



# OPEN Identifying the epileptic network by linking interictal functional and structural connectivity

Ujwal Boddeti<sup>1,2</sup>, Pue Farooque<sup>3</sup>, Hari McGrath<sup>3</sup>, Jennifer Percy<sup>3</sup>, Omar Chishti<sup>3</sup>, Robert B. Duckrow<sup>3</sup>, Dennis Spencer<sup>3</sup>, Hitten P. Zaveri<sup>4</sup> & Alexander Ksendzovsky<sup>2</sup>✉

Over the last two decades, it has become increasingly clear that epilepsy is a network disorder. However, it is unclear whether these networks are established only during seizures or persist interictally. The goal of this study was to identify whether functional seizure networks exist interictally and evaluate if there is a structural basis to these networks. We identified four patients with mesial temporal lobe epilepsy who underwent resective epilepsy surgery. We estimated functional and structural connectivity across intracranial electrode contacts involved in seizure onset, early spread, and uninvolved controls. Across all interictal epochs considered, we found higher functional and white matter connectivity across cortical regions involved in seizure spread. Additionally, we observed that the patient in our cohort with the best seizure outcome had the highest functional connectivity across seizure contacts. Functional connectivity findings suggest the presence of an interictal seizure network that parallels underlying structural connectivity. Furthermore, our findings suggest that disruption or ablation of highly connected seizure regions may be necessary to achieve improved post-operative seizure freedom.

**Keywords** Diffusion tensor imaging, Epilepsy, Functional connectivity, Interictal connectivity, Mesial temporal lobe epilepsy, Seizure networks

Over the past two decades, outcomes in epilepsy surgery have remained largely stagnant, with approximately 50% of patients who undergo epilepsy surgery exhibiting seizure recurrence within one-year of surgery<sup>1</sup>. Until recently, focal epilepsy was considered a disorder of defined epileptogenic foci (EF) with identification and targeting of regions of seizure onset guiding surgical management of drug-resistant epilepsy (DRE)<sup>2,3</sup>. However, despite resection or modulation of EF, complete seizure freedom post-epilepsy surgery is frequently not achieved, with many patients continuing to experience seizures, carrying significant morbidity. As such, it is imperative that we investigate what could be contributing to treatment failure.

Over the past two decades, there has been a shift in our understanding of epilepsy as a disease. Namely, an increasing number of studies have begun to suggest that focal epilepsy is not simply a focal disorder, but rather one of distributed epileptogenic networks<sup>2,4,5</sup>. In fact, recent evidence suggests that seizures likely either hijack pre-existing local circuitry or recruit new pathologic brain networks, forming an aberrant seizure network which ultimately explains why traditional surgical approaches targeting seizure onset foci alone may fail to achieve seizure freedom in some patients<sup>6</sup>.

Of the focal epilepsies, mesial temporal lobe epilepsy (MTLE) is the most common and is often associated with hippocampal sclerosis<sup>7</sup>. Although MTLE is a focal disorder, electrophysiology, histopathology, and neuroimaging studies have all suggested that alterations in localized circuits and white matter tracts exist beyond the hippocampus and are distributed in a network fashion<sup>8</sup>. In fact, this was first suggested by Spencer and Spencer in 1994, when they showed that seizure propagation was facilitated by interactions between hippocampus and entorhinal cortex in a subset of MTLE patients<sup>9</sup>. Since then, there have been numerous studies describing extra-hippocampal neuropathologic and electrophysiologic changes in MTLE patients, such as in the amygdala and entorhinal cortex<sup>2,10–15</sup>. These and a number of other findings ultimately prompted the International League Against Epilepsy (ILAE) in 2010 to redefine focal seizures as “... originating within networks,” and even more recently in a 2017 report, that epilepsy is in fact a network disorder, and not simply “...a symptom of local brain abnormalities...”<sup>16,17</sup>. Perhaps more interesting are the clinical implications of this. Building on the

<sup>1</sup>Surgical Neurology Branch, NINDS, National Institutes of Health, Bethesda, MD 20892, USA. <sup>2</sup>Department of Neurosurgery, University of Maryland School of Medicine, 670 W Baltimore St, HSF3, Rm 9110, Baltimore, MD 21201, USA. <sup>3</sup>Department of Neurosurgery, Yale University, New Haven, CT 06520, USA. <sup>4</sup>Department of Neurology, Yale University, New Haven, CT 06520, USA. ✉email: AKsendzovsky@som.umaryland.edu

understanding that epilepsy is a disorder of circuitry, recent studies have suggested that a primary contributing factor to epilepsy surgery failure is likely ineffective disruption of principal components of the seizure network. For example, in 2019 Andrews et al. showed that patients in whom cortical areas of rapid seizure spread (<10 sec) from ictal onset were unresected experienced significantly higher rates of seizure recurrence within one-year post-resective surgery, suggesting that resecting targets beyond seizure onset may be necessary to achieve adequate seizure control<sup>3</sup>. Since then, a number of studies have similarly reported on the correlation between resection of highly connected cortical and subcortical targets and seizure-freedom outcomes<sup>18</sup>. These studies ultimately lend support to the network theory of epilepsy and suggest that the seizure network must be taken into consideration during surgical decision-making. However, this now begs the question, how can we characterize seizure networks?

To-date, the presence of seizure networks has been suggested based on recordings during seizure events, however, there are currently few studies that explore whether pathologic seizure networks persist interictally. Of the studies reported, many employ non-invasive techniques, such as scalp electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) studies, to characterize resting-state functional connectivity (FC)<sup>18</sup>. Although such studies lend support to the presence of interictal seizure networks, they fail to offer the precise cortical resolution needed to identify key components of the seizure network. We used intracranial EEG (icEEG) recordings obtained during neuromonitoring to ask if seizure networks exist interictally. Specifically, we hypothesized that there exists increased FC and white matter tract connectivity among cortical regions involved in seizure onset and spread, compared to uninvolved regions. Finally, we considered whether resection of seizure regions that were more highly connected was associated with better post-operative seizure outcomes.

