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Epileptic Disorders

CLINICAL COMMENTARY

Responsive neurostimulation detections: "Recognizing the unseen"

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Abstract

Background: Closed-loop responsive neurostimulation (RNS) is an established non-resective neuromodulatory therapy for individuals with drug-resistant epilepsy (DRE). RNS systems are typically programmed to detect and respond to predefined seizure onset patterns, with detector settings often remaining unchanged for extended periods.

Aims: To describe the delayed recognition of a novel seizure onset pattern in the acute and chronic clinical settings.

Methods: The case of a 35-year-old female with history of drug-refractory temporal lobe epilepsy who presented with increasing seizure frequency and headaches was reviewed.

Results: We demonstrate emergence of a new seizure onset pattern in a 35-year-old female with DRE who had undergone RNS implantation 5.5 years prior to presentation. Guided primarily by strong clinical suspicion, with live electrocorticography (ECoG) serving as a confirmatory tool, we identified a previously unrecognized seizure onset pattern linked to a rare, delayed intraparenchymal hemorrhage associated with an RNS lead. Longitudinal ECoG analysis in this patient, who experienced over a 95% reduction in seizures since implantation, revealed evolving seizure patterns over several years that contributed to delayed detections.

Conclusion: This case underscores the risk of misdiagnosis when acute changes in seizure patterns occur, in the context of detections programmed to identify specific patterns. Longitudinal analysis of ECoG in the same patient showed changes in seizure patterns over several years that were detected with delay, highlighting importance of vigilant detection monitoring.

KEYWORDS

intracerebral hemorrhage, neuromodulation, responsive neurostimulator, seizure networks, temporal lobe epilepsy

Aden P. Haskell-Mendoza and Praveen Ramani have contributed equally to this work.

1 | INTRODUCTION

Closed-loop responsive neurostimulation (RNS) has emerged as a mainstay neuromodulatory therapy for drug-resistant epilepsy (DRE) in patients with widespread or unresectable epileptogenic zones.[1–4] The RNS device, implanted in the cranium and connected to two depth or strip leads, allows recording of electrocorticograms (ECoGs) from targeted epileptic foci, while also delivering electrical stimulation on detection of prespecified patterns of abnormal activity. This report explores a complex case of a 35-year-old female with DRE who experienced an acute change in seizure pattern and increased seizure frequency following a spontaneous, lead-associated intraparenchymal hemorrhage (IPH). Despite a negative scalp EEG, high clinical suspicion and the integration of live ECoG led to the discovery of an acute change in seizure pattern that had escaped detection. Further analysis of the patient's ECoG over 5.5 years demonstrated novel seizure patterns over several years, resulting in delayed detections. In this report, we highlight that detection parameters may require dynamic adjustment over time, reinforced by clinical vigilance and patient-centered care to optimize recognition of both acute and chronic alterations in seizure patterns in RNS therapy.

Key points

- Seizure patterns may change due to acute events or evolve over time.
- Static RNS detector settings may miss or delay detection of new seizure onset patterns.
- Live electrocorticography confirmed seizures not visible on scalp EEG.

2 | CASE PRESENTATION

A 35-year-old right-handed female with a history of tobacco use and focal impaired awareness seizures consisting of oral automatisms, paresthesia of the arm and face, tunnel vision, and confusion lasting for approximately 30 seconds. She called to report a headache for 48 hours and an increase in seizures with an aura different from her typical seizures. A review of uploaded ECoG showed a mismatch in frequency of reported versus stored seizures. She was referred for hospital admission due to a worsening headache, concern for frequent epileptic seizures versus psychogenic non-epileptic seizures (PNES), inconsistencies in RNS data uploads, magnet swipes, and reported symptoms—all of which, taken together, could not be adequately evaluated remotely.

Relevant history includes first seizure at age 25, with presurgical workup for DRE indicating seizure onset in the right temporal lobe (MRI-negative, PET hypometabolism in the right temporal lobe, intact verbal and visuospatial memory, long-term EEG with right temporal sharp waves and 7 right temporal seizures). This resulted in a recommendation for an anterior temporal lobectomy; however, in alignment with the patient's preference to avoid resective surgery, RNS was selected as the treatment approach.

The patient underwent RNS with placement of a right-sided hippocampal depth electrode and a sub-temporal strip electrode 5.5 years prior to the current presentation. She experienced a reduction in frequency of seizures from 9–10 daily to 1–2 weekly or less following implantation and programming over 1–2 years.

