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Intracranial electroencephalographic biomarker predicts effective responsive neurostimulation for epilepsy prior to treatment

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CONFLICT OF INTEREST

V.R.R. has served as a paid consultant to NeuroPace, manufacturer of the RNS System, but declares no targeted compensation for this work. D.F. receives salary support for consulting and clinical trial-related activities performed on behalf of the Epilepsy Study Consortium, a nonprofit organization. D.F. receives no personal income for these activities. Within the past 2 years, the Epilepsy Study Consortium received payments for research services performed by D.F. from BioXell, Biogen, Cerebral Therapeutics, Cerevel, Crossject, Engage Pharmaceuticals, Eisai, Lundbeck, SK Life Science, Xenon, and Zynerba. He has also served as a paid consultant for Eisai and Neurelis Pharmaceuticals. He has received travel support from Medtronic, Eisai, and the Epilepsy Foundation. He has received research support from the Epilepsy Foundation, Empatica, Epitel, and NeuroPace unrelated to this study. He serves on the scientific advisory board for Receptor Life Sciences. He holds equity interests in Neuroview Technology and Receptor Life Sciences. He has received royalty income from Oxford University Press. None of the other authors has any conflict of interest to disclose.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Abstract

Objective: Despite the overall success of responsive neurostimulation (RNS) therapy for drug-resistant focal epilepsy, clinical outcomes in individuals vary significantly and are hard to predict. Biomarkers that indicate the clinical efficacy of RNS—ideally before device implantation—are critically needed, but challenges include the intrinsic heterogeneity of the RNS patient population and variability in clinical management across epilepsy centers. The aim of this study is to use a multicenter dataset to evaluate a candidate biomarker from intracranial electroencephalographic (iEEG) recordings that predicts clinical outcome with subsequent RNS therapy.

Methods: We assembled a federated dataset of iEEG recordings, collected prior to RNS implantation, from a retrospective cohort of 30 patients across three major epilepsy centers. Using ictal iEEG recordings, each center independently calculated network synchronizability, a candidate biomarker indicating the susceptibility of epileptic brain networks to RNS therapy.

Results: Ictal measures of synchronizability in the high-γ band (95–105 Hz) significantly distinguish between good and poor RNS responders after at least 3 years of therapy under the current RNS therapy guidelines (area under the curve = .83). Additionally, ictal high-γ synchronizability is inversely associated with the degree of therapeutic response.

Significance: This study provides a proof-of-concept roadmap for collaborative biomarker evaluation in federated data, where practical considerations impede full data sharing across centers. Our results suggest that network synchronizability can help predict therapeutic response to RNS therapy. With further validation, this biomarker could facilitate patient selection and help avert a costly, invasive intervention in patients who are unlikely to benefit.

Keywords

functional connectivity; multicenter; network neuroscience; neuromodulation; synchronizability

1 | INTRODUCTION

Approximately one in 26 people worldwide will develop epilepsy at some point in their lifetime, and nearly one third of people with epilepsy are drug-resistant and experience recurrent seizures. Although surgically removing the seizure onset zone (SOZ) holds the highest promise for medication-resistant patients to become seizure-free, resective surgery is often not a viable option for those patients with multiple SOZs, seizures that originate from eloquent cortex, or a spatially extensive seizure onset.[1] Responsive neurostimulation (RNS) therapy offers a promising alternative to traditional resective surgery for these patients.[2] The current US Food and Drug Administration (FDA)-approved RNS device for epilepsy

consists of an implantable pulse generator affixed to the skull and connected to two subdural electrodes that facilitate continuous intracranial electroencephalographic (iEEG) sensing and direct electrical stimulation when abnormal activity is detected.[3] A recent study of real-world RNS outcomes showed that >50% of patients are RNS responders (≥50% reduction in seizures) after 1 year, and >70% of patients respond at 3 years.[4]

Although RNS is effective for many patients, approximately 10% of those who receive the device demonstrate no change or an increase in seizure frequency after 9 years of RNS therapy.[5] RNS implantation is invasive and costly, and the risk of serious adverse events, including tissue infection, osteomyelitis, and hemorrhage, although small, is especially burdensome for patients whose condition is not improved by the device.[6–8] Additionally, candidates for RNS typically have a multiyear history of failed medications, many have failed surgical interventions,[2,9] and the psychological toll of prolonged treatment failure can exacerbate comorbid anxiety and depression, which are prevalent in the drug-resistant epilepsy population.[10,11] An expanding body of work is uncovering clues to the mechanisms underlying RNS action,[2,12–17] but there is an ongoing need for validated biomarkers to improve RNS therapy. In particular, a biomarker that predicts whether RNS therapy will lead to a successful outcome, given that the current therapeutic guidelines for RNS therapy are followed,[4] and that can be measured before device implantation, would provide a critical tool for guiding therapeutic options for patients.