Materials and methods
Patients

We retrospectively identified 4 patients (2 female, 37.2 ± 11.8 years) with MTLE who underwent resective surgery by a single surgeon (D.D.S.). All patients in the study cohort underwent neuromonitoring between September 1, 2014, and December 1, 2016, for 8.5 ± 4.0 days. The surgical epilepsy evaluation is a multiphase workup, with phase 1 consisting of non-invasive assessment modalities (i.e., scalp EEG, MRI, fluorodeoxyglucose positron-emission tomography (FDG-PET)), phase 2 consisting of an intracarotid Wada test if necessary, phase 3 consisting of icEEG monitoring with stereotactic EEG (SEEG) depth electrodes and subdural strips and grids as needed, and phase 4 consisting of treatment, typically surgical resection, laser ablation, or neuromodulation. In each case, the clinical team determines placement of electrode contacts to localize ictal regions. All surgical procedures and icEEG monitoring were performed at the Yale Comprehensive Epilepsy Center at the Yale New Haven Hospital (YNHH) (New Haven, CT). During neuromonitoring, each patient had 1.75 ± 0.50 seizures, for a total of seven seizures across all patients. Each patient was followed for 3.25 ± 0.96 years and outcome was evaluated using the ILAE classification. All icEEG used in this study was obtained during patients' awake state. Patient information is briefly detailed below and for a full list of patient demographic information, see Table 1. The study was conducted with approval from the Yale Institutional Review Board (IRB) and informed consent was obtained from all participants. The study was conducted in accordance with the relevant guidelines and regulations.

Patient ID	Sex	Age	Sz onset age	Inciting event	Seizure types	Non-invasive workup findings (Phase 1)	icEEG findings (Phase 3)	Procedure (Phase 4)	ILAE outcome
1	Female	41	39	None	Subclinical Focal to BTC	<ul style="list-style-type: none"><li>• MRI - T2 hyperintensity in R hippocampus and temporal cortex</li><li>• FDG-PET - hypometabolism in R lateral temporal cortex</li><li>• EEG - diffuse R temporal 4 Hz sharp waves</li></ul>	High-voltage spikes in R mesial temporal lobe, hippocampus, and amygdala	Resection R lateral temporal lobe, hippocampus, and amygdala	Class 1
2	Male	25	20	None	Subclinical Focal aware, Focal impaired awareness Focal to BTC	<ul style="list-style-type: none"><li>• MRI - normal</li><li>• FDG-PET - hypometabolism in R temporal and frontal opercula</li><li>• EEG - R temporal slowing</li></ul>	Involvement of bilateral hippocampi and R amygdala	RNS bilateral parahippocampi and temporal poles	Class 3
3	Female	31	9	None	Focal impaired awareness Focal to BTC	<ul style="list-style-type: none"><li>• MRI - normal</li><li>• FDG-PET - broad region of hypointensity in the R inferomedial temporal lobe</li><li>• EEG - sharp rhythmic activity in the R posterior temporal lobe</li></ul>	Revealed likely seizure foci to be in R temporal and frontal lobes	Resection R hippocampus and parahippocampus	Class 3
4	Male	52	24	TBI	Subclinical Focal impaired awareness	<ul style="list-style-type: none"><li>• MRI - T2 hyperintensity and atrophy of bilateral hippocampi</li><li>• FDG-PET - severe hypometabolism in L lateral temporal lobe and moderate hypometabolism in R medial temporal lobe</li><li>• EEG - R temporal theta rhythm with rapid involvement of L temporal region within 2 seconds</li></ul>	High-voltage spikes and polyspikes in the R mesial temporal lobe, hippocampus, and amygdala	RNS R hippocampus, amygdala, and entorhinal cortex	Class 4

Table 1. Patient demographic information. icEEG = intracranial electroencephalography; BTC = bilateral tonic clonic; TBI = traumatic brain injury; ILAE - International League Against Epilepsy.

### Patient 1

Patient 1 was a 41-year-old female with new-onset seizures at 39 years of age. The patient had no family history of seizures and no seizure risk factors. She experienced focal seizures which typically progressed to generalized tonic-clonic (GTC) lasting 3–4 min several nights per week. Approximately one time per month, her seizures would involve automatisms involving lip-smacking and nonverbal vocalizations. She presented to YNHH for surgical epilepsy workup after failing management with multiple anti-seizure medications (ASMs). Phase 1 of the surgical epilepsy workup revealed MRI findings of T2 hyperintensity in the right hippocampus and temporal cortex. FDG-PET showed hypometabolism in right lateral temporal cortex. Interictal scalp EEG showed right-sided temporal intermittent rhythmic delta activity (TIRDA) and anterior temporal epileptiform discharges. Ictal scalp EEG findings showed diffuse right temporal 4 Hz sharp waves with spread throughout right hemisphere. The patient was then scheduled for icEEG monitoring to localize cortical and subcortical targets more precisely for epilepsy surgery. Patient was implanted with a combination of a single subdural grid, 11 strips, and four SEEG depth electrodes. Interictal icEEG revealed right inferior frontal lobe spikes (2–3 Hz) and high voltage spikes and polyspikes in the right hippocampus. Ictal icEEG showed onset in the right mesial temporal lobe with spread within 8 s to ipsilateral insula. The patient underwent a right extended temporal lobectomy, 6 cm from the temporal pole and resection of ipsilateral hippocampus and amygdala.

### Patient 2

Patient 2 was a 25-year-old male with new-onset seizures at 20 years of age. The patient had a family history of seizures (patient's mother had three cousins with a reported seizure history). He experienced a combination of focal aware (FA), focal impaired awareness (FIA), and GTC seizures. Partial seizure episodes involved swallowing and speech difficulties at times, with episodes lasting 1–3 min occurring once per week. The patient presented to YNHH for workup after failing management with multiple ASMs. Phase 1 of the surgical epilepsy workup revealed FDG-PET findings of right anterior temporal and right frontal opercular hypometabolism. MRI Brain was normal. Single-photon emission computed tomography (SPECT) revealed bilateral (right > left) medial temporal lobe hypoperfusion. Interictal scalp EEG findings showed right temporal slowing after multiple seizure events and occasional sharp discharges arising from right mid-anterior temporal lobe. Ictal scalp EEG showed epileptiform activity arising from right and left temporal lobes. The patient was implanted with 16 SEEG depth electrodes with coverage of bilateral temporal and parietal regions, including amygdala, hippocampi, medial and inferior occipital lobes, anterior and posterior cingulate, medial orbitofrontal and anterior insula. Interictal icEEG revealed epileptiform discharges from left amygdala and right amygdala with spread to right hippocampus. Ictal icEEG revealed multiple seizure spread patterns, one being onset in the right amygdala with spread to right hippocampus and another being onset in the left hippocampus with spread to left posterior cingulate. The patient was scheduled for bilateral implantation of the Responsive Neurostimulation (RNS) neuromodulation device.

