BRAIN
UPDATE

# Quantitative approaches to guide epilepsy surgery from intracranial EEG

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Over the past 10 years, the drive to improve outcomes from epilepsy surgery has stimulated widespread interest in methods to quantitatively guide epilepsy surgery from intracranial EEG (iEEG). Many patients fail to achieve seizure freedom, in part due to the challenges in subjective iEEG interpretation. To address this clinical need, quantitative iEEG analytics have been developed using a variety of approaches, spanning studies of seizures, interictal periods, and their transitions, and encompass a range of techniques including electrographic signal analysis, dynamical systems modeling, machine learning and graph theory. Unfortunately, many methods fail to generalize to new data and are sensitive to differences in pathology and electrode placement.

Here, we critically review selected literature on computational methods of identifying the epileptogenic zone from iEEG. We highlight shared methodological challenges common to many studies in this field and propose ways that they can be addressed. One fundamental common pitfall is a lack of open-source, high-quality data, which we specifically address by sharing a centralized high-quality, well-annotated, multicentre dataset consisting of >100 patients to support larger and more rigorous studies. Ultimately, we provide a road map to help these tools reach clinical trials and hope to improve the lives of future patients.

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## Epilepsy surgery and traditional localization of the epileptogenic zone

Clinicians plan epilepsy surgery by localizing the regions which causally generate seizures known as the epileptogenic zone (EZ), a process which often involves using intracranial EEG (iEEG)[1] (Fig. 1A) to record seizures directly over a 1–2 week period. Teams of epileptologists analyse the temporal, spatial, and spectral characteristics of these events to select the areas from which they most likely originate. The insights from iEEG are then combined with findings from the patient's history, seizure semiology, scalp EEG, neuropsychological testing, as well as structural and functional neuroimaging to determine the ultimate surgical strategy.

The primary method of EZ identification from iEEG is the qualitative recognition of specific seizure onset patterns that indicate a well-localized onset.[4,5] Common patterns include (i) low voltage fast activity; (ii) 'DC shift' or 'diffuse electrodecremental event'; (iii) preictal rhythmic spiking of low frequency and high amplitude; and (iv) bursts of polyspikes or spike-and-wave activity (Fig. 1A). Such onset patterns are known to vary by anatomical location and aetiology of epilepsy,[4] which aids clinicians in their approach to localization. Occasionally, typical onset patterns are not observed and instead poorly localized, lower frequency or 'propagated' patterns are seen, leaving clinicians to wonder if the implant has somehow missed the region driving seizures, or if the EZ is 'distributed',[2,3] and better treated with broader neuromodulation than focal intervention (Fig. 1B).

Traditional methods of EZ localization lead the majority of patients to become seizure free. However, even when clinicians feel that epileptogenic networks have been well defined, many patients relapse after surgery.[6,7] These poor outcomes may reflect inherent challenges in qualitative iEEG interpretation, limited spatial sampling, as well as our incomplete understanding of how seizures arise from brain networks in epilepsy. Furthermore, concerns about financial cost, potential neurologic morbidity, and the dependence on referral to a limited number of highly experienced clinicians restrict the access of epilepsy surgery to a small fraction of potential candidates.[8-10] Overall, there is a substantial need to leverage quantitative tools to improve surgical decision making while reducing cost and morbidity and increasing access.

In this article, we briefly review prior efforts to build quantitative tools intended to guide iEEG evaluation, identify barriers and potential solutions to clinical translation, and publicly release a large, multicentre dataset to accelerate research and clinical translation. Intracranial EEG, including microelectrode arrays have also provided substantial progress towards seizure prediction[11-14] uncovering the mechanisms underlying seizure generation[15-17]; however, an in-depth review of these topics is beyond our current scope. Here, we focus on the potential of quantitative iEEG as a tool for precision medicine in epilepsy.

## Quantitative localization of the epileptogenic zone

### Interictal methods

Methods of identifying epileptogenic surgical targets using interictal data could significantly reduce the need for long hospital stays waiting for unpredictable seizures to occur and increase the diagnostic yield for the patients who do not have seizures while implanted with iEEG. Many promising methods have been developed, including those studying high-frequency oscillations (HFOs; Fig. 2B), interictal spikes,[18-26] resting-state signal analysis, and functional connectivity.