On admission to the general neurology service, the patient reported difficulty obtaining her antiseizure medications (ASMs) (levetiracetam and cenobamate). After optimizing her ASMs and treating her headache, she reported significant improvement in headache; however, there was minimal improvement in her seizures. Despite multiple reported seizures by the patient during the recording, no correlate was found on scalp EEG. On the second day of admission, the RNS device was interrogated and showed a marked increase in impedances on both leads relative to the last interrogation (Figure 1). An earlier-ordered CT head was obtained, revealing a 3.9 × .8 × 1.8 cm IPH extending along the hippocampal depth lead. Extensive workup, including vessel imaging, did not reveal the exact cause of the bleed. ECoG review showed the development of new mesial temporal theta and delta activity (Figure 1), but did not initially show seizures corresponding to the patient's reported events. A second interrogation of the RNS device was performed and live ECoG showed multiple seizures with onset in the hippocampal contacts with a seizure pattern that was different from prior seizures. These seizures were not detectable with the device's current detection parameters (Figure 2).

After changing detections to deliver stimulation for the new seizure onset pattern and further increasing her antiseizure medications, the patient was discharged. Given anticipated changes in electrographic pattern with resolution of IPH and to ensure established seizure patterns were not missed, close outpatient follow-up was obtained. At 3 months from discharge, the patient has remained seizure-free with non-explanatory workup for the IPH.

An in-depth review of ECoG recordings was performed to understand seizure patterns across the lifecycle of this patient's implant. This revealed evolving seizure onset patterns over time as the patient achieved improved seizure