### Patient 3

Patient 3 was a 31-year-old female with new-onset seizures at 9 years of age. Patient reported a significant family history, having a son with generalized epilepsy. She experienced secondary generalized seizures, lasting up to 1 min in duration, occurring two-four times per month, with all episodes consisting of a déjà vu aura. She presented to YNHH for surgical epilepsy workup after failing multiple ASMs. Phase 1 of the surgical epilepsy workup revealed FDG-PET findings of region of hypometabolism in the right inferomedial temporal lobe. MRI Brain was normal. Ictal scalp EEG showed sharp rhythmic activity arising from the right posterior temporal region. Interictal scalp EEG showed rare discharges and high amplitude rhythmic theta activity in the right posterior temporal lobe. Ictal scalp EEG showed right temporal onset with spread to bilateral hemispheres. The patient was then scheduled for icEEG monitoring. A combination of a single subdural grid and 15 strips were used, with coverage of right frontal pole and orbitofrontal area, right temporal lobe with hippocampus and amygdala, right parietal lobe, right occipital pole, and left anterior frontal region. Interictal icEEG revealed spike wave discharges arising from right temporal pole, medial temporal lobe, and frontal region. Ictal icEEG revealed onset in right entorhinal cortex with spread to ipsilateral hippocampus and amygdala. The patient was scheduled for surgical resection of right hippocampus and parahippocampus.

### Patient 4

Patient 4 was a 52-year-old male who presented with new-onset seizures at 24 years of age secondary to a traumatic brain injury (TBI), at which time patient experienced a GTC seizure. After TBI, the patient continued to experience refractory seizures, with several GTCs and FIAs occurring per month. Six months after the injury, the patient had an episode of status epilepticus, after which he had significant worsening memory and cognition. The patient's GTCs resolved, and he now has FIA seizures characterized by lip-smacking and bimanual automatisms that last 1–2 min and occur one-two times per week. Patient had no family history of seizures. The patient presented for surgical epilepsy workup after failing multiple ASMs. Phase 1 of the surgical epilepsy workup revealed MRI findings of focal encephalomalacia in left lateral temporal area and increased T2-weighted-Fluid-Attenuated-Inversion-Recovery (FLAIR) signal and atrophy in bilateral hippocampi. FDG-PET showed severe hypometabolism in left lateral temporal lobe and moderate hypometabolism in right medial temporal lobe. Interictal scalp EEG showed left temporal slowing. Ictal scalp EEG showed rhythmic theta waves in the right temporal region with rapid expression in the left temporal region within two seconds. The patient was scheduled for icEEG monitoring with SEEG depth electrodes, five left-sided covering medial and lateral temporal lobe and four right-sided covering hippocampus. Interictal icEEG revealed discharges in right mid and posterior hippocampus and right amygdala. Ictal icEEG revealed onset in right mid hippocampus with spread to ipsilateral posterior hippocampus, amygdala, finally cortex (in 20–30 s). Patient was scheduled for implantation

of the RNS neuromodulation device, with one electrode in the right hippocampus and amygdala and one in the right entorhinal cortex. RNS was chosen as the patient was noted to have global memory dysfunction on neuropsychological assessment.

### Intracranial recording acquisition and preprocessing

Each patient underwent an intracranial study with platinum recording contacts (Ad-Tech, Racine, WI) implanted subdurally and/or with depth electrodes. Continuous icEEG was sampled from each electrode contact at 1024 Hz. Subdural contacts were arranged in grid and strip configurations with inter-contact spacing of 10 mm. Two epileptologists independently (P.F. and J.P.) identified contacts of seizure onset (SOZ) and early spread (SP) (i.e., first electrode contact over 2 cm away to exhibit ictal activity after seizure onset at SOZ). After identification of SOZ and SP contacts, control (never exhibited ictal or interictal activity) contacts were selected such that SP and control contacts were both approximately equidistant from their respective SOZ contact. We show a representative schematic in Fig. 1A delineating contact selection.

Following identification of SOZ, SP, and control contacts, interictal epochs were identified by a single epileptologist (P.F.). Interictal epochs were defined as periods of no electrographic ictal activity at least 6 h from any seizure event. For each patient, interictal epochs  $5.0 \pm 2.1$  min in duration were selected for further analysis. We excluded contacts showing obvious artifacts during visual inspection. After obtaining icEEG, we bandpass-filtered raw signals between 0.1 and 512 Hz using a Butterworth filter (order = 4) to remove low-frequency drift and DC offset. We finally applied a notch filter to remove 60 Hz line noise.