HFOs are transient oscillatory events in the frequency range of 80 to 500 Hz, often separated into ripples (80–250 Hz) and fast ripples (250–500 Hz), that stand out from background activity.[18,20,27] It has been reported that high rates of HFOs are present in epileptic tissue and that removal of regions with high HFO rates results in more favorable outcomes.[28-31] However, as HFO analysis has moved to automatic detection due to the poor inter-rater reliability of visual review,[32-35] recent prospective studies[36] and meta-analyses[37,38] have reported little advantage in using HFOs for surgical planning. The performance of HFOs in predicting surgical outcome may be biased by several factors. First, HFOs are present physiologically, and this confounds the distinction of pathological HFOs.[39-41] Efforts to create an HFO atlas[42] and to assess HFO rates during cognitive tasks[43] may help distinguish pathological tissues. Second, though fast ripples were shown to be more specific to epileptogenic tissues,[44] clinical viability may rely on fast ripple detection combined with epileptic spikes or post-resection recordings.[45,46] However, the mechanistic theory that HFOs are network-driven phenomena may explain this discrepancy in fast ripple specificity.[45,47,48]

Interictal spikes are brief, abnormal electrical discharges seen in epileptic patients during seizure-free intervals. The mechanistic relationship between spikes and seizures is still unknown, although they are temporally related in many patients[49] and both are observed to manifest similar multi-day cycles.[50] Given that spikes occur more frequently than seizures, they have been extensively studied for their ability to guide epilepsy surgery. Examining their location in frequency in iEEG has revealed that their spatial distribution fluctuates over time,[26] but that good surgical outcome is associated with the resection of regions which generate the highest frequency of spikes.[51,52] Furthermore, gamma activity preceding spikes provides additional sensitivity for discharges which mark the EZ.[53] However, spikes often arise outside regions of seizure onset,[54] complicating the presumed relationship between spike and seizure generation. These areas remain under active investigation, spanning research protocols that vary widely across institutions.

With epilepsy increasingly conceptualized as a network disorder, various network-based measures have been proposed to characterize the connectivity patterns in the epileptic brain network.[55-61] Recent studies suggest that the epileptic network not only demonstrates abnormalities during seizures but also at rest[55,62,63] and information about epileptogenic regions can be gleaned from the resting-state network.[57,58,64] Several studies have demonstrated increased synchronization in seizure-onset regions.[56,65] and a high influence of epileptogenic regions on the brain network during interictal periods.[55,57,58,62,64,66] To construct iEEG networks, graph-theoretic measures computed from an adjacency matrix that represents pairwise dependencies (correlation or coherence) between iEEG channels[56,64,67] are often used. These metrics are not always easily interpretable as different networks can result in identical metrics.[68] To overcome this, others have derived dynamical models of the iEEG signals,[57,58,69] which are designed to capture the underlying dynamical properties of the epileptic network responsible for seizure generation. A recent study implemented a time-varying autoregressive model to conceptualize source and sink nodes (regions) in the epileptic network where the sinks, regions being inhibited by sources, are correlated to epileptogenic regions during interictal periods.[58,70]

