

Node Degree Volatility for Seizure Onset Zone Localization

Igor Belykh

ibelykh@gsu.edu

Georgia State University <https://orcid.org/0000-0002-5683-0754>

Kevin Slote

Georgia State University <https://orcid.org/0009-0008-3167-3992>

Kelley Smith

Georgia State University

Marrium Shamshad

Georgia State University

Aditi Trivedi

Georgia State University

Charles Epstein

Emory University

Mukesh Dhamala

Georgia State University

Article

Keywords:

Posted Date: November 27th, 2025

DOI: <https://doi.org/10.21203/rs.3.rs-8061650/v1>

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Additional Declarations: There is **NO** Competing Interest.

1 Node Degree Volatility for Seizure Onset Zone

2 Localization

3 Kevin J. Slote¹, Kelley M. Smith¹, Marrium Shamshad¹, Aditi Trivedi¹, Charles M. Epstein²,
4 Mukesh Dhamala^{3,4*}, and Igor Belykh^{1,4*}

5 ¹Department of Mathematics and Statistics, Georgia State University, Atlanta, USA

6 ²Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, USA

7 ³Department of Physics and Astronomy, Georgia State University, Atlanta, USA

8 ⁴Neuroscience Institute, Georgia State University, Atlanta, USA

9 *These authors share senior authorship

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Abstract

13 Drug-resistant epilepsy, in which seizures cannot be controlled with medication, often requires
14 invasive treatment interventions such as surgical resection, laser ablation, or neuromodulation
15 targeting the seizure onset zone (SOZ). However, precise biomarkers for localizing the SOZ remain
16 lacking, limiting treatment success. Here, we introduce a novel biomarker: *node degree volatility*,
17 defined as the rate of change in a node's functional connectivity over time. We analyze 82 seizures
18 from 80 patients, reconstructing Granger-causal networks from intracranial EEG (iEEG) recordings,
19 where nodes represent iEEG channels and edges denote directed causal influences between
20 them. Nodes with the highest degree volatility at seizure onset predict the clinically identified SOZ
21 in 75% of successful surgical cases, using a stringent 5% top-quantile threshold to designate SOZ
22 nodes. On the analyzed dataset, this biomarker outperforms established iEEG-based methods,
23 including neural fragility and conventional network metrics such as node degree and betweenness
24 centrality, highlighting the value of capturing local temporal dynamics in functional brain networks.
25 Unlike many machine learning methods that can be computationally intensive and often lack

transparency, our approach is direct and interpretable, offering a clear and clinically actionable path to SOZ localization. Beyond epilepsy, node degree volatility may provide a framework for identifying dynamically critical nodes in evolving biological, social, and engineering networks.

Introduction

Epilepsy is one of the most prevalent chronic neurological disorders, affecting approximately 50 million people worldwide and contributing significantly to the global burden of disease¹. Despite the availability of antiepileptic medications, about one-third of patients experience drug-resistant epilepsy, in which seizures persist despite pharmacological therapy². For these individuals, surgical resection remains the most effective therapeutic option, particularly in focal epilepsy where seizure activity arises from a localized cortical region³. The clinical goal of such interventions is to accurately delineate and remove the seizure onset zone (SOZ)—the cortical area where seizures originate⁴. Precise identification of the SOZ is crucial for achieving favorable outcomes, as it enables the targeted disruption of the pathological circuitry underlying seizure generation⁵. The Engel Epilepsy Surgery Outcome Scale is commonly used to evaluate the success of surgical interventions, ranging from Engel class I (free of disabling seizures) to Engel class IV (no worthwhile improvement)⁶. The lack of a universally accepted biomarker for the SOZ hampers surgical efficacy, often leading to less-than-optimal results, with long-term Engel class I outcomes varying between 16% and 66% depending on the type of epilepsy and surgical intervention⁷. Given the invasive and costly nature of resective surgery, improving localization accuracy remains a critical and urgent goal⁸.

A growing body of work has reframed epilepsy as a disorder of large-scale network dysfunction rather than isolated neuronal hyperexcitability^{9–29}. Modeling epileptic seizures using synthetic or patient-specific data has emerged as an essential framework for understanding the transition from normal to pathological brain states^{9,11–13,30}. The Virtual Epileptic Patient platform^{21,28,31} exemplifies this personalized modeling approach by combining diffusion-weighted MRI-derived structural connectivity with coupled neural mass oscillators to simulate seizure spread and evaluate hypothetical resections in silico. Similarly, the virtual resection framework²² reconstructs brain networks from intracranial recordings, treating electrode contacts as nodes and pairwise functional relationships as

edges. By iteratively removing nodes and recalculating network synchronizability, it estimates the control centrality of each region in seizure dynamics.

Spectral biomarkers represent another established class of SOZ localization tools. High-frequency oscillations in the 80-500 Hz range have long been associated with epileptogenic tissue^{32,33}, while recent work suggests that the aperiodic component of neural power spectra may capture the excitation–inhibition imbalance characteristic of seizure-prone regions³⁴. Complementary imaging modalities, such as iEEG–fMRI mapping, have also shown promise in predicting postsurgical outcomes³⁵.

Network-based and graph-theoretic analyses of iEEG recordings offer an alternative and increasingly influential perspective. These approaches reconstruct evolving functional or effective connectivity networks across interictal, ictal, and postictal seizure epochs to identify nodes that play critical roles in seizure generation and spread^{36–39}. Connectivity is typically estimated using measures such as mean phase coherence, imaginary coherence, or phase-locking value, and translated into graph-theoretic features such as node degree (the number of functional connections a node maintains)^{38,40,41} and betweenness centrality (a measure of a node’s influence based on shortest-path routing)³⁷. Despite their interpretability, these static measures often show limited ability to accurately localize the SOZ.

A key benchmark in computational biomarker development is the concept of neural fragility⁴², which quantifies the susceptibility of a neural network to small perturbations that can induce instability. Nodes requiring minimal perturbation to destabilize the system are hypothesized to coincide with the SOZ. Although this method performs well in identifying surgical failures, its sensitivity for successful outcomes remains limited, highlighting the need for complementary and interpretable metrics. Machine-learning frameworks that integrate multiple SOZ features⁴³ have also improved predictive performance, but often at the expense of interpretability and computational efficiency.

To address these limitations, we introduce a new dynamical network biomarker, termed *node degree volatility*, which quantifies the rate of change in a node’s degree within the functional network over time. Building on the established framework of evolving temporal networks studied across scientific domains^{44–49}, this approach extends graph-theoretic analysis to capture rapid reconfigurations in brain connectivity that characterize seizure onset. Leveraging Granger-causal networks reconstructed

81 from broadband iEEG recordings^{17,50–52}, we hypothesize that nodes within the SOZ exhibit distinct
82 temporal signatures reflecting localized network instability during ictogenesis. An overview of the
83 study design and computational pipeline is shown in Fig. 1.

84 In a cohort of 80 patients comprising 82 seizures, nodes with the highest degree volatility at seizure
85 onset correctly predicted the clinically annotated SOZ in 75 % of successful Engel class I surgical
86 cases, under a stringent 5% top-quantile criterion. Across datasets, this biomarker outperformed both
87 neural fragility and conventional network measures, offering a simple, interpretable, and clinically
88 actionable tool for SOZ localization. Beyond epilepsy, node degree volatility promises to offer a
89 general framework for identifying dynamically critical nodes in complex evolving systems spanning
90 biological, social, and engineering networks.