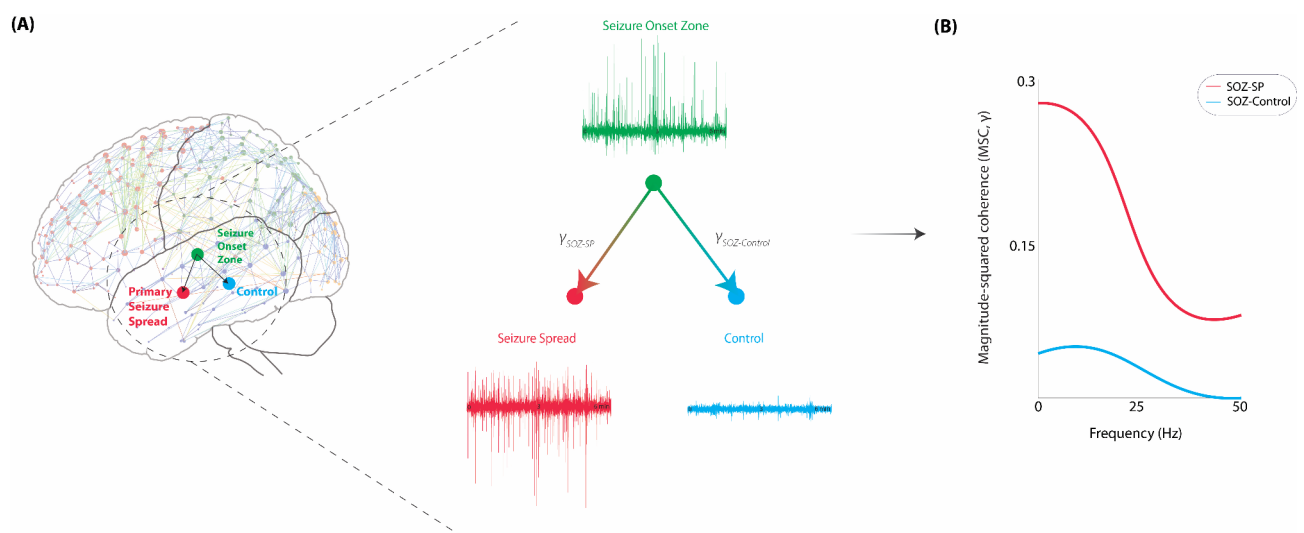
### Electrode distance calculation

To show that control contacts within each electrode pair were truly equidistant to respective SOZ contacts, we calculated inter-electrode distances across all SOZ-SP and SOZ-control pairs. Electrode contacts were identified on post-implant images and transformed to pre-implant images using the non-linear transformation BioImage Suite software<sup>19</sup>. Then, we obtained coordinates for each contact and calculated Euclidean distances between each pair of SOZ-SP and SOZ-control contacts by expressing the distance between two points,  $p_1 (x_1, y_1, z_1)$  and  $p_2 (x_2, y_2, z_2)$  as follows:

$$d_{p_1, p_2} = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2} \quad (1)$$

### Interictal magnitude-squared coherence analysis

We quantified FC using magnitude-squared coherence (MSC), a measure of the linear correlation between two signals  $x(f)$  and  $y(f)$  at each frequency  $(f)$ <sup>20</sup>. Coherence can be considered as a measure of the correlation of two signals indexed by frequency and can be estimated from the Fourier Transform (FT) of the two signals<sup>21</sup>. We specifically chose this measure as we were unconcerned with phase information but rather the magnitude of the relationship between the signals at each frequency. MSC is calculated as follows:



**Fig. 1.** Experimental workflow. **(A)** Here, we show a schematic of the experimental workflow. SOZ and SP contacts were identified by two epileptologists (P.F. and J.P.) through examination of seizure recordings during intracranial neuromonitoring. Equidistant control contacts were identified, with the aim of choosing cortical areas covered by subdural electrodes that were approximately equidistant from the SOZ. Subsequent analysis involved extraction of interictal (at least 6 h from any seizure event) ECoG and comparison of MSC between SOZ-SP and SOZ-control contact pairs. **(B)** Here, we show a representative MSC plot for a single pair of SOZ-SP (red) and SOZ-control (blue) observations. Abbreviations: ECoG - electrocorticography, SOZ - seizure onset zone, SP - primary seizure spread zone, MSC ( $\gamma$ ) - magnitude-squared coherence.

$$MSC_{xy}(f) = \frac{|G_{xy}(f)|^2}{G_{xx}(f)G_{yy}(f)} \quad (2)$$

where,  $G_{xy}(f)$  is the cross-spectral density (CSD) between the two signals  $x(t)$  and  $y(t)$  and  $G_{xx}(f)$  and  $G_{yy}(f)$  are the autospectral densities (ASD) of  $x(t)$  and  $y(t)$ , respectively<sup>22</sup>. MSC varies from 0 to 1, with higher values suggesting stronger correlation between the two signals at the considered frequency. MSC analysis was performed using a Hamming window with window size 1024 to adequately capture the spectral bands of interest. Furthermore, we used a window overlap of 25% ( $f_s/4=256$  samples). MSC signals were smoothed by convolution with a Gaussian kernel ( $\sigma=10\%$  of original signal size) for visualization purposes (Fig. 1B). To obtain MSC estimates for each spectral band of interest, we averaged MSC values across all frequencies within the spectral band. Specifically, we considered the following spectral bands: delta ( $\delta$ , 1–4 Hz), theta ( $\theta$ , 4–8 Hz), alpha ( $\alpha$ , 8–13 Hz), beta ( $\beta$ , 13–30 Hz), low-medium gamma ( $\gamma$ , 30–80 Hz), and broadband (1–30 Hz).

### Structural connectivity from diffusion tensor imaging

In addition to characterizing FC using MSC, we were also interested in investigating structural connectivity patterns and whether FC was correlated with underlying white matter tract connectivity. White matter connectivity was determined from diffusion tensor imaging (DTI) of normal healthy adults. Over the past decade, DTI scans from 1200 healthy young adult individuals have been made available by the Human Connectome Project<sup>23–27</sup>. We used data from 1065 of these subjects that had been pre-processed and registered to MNI space. A deterministic fibre tracking algorithm was used and an end-to-end structural connectivity matrix in the Yale Brain Atlas space was calculated using the white matter streamline count metric for each parcel pair. The Yale Brain Atlas uses high-resolution cortical parcellation based on icEEG to divide the brain into 690 one-square centimeter parcels<sup>28</sup>. This serves to capture all anatomical features in the brain with no ambiguity and thus allows for standardized localization of SOZ, SP, and control regions. We used the number of streamlines calculated between each SOZ-SP and SOZ-control parcel-pair to quantify and compare the degree of structural connectivity between contacts involved in seizure spread and uninvolved controls. Using this information, we then quantified the linear relation between number of streamlines and MSC values to see whether structural and functional connectivity patterns were correlated. We also quantified the linear relation between number of streamlines and seizure spread times (i.e., time from seizure onset to observation of ictal activity in SP contact) to see whether greater degree of white matter tract connectivity between seizure regions was associated with more rapid seizure spread.

### Data visualization and statistical methods

All data analysis was conducted using MATLAB (MathWorks, Natick, MA) and all statistical analyses were performed using GraphPad Prism (San Diego, CA). Before conducting statistical tests, we quantitatively evaluated the normality of MSC values (Shapiro-Wilk test, SOZ-SP:  $p=0.0235$ , SOZ-control:  $p=0.0004$ ). We found that MSC values deviated significantly from normality, concordant with prior understandings of the statistical characteristics of the coherence estimator<sup>20,29</sup>. As such, we used nonparametric measures (ex. Wilcoxon signed-rank test) to compare coherence values, unless otherwise noted. Corrections for multiple comparisons were made using Tukey's multiple comparisons test. A threshold of  $p=0.05$  was used to denote statistical significance. Asterisks (\*), (\*\*), (\*\*\*), and (\*\*\*\*) indicates significance  $p<0.05$ ,  $p<0.01$ ,  $p<0.001$ , and  $p<0.0001$ , respectively. Data are reported as mean ( $\bar{x}$ )  $\pm$  standard deviation ( $\sigma$ ), unless otherwise stated. Difference in medians ( $\Delta\bar{x}$ ) is reported where relevant. Plots depict points jittered for visualization purposes.