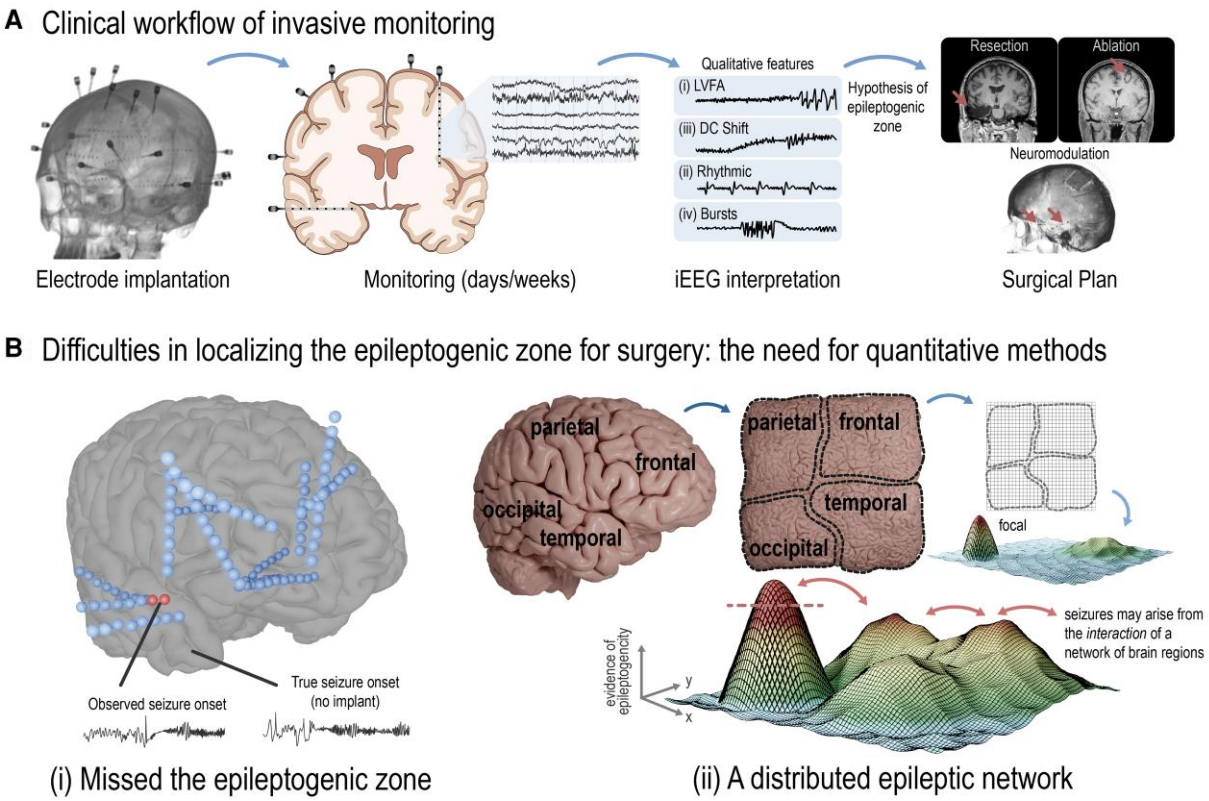


**Figure 1 Clinical workflow and the need for quantitative methods to localize the EZ.** (**A**) Clinicians often localize the EZ for surgery using iEEG. Qualitative recognition of specific seizure onset patterns are primary used, including the identification of (i) low voltage fast activity; (ii) 'DC shift'; (iii) preictal rhythmic spiking; and (iv) bursts of polyspikes or spike-and-wave activity (**B**) Difficulties in localizing the EZ may arise due to many factors. These can include (i) the implant somehow missed the region driving seizures; and (ii) the EZ is not a singular focus *per se*, but rather, seizures arise from a distributed interaction of brain regions in some patients. This is called the distributed epileptic network hypothesis.[2,3] Given relevant iEEG and other clinical data, a singular focus may present itself as the EZ (red dashed line, adapted from Khambati *et al.*[2] and Revell *et al.*[3] with permission); however, other regions across the brain are involved in seizure generation, too. Removal of the primary seizure focus may not result in complete seizure freedom. Thus, there is the need for quantitative methods to (i) better localize seizure onset given imperfect implantation schemes; and (ii) quantify if a patient may be better treated with broader neuromodulation over focal intervention.