91 Results

92 Patient cohort

93 To evaluate the potential advantages of node degree volatility over existing SOZ localization metrics,
94 we analyzed intracranial iEEG recordings from two retrospective datasets, referred to as Dataset A
95 and Dataset B.

96 The study was motivated by a representative case from Emory University Hospital, hereafter
97 designated as patient 0 (this internal label carries no clinical implication). This patient offered a
98 rare opportunity for precise SOZ localization, as the seizures were consistently preceded by a
99 distinct symptom, such as reproducible left thumb tingling, consistent with the activation of the
100 thumb representation in Brodmann area 3b of the primary somatosensory cortex. Responsive
101 neurostimulation targeting this region achieved complete seizure freedom (Engel Class I outcome),
102 and clinical evaluation identified the SOZ within ten adjacent channels along a single electrode.
103 Because of the unambiguous localization and favorable clinical response, patient 0 served as an ideal
104 benchmark for evaluating new SOZ localization methods. Three seizures of varying intensity were
105 recorded on separate days and used as the initial testbed for our analysis.

106 Dataset A included these three seizures from patient 0 along with 24 seizure episodes from 24
107 patients with drug-resistant epilepsy, sourced from the publicly available Epilepsy iEEG Multicenter

Dataset (OpenNeuro accession ds003029). The dataset comprises electrocorticography (ECoG) recordings from four major epilepsy centers. All patients underwent surgical resection, and seizure onset times were determined by clinical experts. Only recordings with clearly annotated ictal periods were retained for analysis. Among the 27 total episodes, 20 corresponded to Engel Class I surgical successes, while 7 were classified as Engel Class II or IV outcomes.

To validate findings in a larger and more diverse population, we analyzed Dataset B, which contained 55 ictal episodes from 55 patients in the Hospital of the University of Pennsylvania (HUP) iEEG Epilepsy Dataset (OpenNeuro accession ds004100). This cohort included both stereotactic EEG (35 patients) and ECoG (20 patients) recordings. Clinical outcomes were categorized as 36 Engel Class I, 7 Class II, 10 Class III, and 2 Class IV cases.

Across Datasets A and B, we examined 82 seizures from 80 unique patients across multiple clinical centers, encompassing a broad spectrum of seizure types, implantation modalities, and surgical outcomes. Comprehensive demographic, clinical, and recording information for both datasets is provided in the Methods section.

Node degree volatility in Engel Class I patients

Figure 2a shows the iEEG recording of seizure episode 1 from patient 0. Channels are ordered by electrode contact and downsampled for clarity. The corresponding electrode map, shown in Fig. 2b, includes 120 channels distributed across multiple depth electrodes placed according to the pre-surgical evaluation. The SOZ was clinically localized to contacts on electrode pin 8, situated in the primary somatosensory cortex and identified based on symptomatology (tingling of the left thumb). As outlined in Fig. 2, we pre-process iEEG recordings and reconstruct evolving causal functional networks using Granger causality applied to broadband frequency data within an 8-second sliding window. The resulting adjacency matrices are binarized using a 95th percentile threshold to define directed connections (see Methods). For a sequence of evolving functional networks, we compute and track baseline local graph theoretic measures of in-degree (the incoming connections to a node), out-degree (the outgoing connections from a node), node degree (the sum of incoming and outgoing connections), and the global graph theoretic metric of betweenness centrality (how often a node acts

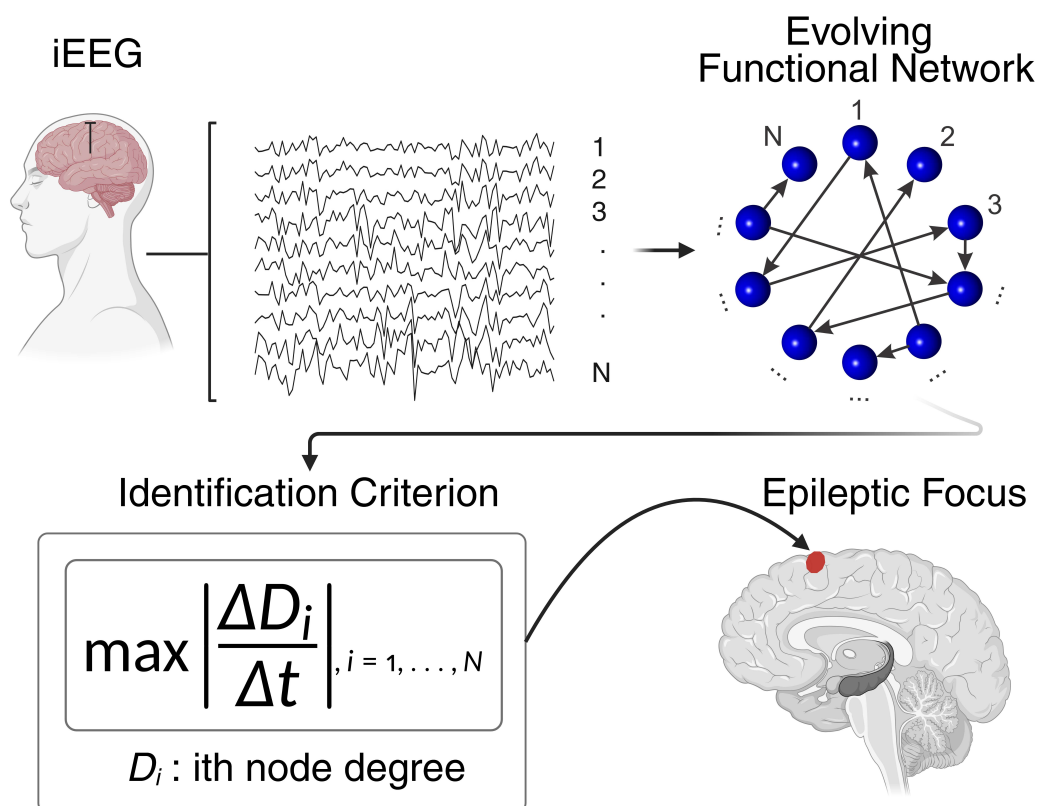


Figure 1. Schematic overview of the study design. iEEG recordings undergo minimal preprocessing before being used to reconstruct evolving functional networks via Granger causality. After computing the rate of change of node degree D_i , where Δt is equivalent to one time step, the maximum of the absolute values $D_i(t)$ is calculated over a 16-second window centered around seizure onset. Channels with maxima in the top 5% of this distribution, yielding the highest node degree volatilities, are identified as candidate SOZ nodes.

as a bridge along the shortest path between two other nodes).

A pronounced rise in node degree was observed in SOZ channels immediately following seizure onset (Fig. 2c,d), most notably at contact 8Rd5 (node 26), corresponding to the clinically defined seizure origin. To quantify this rapid reconfiguration, we introduced node degree volatility, defined as the rate of change in a node's degree across successive time steps. The resulting spatiotemporal map of node degree volatility (Fig. 3a) revealed sharp, localized peaks centered on seizure onset that distinguished SOZ channels from surrounding tissue. Four of the ten clinically labeled SOZ contacts (nodes 23, 25, 26, and 28) fell within the top 5 % of the maximum node degree volatility distribution (Fig. 3b), the stringent threshold used throughout this study to identify SOZ nodes. Consistent

144 patterns were observed across two additional seizure episodes from patient 0 (Supplementary Fig. 1).