## Results

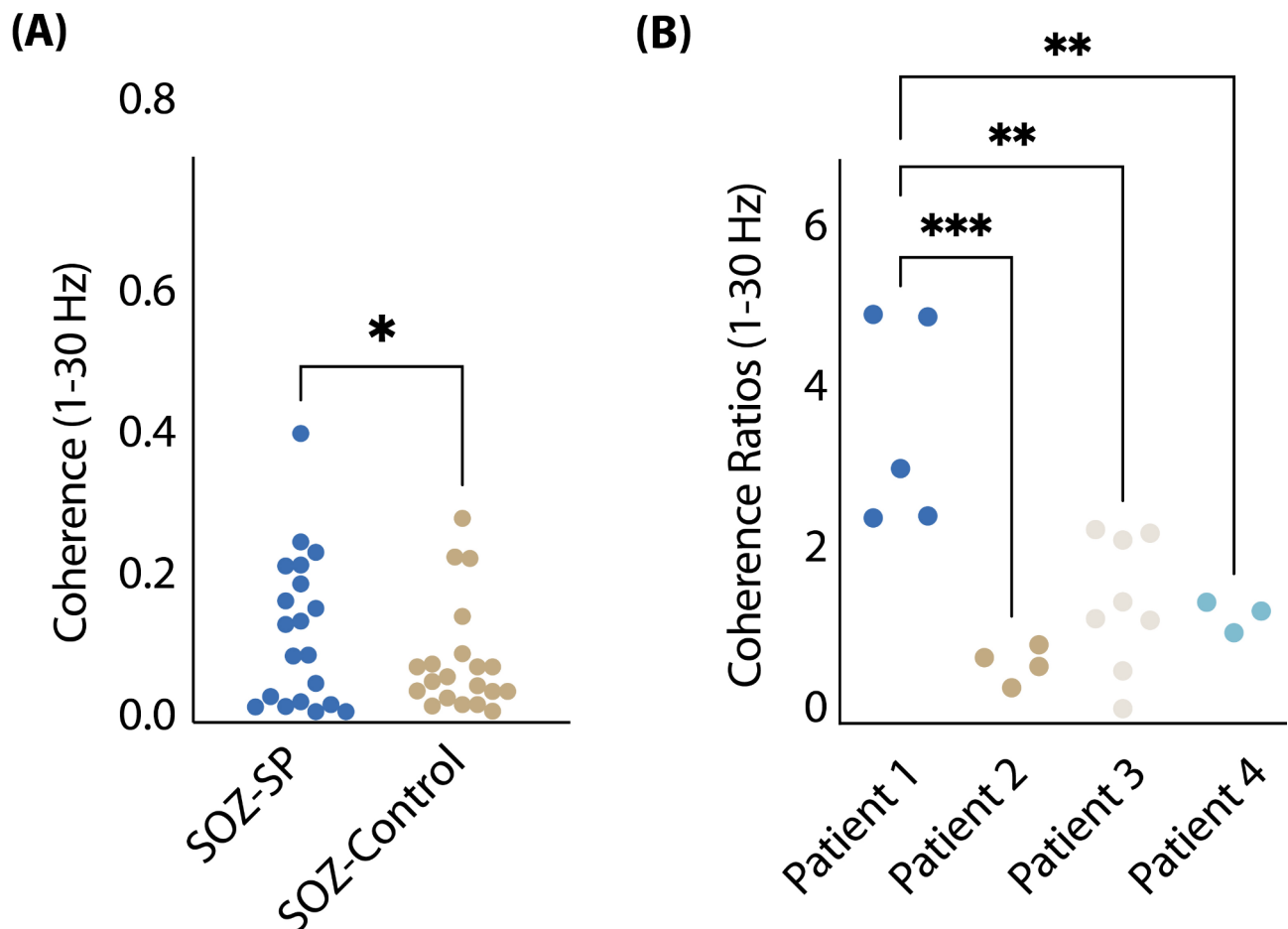
In this study, our primary objective was to investigate whether seizure networks persist and can be detected interictally. To this end, we calculated interictal FC using icEEG recordings and compared strength of connectivity between seizure and control regions. Our secondary objective was to quantify structural connectivity to investigate whether the two were correlated and better understand whether there might be a structural basis to seizure networks in our cohort. Finally, we sought to investigate whether there were differences in seizure outcomes following disruption (via resective surgery or neuromodulation) of networks between more highly connected seizure regions.

### Increased interictal functional connectivity between seizure regions

We observed significantly higher interictal FC, as quantified by MSC, between seizure spread contacts compared to controls in the following spectral bands: delta ( $\delta$ , 1–4 Hz): ( $\Delta\bar{x} = 0.02685$ ,  $p=0.0215$ ), theta ( $\theta$ , 4–8 Hz): ( $\Delta\bar{x} = 0.02957$ ,  $p=0.0215$ ), alpha ( $\alpha$ , 8–13 Hz): ( $\Delta\bar{x} = 0.03220$ ,  $p=0.0192$ ), beta ( $\beta$ , 13–30 Hz): ( $\Delta\bar{x} = 0.02139$ ,  $p=0.0296$ ), and broadband (1–30 Hz) ( $\Delta\bar{x} = 0.02608$ ,  $p=0.0240$ ) (Fig. 2A, Supplementary Fig. 2, Table 2). Significant differences were not noted in low-medium gamma ( $\gamma$ , 30–80 Hz) ( $\Delta\bar{x} = 0.006480$ ,  $p=0.4980$ ) (Supplementary Fig. 2, Table 2).

FC measures are susceptible to influence by volume conduction, which could bias estimates of connectivity. To ensure that MSC values computed between seizure spread regions were not biased by SP contacts being in closer proximity to SOZ contacts compared to control contacts, as a verification measure, we calculated pairwise distances between each SP and SOZ contact and between each control and SOZ contact. We found that inter-contact distances were not significantly different across the two groups ( $p>0.05$ ), suggesting that MSC estimates were not influenced by proximity to SOZ (Supplementary Fig. 1).