## Ictal methods

Quantitative evaluation of ictal recordings can provide additional localizing value beyond clinician recognition of canonical seizure onset patterns. Many such approaches analyse the spectral characteristics of seizure onset patterns to determine which channels are most critically involved in seizure generation. One method leverages a wavelet transform (Fig. 2B) of the iEEG signals recorded on each individual channel in patients that became seizure free, to identify a 'fingerprint of the epileptogenic zone'.[71,72] Approaches from computer vision were used to extract features from the time-frequency plot, which were then classified as epileptogenic using a support vector machine. Another widely studied, non-linear univariate metrics is the epileptogenicity index (EI; Fig. 2B),[73] which quantifies clinically-observable patterns based on both the spectral and temporal delay patterns of iEEG. To compute EI, two specific metrics are calculated over a sliding window: (i) the 'ER', or the signal energy ratio between the beta and gamma bands compared to the theta and alpha bands; and (ii) a cumulative sum algorithm used over the 'ER' signal to determine when it significantly changes, marking a shift from low frequency to high frequency activity. Additionally, cross-frequency coupling has proved to be an important characteristic of epileptogenic tissues. For example, channels within the ictal core contain a high degree of phase locking between the high-gamma band and lower frequencies.[74] Studies have shown that using this method to localize epileptogenic networks accurately predicts surgical outcomes better than experts marking the seizure onset zone alone.[74]

Connectivity-based, or 'network' approaches for analysing ictal activity generally estimate connectivity values between channels, via either a bivariate, or multivariate statistical approach[75] (Fig. 2A). Analysing eigenvector centrality (EC), a measure of a node's influence within a network, (Fig. 2B) of the iEEG correlation graph in frequency space shows a network transition from the interictal to ictal state.[76] A similar analysis correlates the EC with the clinically hypothesized epileptogenic regions of a retrospective pool of patients.[59] Analysing the network during ictal periods may also help predict surgical outcomes.[77] Assuming the network is estimated sufficiently, virtual resection in the context of the model may help predict surgical outcomes.[65,78] In a recent study, analysis of time-varying dynamical connectivity enabled computation of 'neural fragility' metric (Fig. 2B) that predicted surgical outcome in a large retrospective multicentre cohort of 91 patients.[79-81] The study showed this by conditioning on the clinically hypothesized epileptogenic regions, indirectly suggesting that neural fragility could be useful for localization. Interestingly, neural fragility was also shown to increase across the course of epileptogenesis in a small animal study,[82] implying that it provides not only localizing but perhaps mechanistic implications towards seizure generation.