To date, many of the biomarkers associated with RNS patient outcomes such as interictal spike frequency, spontaneous seizure interruption, and functional network connectivity have been extracted from long-term RNS device recordings after device implantation.[13,17,18] However, data collected in the epilepsy monitoring unit (EMU) during presurgical monitoring remains an unexplored resource for guiding RNS placement beyond localizing the SOZ, and holds promise for discovering RNS biomarkers that can predict patient outcome. iEEG recordings in particular have been used to predict outcomes from resective surgery,[19,20] indicate effective locations and time points for seizure control,[21] predict dynamics of seizure spread,[22] and functionally map brain networks through corticocortical evoked potentials.[23,24] It is likely that multiple factors, such as medication schedule, RNS implant location, and stimulation parameters, contribute to a patient's therapeutic response. Nonetheless, evidence that RNS therapy has a gradual effect leads to the hypothesis that the organization of brain network connectivity may help predict response to targeted RNS therapy.

In this study, we present a candidate biomarker—network synchronizability—calculated from iEEG recorded during presurgical evaluation, for predicting whether a patient will respond to RNS therapy. Network synchronizability is a metric borrowed from the field of graph theory and is a theoretical measure of the diffusion of information throughout a network under certain assumptions of system dynamics.[25,26] Preliminary studies show that network synchronizability at seizure onset is a promising candidate biomarker for identifying patients most likely to benefit from resective surgery.[19,27] Here, we test the hypothesis that global ictal brain network dynamics recorded before RNS implant can indicate whether a patient will respond to RNS therapy. We also establish a set of shared inclusion criteria, computational pipelines, and data repositories to analyze intracranial

electrophysiology and clinical metadata in a federated manner across our three epilepsy centers.

2 | MATERIALS AND METHODS

2.1 | Patient selection and data collection

We aggregated a retrospective cohort of 30 patients by randomly selecting 10 patients who were implanted with the NeuroPace RNS System between June 2014 and September 2018 at each of three major epilepsy centers. We included patients that met the following criteria: patients who were >18 years of age, underwent at least 2 years of RNS treatment, experienced at least one seizure per month before RNS treatment, and underwent iEEG monitoring during presurgical evaluation in the EMU of their epilepsy center as part of standard clinical care before RNS device implantation. Ten of 19 consenting patients from the Hospital of the University of Pennsylvania (HUP) met the inclusion and exclusion criteria at the time of data assembly and were selected for this study. Ten patients meeting the inclusion and exclusion criteria at both New York University (NYU) Langone Comprehensive Epilepsy Center and the University of California, San Francisco (UCSF) Comprehensive Epilepsy Center were additionally selected as a convenience sample to ensure equal representation from each center (Table S1). iEEG data were recorded from cortical grids and strips, depth electrodes, stereo EEG electrodes, or a mixture of electrode types across centers, sampled at either 500 Hz, 512 Hz, or 1024 Hz (with one exception; recordings of Patient NP47 were downsampled from an 8192-Hz sampling rate to a 1024-Hz sampling rate before further processing). At each center, iEEG signals were recorded referentially, with the reference electrode placed distant to the site of seizure onset. Patients were determined to be good candidates for the RNS System based on consensus of each center's multidisciplinary epilepsy care team during epilepsy surgical conference. Data from these evaluations were collected solely for clinical use and incorporated into this study retrospectively. Data collection for research purposes at HUP was approved by the HUP institutional review board under the collaborative and iEEG protocols; all HUP subjects provided consent to have their full-length iEEG recordings and anonymized imaging and metadata publicly released on the ieeg.org portal, an open-source online repository for electrophysiologic studies. The NYU Langone institutional review board granted approval for data collection and allowed that informed consent could be waived for studies involving sharing of deidentified EEG and imaging data. Finally, data collection at UCSF was approved by the UCSF Committee on Human Research, which ruled that informed consent could be waived for studies involving sharing of deidentified EEG and imaging data.

We quantified a patient's response to RNS treatment as the percent change in seizure frequency after stimulation therapy was turned on compared to their preimplant baseline frequency, as reported in the patient's seizure diary and clinical notes. For our main analysis, we used the reported outcome nearest to the second year of implantation after stimulation therapy commenced (median = 2.0 years, interquartile range [IQR] = 1.9–2 .1). We classified patients who achieved ≥50% seizure reduction as "responders" (n = 16), a standard threshold for treatment evaluation, whereas those who had a lesser reduction or increase in seizures were classified as "nonresponders" (n = 14).[7] In an additional analysis

step, we separated patients into three bins associated with their degree of RNS response. Because outcomes are documented differently across centers—some report percent decrease in seizure frequency as a single value, whereas others report a range of seizure reduction values—we arrived at our bin boundaries of 15% and 83% by assigning each patient a value in the middle of their reported outcome range (e.g., a patient with a 50%–74% outcome range would be assigned 62%), then we calculated the two tertile values of all assigned outcomes.

