Hippocampal seizure-onset laterality can change over long timescales: A same-patient observation over 500 days

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Bilateral temporal lobe epilepsy is not uncommon [1,2]. Unilateral surgical resection in this setting, if offered, is more potentially palliative than curative treatment although some patients with BTLE experience seizure freedom when preoperative diagnostic tests identify a predominant laterality [1,3]. Thus, identifying patients with bilateral mesial temporal onsets is critical to outcome prognostication and surgical decision-making. However, the limited sampling that is practical during noninvasive or invasive video-EEG monitoring [4] presents statistical limitations in determining whether seizure onsets are truly unilateral or bilateral, although it has been suggested that a sampling of five seizures has a high likelihood of identifying bilateral onsets [5].

For patients with BTLE, hippocampal deep-brain stimulation (DBS) is an investigational alternative therapy [6,7]. In particular, the NeuroPace RNS™ System uses implanted electrodes to measure continuous electrocorticography (ECoG), perform real-time signal analysis for specified seizure detection, and trigger electrical DBS through the same electrodes [8]. Acquiring long-term ambulatory ECoG via the RNS™ affords an unprecedented opportunity to study electrical brain activity over months [9] and years, in contrast to the week-long period allowed during routine presurgical evaluation. For instance, this report describes results of monitoring ECoG seizures for two years in a patient with bilateral hippocampal DBS electrodes to treat medically refractory BTLE discharges as part of the ongoing clinical trial of the efficacy and safety of the RNS™ [10]. We track monthly and daily seizure counts, observing a nonstationary epileptic focus.

2. Case report and methods

2.1. History and examination

The patient, a 27-year-old right-handed woman, began having complex partial seizures at age 8. Her seizures were characterized by unintelligible speech, a blank stare, lip-smacking, and periodic progression to left-arm extension and secondary generalization. Epilepsy risk factors included premature birth and a neonatal stroke. At the time of operation, she had about 5 seizures with frequent generalization per month which failed polytherapy with medicines including carbamazepine and levetiracetam. Magnetic resonance imaging displayed dysmorphic changes in the right temporal lobe, but normal hippocampal architecture without sclerosis. Fludeoxyglucose positron emission tomography (FDG-PET) revealed left mesial temporal lobe hypometabolism. Neuropsychological testing showed no sign of depression, anxiety, psychosis, or hallucinations. Her selective Wada test showed poor memory...
Video-EEG recorded five complex partial seizures, with three exhibiting generalization: one had a clear left-sided temporal onset, and four had left temporal maxima but ambiguous onsets. To definitively identify the seizure-onset region, bilateral iEEG monitoring was performed with orthogonally implanted depth electrodes in the amygdala and hippocampus and strip electrodes implanted over the parahippocampal gyrus plus the basal and lateral temporal lobes. Unexpectedly, a 1-month video-iEEG monitoring recorded three right mesial temporal lobe seizures.

Juxtaposing all presurgical evaluation results provided convincing evidence for bilateral hippocampal onsets. The patient was considered an unsuitable candidate for hippocampal resection but satisfied inclusion criteria for the RNS™ clinical trial for intractable epilepsy.

The protocol (IRB00003952) was approved by the Emory University Institutional Review Board (IRB).

2.2. Implantation and intraoperative electrophysiology

A track per DBS lead (NeuroPace, Mountain View, CA) targeted each anterior hippocampus using the microTargeting WayPoint Planner 2.0 software (FHC, Inc., Bowdoin, ME). Occipital lead entry points were chosen to avoid the ventricles, prominent veins, and arteries as visualized by the preoperative coregistered volumetric MRI and CT scans. On each side, a recording (Figs. 2A–E) was performed before implanting one four-electrode DBS lead, which was then connected to the pulse generator embedded in the right side of the skull (Fig. 1A).

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**Fig. 1.** Image coregistration after device implantation. (A) The pulse generator is affixed within a ferrule in the skull and attached to the leads in the brain (not visible) by an insulated electrical conductor that is tunneled under the scalp. (B–F) Implanted electrodes in coronal view of coregistration where each aspect is orthogonal to the long axis of the hippocampus.
2.3. Extraoperative electrocorticography and seizure monitoring

The RNS™ device automatically stored four bipolar ECoG signals for each seizure: signals L1, L2, R1, and R2 respectively represented left electrodes 1–2, left electrodes 3–4, right electrodes 1–2, and right electrodes 3–4 (Figs. 1B–I). For each seizure, the RNS™ stored the four signals with corresponding date and timestamps (60 s before and 30 s after detection).

The seizure-onset zone (SOZ) and the seizure-onset time (SOT) were visually annotated for 51/54 consecutive unequivocal electrographic ECoG seizures by an epileptologist (C.M.E.) without a priori knowledge about the location or laterality of each seizure or the label of each ECoG signal. The signal with the earliest definite electrographic change was declared the SOZ, and the time point at which the change occurred was declared the SOT. Additionally, the epileptologist noted if each seizure spread from ipsilateral to contralateral electrodes. We ignored from further analysis 3/54 seizures for which SOZs were too ambiguous to determine. We illustrated the first (Fig. 2F) and final (Fig. 2G) recorded seizures with their annotation.