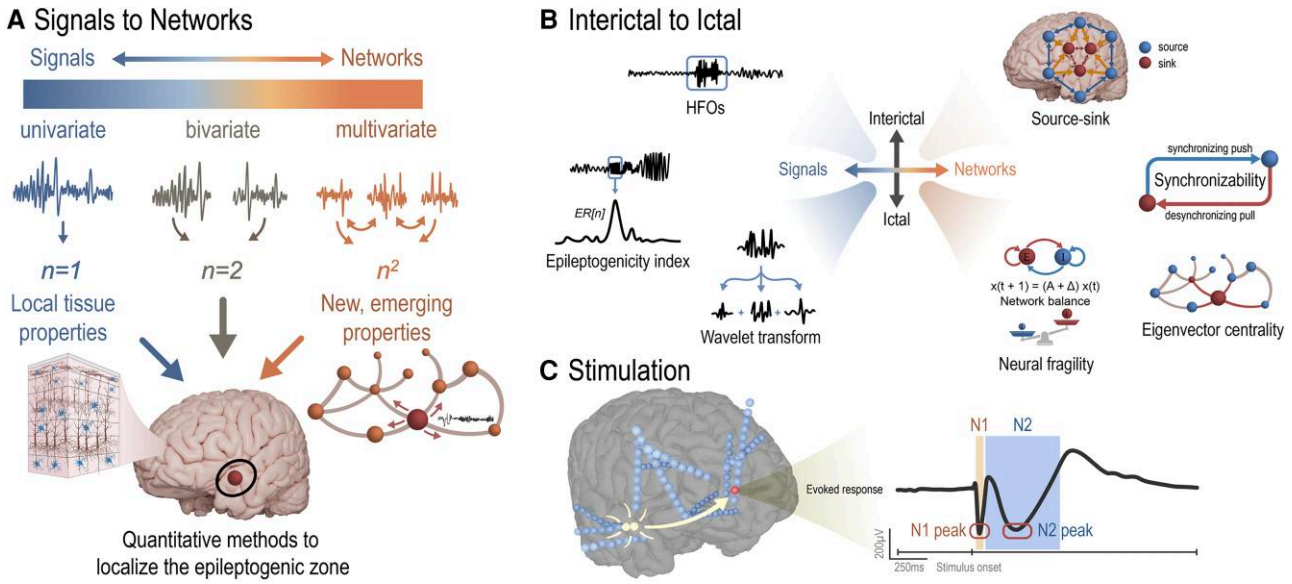


**Figure 2 Quantitative methods to localize the EZ.** (**A**) Methods of iEEG analysis range from univariate signal processing analyses of individual channels to bivariate analyses on pairs of channels, and to networks in which connectivity between all pairs of channels are assessed and emergent network properties are studied. (**B**) Various methods of quantitative seizure onset zone localization have been studied using both interictal and ictal data (**C**) Stimulation-based mapping is an effective method of probing the dynamics of epileptogenic networks.

### Stimulation-based mapping

Investigations of the EZ using electrical stimulation (Fig. 2C) have undergone a resurgence in the past two decades since the first pioneering experiments by Penfield, Jasper, Ojemann and others.[83-85] Specifically, single pulse electrical stimulation (SPES) has gained popularity as a measure of effective connectivity, where brief (150–300 μs per phase) pulses evoke responses in local and remote regions to indicate a structural or functional connection to the stimulation site.[86-88] These cortico-cortical evoked potentials (CCEPs) have been used to map interregional connectivity *in vivo* in the language network,[89] motor cortex,[89] limbic network,[90] parietal-frontal connections,[91] and deep brain structures.[87,92] SPES is safe,[93] reveals local and distant functional networks,[89,94,95] and provides complementary information when combined with other neuroimaging modalities.[96]

To delineate seizure networks, differences in features of the CCEP waveform have been associated with increased cortical excitability.[90,97,98] The amplitude of the N1 response (typically 10–50 ms post-stimulus) is often greater in seizure onset regions and early spread regions when compared to healthy tissue,[90,97-99] and stimulating the seizure onset region produces larger remote responses with increased connectivity.[99-101] More recently, greater cortico-cortical spectral responses and induced high-frequency activity have been shown to localize epileptogenic tissue.[102-106] Additionally, 'delayed responses', neuronal activities that resemble spikes or slow waves that occur 100 ms to 1 s after stimulation onset, are more frequently observed in seizure onset zone regions,[107,108] and removal of these areas result in improved outcomes.[107,109]

In contrast to these signal properties, systems-level analysis of CCEP data to localize the epileptogenic network has been recently proposed.[110-113] In a recent study, authors tested the hypothesis that dynamical network models derived from CCEPs can reveal epileptic network connections and the underlying dynamics of seizure generation. Specifically, they posit that brain regions where small periodic inputs produce large amplitude oscillations in the intracranial EEG correspond to the seizure onset zone. Such responses occur when there is a resonant frequency of the brain network, and this frequency can be detected by a sharp peak in the frequency response curve.[113]

Several factors that affect the CCEP waveform remain open questions, impeding the widespread use of SPES in surgical planning for epilepsy. SPES and CCEPs were first defined with electrocorticography (ECoG) grids, but the increased use of stereo-EEG (SEEG) raises questions about optimal stimulation parameters, volume of activated tissue, and artifact considerations.[85,114-116] The CCEP waveform depends heavily on location of the stimulating and response electrodes,[66] whether in grey or white matter[117,118] or in highly functional regions.[119] Larger validation studies answering these questions will ease implementation of stimulation-based investigations of seizure networks in the clinical workflow.

In a broader context, electrical stimulation has been used to evoke seizures to aid in seizure network inference.[113,120,121] There are relatively few studies that directly examine the improvement in surgical outcome when using clinical information derived from stimulation-induced seizures,[122] but a general trend towards adoption of stimulation-derived investigations of seizure networks provides a unique and timely opportunity for further investigation.[113]

## Challenges and opportunities

In this section, we review a series of challenges that have prevented most quantitative methods of localizing the EZ from becoming clinical tools which routinely impact clinical practice for patients undergoing epilepsy surgery (Fig. 3). For each of these challenges, we propose ways of adapting future studies to mitigate their effects on results and clinical translatability.