2.2 | iEEG processing and functional network generation

Seizures were identified in the iEEG recordings at each center during clinical presurgical evaluation, and the seizure onset and seizure termination time points were annotated by board-certified epileptologists (B.L., V.R.R., D.F.).[28] In total, 151 seizures across 30 patients were identified for analysis (median = 2.5 seizures/subject, IQR = 2–5). Artifactual channels were identified by visual inspection and removed. Next, data clips containing each seizure were formatted to enter the preprocessing and network generation pipeline described in previous publications (median seizure length = 1.4 min, IQR = 45 s to 2.6 min).[19,27] Briefly, the raw iEEG recordings were denoised using a common average referencing (CAR) technique, wherein the mean across recording channels at a given time point is subtracted from all channels at the same time point.[27,29] Importantly, CAR is robust to the placement of the reference electrode used for signal recording, thus mitigating one potential difference in recording technique between centers.

Metrics from network theory can be applied to electrographic neural data by constructing functional connectivity networks in consecutive time windows, using iEEG electrodes as nodes and assigning the strength of coherence between pairs of electrode recordings as weighted edges. Accordingly, each event clip was split into a total of T nonoverlapping 1-s time windows and functional networks were generated for each time window such that the N recording electrodes represented N network nodes, and an estimate of coherence between each pair of 1-s channel recordings represented the edge weight between respective electrode pairs. We used multitaper coherence, a measure of similarity in spectral power between two signals at a given frequency, to calculate network edge weight as the average coherence value across frequencies in a given frequency band. Studies of neural communication in a variety of behavioral contexts find that neuronal coherence may increase within distinct frequency bands to achieve specific neurophysiological aims, with feedforward communication signals mediated by higher frequencies and feedback signals mediated by lower frequencies.[30] Thus, coherence networks built using specific frequency bands can tease apart band-specific dynamics of neural communication. Therefore, a multitaper coherence network was generated over the β band (15–25 Hz) and high-γ band (95–105 Hz) respectively, as well as a cross-correlation network calculated over a broad band range (5–115 Hz) for each time window.[19] We were left with three functional connectivity networks with N nodes for each of the T time windows across each seizure (Figure 1A).

2.3 | Network synchronizability

The metric of network synchronizability is a global network metric that can be interpreted as the ease by which neural activity propagates throughout a functional connectivity brain network.[27,31] Although related to synchrony, synchronizability is not a measure of how well brain signals are synchronized throughout the network, but rather is a measure of the potential for activity in all regions to fully synchronize with one another. Synchronizability for a given time window is calculated by first representing a network as an N × N adjacency matrix, $\boldsymbol{A}$, where the ij^{th} element holds the value of the edge weight between nodes i and j. The Laplacian matrix is then calculated as $\boldsymbol{L} = \boldsymbol{D} - \boldsymbol{A}$, where $\boldsymbol{D}$ is a diagonal matrix of node strength.[25] Importantly, the edges $l_{i,j}$ of the Laplacian matrix quantify how easily information can diffuse between nodes i and j, and the spread of the Laplacian eigenspectrum reflects the stability of the fully synchronized state.[32] Synchronizability is given as the ratio of the second smallest to the largest eigenvalue of the Laplacian matrix; thus, a larger synchronizability value indicates a system with a greater eigenvalue spread and a greater potential to synchronize.[32] Additional information on the synchronizability measure can be found in the Supporting Information.

We calculated the synchronizability value for consecutive functional connectivity networks to create a synchronizability curve as a function of time, $s(t)$. Once we obtained a synchronizability curve for each seizure event, the curve was normalized such that the ictal period had unit length. For each patient with multiple seizures, all normalized synchronizability curves were averaged at each time point, resulting in a single representative curve per patient, used for group level analysis (Figure 1C).

2.4 | Aggregating data in a federated framework

We created a framework that allowed for distributed processing of clinical neuromonitoring data across epilepsy centers in a standardized manner. Ten patients were selected using the same exclusion and inclusion criteria at each center, respectively, and gave their written informed consent to share their deidentified neuromonitoring data. Mutual data-use agreements were prepared between each institution to allow the investigators to share limited datasets and postprocessed results on the International Epilepsy Electrophysiology Portal (www.ieeg.org)[33], a centralized Health Insurance Portability and Accountability Act (HIPAA)-compliant cloud repository. The same pipeline for electrophysiological data preprocessing and network generation was distributed across centers,[27] ensuring that the data processing steps were identical across sites.