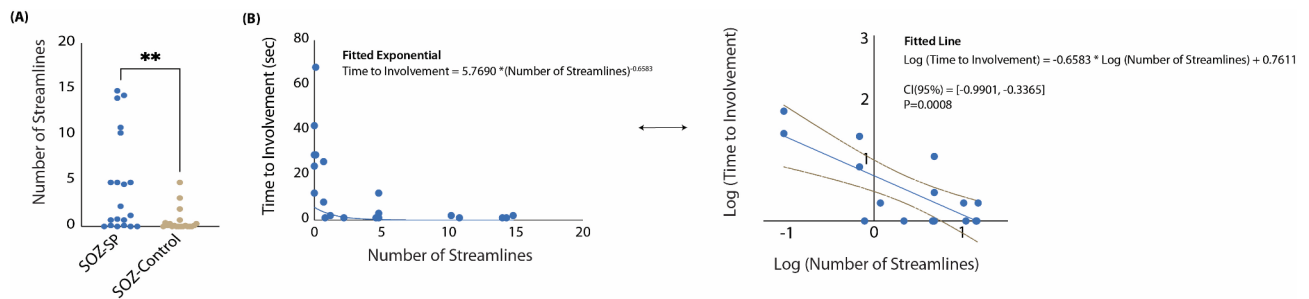
**Fig. 2.** Increased interictal functional connectivity. Here, we show plots of coherence-based FC using MSC in the 1–30 Hz spectral band. **(A)** Here, we show that pooled MSC values are significantly higher for all SOZ-SP pairs compared to SOZ-control pairs (Wilcoxon matched-pairs signed rank test,  $p=0.0240$ ). In other words, there is higher FC interictally between cortical regions involved in seizure activity compared to equidistant control regions, suggesting the presence of a pathologic epileptic network that persists interictally. **(B)** Here, we took the ratio of MSC of SOZ-SP with respect to SOZ-control, to normalize for within patient variability. Each data point refers to the coherence ratio computed from a single interictal ECoG recording from each patient. Specifically, we show that the patient with the best post-operative seizure outcome at follow-up (Patient 1, ILAE = 1) had significantly higher MSC ratios compared to those with poor outcome (Patients 2–4, ILAE  $\geq 2$ ) ( $F(3,16) = 10.91$ ,  $p = 0.0004$ , ordinary one-way ANOVA with corrections for multiple comparisons). Abbreviations: MSC - magnitude-squared coherence, FC - functional connectivity, SOZ - seizure onset zone, SP - primary seizure spread zone, ECoG - electrocorticography.

Patient ID	$\delta$ : 1–4 Hz	$\theta$ : 4–8 Hz	$\alpha$ : 8–13 Hz	$\beta$ : 13–30 Hz	1–30 Hz	$\gamma$ : 30–80 Hz
1	$3.5 \pm 1.7$	$3.5 \pm 1.6$	$3.5 \pm 1.4$	$3.7 \pm 1.1$	$3.6 \pm 1.3$	$5.0 \pm 2.3$
2	$0.9 \pm 0.2$	$0.8 \pm 0.1$	$0.7 \pm 0.2$	$0.6 \pm 0.4$	$0.6 \pm 0.2$	$0.8 \pm 0.4$
3	$1.5 \pm 1.0$	$1.5 \pm 1.0$	$1.5 \pm 0.9$	$1.4 \pm 1.0$	$1.4 \pm 0.8$	$2.1 \pm 2.8$
4	$1.1 \pm 0.2$	$1.1 \pm 0.2$	$1.2 \pm 0.2$	$1.3 \pm 0.2$	$1.3 \pm 0.2$	$1.1 \pm 0.1$

**Table 2.** Interictal MSC ratios. MSC ratio = SOZ-SP MSC/SOZ-control MSC. MSC - magnitude-squared coherence.

### Higher white matter tract connectivity between seizure spread contacts

Our secondary objective was to quantify structural connectivity between cortical regions involved in seizure spread. We quantified average white matter tract connectivity by computing the number of streamlines for all parcel-parcel pairs represented in the Yale Brain Atlas from 1065 healthy young adult subjects. Each SOZ, SP, and control contact was mapped on to the Yale Brain Atlas, with each subsequently being represented by unique parcels. Then, white matter tract connectivity between all SOZ-SP and SOZ-control pairs was identified.



**Fig. 3.** Higher structural connectivity among seizure regions. **(A)** Here, we obtained white matter tract connectivity estimates across all parcel pairs of interest (i.e., SOZ, SP, and control). We show that there is significantly increased white matter tract connectivity across cortical regions involved in seizure activity (SOZ-SP) compared to uninvolved (SOZ-control) (Wilcoxon matched-pairs signed rank test,  $p = 0.0073$ ). **(B)** Here, we fit a model to time to involvement and white matter tract connectivity data to see if white matter tract connectivity could be informative of seizure spread time. Specifically, we fit a linear model on log transformed time to involvement and white matter tract connectivity values, given that the data appeared to follow a logarithmic fit. We show that slope of the line of best fit of the log-transformed data is significantly nonzero ( $Y = -0.6583 \cdot X + 0.7611$ ,  $p = 0.0008$ ). In other words, higher white matter tract connectivity is significantly negatively correlated with seizure spread time, suggesting a role for structural connectivity patterns in seizure spread and the utility of DTI in elucidating the epileptic network in patients implanted with cortical grid and depth electrodes. Abbreviations: SOZ - seizure onset zone, SP - primary seizure spread zone.

We made two key observations. First, there was significantly greater white matter tract connectivity between seizure onset and spread contacts compared to control contacts ( $p = 0.0073$ , Fig. 3A). Second, we observed that higher white matter tract connectivity was significantly correlated with faster seizure spread times ( $\beta = -0.6583$ ,  $CI(95\%) = [-0.9901, -0.3365]$ ,  $p = 0.0008$ ) (Fig. 3B), suggesting that seizures may use extant white matter tracts to spread across cortical regions involved in the pathologic seizure network and that stronger underlying structural connections may portend more rapid ictal spread.

