEGs accurately detect seizure onset zones. ECoG studies have helped understand gamma oscillations in cognitive tasks involving firing of only a thousand neurons [6]. Examples include studies that used subdural electrodes to identify specific cortical functions such as by Miller et al. [7], 'laughing and smiling' by Kern et al. [8], and word production by Crone et al. [9].

However, there are some limitations with subdural and deep electrode recordings. Subdural recordings tend to have extensive cortical coverage, they are limited in recording deeper locations. Depth electrodes have sampling limitations due to incomplete and irregular cortical coverage [10,11].

Locating seizure networks in medically refractory epilepsy patients offers options to treat using neuromodulation or targeted therapies like ablation. Both cases in our study achieved a significant degree of seizure freedom using RNS. RNS is a cortical based device placed at the seizure focus using 1-2 depth electrodes that continuously monitor ECoG patterns and deliver a stimulation in response to them. The pattern to be detected is pre-programmed according to the patient [12]. Class 1 evidence supports that responsive neurostimulation improves quality of life and is safe in patients with medical refractory epilepsy especially with 1-2 foci [13]. There is also a 9-year prospective trial providing class IV evidence that supports seizure freedom for at least 3.2 years on average in patients with medically intractable focal onset seizures [14].

Heck et al. also demonstrated that over a 1-2 year follow up since implantation of RNS there was significant seizure reduction and improved quality of life (QOL) [15].

Although stereotactic EEGs are invasive, the future of treatment is accurate localization of seizure networks using different techniques. Fyfe et al. predicted deep epileptic foci in 40% of the cases based on noninvasive algorithms [16]. RaviPrakash et al. demonstrate accuracy of epileptic foci detection using deep learning algorithms with stereotactic

EEG based functional mapping [17]. Hence, building systems that use noninvasive methods is the future for treating scalp negative seizures.

Conclusions

Intracranial EEGs help determine accurate localization data for epileptogenic foci which can be missed by scalp EEGs. These accurate foci can then be targeted by therapies such as RNS, ablation or other techniques that can remarkably improve seizure freedom and quality of life

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and or publication of this article.

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