2.5 | Statistical analysis

We used the Mann–Whitney U-test to compare the mean value of each patient's synchronizability curve in responders versus nonresponders. In our sensitivity analysis, we generated a receiver operating characteristic (ROC) curve to measure how well the mean synchronizability value during the ictal period could identify a patient as a responder or a nonresponder for a sweep of classification thresholds. The area under the ROC curve (AUC) was measured, with a value of 1 representing perfect classification, and a value of .5 representing chance assignment of a patient to one of the two groups.

2.6 | Data availability

We share all functional connectivity networks and synchronizability curves derived from iEEG recordings obtained during a patient's stay in the EMU on the free and HIPAA-secure web portal ieeg.org.[33] The code used for generating functional networks and calculating synchronizability is freely available at https://github.com/akhambhati/Echobase.

3 | RESULTS

We began our analysis by examining whether quantifiable clinical factors alone were associated with patients' RNS response. We found no significant difference between responder and nonresponder groups based on years of RNS therapy at the time of outcome measurement (responder IQR = 2.0−2.0, nonresponder IQR = 1.9−2.0, Mann–Whitney $U = 275$, $p = .3$), years with epilepsy (responder IQR = 12.5−20, nonresponder IQR = 13−24, $U = 232$, $p = .5$), or the location of RNS lead implants (mesial temporal implant vs. neocortical, $U = 186$, $p = .3$; unilateral vs. bilateral, $U = 239$, $p = .99$). Additionally, there was no significant difference in number of implanted iEEG electrodes between groups (responder IQR = 86−124, nonresponder IQR = 110−121.5, $U = 249$, $p = .98$). Given that clinical features did not distinguish responders from nonresponders, we next turned to our hypothesis that synchronizability, a measure based on the connectivity of functional brain networks, might have value for predicting treatment response.

The synchronizability value measured from functional brain coherence networks estimates the capacity for neural information to diffuse throughout a network.[27,34,35] Thus, synchronizability after seizure onset is a measure of how much the neural channels for communication are impeded or facilitated during the seizure. We quantified how synchronizability during seizure onset differed between the 16 RNS responders (patients showing at least a 50% reduction in seizure frequency compared with baseline) and the 14 nonresponders, where outcomes were measured after 2 years of RNS titration. We computed synchronizability curves using networks in two frequency bands, β (15– 25 Hz) and high-γ (95–105 Hz), and broad band (5–115 Hz), and found that RNS responders demonstrated a significantly smaller value of network synchronizability in the high-γ band compared with patients who were nonresponders ($U = 173$, $p = .002$). Even after using a Bonferroni correction for multiple comparisons across the three distinct network types, the high-γ band maintained significance ($p < .0167$). In contrast, synchronizability values were similar between groups in the β band and broad band ($p > .05$), suggesting that these bands do not generate network characteristics pertinent to predicting patient response (Figure 2B). In a sensitivity analysis, synchronizability change for high-γ band networks was able to predict responder status with an AUC value of .83 (95% confidence interval = .63–.94; Figure 2C).

Noting that synchronizability values in the high-γ band were lower for responders, we next asked whether the degree of response to RNS therapy at 2 years was inversely related to ictal synchronizability. We separated patients into three outcome bins based on percent seizure reduction (≥83%, 15%–83% exclusive, and ≤15%) with 10 patients per bin. We found that the mean synchronizability value for each bin increased with decreasing seizure reduction, providing further evidence that measures of brain connectivity obtained prior to device

implantation may indicate the extent of therapeutic response within the first few years of therapy (Figure 2D).

We next performed two subanalyses to determine whether the main effect of a smaller synchronizability value in responders held after patients were grouped by iEEG electrode type and by location of implanted RNS leads. The trend of lower synchronizability in responders was maintained in each category for the high-γ band, whereas directionality of the difference between responder groups was variable in the β band and broad band. Specifically, there was a significant difference in the high-γ band for patients with majority depth electrodes (responders $n = 10$, nonresponders $n = 5$, $U = 62$, $p = .028$) and patients with unilateral RNS lead implantation (responders $n = 9$, nonresponders $n = 9$, $U = 61$, $p = .017$; Figure 3). An additional analysis on patients within each center also demonstrated trends consistent with the main findings in the high-γ band, although the individual center results were statistically underpowered, with only one center reaching a significant result (UCSF, responders $n = 4$, nonresponders $n = 6$, $U = 12$, $p = .038$; Figure S1). Furthermore, we repeated the main analysis at two additional time points and found that synchronizability in the high-γ band remained significantly different between responder groups after 1 and 3 years of stimulation therapy ($p < .015$; Figure S2, Figure S3). Finally, we determined that an electrode-specific effect due to our choice of reference method was not biasing our conclusions (Figure S4), and found no evidence for biases due to circadian rhythm (Figure S5). Taken together, our results illustrate that neither laterality of implant, type of intracranial electrodes, nor treatment center bias the main finding that high-γ synchronizability is predictive of RNS outcome.