145 In patient 0, where the SOZ was clearly localized, we verified that conventional network measures
146 performed as expected. The median node degree calculated over the ictal period identified SOZ nodes
147 within the top 5 % of the node degree distribution (Supplementary Fig. 2c,d), consistent with previous
148 studies based on correlation-derived functional networks^{36,38}. In contrast, the present approach
149 employs Granger-causal network reconstruction, which captures directed temporal dependencies
150 rather than mean phase coherence⁵³, a distinction that may enhance localization specificity.

151 We further applied the benchmark neural fragility method to all three seizure episodes from patient
152 0 using the EZFragility R package⁵⁴. Neural fragility successfully identified the surgeon-labeled
153 SOZ contacts but yielded a greater number of false positives and a lower interpretability ratio⁴²
154 compared to node degree volatility (Supplementary Fig. 2e,f). Although node degree volatility aligns
155 with established biomarkers in the clearly localized case of patient 0, conventional metrics such as
156 median node degree may fail in more diffuse or multifocal cases. Importantly, node degree volatility,
157 while derived from the same underlying connectivity structure, captures temporal reorganization
158 that static measures inherently overlook, providing a more sensitive representation of ictal network
159 dynamics.

160 To further evaluate the effectiveness of node degree volatility, we analyzed an Engel class I case
161 (patient 14 from Dataset A). The node degree volatility metric accurately identified both electrodes
162 labeled as the SOZ in the clinical summary, corresponding to nodes 4 and 5 in our analysis. These
163 nodes ranked within the top 5 % of the node degree volatility maxima and appeared as prominent
164 outliers in the distribution of maxima (Fig. 3d).

165 By contrast, conventional graph-theoretic measure such as node degree, in-degree, out-degree,
166 and betweenness centrality, failed to detect the SOZ nodes, often assigning high values to non-
167 epileptogenic contacts (Supplementary Figs. 3c,d and 4) The neural fragility analysis of the same
168 episode also did not recover nodes 4 and 5 among the top 5 % of its distribution (Supplementary Fig.
169 3e,f); instead, they appeared near the lower tail. In technical terms, neural fragility employs linear
170 algebraic techniques to quantify the smallest column perturbation required to inject an eigenvalue of
171 a specified complex modulus into the Koopman operator, thereby destabilizing the functional network

reconstructed from iEEG data⁴². In this case, the result indicates the opposite phenomenon: nodes 4
and 5 correspond to regions that are more dynamically stable, as their associated eigenvalues are
shifted back within the unit circle of stability in the complex plane.

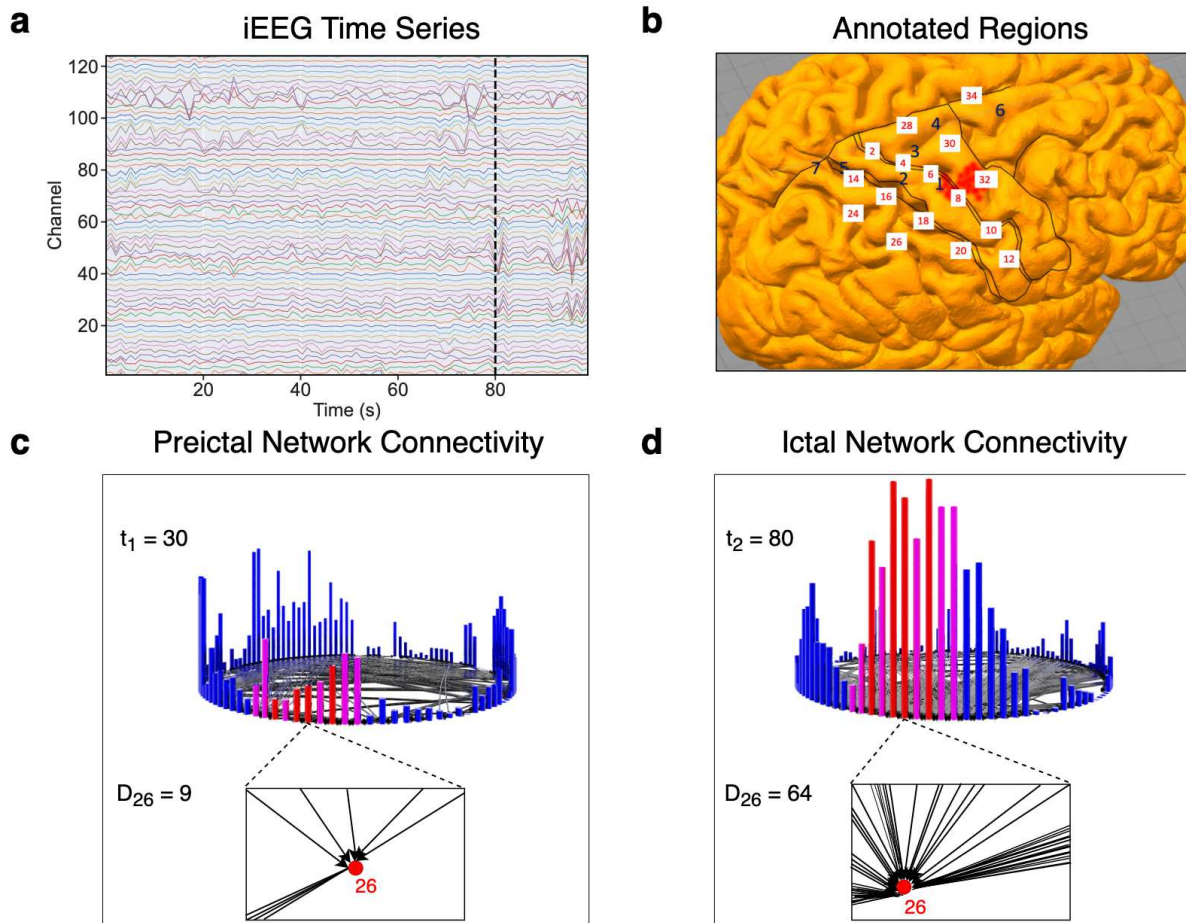


Figure 2. Dynamical reorganization of functional brain networks during seizure onset. (a) iEEG recording of episode 1 from patient 0; channels (downsampled) on the y -axis and time on the x -axis. The black dashed line indicates seizure onset, as determined by clinical observation. (b) Anatomical mapping of depth electrodes. The red region indicates clinically identified SOZ (contacts 8Rd1–8Rd10 on electrode pin 8) localized to the primary somatosensory cortex based on symptomatology. (c) Preictal functional network at $t_1 = 30s$. Channels are represented by nodes arranged in a ring; binarized Granger-causal links are shown in black, and node degree is encoded by cylinder height. SOZ nodes (in red) are not among the most highly connected (node degree $D_{26} = 9$). (d) Ictal functional network at $t_2 = 80s$; SOZ nodes show a sharp increase in connectivity ($D_{26} = 64$). Insets show incoming connections for node 26, clinically identified as part of the SOZ. Arrows represent incoming links; node degree is the sum of incoming and outgoing connections in the directed network.