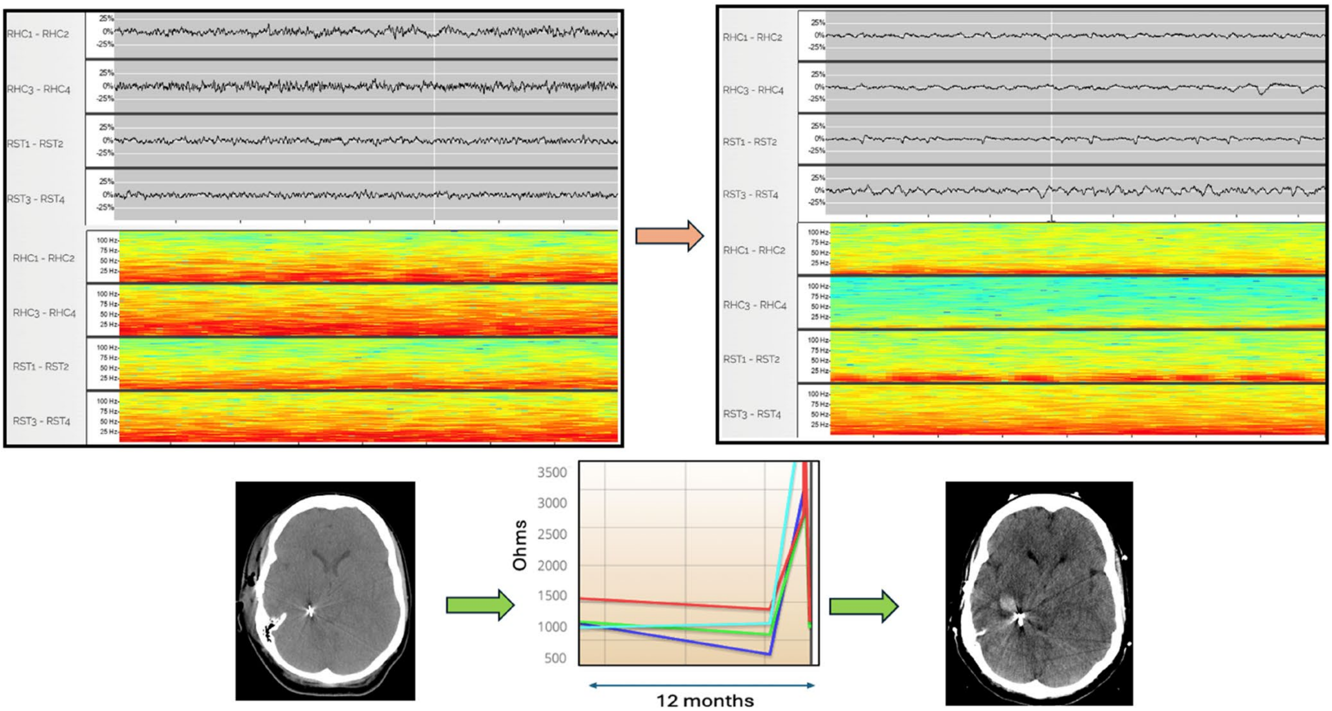
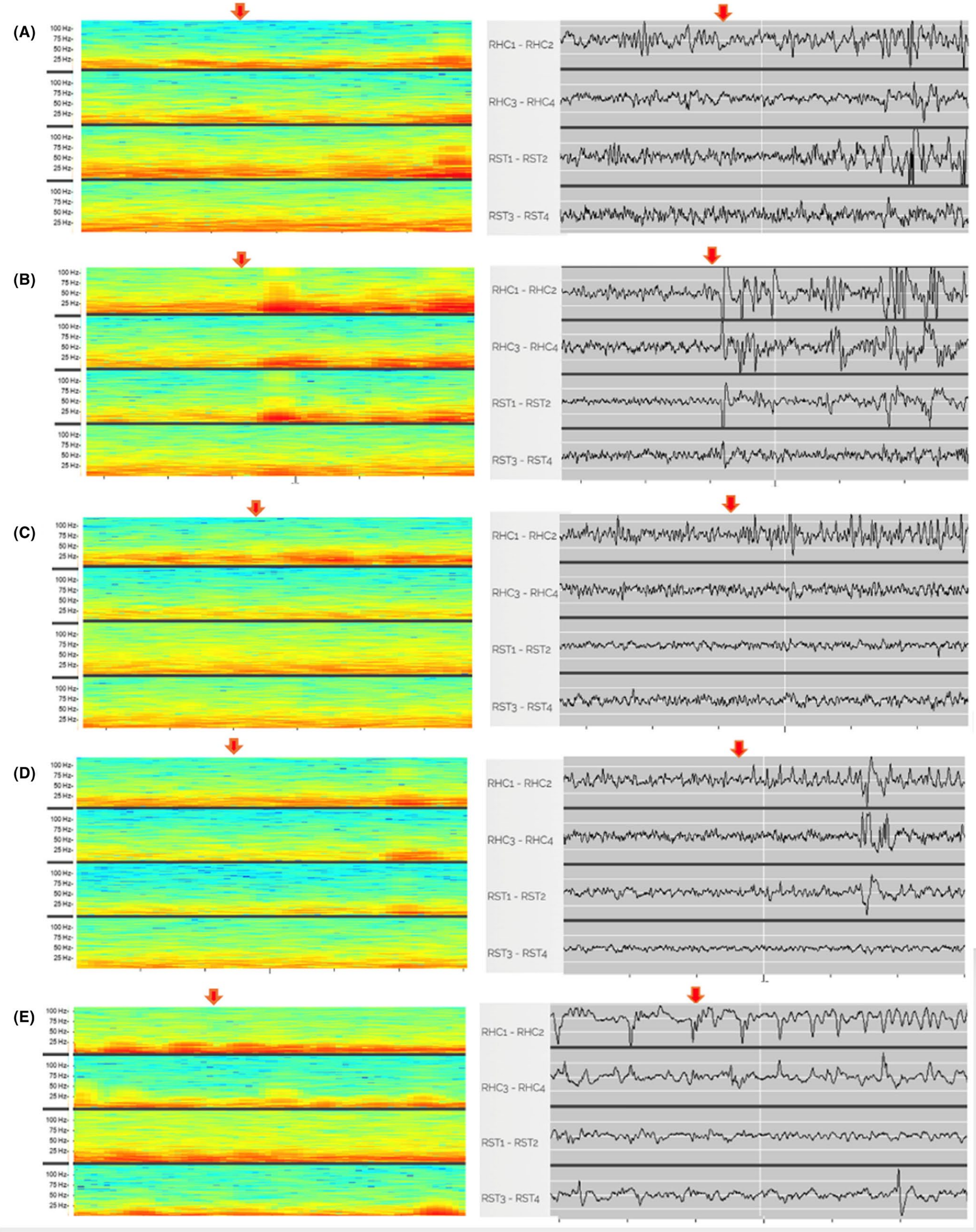