### Relationship between functional connectivity and white matter tract connectivity

We were interested in investigating whether there was a relationship between FC and structural connectivity. To this end, we ran linear regressions looking at the relationship between MSC (exclusively considering broadband 1–30 Hz) and white matter connectivity. We obtained MSC ratios as opposed to simply using MSC values obtained from SOZ-SP pairs to normalize for potential intracortical variability. Given that each patient's respective MSC calculations are strictly reflective of their own individual underlying network connectivity, MSC values could be higher on average for all contact pairs in one patient compared to others. Since direct SOZ-SP MSC comparisons could be biased by a patient's unique network connectivity patterns or icEEG recording conditions, we chose to normalize MSC values by obtaining the ratio between SOZ-SP MSC and SOZ-control MSC for each observation. To conduct like comparisons between ratios, we similarly normalized white matter tract connectivity by taking the ratio between each observation's SOZ-SP number of streamlines and SOZ-control number of streamlines. As shown in Supplementary Fig. 4A, we observed that FC was positively correlated with white matter tract connectivity, with higher MSC ratios being associated with higher white matter tract connectivity ratios ( $p = 0.1221$ ), though it is important to note that this correlation was not significant. Additionally, we observed that on average, higher MSC ratios were correlated with faster ictal spread from SOZ to SP (Supplementary Fig. 4B), though once again, it is important to note that this correlation was not significant.

### Improved outcome in patient with stronger interictal network

After quantifying FC and white matter tract connectivity between seizure and control contacts, we were interested in whether resection or modulation of more strongly connected interictal seizure networks was associated with improved post-operative seizure outcomes. We considered all MSC ratios (see “[Relationship between functional connectivity and white matter tract connectivity](#)” section) for each patient and their ILAE outcome on follow-up. Interestingly, we observed that the patient in our cohort with the best ILAE outcome on follow-up (Patient 1, ILAE = 1) also had a significantly higher MSC ratio when compared to the remaining patients in the cohort ( $F(3,16) = 10.91$ ,  $p = 0.0004$ , ordinary one-way ANOVA with corrections for multiple comparisons) (Fig. 2B; Table 2).

## Discussion

### Network perspective of epilepsy

Despite resective surgery targeting regions of ictal onset, seizure freedom rates have remained stagnant, suggesting a failure to address the disease's underlying mechanisms<sup>5,30</sup>. Over the past two decades, studies have increasingly suggested that pathologic alterations in cortical networks play a crucial role in epileptogenesis. Even more recently, intracranial studies have suggested that treatment failure in epilepsy surgery patients may be due to untreated elements of a distributed epileptogenic network<sup>2,3,31–34</sup>. As such, there has been a shift towards identifying seizure networks with the ultimate hope of being able to tailor epilepsy surgery towards

addressing the most critical nodes in the pathologic seizure network. For example, a recent study by Rijal et al. showed in a subset of DRE patients that those who had resection of cortical regions associated with high FC had improved post-operative outcomes<sup>35</sup>. There have been few similar studies considering FC from intracranial electrophysiology to characterize the seizure network outside the SOZ, although there have been a number of studies over the years exploring FC using Blood Oxygenation Level-Dependent (BOLD) signals from fMRI<sup>21,36,37</sup>. As such, our study aims to address this gap by correlating FC with structural connectivity utilizing intracranial electrode recordings. Considering the limited number of studies using interictal FC derived from icEEG to characterize the seizure network, here we sought to use MSC to identify interictal functional seizure networks and assess their relationship with underlying white matter tract connectivity.

### Evidence of interictal seizure networks

We characterized FC using MSC, a measure of the linear correlation between two signals in the frequency-domain. By design, we considered MSC across SOZ-SP and SOZ-control pairs, to (i) determine the extent of FC between cortical regions identified empirically as SOZ and SP and (ii) compare that measure to the degree of FC between SOZ and an equidistant control, to effectively control for within-patient variability. Across our cohort, we show that FC is significantly higher among seizure spread contacts (SOZ-SP) compared to control (SOZ-control) (Fig. 2A), suggesting the presence of an interictal functional network along which seizures propagate. In addition, we aimed to see if disruption of cortical regions deemed highly connected per FC analysis was associated with improved post-operative seizure freedom by comparing MSC ratios between seizure and control pairs (SOZ-SP MSC / SOZ-control MSC) across patients with good (ILAE class = 1,  $N = 1$ ) and poor outcomes (ILAE class  $\geq 2$ ,  $N = 3$ ). All patients in our cohort had either resection of or neuromodulatory intervention at SOZ and SP regions. We found that the single patient in our cohort with the best seizure freedom outcome coincidentally had the highest FC (MSC ratio of  $3.6 \pm 1.3$ ), compared to the rest of the cohort (Table 2). Our findings suggest that when more highly connected interictal functional networks are surgically disrupted, this may portend a higher chance at post-operative seizure freedom. Furthermore, our observations are concordant with recent studies by Shah et al. and Rijal et al., which support the presence of increased interictal FC within clinically relevant epileptic networks<sup>35,38</sup>. In addition, our results also corroborate Andrews *et al.*'s findings, which indicated that patients who underwent resection of nodes with rapid seizure spread experienced better postoperative outcomes, as described above. While their study focused on the ictal period and used timetoinvolvement to characterize epileptic networks, our study provides evidence of an interictal seizure network characterized by FC that persists at baseline.

### Structural underpinnings of functional networks

Studies have shown that there is a link between FC and structural connectivity patterns, however, often studies characterize this relationship by focussing on global network patterns<sup>39–42</sup>. More recent studies have begun to suggest that ictal oscillations likely propagate through direct corticocortical and additional subcortical and multisynaptic white matter pathways<sup>43,44</sup>. As such, after characterizing FC among seizure regions interictally, we sought to investigate whether white matter tract connectivity would be correlated with observed FC strength. Our findings revealed significantly higher white matter tract connectivity between seizure contacts (SOZ-SP) compared to control (SOZ-control) (Fig. 3A). We believe that these findings explain observed FC patterns, by enabling seizures to traverse extant white matter tracts during seizures and lends support to hypotheses of how pathologic seizure networks form. Namely, one hypothesis for how seizure networks develop is that pre-existing cortical and subcortical networks are effectively hijacked over repeated seizure events<sup>6</sup>. Our findings may lend support to this idea by showing that seizures propagate along structurally and functionally connected regions that persist interictally.

Additionally, using linear regression, we showed a significant negative correlation exists between white matter tract connectivity and speed of seizure spread from SOZ to spread contacts, indicating that regions with greater white matter tract connectivity facilitate faster seizure spread (Fig. 3B). Our findings suggest that underlying structural connections may play a role in seizure propagation, with stronger connections portending faster ictal spread, a phenomenon found to be critical in affecting post-operative outcomes, as described in Andrews *et al.*'s work<sup>3</sup>. Our findings suggest a relationship between FC and structural connectivity patterns may exist in epilepsy, suggesting pathologic seizure networks may preferentially exploit pre-existing brain networks established before the initial seizure insult. From a surgical decision-making perspective, this idea could influence epilepsy surgery, by potentially coupling corticocortical pathway characterization with icEEG studies to more precisely characterize seizure networks and identify targets for surgery. However, determining the exact mechanism behind epilepsy network formation remains challenging, particularly in retrospective human studies. We propose future animal research to explore this, where structural connectivity patterns are analyzed before and after epileptogenesis. This approach could clarify whether seizures take over pre-existing networks or contribute to the formation of new ones.