### Challenge 1: clinical heterogeneity

One of the primary barriers to deploying quantitative methods to guide epilepsy surgery is the vast clinical heterogeneity that exists

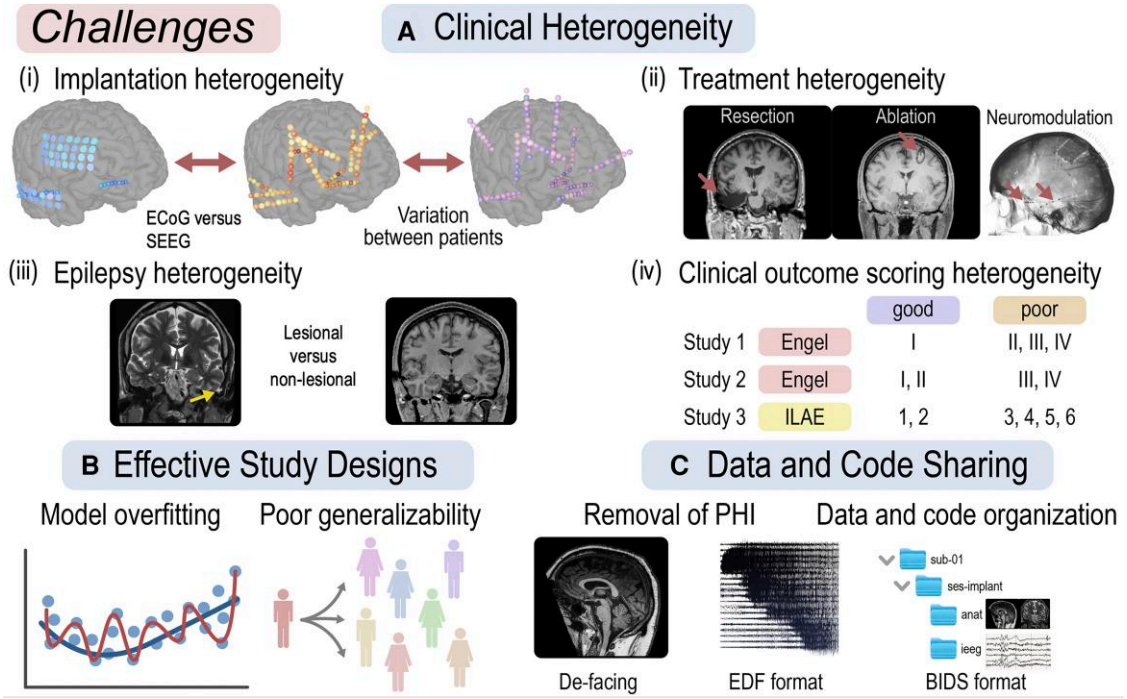


**Figure 3 Challenges and opportunities.** (**A**) Clinical heterogeneity is a primary challenge in deploying quantitative iEEG methods in epilepsy surgery, and encompasses variability in implant type, therapy, underlying pathology, and outcome metrics. (**B**) Effective study design should include development, validation, and test cohorts to minimize overfitting and maximize generalizability. (**C**) Data and code sharing should be a standard practice in iEEG studies in epilepsy and should incorporate de-identification and standardized formatting of raw data, imaging, and metadata such as using the BIDS framework.

across patients with epilepsy (Fig. 3A). We identify the main sources of heterogeneity which may influence network models as (i) variability in electrode implantation types and placement, such as ECoG and SEEG; (ii) variability in treatment approaches, such as resection, ablation, and neurostimulation; (iii) variability in types of epilepsy, aetiology and underlying genetic and pathological substrates; and (iv) variation in the methods of assessing clinical outcome.

The type of data recorded from ECoG and SEEG are inherently different. ECoG records from the surface of the brain capturing grey matter often with a uniform spacing between contacts on a grid electrode array. SEEG depth electrodes capture white matter in addition to grey matter, which differ in both qualitative and quantitative properties during interictal and seizure periods. These differences in implants are known to impact the utility of network models in each type of implant[123] and the effects are different across different network statistics.[124,125] We propose that future studies validate their methods using SEEG subjects when possible.