To further evaluate the performance of node degree volatility, we conducted a patient-by-patient

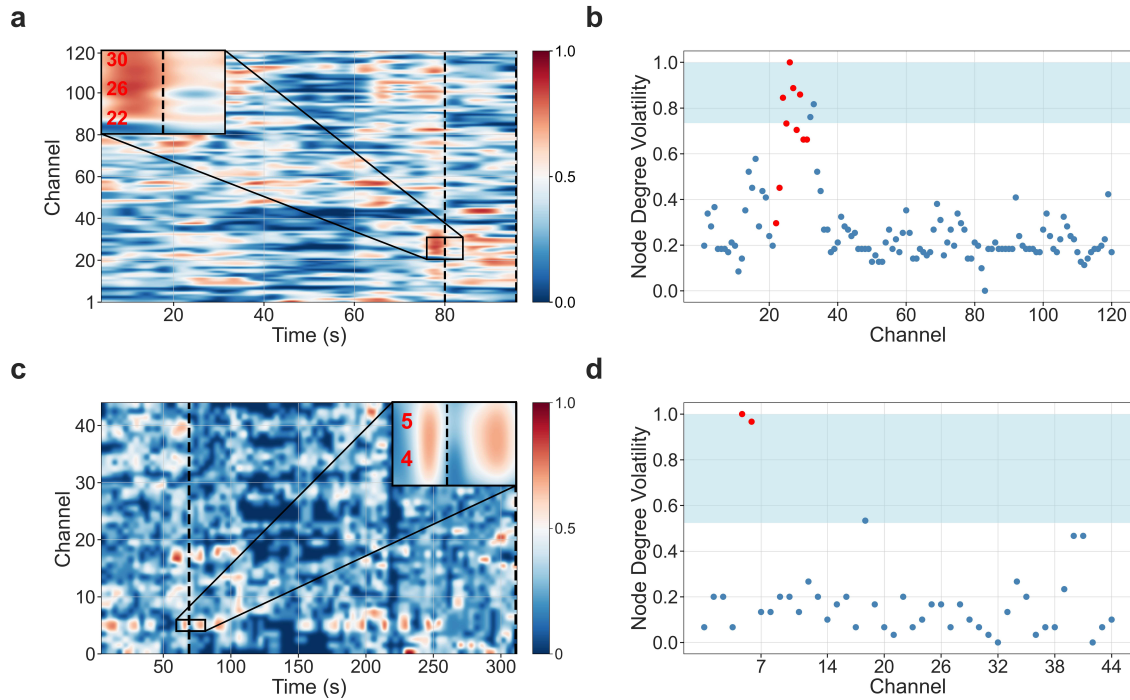


Figure 3. Node degree volatility identifies seizure onset zone channels in representative Engel class I cases. (a–b) Patient 0 (episode 1). (a) Heatmap of normalized node degree volatility over time. Black dashed lines indicate the ictal epoch. (b) Maximum normalized node degree volatility within a 16-second window centered on seizure onset. Red circles denote SOZ channels; blue circles denote non-SOZ channels. Four SOZ nodes (23, 25, 26, and 28) rank within the top 5% of the distribution (shaded blue region). (c–d) Patient 14. Panels follow the same structure as (a–b). Both clinically labeled SOZ nodes (4 and 5) appear as distinct outliers within the top 5% of the distribution.

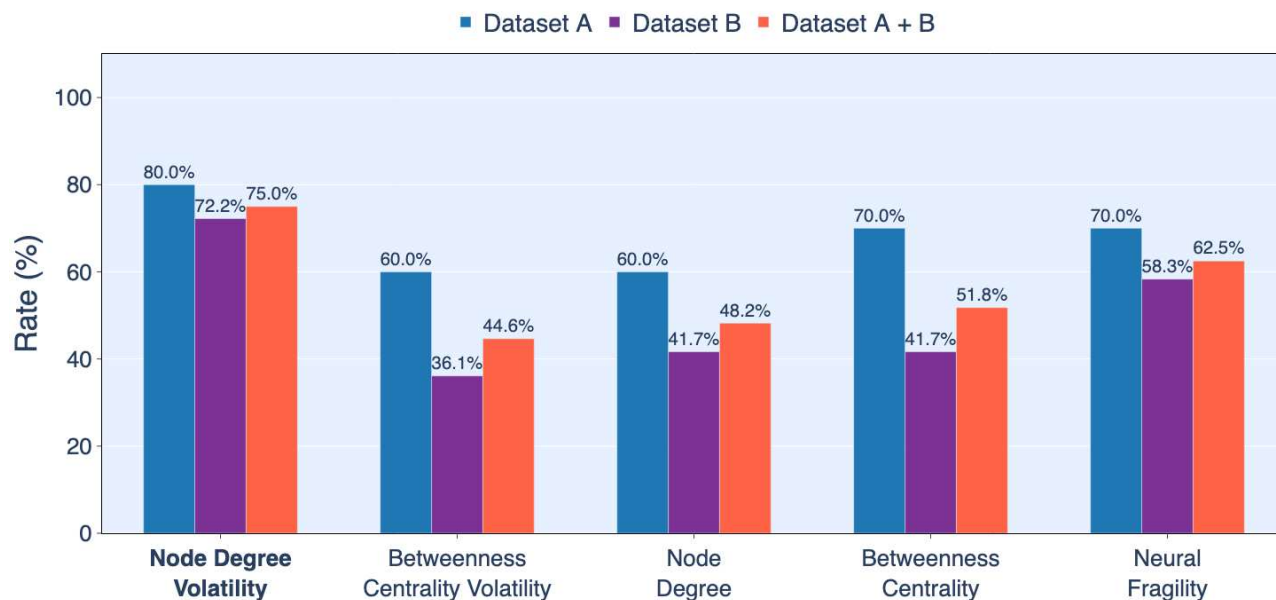


Figure 4. Comparative sensitivity outcomes for SOZ localization in Engel class I patients. The metrics were validated on 20 seizure episodes from Dataset A and 36 episodes from Dataset B, covering a broad range of cortical implantations and seizure morphologies. Node degree volatility consistently outperformed all benchmark methods, including static node degree, betweenness centrality, and neural fragility. In both datasets and in the combined analysis ($n = 56$), it achieved higher sensitivity than either static or dynamic alternatives. For each episode, a localization was deemed successful when at least one clinically annotated SOZ node appeared within the top 5% of the metric distribution.

analysis across Datasets A and B. Applying the same procedure as for patients 0 and 14, the metric reliably identified SOZ candidates in 16 of 20 Engel Class I episodes from Dataset A (80 % sensitivity) and in 26 of 36 Engel Class I episodes from Dataset B (72.2 % sensitivity) (Supplementary Tables 1-3). A result was considered successful when at least one clinically marked SOZ node fell within the top 5 % of the volatility distribution, following standard evaluation practice^{37–39}.

Figure 4 summarizes the comparative sensitivity of node degree volatility against established SOZ localization metrics across both datasets. The proposed metric consistently outperformed static measures, including node degree and betweenness centrality, as well as the benchmark method, neural fragility. It also exceeded the performance of a dynamic analog based on betweenness centrality volatility, computed using the same time-resolved framework. These findings suggest that local network dynamics, captured through rapid changes in node degree, provide greater predictive power than global reconfiguration patterns described by centrality measures. Furthermore, node degree volatility, defined as the rate of change of the sum of in-degree and out-degree, outperformed both node in-degree and out-degree volatility individually, as well as their static counterparts (Supplementary Fig. 5), reinforcing its role as a robust and sensitive dynamic biomarker for SOZ localization.