### Clinical implications

As our understanding of DRE evolves from a focal disorder to a distributed network concept, our treatment approaches must also adapt. Surgical strategies may shift from targeting focal regions of ictal onset to also addressing those playing a key role in the pathologic epileptic network. This novel treatment strategy may simply involve using timing of seizure spread to dictate surgical targets or analyzing FC patterns during interictal periods to identify abnormally connected cortical areas for intervention. This network-based approach could lead to improved outcomes, as suggested by our work. Anecdotally, in our clinical experience, we have observed increasingly positive outcomes in patients who receive treatment targeting regions of rapid seizure spread, in addition to those of ictal onset. In these patients, our treatment paradigm involves resection, thermal ablation,



or neuromodulation of the SOZ and site of rapid seizure spread. This combination of targeting multiple critical nodes in the seizure network has been suggested to potentially improve post-operative seizure freedom, compared to resection of the SOZ alone, further supporting the idea of a network-targeted approach to epilepsy surgery<sup>45</sup>. Finally, an interictal network-based approach to surgical management could reduce the need for prolonged stays in the Epilepsy Monitoring Unit (EMU), which are currently required for localizing seizure onset and spread. If a pathologic seizure network exists interictally, as our work here suggests, prolonged EMU stays waiting for seizure events may be unnecessary as connectivity analysis using interictal iEEG recordings can help identify principal nodes in the seizure network that can inform surgical decision making.

### Limitations

It is important to contextualize our findings by acknowledging relevant limitations. A primary limitation in our study is the small size of our patient cohort. With four patients, we are limited in power needed to draw strong conclusions, with significance only being attained when considering large effect sizes. This could explain the non-significant relationship between FC and white matter tract connectivity we observed, although trends can be observed qualitatively. One reason for the limited sample size is the intentional restriction of our study to patients with exclusively MTLE. Another reason is the inherent design of our study. Specifically, we directly compare SOZ-SP and SOZ-control FC. This comparison is most appropriately captured using iEEG from subdural grid electrodes, as this allows for direct selection of equidistant controls and also similar tissue density across seizure and control areas, which could otherwise bias FC measurements. However, epilepsy neuromonitoring across most institutions typically involves use of SEEGs, making subdural grid data more challenging to come by<sup>46</sup>. For these reasons, our sample size is small, however, we plan to investigate FC in larger cohorts by including extra-temporal epilepsy patients in future studies. Furthermore, considering the distribution of ILAE outcomes in our cohort, with one patient having a relatively better post-operative outcome than others (ILAE = 1,  $N = 1$  vs. ILAE = 3–4,  $N = 3$ ), we are unable to make strong conclusions regarding the relationship between connectivity and patient outcomes. Additional limitations include the fact that our study is retrospective. As such, our study carries the inherent limitation that outcome findings may not be generalizable given that we are unable to control for all potential confounding factors. Furthermore, given the retrospective nature of our study, it precludes our ability to draw causal relationships, and limits us to correlation inferences. Additionally, given that our cohort specifically focused on MTLE, as discussed above, our findings are limited in that they do not inform us of structural and interictal FC in temporal neocortical or extra-temporal lobe epilepsies (i.e., frontal, parietal, or occipital involvement), although recent studies would suggest they do<sup>47</sup>. An additional limitation in our study is that FC was measured in individual subjects, while structural connectivity was estimated based on data collected in normal subjects. Despite these limitations, our study provides crucial evidence in support of the network theory of epilepsy in the context of one of the most common drug-resistant epilepsies, which can be informative of the role of pathologic networks in DRE and potential management. An additional limitation, any study considering electrophysiology-based FC bears the inherent confounding effects of volume conduction/field spread problems. To minimize these effects from potentially biasing FC estimates, we chose control contacts that were equal Euclidean distances to SOZ contacts (see Methods) and compared distances between SOZ-SP contacts and SOZ-control contacts to validate that chosen contacts were in fact equidistant. A further limitation, although in this study we provide a characterization of potential seizure networks using functional and structural connectivity measures, it is important to note that it is yet to be shown whether seizures alter underlying structural connectivity patterns or hijack preexisting ones. Finally, as discussed above, surgical treatment for focal epilepsy includes a variety of options, with treatment approaches varying from patient-to-patient<sup>48</sup>. As such, these differences must be taken into consideration when interpreting comparisons in outcome. However, although treatment approaches may vary, what remains consistent is that all surgical treatment methods presented in our study involve disruption of SOZ and SP regions, hence representing disruption to the underlying functional seizure network.

### Conclusion

In summary, over the past two decades, it has become increasingly clear that epilepsy is a network disorder and appropriately targeting principal nodes in the seizure network may be necessary for improving epilepsy surgery outcomes. However, we are yet to see this newfound understanding translate to improved patient outcomes. Here, we show using FC and white matter connectivity measures that epileptic networks exist not only during active seizures, but also interictally. Additionally, our findings suggest that resection of highly connected regions of seizure spread may be important in achieving post-operative seizure freedom. Future research should focus on replicating and expanding upon these results in larger, more diverse cohorts, and exploring the clinical implications of network-based approaches, including their potential for personalized treatment strategies. Ultimately, we believe that our findings lend strong support to clinical considerations of epileptic networks and the potential to achieve seizure freedom by targeting these networks in patients with DRE.

### Data availability

The data that support the findings of this study are available on request from the corresponding authors. The data are not publicly available because they could compromise research participant privacy and consent.

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## Author contributions

U.B., D.S., H.P.Z. and A.K. designed the study and wrote the manuscript. U.B., H.M., O.C., and H.P.Z developed the data pipeline analysis tools, analyzed the data, and created all figures. P.F., J.P., and R.B.D. identified the onset of seizures. D.S. and A.K. provided the location of icEEG electrodes with respect to resection. D.S. and A.K. provided the surgical outcome of patients. All authors reviewed the manuscript.

## Declarations

### Competing interests

The authors declare no competing interests.

## Additional information

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**Correspondence** and requests for materials should be addressed to A.K.

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