4 | DISCUSSION

To our knowledge, our results are the first to demonstrate the prognostic value of iEEG data collected before RNS implantation to determine whether patients are likely to respond to RNS therapy. In our analysis, we find that ictal synchronizability has the ability to distinguish RNS responders from nonresponders over the first 3 years of therapy, with trends maintained even after segmenting patients by onset location, iEEG electrode type, and treatment center. Additionally, our study serves as a proof-of-concept for multicenter collaborative RNS biomarker discovery on federated datasets.

Much evidence suggests that epilepsy is a disorder of brain networks,[36] and incorporating measures of complex macroscale neural dynamics is promising for guiding surgical resection in cases of drug-resistant epilepsy.[37,38] In prior work, the network measure of broad band synchronizability at seizure onset predicted a good outcome after surgical resection, reflecting the network's ability to isolate seizure propagation after onset.[19] Our finding that RNS responders exhibit a smaller synchronizability magnitude during seizures is consistent with the previous study, although our results are significant in the high-γ band, suggesting that biomarkers for neurostimulation outcomes may be more frequency-specific. Prior work found that RNS stimulation acutely suppresses γ-band phase-locking, a measure of synchrony, between signals in adjacent electrode channels, although phase-locking in lower frequencies was not significantly affected.[15] Paired with our results, it is possible that RNS stimulation is more effective at suppressing phase-locking in patients with low

synchronizability networks that take longer to naturally synchronize. In another study of brain synchronizability in epilepsy patients, a smaller preictal synchronizability magnitude in the high-γ band was shown to be a hallmark of network focality.[27] Recent longitudinal analysis of RNS recordings supports the theory that stimulation also actuates gradual, frequency-specific plasticity changes that differ for responders versus nonresponders.[17] A purely speculative possibility is that networks of RNS responders are more focal and thus exhibit a greater resistance to spreading epileptic activity throughout the network, making it easier for stimulation to further decouple epileptic brain regions from the broader network.

The mechanism of RNS remains poorly understood, and undoubtedly a number of external factors may influence responder status over time, including programmed detection and stimulation parameters and interactions between RNS therapy and pharmaceutical treatments.[14,39] Our results suggest that the intrinsic connectivity of epileptic networks may be a significant predictive factor of their susceptibility to RNS therapy within the first 3 years. It is unknown whether synchronizability predicts outcome at later time points, as many patients ultimately improve over time.[4,5] We propose that there is still clinical utility in a biomarker that can indicate whether a patient will respond within the initial years of therapy, as they may benefit from a different approach to device programming or medication management that departs from the typical treatment strategy, in an effort to decrease time to response.

Using iEEG during presurgical evaluation to determine whether a patient should be implanted with an RNS device is not a novel concept. Patients are typically referred for RNS therapy after iEEG implant when seizures are found to emanate from an eloquent region that cannot be resected, when there are multiple, spatially distinct generators for seizures (e.g., independent bitemporal seizure onsets), or when seizures are poorly localized and focal resection or ablation is not an option.[2] It is typically presumed that RNS is more likely to be effective in the first two situations, although we know that rapidly synchronized networks can exist in well-localized focal or multifocal epilepsies, likely related to their underlying cause. It is our long-term vision that our biomarker may identify these poor responders early, and that it may also identify potential good responders whose seizures spread rapidly or are poorly localized. In our study, there were no features in the iEEG seizure onset pattern that distinguished likely responders from nonresponders, even on review by expert epileptologists. We do not yet know whether the utility of ictal network synchronizability as a biomarker of treatment response is unique to RNS or is a general marker of the susceptibility of the epileptic network to neuromodulation, including deep brain stimulation and vagus nerve stimulation. Rigorous quantitative analysis of many more patients over more time points will be required to more precisely understand the physiologic underpinnings of our predictions.