Node degree volatility in Engel Class II-IV patients

Having established the sensitivity of node degree volatility for SOZ localization in Engel Class I cases, we next examine its performance in patients with less favorable surgical outcomes. An effective biomarker should demonstrate both high sensitivity and specificity, identifying SOZ regions in seizure-free patients while avoiding false positives in patients with unsuccessful surgeries (Engel Classes II–IV). In such cases, the absence of clinically marked SOZ nodes among the top 5% of the maximum volatility distribution could indicate that the metric does not reinforce incorrect hypotheses. This property is particularly valuable when revisiting cases where surgical results suggest incomplete resection or inaccurate localization.

Patient 9 from Dataset A (Engel Class II) exemplifies this scenario. The clinically hypothesized SOZ was localized to the right anterior temporal lobe, with onset channels annotated on the TT, AST, and MST electrodes (see Data Set description). The patient achieved seizure freedom for two years

206 post-surgery, but later relapsed after tapering antiepileptic medication. As shown in Fig. 5a, the node
 207 degree volatility heatmap centered at the seizure onset reveals that none of the nine clinically labeled
 208 SOZ channels fall within the top 5 % of the volatility distribution (Fig. 5b). Instead, the highest-volatility
 209 nodes correspond to non-SOZ contacts, suggesting alternative candidate regions that may warrant
 210 further investigation or re-analysis.

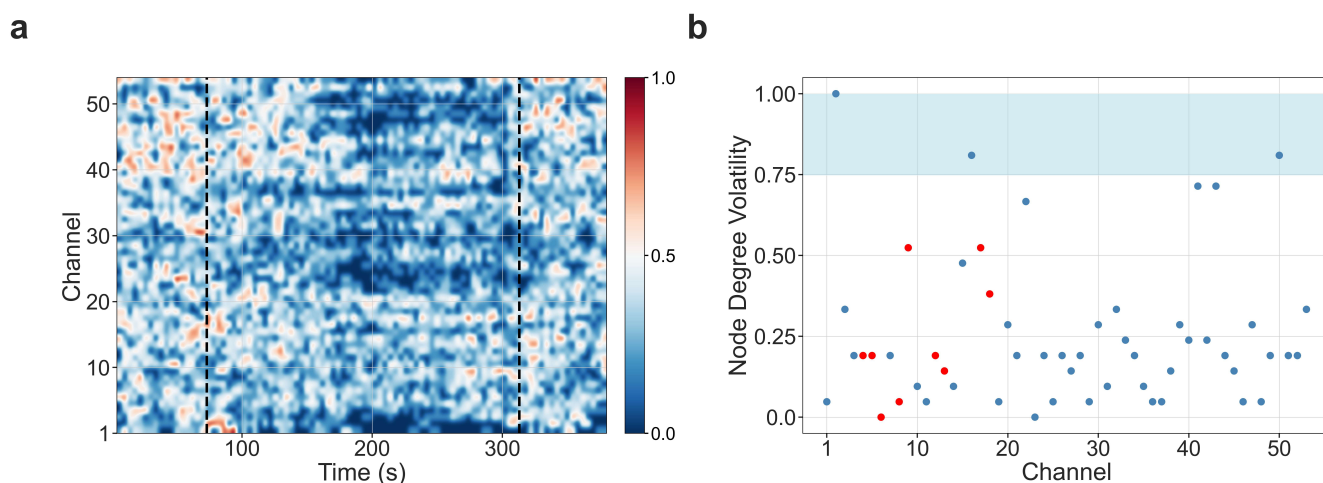


Figure 5. Node degree volatility in a patient with unsuccessful surgical outcome. (a) Heatmap of normalized node degree volatility over time during the seizure recording for patient 9 (Engel class II). The black dashed lines indicate the duration of the seizure. (b) Maximum normalized node degree volatility within a 16-second window centered on seizure onset. None of the clinically labeled SOZ nodes appear within the top 5% of the distribution (shaded blue). High-volatility non-SOZ nodes may represent alternative candidate regions for re-evaluation following seizure recurrence.

211 In contrast, static network measures performed poorly in this case. The median node degree
 212 metric assigned all top 5 % values to clinically labeled SOZ nodes (Supplementary Fig. 6c,d), resulting
 213 in a hypothesized false-positive identification. We also evaluated neural fragility, which, like node
 214 degree volatility, did not identify the clinically labeled SOZ nodes within the top 5 % of the distribution,
 215 consistent with its established effectiveness in predicting surgical failure cases⁴². However, in patient
 216 9, neural fragility yielded a broader set of high-ranking nodes near the 5 % threshold, resulting in
 217 reduced interpretability and overall performance compared with node degree volatility (Supplementary
 218 Fig. 6e,f). These findings indicate that node degree volatility not only captures clinically effective
 219 targets in successful cases but also avoids reinforcing incorrect hypotheses in failed ones. This
 220 specificity highlights its potential utility for postoperative evaluation and hypothesis refinement in

221 complex or ambiguous clinical scenarios.

222 We extended the analysis to all Engel class II–IV patients from Datasets A and B to evaluate the
223 specificity (true negative rate) of node degree volatility relative to static graph-theoretic measures
224 and neural fragility. Across these cases, node degree volatility consistently demonstrated the lowest
225 false-positive rate (Fig. 6). In Dataset A, only 2 of 7 patients showed surgeon-labeled SOZ channels
226 within the top 5% of the node degree volatility-based metric, corresponding to a hypothesized false
227 positive rate of 28.6%, outperforming all baseline methods.

228 Similarly, in Dataset B, only 6 of 19 patients met the same criterion, yielding a false positive rate of
229 31.6 %. Detailed performance statistics for node degree volatility across both datasets are provided in
230 Supplementary Tables 1-3. The computational procedures for all static, dynamic, and fragility-based
231 metrics are described in the Methods section.