FIGURE 1 Change in ECoG background pattern following RNS lead-associated IPH: Upper panel, left-to-right: Raw ECoG recordings and time-frequency plot ~12 months prior to and after detection of the intraparenchymal bleed. Recordings consist of 10s of time-matched ECoG at 2X gain showing background activity dominant beta and gamma frequencies versus post-hemorrhagic dominant delta and theta slowing. Lower panel, left-to-right: Immediate post-implant CT head demonstrated no hemorrhage. At the time of delayed intraparenchymal hemorrhage, a sudden increase in impedance was identified (showing sub-temporal strip impedances, X axis shows ~12 months duration, Y-axis in ohms), CT showing IPH along the hippocampal lead.

control (Figure 2). Inconsistent uploading of data and programming visits led to a delay in identifying new patterns and subsequent modification of detector settings. It was noted that seizure patterns had slowly evolved over several years even prior to the IPH and were not triggering early detections although they continued to trigger late detections (Figure 2). We further confirmed that this variability and patterns of seizure onsets were not present at baseline or within the first 6 months post-implantation.

3 | DISCUSSION

RNS therapy delivers closed-loop electrical stimulation in response to the detection of various electrographic patterns. Clinicians often adjust RNS detectors to be more sensitive to early detection of ictal activity and may or may not allow frequent triggering with interictal activity to balance battery usage. Typical RNS programming workflows enable detection via changes in power with line length detection, alterations in rhythmicity or spikes with bandpass detectors, and less commonly, sustained changes using area detectors.[4,5] Once programmed to recognize seizure onset patterns, these detectors are often left unmodified for years. We describe a case of a 35-year-old female with DRE who underwent RNS implantation 5.5 years earlier and later developed a new seizure onset pattern, not "seen" by the preset detector or on scalp EEG. A rare, delayed idiopathic lead-associated IPH (Figure 1) was identified as the underlying cause. The discovery of electroclinical seizures was made possible through a combination of strong clinical suspicion and the use of live ECoG as an adjunct, which revealed the novel seizure pattern. This case emphasizes the risk of missing acute seizure pattern changes and misdiagnosis, particularly when detectors remain configured to detect pre-specified patterns. Despite negative scalp EEG findings and the absence of recorded seizures on ECoG, the strong clinical suspicion—based on patient-reported symptoms—prompted the epileptologist to perform live ECoG monitoring during an event. This approach confirmed the presence of ictal activity and conclusively ruled out non-epileptic events. While magnet swipes combined with a review of stored events could have yielded a similar clinical insight, the use of live ECoG during inpatient RNS interrogation allowed for immediate electrographic correlation as the patient reported her symptoms as they occurred. Overall, this work underscores the promise of closed-loop technology as a complementary modality, while recognizing its present limitations.



Delayed, atraumatic hemorrhage in the setting of RNS placement for temporal lobe epilepsy is infrequent based on current evidence, with an overall rate at any timepoint/etiology of 3/111 (2.7%).[6] Further, while our patient was young and without other vascular risk factors, it is possible that tobacco use in the setting of a chronically implanted

FIGURE 2 Seizure onset patterns on sampled ECoG over 5.5 years: Left column: Time-frequency plots and right column: ECoG from RNS implant showing 6 s of recordings with interictal to ictal transitions (red arrow). Displayed ECoG patterns are representative of most seizures that occurred around this time period after implantation (A) 2 months post- implantation showing desynchronization followed by rhythmic polyspikes at onset (B) 18 months post-implantation with higher amplitude rhythmic slow spikes at onset (C) 36 months post-implantation, reported excellent seizure control, showing fast activity at onset (D) 60 months post-implantation showing pre-ictal spiking pattern (E) 65 months post-implantation in the setting of intraparenchymal hemorrhage showing new slowing intermixed with pre-ictal spiking pattern recorded by the new detector.

device may have heightened hemorrhage risk. The underlying cause of the IPH remains unclear after extensive evaluations. This study focuses on identifying acute changes in seizure patterns that may go undetected by preconfigured detection settings, as demonstrated in the setting of IPH. Clinicians are encouraged to leverage the advanced capabilities of the RNS device, such as magnet-based recordings or live ECoG, as adjunctive tools in the diagnostic evaluation of acute changes, in the appropriate clinical context.