3. Results

3.1. Total seizure counts

We examined whether one side had greater seizure preponderance than the contralateral side. We found no statistically significant difference in total seizure counts on the left and right sides ($p = 0.893$, $\chi^2$ test) (Fig. 3A) but found a statistically significant difference in seizure counts (Fig. 3C) across the signals ($p < 0.001$, $\chi^2$ test), suggesting that the SOZ localized to a specific brain area despite ambiguous laterality. Further analysis showed more seizures in L1 than in L2 or R1 ($p < 0.004$, $\chi^2$ test) but not R2 ($p = 0.058$, $\chi^2$ test). Signal L2 exhibited the fewest seizures (versus R1: $p < 0.035$, others: $p < 0.003$, $\chi^2$ test). We found no statistically significant difference in seizure counts between R1 and R2 ($p = 0.297$, $\chi^2$ test).

3.2. Time-varying seizure counts

We examined whether the laterality or the location of seizures remained constant over two years, providing an appreciation for the long-lasting dynamical nature of the epileptic brain. Results showed nonrandom ($p < 0.0001$, nonparametric test run) time-variant laterality (Figs. 3A and B) and localization (Figs. 3C and D) over monthly and daily timescales with a very dramatic side shift arising between four and five months (183 and 192 days postop) after the first recorded seizure (79 days postop). Seizure occurrences initially increased in three months postop but eventually decreased from monthly to none (Figs. 3B and D).

Changing either the stimulation or detection parameters of the system did not immediately result in onset side shifts (Figs. 3A and C). Between 400 and 535 days postoperation, the final system detection parameters were set to sense signals L1 and R1, which exhibited all the ictal episodes (L1: 4/9, R1: 5/9) before patient’s seizure freedom (i.e., Engel Class I [14]). The stimulation parameters, which remained relatively
Fig. 2. Intraoperative (A–E) and extraoperative (F–G) recordings from both hippocampi. (A) Left and (B) right hippocampal action potentials (APs). (C) Left side with interictal spikes and (D) right side without interictal spikes. (E) Left interictal spikes (red) coincided with multiunit AP bursts (black). (F) The 1st and (G) 54th ECoG seizures with L1 and R1 SOZs, respectively (arrow). The RNS™ delivers therapy upon seizure detection (vertical line).
Fig. 3. Tracking (A, C), tallying (B, D), and clustering (E–F) the ECoG seizures. Tracking the SOZ laterality (A, B) and localization (C, D) shows shifts from the left (L1 and L2) to the right (R1 and R2) side over daily (A, C) and monthly (B, D) timescales for the seizures (black asterisk) unrelated to changes in RNS™ detection or stimulation parameters (solid vertical lines). Total seizure preponderance does not indicate lateralization (A) but may indicate localization (C). (E) Seizure clusters mostly occur within a week, where (F) time between consecutive seizures models a negative binomial distribution.
constant throughout the change of the detection parameters since 85 days postop, did not correlate with any onset side shift (Fig. 3A). A key stimulation-parameter change was a 35-day-long charge-density increase by pulse-width widening 111 days postop, which occurred well before the first significant SOZ laterality shift 192 days postop.

Changes in chronic antiepileptic medication, all after 500 days postop, did not affect our findings (Fig. 3). In summary, our case raised an important question about the most reliable period to record the true SOZ during presurgical evaluation while illustrating seizure laterality and focus dynamics in the human brain over months to a couple years.

4. Discussion

Both EEG and iEEG for presurgical seizure lateralization assume some degree of stationarity about ictal events. Yet, previous studies have revealed that epileptic tissue possesses highly dynamic mechanisms [11–13]. Much time (weeks to month) may elapse during and between each diagnostic test, while heterogeneous dynamical brain-network changes can proceed, including distinct shifts in SOZ lateralization and localization, even for an abbreviated period. Until recently [9], the timescale and pattern of SOZ laterality shifts have not been examined for obvious ethical and practical limitations in continuous EEG or iEEG testing. This case presents evidence that SOZs and epileptic networks can be a ‘moving target’ throughout the years.

By exploiting the feedback functionality of the RNS™, ictal onsets can be studied extensively, essentially establishing a real-time continuous postsurgical evaluation while providing a true appreciation for the time-varying dynamics of epileptic seizures and seizure-generating foci. Moreover, the technology can record brain activity while the patient is in a more naturalistic environment than a hospital, becoming an invasive ambulatory EEG. The iEEG monitoring in a hospital clearly transpires under contrived circumstances such as diet, being bedbound, sleep deprivation, and medication withdrawal. Often, “clinical” seizures during hospitalization do not mimic the actual seizures that a patient experiences in their natural milieu. These results imply that ambulatory electrographic monitoring may better indicate the complexity and behavior of the epileptic physiological system (i.e., patient and environment).

Overall, this study presents results that challenge traditional perspectives on pinpointing the SOZ during presurgical evaluation and highlights why epilepsy surgery may fail in some patients. For instance, there was a reasonable possibility that this patient would have had mainly left-onset seizures during video-iEEG monitoring. Since this finding would have agreed with video-EEG, PET, and Wada diagnostics, this patient would have undergone a left hippocampectomy, and postop right hippocampal seizures would have been considered de novo, possibly representing disinhibition from eliminating cross-temporal suppression [2]. The RNS™ may become, in the future, a useful instrument for extended iEEG in BTLE cases with abstruse lateralization.

Disclosures

None of the authors has any conflict of interest to disclose. This research was conducted in accordance with the policy and ethics of this journal. None of the work in this manuscript has been previously presented or published.

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