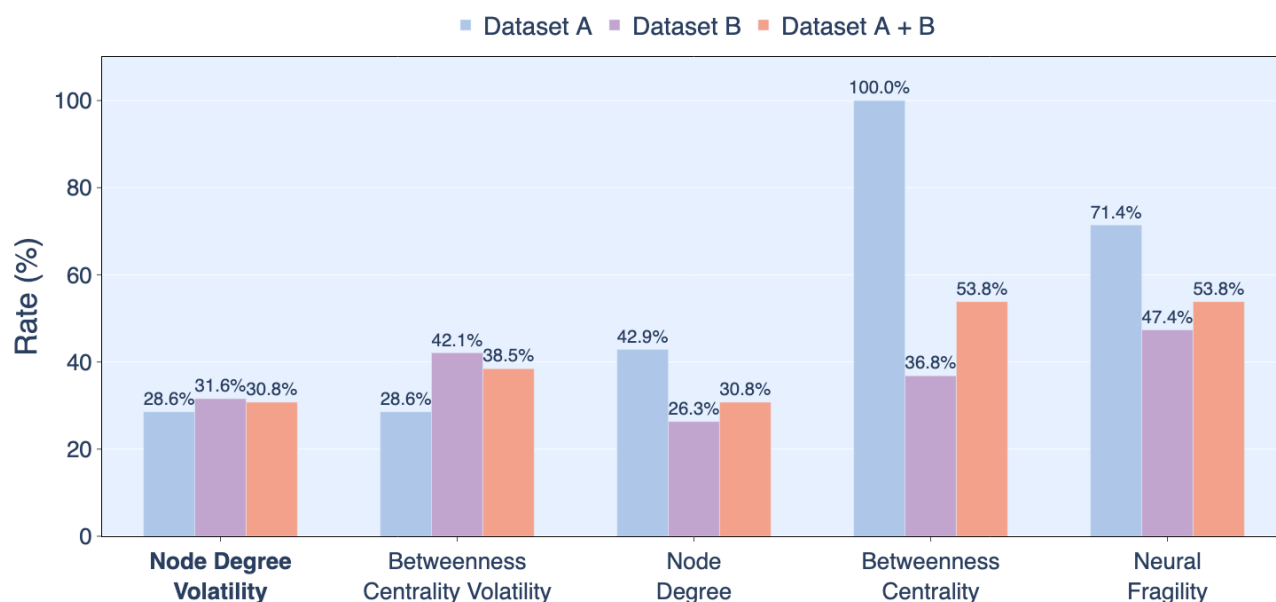


Figure 6. False positive rates for SOZ localization in patients with unsuccessful surgical outcomes. Lower false positive rates indicate better specificity. Results are shown for Dataset A (7 episodes, Engel classes II and IV) and Dataset B (19 episodes, Engel classes II–IV), comparing node degree volatility and betweenness centrality volatility to traditional static metrics and neural fragility. A false positive is defined as any case in which at least one clinically labeled SOZ node falls within the top 5% of the metric distribution.

232 **Overall performance of node degree volatility**

233 To assess the overall performance of node degree volatility across both correctly identified and missed
234 cases, we computed standard classification metrics using the combined Datasets A and B. The
235 proposed method achieved a precision (positive predictive value) of 84 %, a sensitivity of 75 %, and a
236 specificity of 69.2 % (Supplementary Table 3).

237 Beyond case-level validation, we examined whether node-degree volatility distinguishes SOZ
238 channels from non-SOZ channels at the population level (Fig. 7). For each patient, node degree
239 volatility values were first normalized to the min–max range. Summary statistics were then obtained as
240 the median of 5,000 as outlined strap-resampled means, computed separately for SOZ and non-SOZ
241 channels. Node degree volatility exhibited a clear separation between SOZ and non-SOZ channels in
242 patients with successful surgical outcomes (Engel Class I). In contrast, this distinction was absent
243 in patients with unsuccessful outcomes (Engel Classes II–IV). The direction and strength of these
244 effects were consistent across datasets, indicating that elevated node degree volatility is a reliable
245 signature of epileptogenic regions only in patients who achieve durable postoperative seizure control.

246 **Discussion**

247 This study demonstrates that a simple, dynamical readout of evolving connectivity, such as node
248 degree volatility, can identify seizure-initiating tissue with high fidelity while remaining transparent
249 enough for clinical use. When applied to time-resolved Granger-causal networks derived from iEEG
250 recordings, this measure isolates channels that undergo rapid, localized reconfiguration at seizure
251 onset. Across two independent datasets, these patterns consistently aligned with clinically annotated
252 SOZ regions more often than existing benchmarks.

253 Two features likely explain this performance advantage. First, node degree volatility is inherently
254 local and time-sensitive, allowing it to capture ictal reorganization that static summaries tend to blur.
255 Second, it is computed on directed interactions, focusing analysis on changes in effective influence
256 rather than undirected covariation. Together, these properties help clarify why global graph metrics
257 such as betweenness centrality, which are prone to information loss in sparsely sampled networks,
258 were less discriminative in our analyses.

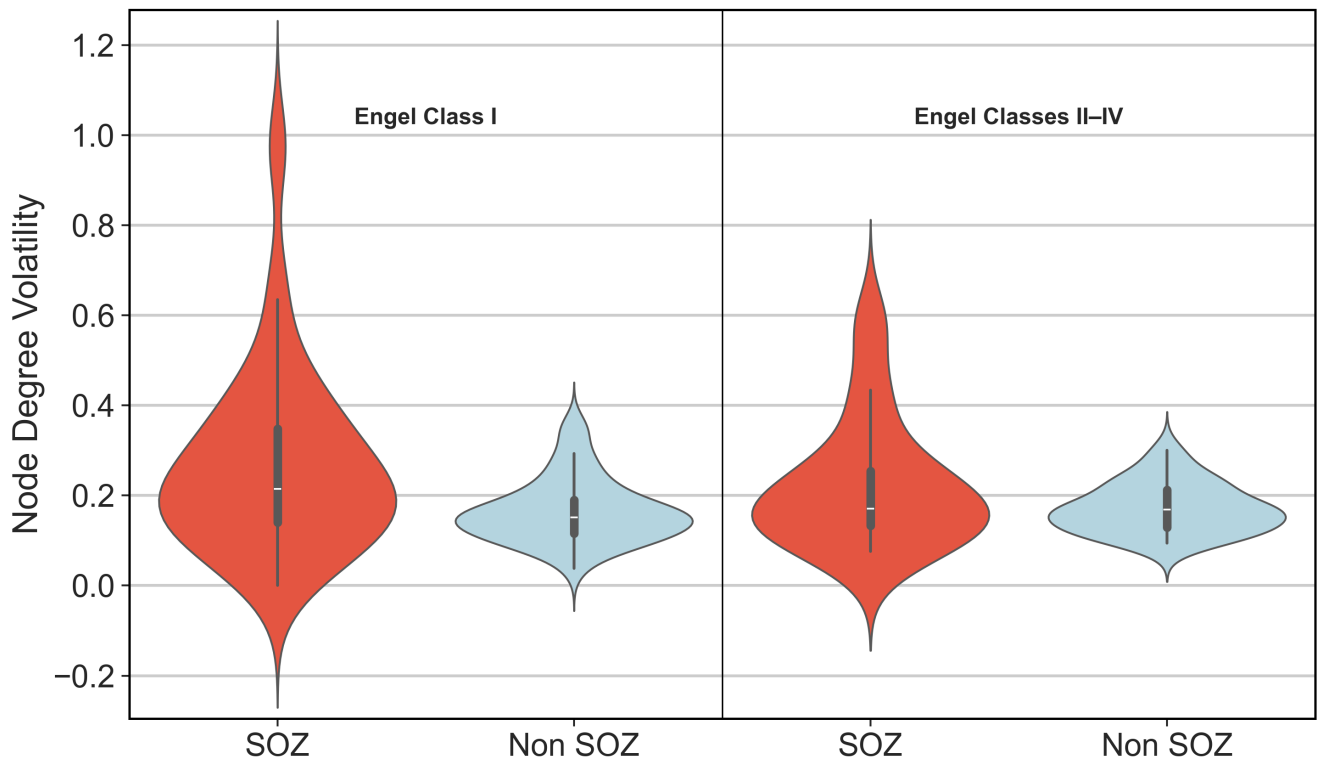


Figure 7. Node degree volatility shows significant SOZ vs non-SOZ separation only in successful outcomes (Engel Class I). Violin plots represent the distribution of patient-level summary values, where each patient contributes the median SOZ and non-SOZ values. In Engel Class I patients, SOZ values were significantly higher than non-SOZ values (Mann-Whitney $U = 2102.5$, $p = 9.4 \times 10^{-4}$; Cliff's $\Delta = 0.34$, medium effect size), indicating greater volatility in clinically identified epileptogenic regions. In Engel Classes II–IV, no significant group difference was observed ($U = 386.0$, $p = 0.192$; Cliff's $\Delta = 0.14$, negligible), consistent with reduced differentiation between SOZ and non-SOZ regions in unsuccessful surgical outcomes.