Given the scarcity of available data, there is currently no established guidance to inform the use of RNS-mediated electrical stimulation for the treatment of acute symptomatic seizures in the setting of hemorrhage. In response to the acute change, we adjusted the detection settings to capture this "new pattern," recognizing that such a pattern could shift or resolve over time. Importantly, our intention was not to pursue chronic stimulation for this emergent pattern unless warranted, which is why we arranged for close clinical follow-up—to ensure that the patient's established ictal patterns were not overlooked as the situation evolved. It also remained unclear whether the hemorrhage itself would ultimately become a new focus for long-term stimulation. From a network-based perspective, our approach simply resulted in an increase in network-level stimulations during a period when the patient was experiencing frequent seizures, at least in the short term.

In addition to detecting and delivering stimulation with triggering of the detector, the device also stores epochs of electrographic data with magnet swipes, long events triggered by the detector, or amplitude saturations.[5] Therefore, RNS provides a unique opportunity to record electrographic activity acutely as well as chronically over several years.[1,3,7] There is evidence that the efficacy of RNS is not only mediated by immediate stimulation-induced cessation of seizures but primarily by long-term remodeling of epileptogenic networks.[1,6,8–10] During the years following RNS implantation, our patient had reported a significant improvement in her seizures. In addition to the acute changes in the setting of IPH, longitudinal ECoG analysis revealed chronic changes in seizure patterns (Figure 2) that were being detected with a delay. Within the limitations of sampling, as shown in Figure 2, the displayed ECoGs represent the predominant seizure onset patterns as older patterns were replaced. This finding suggests that detection algorithms may require updates rather than remaining static, to ensure accurate seizure counts if seizure patterns change.[1,5,8–10] Regarding seizure count comparisons across different detection settings, maintaining stable parameters helps avoid inappropriate comparisons. However, if unchanged settings lead to missed or delayed detections, stability alone does not justify leaving detectors unadjusted. Seizure networks are dynamic and evolve over time, which may play a role when choosing and re-evaluating detectors.[1,8,9,11,12] Kokkinos et al. hypothesized that chronic stimulation may isolate interconnected epileptogenic networks by the creation of electrical barriers leading to desynchronization of these networks, resulting in changes in electrographic signatures.[11] In our patient, whether these changes in seizure onset patterns are related to chronic neuromodulatory effects on seizure networks, changes in medications, or are unique to this case given the rare IPH is difficult to ascertain. A larger study analyzing background and ictal ECoG recordings from patients over several years, accounting for all variables, would be valuable to understand the progressive network-level effects achieved with seizure control from RNS.

Traditional, subjective reports of seizures utilizing diaries are limited by lack of recognition of seizures, incomplete or inaccurate data, and potential underreporting.[13–15] There is a growing trend toward utilizing ECoG from RNS devices as objective evidence to address these limitations. However, its utility hinges on understanding detection limitations. In this patient, who had a mismatch in subjective reporting and scalp EEG/ stored ECoG, integration of live ECoG and imaging was beneficial to make a clinical diagnosis. However, in patients with RNS devices, seizures can originate from regions outside of the sampled regions, limiting the utility of ECoG and highlighting the critical role of clinical suspicion. It is possible that, in similar cases, a more detailed history or consistent symptom correlated magnet-stored ECoGs might lead to an earlier, outside hospital diagnosis and more prompt therapeutic intervention. In this case, the patient was treated with optimization of her antiseizure medications, management of her headache, and underwent CT imaging and a full workup for intracerebral hemorrhage, irrespective of the

RNS interrogation results. However, live ECoG served as an adjunctive objective measure, supporting the clinical correlation with her focal symptoms. Although objective metrics are important, clinicians should aim to combine these with the patient's subjective reports rather than relying on them exclusively. In our case, where a distinct pattern emerged after an intracranial bleed, reliance on prior ECoG recordings or scalp EEG alone might have incorrectly indicated the patient was “seizure-free” or experiencing “non-epileptic events” Consequently, acute changes in seizure frequency or type, even if apparently “ECoG negative” should raise clinical suspicion and prompt a complete workup that leverages both the advanced and traditional tools for patient-oriented care.

4 | CONCLUSION

This study highlights the nuanced application of closed-loop neuromodulation to detect seizures associated with a rare, idiopathic RNS lead-associated IPH. While preset detectors failed to identify these seizures, the use of live ECoG successfully revealed an electrographic correlate to the patient's reported seizures. Additionally, over 5.5 years of ECoG data from this case showed an evolution of seizure patterns, with delayed triggering of preset detectors. Ultimately, this underscores the critical importance of “recognizing the unseen”—where real-time data and adaptive detection strategies can uncover seizure activity hidden from static detectors. Further, this case reinforces the value of patient-reported symptoms in guiding clinical decision making, ensuring that the full capabilities of RNS technology are harnessed for an individualized patient-centric approach.