4.1 | Building a multicenter collaborative pipeline

Procedures for preimplant evaluation and RNS treatment, including patient selection, lead placement, and device programming, are not standardized across epilepsy centers and differ from protocols used in RNS clinical trials.[4] Thus, results from clinical trials will need to be augmented by quantitative biomarkers, not just to select patients for RNS therapy, but also

to select regions for stimulation and to titrate stimulation parameters. Although candidate biomarkers to predict RNS response exist, discovering robust biomarkers and validating them is challenging due to the heterogeneity of the patient population, nonstandardized clinical methods, and limited access to centralized clinical data, including outcome measures and medication regimens.

For these reasons, we elected to unify data formats, annotation protocols, electrode coregistration, and analysis code so that our experiments could be federated, or performed separately and in parallel across our sites, and then the results aggregated centrally. Despite some initial up-front effort to make this protocol run smoothly, we found this approach to be very feasible and efficient. In this way, our study lays the groundwork for streamlined collaboration on RNS biomarker discovery. We only discovered the broadly significant differences in synchronizability change based on RNS outcome after combining data across multiple centers, a result that is a powerful demonstration of how biomarker evaluation using any one institution's dataset is statistically underpowered. We believe that this same paradigm could be extremely useful in other difficult "medical informatics" problems that require analyzing large amounts of data across institutional and industry boundaries. By utilizing centralized tools that can be ported into center-specific data environments, investigators can uphold privacy and firewall restrictions on original data while sharing their processed derivatives.

4.2 | Methodological considerations

One clinical challenge presented in the study of RNS patients involves assessing clinical outcome. For this pilot study, we chose to use each patient's self-reported seizure diary, which is the currently accepted gold standard for calibrating RNS therapy, as our measure of therapy response. The limits of relying on seizure diaries is well documented; however, we chose this outcome measure because it was used in the clinical trials leading to RNS device approval and is the gold standard for judging response for other treatments by the FDA.[40]

There are a number of additional limitations to our study. As a proof-of-principle study, our sample size of 30 patients is small, and gives us limited ability to fully account for center-specific factors and patient variability or to perform a more detailed breakdown analysis. We mitigated variability in data processing by implementing a shared, well-documented pipeline that will easily scale to a larger number of epilepsy centers as we expand patient numbers in future work.[27] Another limitation is in the retrospective nature of this work. A prospective, randomized clinical trial will ultimately be required to fully assess the benefit of any clinical biomarker or computational model for surgical planning.

In this study, we take the first step toward translating our work into clinical practice by preparing a framework to support large-scale validation of our biomarker collaboratively across centers. We hope that our approach and the infrastructure we employ will accelerate the progress of the epilepsy community toward answering the urgent questions about how to optimize RNS therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Validated clinical biomarkers that can predict the success of RNS therapy do not currently exist
- Intracranial EEG data are an unexplored resource that may hold biomarkers of RNS outcome, measurable before the RNS device is implanted
- We find that differences in synchronizability, a measure of dynamic brain connectivity, can separate RNS responders from nonresponders
- A federated framework for data analysis allows for scalable biomarker discovery, while keeping private health information secure

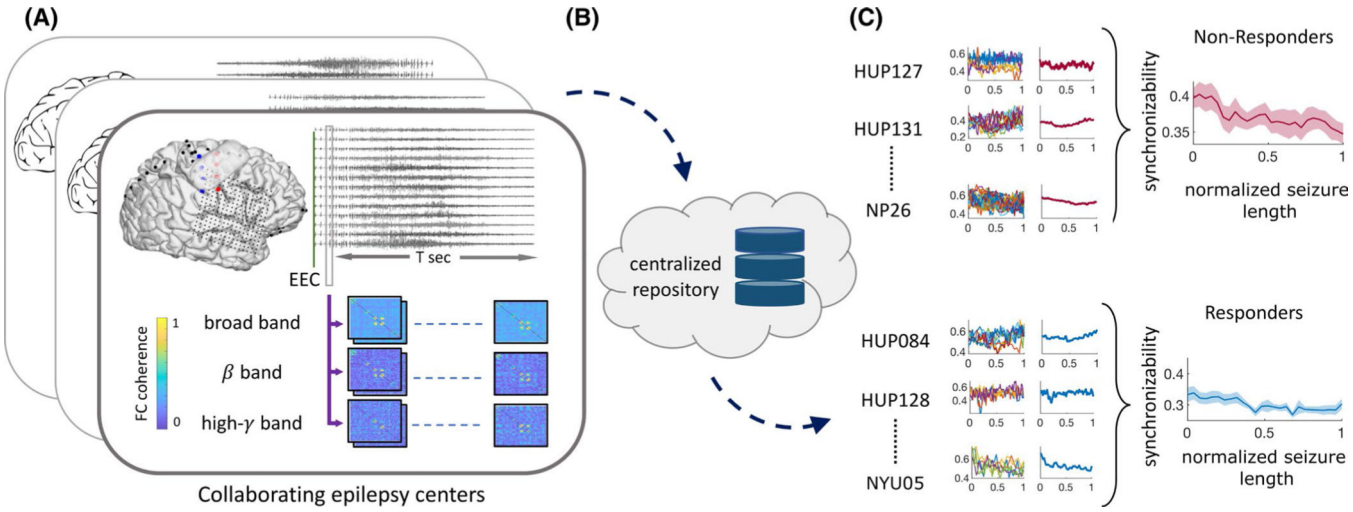

FIGURE 1.