259 Differences between datasets provide additional insight. Sensitivity was higher in Dataset A,
260 composed entirely of ECoG recordings, than in Dataset B, which included both ECoG and SEEG
261 modalities. This outcome likely reflects sampling geometry: ECoG provides dense and contiguous
262 coverage of cortical surfaces, which better captures rapid local reconfiguration, whereas SEEG offers
263 broader anatomical reach but sparser spatial sampling. Because node degree volatility depends
264 on the extent of the onset region, denser sampling improves both detectability and contrast with
265 surrounding tissue. Differences in implantation strategies and treatment modalities may also contribute
266 to this variation.

267 Clinically, node degree volatility supports two complementary applications. In Engel Class I
268 cases, it produces a concise and interpretable shortlist of onset-candidate channels that align with
269 surgical success. In less favorable outcomes, its specificity can help prevent reinforcement of incorrect
270 hypotheses and instead suggest alternative targets for re-evaluation. The metric's computational
271 efficiency and minimal preprocessing requirements make it suitable for integration into presurgical or
272 intraoperative workflows.

273 Several limitations should be acknowledged. Except for a rare case with near-ground-truth local-
274 ization (patient 0), SOZ annotations rely on expert interpretation, introducing unavoidable uncertainty.
275 While the chosen sliding window balances temporal precision and stability, adaptive windowing and
276 multiscale analyses could better capture rapid transitions. Future work should also explore frequency-
277 resolved volatility to reveal band-specific mechanisms of ictogenesis. Finally, although a stringent
278 5-percent threshold aided interpretability and standardization, threshold optimization could be tailored
279 to clinical priorities using receiver operating characteristic analysis.

280 Looking forward, node degree volatility complements rather than replaces existing biomarkers.
281 It can be combined with spectral and structural features or used as a transparent, physiologically
282 grounded input to machine-learning frameworks. Prospective multicenter validation and real-time
283 applications represent promising next steps.

284 Beyond epilepsy, this concept, which identifies nodes that undergo rapid changes in effective
285 connectivity during critical state transitions, offers a general framework for detecting dynamically
286 influential elements in evolving biological, social, and engineered systems.

287 **Methods**

288 **Patients**

289 iEEG data were analyzed from two retrospective datasets, referred to as Dataset A and Dataset B.

290 Dataset A comprised 27 seizure episodes from 25 patients with drug-resistant epilepsy, including
291 three seizures from a single benchmark case (patient 0) treated at Emory University Hospital. The
292 remaining 24 episodes were drawn from the publicly available Epilepsy iEEG Multicenter Dataset
293 (OpenNeuro accession: ds003029), which includes ECoG recordings from four major epilepsy centers.
294 All patients underwent surgical resection, and seizure onset times were determined by expert clinical
295 teams. Only episodes with clearly annotated ictal periods were included. Among the 27 episodes,
296 20 were classified as Engel class I and 7 as Engel class II or IV outcomes. Two class III cases were
297 excluded due to incomplete metadata.

298 Across Dataset A, 1,980 electrode contacts were analyzed, with a mean of 73.3 per patient
299 (range 43–136). This included 284 surgeon-identified SOZ contacts, with a mean of 10.5 per patient
300 (range 2–33). Recordings included both subdural grid and stereotactic depth electrodes sampled
301 at 250–3000 Hz (typically 1000 Hz). Patient 0, implanted with a combination of subdural grids,
302 strips, and depth electrodes tailored to the clinical hypothesis, served as a high-confidence test case
303 due to reproducible seizure semiology and a seizure-free (Engel I) outcome following responsive
304 neurostimulation.

305 Dataset B consisted of 55 seizure episodes from 55 patients obtained from the Hospital of the
306 University of Pennsylvania iEEG dataset (OpenNeuro accession: ds004100). This cohort included 36
307 Engel I, 7 Engel II, 10 Engel III, and 2 Engel IV cases, with recordings from both stereotactic EEG
308 (SEEG; 35 patients) and ECoG (20 patients). A total of 5,913 electrode contacts were analyzed, of
309 which 663 were labeled as SOZ channels. Sampling rates ranged from 256 Hz to 1024 Hz.

310 SOZ annotations across both datasets reflected the original surgical team's consensus, incorporat-
311 ing presurgical evaluations and postoperative outcomes. Seizure onset and offset times provided by
312 clinicians were used without modification in nearly all cases. Minor timing adjustments were applied
313 to align the onset with the observed ictal envelope in a small number of recordings (four Engel I and

314 five Engel II–IV cases in Dataset B). These adjustments had a negligible effect on the study’s overall
315 statistics and conclusions. All data analyzed in this study were obtained from publicly accessible
316 repositories or retrospectively collected institutional recordings.

317 **Data preprocessing**

318 All iEEG recordings were preprocessed using the EEGLAB toolbox (MATLAB, MathWorks). Channels
319 identified as poor quality or containing artifacts, such as those labeled by clinicians as bad contacts
320 or exhibiting abnormally high standard deviation or signal dropout, were excluded from analysis.
321 Additionally, segments contaminated by significant artifacts, particularly near the end of the time
322 series, were manually removed.

323 To suppress line noise, a 60 Hz notch filter was applied using a finite-impulse-response design with
324 a 2 Hz cutoff frequency, a filter order of 256, and a bandwidth of 4 Hz. The data were also band-pass
325 filtered using a fourth-order Butterworth filter with cutoff frequencies from 0.5 Hz to the Nyquist
326 frequency to retain physiologically relevant components. Both filters were applied bidirectionally to
327 preserve signal phase. Signal baselines were normalized by subtracting the mean voltage of the
328 preictal period from each channel, producing a zero-mean signal centered on pre-seizure activity.
329 The fully preprocessed datasets, including artifact-free recordings and electrode-level annotations,
330 are publicly available on Hugging Face as described in the Data availability section.

331 **Functional network reconstruction**

332 Functional connectivity, defined as the statistical dependence between neural signals irrespective
333 of anatomical connections, was estimated from iEEG recordings to capture the evolving network
334 dynamics of epileptic seizures. This approach enables the characterization of the spatiotemporal
335 spread of activity during ictogenesis, facilitating the localization of the epileptogenic zone.

336 Time-resolved functional brain networks were reconstructed using Granger causality as a di-
337 rected measure of connectivity. Granger causality evaluates whether past values of one time series
338 improve the prediction of another and is therefore well-suited to detecting directional influences in
339 electrophysiological data. For each pair of iEEG channels, linear autoregressive models were fitted
340 in both unrestricted (bivariate) and restricted (univariate) forms, and causality was quantified as the

341 logarithm of the ratio of residual variances between these two models^{55–57}. Specifically, the Granger
 342 causality from signal Y to X was computed as $F_{Y \rightarrow X} = \ln[\text{var}(\varepsilon_X)/\text{var}(\varepsilon_X^*)]$, where ε_X and ε_X^* denote
 343 the residuals of the restricted and unrestricted models, respectively. The same formulation was
 344 applied, with the roles of Y and X reversed in the linear autoregressive models, to estimate $F_{X \rightarrow Y}$.