AUTHOR CONTRIBUTIONS

Conceptualization – SA, APH, PR; methodology – SA, PR, APH; software – SA; figures – SA, APH; writing – original draft – APH, SA, PR; writing – review & editing – all authors; supervision – SA.

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CONFLICT OF INTEREST STATEMENT

DS is a paid consultant for NeuroOne, and has prior paid speaking engagement for NeuroPace, as well as sponsored research for Neurona Therapeutics. CM is a consultant for Livanova and Monteris. SA is a consultant for BlackRock Neurotech. BF has received honoraria from UNEEG, Natus, Paladin Labs, UCB, and Eisa within the past 3 years. None of the other authors have relevant conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

IRB STATEMENT

IRB approval and patient consent were not required for preparation of this case report in accordance with institutional policy. The manuscript was prepared according to published guidelines for case reports.[16]

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REFERENCES

1. Rao VR, Rolston JD. Unearthing the mechanisms of responsive neurostimulation for epilepsy. Commun Med. 2023;3(1):166.
2. Morrell MJ, RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77(13):1295–304. https://doi.org/10.1212/WNL.0b013e3182302056
3. Nair DR, Laxer KD, Weber PB, Murro AM, Park YD, Barkley GL, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology. 2020;95(9):e1244–e1256.
4. Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS system pivotal trial. Epilepsia. 2014;55(3):432–41.
5. Sun FT, Morrell MJ. The RNS system: responsive cortical stimulation for the treatment of refractory partial epilepsy. Expert Rev Med Devices. 2014;11(6):563–72.
6. Geller EB, Skarpaas TL, Gross RE, Goodman RR, Barkley GL, Bazil CW, et al. Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. Epilepsia. 2017;58(6):994–1004.
7. Razavi B, Rao VR, Lin C, Bujarski KA, Patra SE, Burdette DE, et al. Real-world experience with direct brain-responsive neurostimulation for focal onset seizures. Epilepsia. 2020;61(8):1749–57.
8. Sperling MR, Wu C, Kang J, Makhalova J, Bartolomei F, Southwell D. The temporal lobe Club: newer approaches to treat temporal lobe epilepsy. Epilepsy Curr. 2024;24(1):10–5.
9. Piper RJ, Richardson RM, Worrell G, Carmichael DW, Baldeweg T, Litt B, et al. Towards network-guided neuromodulation for epilepsy. Brain. 2022;145(10):3347–62.
10. Khambhati AN, Shafi A, Rao VR, Chang EF. Long-term brain network reorganization predicts responsive

neurostimulation outcomes for focal epilepsy. Sci Transl Med. 2021;13(608):eabf6588.

11. Kokkinos V, Sisterson ND, Wozny TA, Richardson RM. Association of closed-loop brain stimulation neurophysiological features with seizure control among patients with focal epilepsy. JAMA Neurol. 2019;76(7):800–8.
12. Haneef Z, Vallera AC, Vedantam S, Feygin MS, Cleboski S, Gavvala JR. Characterizing seizure-onset patterns with the responsive neurostimulation system. J Clin Neurophysiol. 2025;42(2):156–63.
13. Brinkmann BH, Karoly PJ, Nurse ES, Dumanis SB, Nasseri M, Viana PF, et al. Seizure diaries and forecasting with wearables: epilepsy monitoring outside the clinic. Front Neurol. 2021;12:690404.
14. Fisher RS, Blum DE, DiVentura B, Vannest J, Hixson JD, Moss R, et al. Seizure diaries for clinical research and practice: limitations and future prospects. Epilepsy Behav. 2012;24(3):304–10.
15. Tatum WO, Winters L, Gieron M, Passaro EA, Benbadis S, Ferreira J, et al. Outpatient seizure identification - results of 502 patients using computer-assisted ambulatory EEG. J Clin Neurophysiol. 2001;18(1):14–9.
16. Sohrabi C, Mathew G, Maria N, Kerwan A, Franchi T, Agha RA. The SCARE 2023 guideline: updating consensus surgical CAse REport (SCARE) guidelines. Int J Surg. 2023;109(5):1136–40.

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