Construction of functional networks and synchronizability curves. (A) Functional connectivity networks, represented by square adjacency matrices, are generated from consecutive 1-s windows throughout the duration of each seizure event. The same processing pipeline, represented by purple arrows, is used within the data environment of each institution to estimate multitaper coherence networks in the β and high-γ bands, as well as broad band cross-correlation networks. (B) All processed networks are shared in a centralized cloud repository. (C) Synchronizability curves are calculated for each seizure and normalized to a unit length. Patient curves are grouped by outcome status and averaged to yield representative responder and nonresponder curves. EEC, earliest electrographic onset; FC, functional connectivity

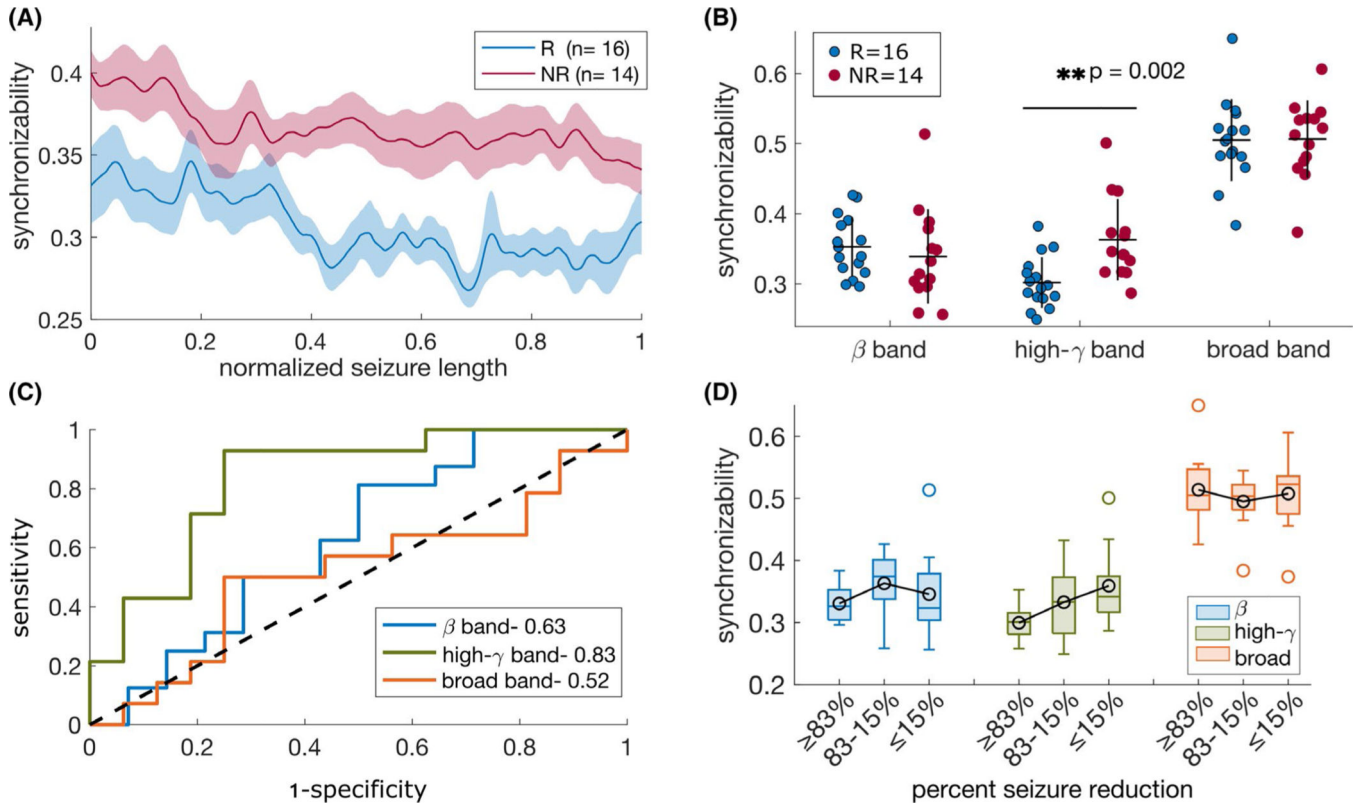

FIGURE 2.