345 Networks were reconstructed within sliding time windows of 8 s with a 4-s step size, using an
 346 autoregressive model order of 5 determined by the Bayesian Information Criterion. This window length
 347 ensured the inclusion of at least two complete cycles of the lowest frequency of interest, thereby
 348 preserving broadband spectral content^{17,58}. The analysis was implemented using the *netrd* Python
 349 library⁵⁹. Stationarity of each time window was verified using the augmented Dickey–Fuller test, and
 350 all analyses were performed on filtered, zero-mean iEEG signals. The reconstructed time-varying
 351 networks formed the basis for subsequent computation of graph-theoretic measures, including node
 352 degree and node degree volatility.

353 Graph-theoretic measures

354 Time-resolved networks reconstructed from iEEG recordings were analyzed using standard graph-
 355 theoretic measures⁶⁰ to quantify local and global properties of seizure dynamics. Adjacency matrices
 356 were generated from the Granger-causal connectivity values using the Python package *networkX*⁶¹.
 357 To focus on the strongest interactions, each matrix was binarized at the 95th percentile threshold,
 358 yielding directed graphs from which in-degree, out-degree, node degree, and betweenness centrality
 359 were computed.

360 For each node i , the out-degree was defined as the sum of outgoing connections, $d_i^{\text{out}} = \sum_j A_{ij}$,
 361 where $A_{ij} = 1$ if a directed edge exists from node i to node j , and 0 otherwise. Similarly, the in-degree
 362 was defined as $d_i^{\text{in}} = \sum_j A_{ji}$. The total node degree, quantifying overall connectivity, was computed as
 363 $D_i = d_i^{\text{in}} + d_i^{\text{out}}$.

364 Betweenness centrality was also calculated to assess the influence of each node on network
 365 communication. For a node v , betweenness centrality was defined as $B(v) = \sum_{s \neq v \neq t} \sigma_{st}(v)/\sigma_{st}$, where
 366 σ_{st} is the number of shortest paths between nodes s and t , and $\sigma_{st}(v)$ is the number of such paths
 367 that pass through v . Nodes with high betweenness centrality can thus be interpreted as critical

368 intermediaries for information flow across cortical regions.

369 Static measures were calculated for each node during the ictal epoch, defined as the interval
370 between seizure onset and seizure offset. Seizure onset and offset times were obtained from the
371 `events.tsv` metadata accompanying each recording. For each node, the median value of a given
372 measure across this interval (for example, node degree) was computed by taking the median along
373 the time axis, yielding a single representative value per node. These static metrics summarize the
374 steady-state network structure during seizure propagation.

375 Dynamic, or volatility-based, measures were designed to capture rapid fluctuations in network
376 organization surrounding seizure onset. For each node and each metric (including node degree
377 volatility, in-degree volatility, out-degree volatility, and betweenness centrality volatility), the rate of
378 change was computed between consecutive time steps. The node degree volatility for node i is
379 defined as $V_i(t) = |D_i(t + \Delta t) - D_i(t)| / \Delta t$ with $\Delta t = 1$. This quantity, which captures how rapidly a
380 node's changes over time, was calculated within a 16-second window centered on seizure onset.
381 Each resulting vector of node-wise values was then normalized to the $[0, 1]$ range, and nodes in the
382 top 5% of this distribution were identified as exhibiting the most pronounced dynamical changes.

383 **Neural fragility**

384 Neural fragility was computed using the *EZFrailty* R package⁵⁴, applied over a time window
385 extending from 10 seconds before seizure onset to the first 5% of the seizure duration. This approach
386 follows the methodology of Li et al.⁴² to ensure consistency with prior work. Within this interval, each
387 node's fragility was quantified as the maximum normalized instability value across time, where all
388 values range between 0 and 1. The analysis window was defined for each seizure using onset and
389 offset times obtained from the `events.tsv` metadata accompanying the recordings. This measure
390 captures each node's relative susceptibility to network destabilization near seizure initiation, providing
391 a benchmark for comparison with node degree volatility.

392 **Classification performance and statistical evaluation**

393 Classification outcomes were defined according to clinical Engel scores to evaluate the performance
394 of each localization metric. A case was considered a true positive (TP) if an Engel class I patient

395 had at least one clinically identified SOZ node within the top 5%; a false negative (FN) if no SOZ
396 nodes were identified in this range; a true negative (TN) if an Engel class II–IV case exhibited no SOZ
397 nodes within the top 5%; and a false positive (FP) if at least one non-SOZ node from an Engel class
398 II–IV case appeared within the top 5%. Sensitivity was computed as $TP/(TP + FN)$, and specificity as
399 $TN/(TN + FP)$.

400 For the pooled analyses shown in Fig. 7, we compared node degree volatility between SOZ and
401 non-SOZ regions across patients. For each patient, channel-level node degree volatility values were
402 resampled with replacement over 5,000 bootstrap iterations, and the median of the resulting mean
403 values was used as a single summary statistic per region. All values were min–max normalized within
404 the patient to the $[0, 1]$ range before aggregation. Group-level differences between SOZ and non-SOZ
405 distributions were evaluated using a one-sided Mann–Whitney U test implemented in `scipy.stats`
406 (Python version 3.9), with statistical significance defined as $p < 0.05$.

407 **Ethics approval**

408 All analyses were conducted on retrospectively collected data. The study protocol was reviewed and
409 approved by the Institutional Review Board of Georgia State University (IRB H25299) and complied
410 with all relevant guidelines and regulations.

411 **Data Availability**

412 All data supporting the findings of this study are available to reviewers upon request and will be
413 publicly released upon publication. During peer review, the dataset can be accessed through a private
414 Hugging Face repository ([Belykh-Lab/hup-multi-center-cleaned-combined-ieeg](https://huggingface.co/Belykh-Lab/hup-multi-center-cleaned-combined-ieeg)) using the access
415 credentials provided to the journal. The dataset includes curated references to clinically verified SOZ
416 channels, seizure onset times, neural fragility heatmaps, and node degree volatility networks used in
417 this study.

Code Availability

All custom code supporting the analyses and visualizations in this study is available to reviewers upon request and will be made publicly accessible upon publication. Reviewers can access the repositories via private GitHub links using credentials provided to the journal. The main analysis code for interpretability and benchmarking is hosted at github.com/Belykh-Lab/node-volatility-neural-fragility-interpretability, and the implementation for evolving Granger-causal networks is available at github.com/Belykh-Lab/evocausality. Code for generating Blender-based 3D visualizations of network degree distributions is hosted at github.com/Belykh-Lab/blender-ictal. All repositories will be publicly released upon acceptance.

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595 **Acknowledgments**

596 This work was supported by Georgia State University's Brains & Behavior Program. It was also
597 partially supported by the National Science Foundation (USA) under grants CMMI-1953135 (to I.B.
598 and K.J.S.) and DMS-2510860 (to I.B.).

599 **Author contributions**

600 I.B. and M.D. conceived and supervised the study. K.J.S. designed and implemented the computational
601 framework and analysis software. K.J.S., K.M.S., and M.S. performed the computational and iEEG
602 data analyses. K.M.S. and M.S. led the statistical analysis and validation of results. K.M.S., M.S.,
603 and A.T. collected and pre-processed the datasets. C.M.E. provided expertise on surgical outcomes
604 and facilitated data acquisition. I.B. drafted the manuscript with input from all authors. All authors
605 discussed the results and approved the final version of the manuscript.

606 **Additional information**

607 Supplementary Information is available for this paper.

608 **Competing interests**

609 The authors declare no competing interests.

610 **Corresponding authors**

611 Igor Belykh (ibelykh@gsu.edu), Mukesh Dhamala (mdhamala@gsu.edu).

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