Synchronizability magnitude during ictal period separates responsive neurostimulation responders from nonresponders. (A) Synchronizability curves over the ictal period for the high-γ band (95–105 Hz) normalized to unit length. Solid lines show the averaged synchronizability curves of subjects sharing the same outcome status (NR, nonresponder; R, responder) at 2 years since stimulation began. The envelope indicates the standard error of the mean. (B) Mean synchronizability value during a patient's seizures, calculated using networks in multiple frequency bands for responders versus nonresponders at 2 years (significant for high-γ band, Mann–Whitney $U = 173$, $p = .002$). Dots represent patients, horizontal (vertical) lines represent mean (SD) of outcome group. (C) Receiver operating characteristic (ROC) curves show the true positive rate (sensitivity) versus the false positive rate (1 − specificity) at each classification threshold. Data were generated for the two frequency bands and broad band. The area under the ROC curve (AUC) was greatest for high-γ networks, with an AUC of .83. (D) Patients were divided into three outcome groups bounded by 15% seizure reduction and 83% seizure reduction, with 10 patients per group. Box plots show the distribution of mean synchronizability values for 10 patients in a given outcome group with 75% confidence interval (box), median (solid line), 95% confidence interval (whiskers), and mean trend (connecting line)

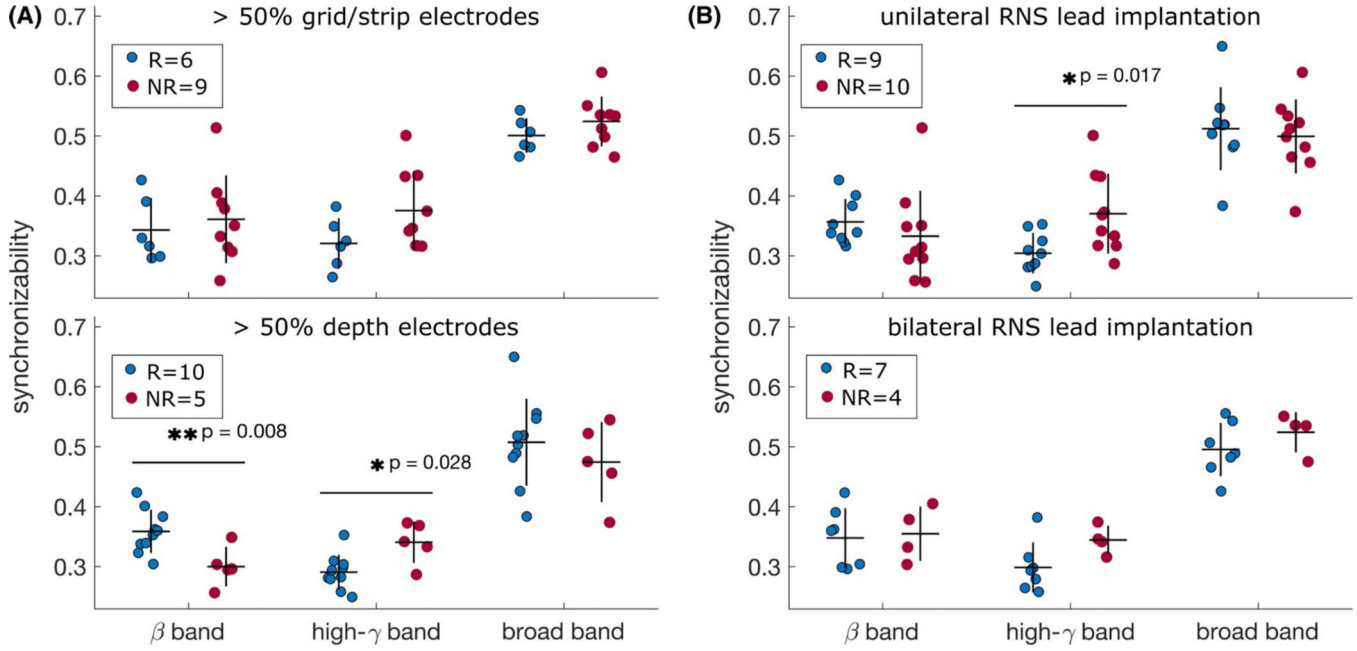

FIGURE 3.

Synchronizability values among patient subgroups. Separation of responders (R) and nonresponders (NR) in each synchronizability band for patients with >50% grid/strip electrodes versus patients with majority depth electrodes (A), and in patients with unilateral versus bilateral onset foci (B). Horizontal lines represent the mean ictal synchronizability value within a response group; vertical lines represent the SD within a group