Treatment type is also an important factor because resections typically cover a larger (and possibly even different) portion of the brain than the clinically hypothesized epileptogenic region. Laser ablations target less tissue but are typically only used if clinicians have a strong hypothesis for a focal epileptogenic network. Finally, implanted neurostimulators do not remove tissue at all, but rather stimulate to suppress activity in regions hypothesized as epileptogenic or exert functional influence over it (e.g. thalamic stimulation).[126] Understanding possible treatment and selection bias is vital to conducting large, controlled multicentre studies involving multiple treatment modalities.[127] We propose that future efforts control for the type of surgical intervention, and exercise caution when cohorts contain both subjects that underwent surgery with curative intent (resection, ablation) and those with palliative intent (e.g. neurostimulation).

Epilepsy is a clinically heterogeneous disorder which encompasses a variety of underlying aetiologies, pathologies and anatomic distributions. Aetiologies of focal epilepsy include both clearly delineated lesions, such as mesial temporal sclerosis, focal cortical dysplasias, and cavernomas. Poorly localized or multi-focal processes can also cause epilepsy, including traumatic brain injury, stroke, or infection. As seizure onset patterns differ between different lesions and aetiologies, even for the same brain region,[5] it follows that the mechanisms underlying seizure generation and therefore quantitative variability could also differ and affect the accuracy of quantitative models. Furthermore, distinct anatomic distributions of hypothesized epileptogenic lesions lead to different network sampling and therefore distinct quantitative properties evident on iEEG. We suggest that future models document both performance on mesial temporal lobe epilepsy and neocortical epilepsy where possible.

Finally, there is substantial bias in quantitative iEEG studies as a result of different clinical assessments of surgical outcome. Criteria for defining which patients achieve ‘good’ versus ‘poor’ outcome are not universally accepted, and even the term ‘seizure free’ may or may not encompass non-disabling auras. Additionally, these metrics change over time as patients relapse, so the results of a single study may only hold valid at a single point in time. Finally, appropriate outcome scales do not exist for neuromodulatory devices or surgical interventions intended to be palliative. We propose that studies document both early and late outcomes when feasible, and that patients with true seizure freedom are treated separately from those with a favorable clinical outcome but remaining auras.

Overall, few single centres have a sufficient clinical volume to study a clinically homogeneous cohort. Rigorous documentation of subject-level clinical metadata will increase the interpretability of future studies, and renewed efforts towards cross-centre collaboration and data-sharing will permit the aggregation of subjects with similar implants, surgery, and pathology to more finely probe the factors which drive seizure freedom and relapse.

### Challenge 2: effectively designing retrospective studies

Another significant barrier to clinical translation is variability in retrospective study design (Fig. 3B). We propose that methods should be developed on a training cohort, optimized on a validation cohort, and performance quantified on a held-out test cohort to prevent overfitting to small datasets.[128] Ideally, the set of clinically hypothesized regions are well within the surgically resected/ablated areas in training data to provide the most accurate representation of epileptogenicity possible.

Additionally, most retrospective studies aim to localize tissue that should be removed, but do not explicitly identify regions that should be preserved. In clinical practice, the selection of surgical approach and extent weighs the benefit of seizure freedom with the risk of neurologic morbidity and patient preference. Besides the avoidance of eloquent cortex, regions which have a desynchronizing effect on the epileptogenic network also may be important to preserve for an optimal seizure outcome. Practically, future studies should indicate which subjects had resection strategies limited by their EZ localized to eloquent cortex and models should take neuro-cognitive testing and cortical mapping into account for symptom avoidance.

A recent trend in designing studies to validate localization algorithms is to predict surgical outcomes instead of identifying the EZ, since these regions are not observed. However, one should be aware of non-causal covariates that may bias results to be overly optimistic. For example, if the number of channels is higher in patients with surgical outcomes Engel II, or greater, and a prediction algorithm adds the number of channels to its set of features then the prediction algorithm leverages a spurious correlation of the number of channels to predict outcome, which has no real clinical utility.[129] Designing effective studies that fairly evaluate a proposed biomarker of epileptogenicity requires a deep understanding of the data and statistical challenges.

Finally, some models have a high predictive value but low explanatory value—addressing this trade-off is another challenge. For example, quantitative models that have high physiological plausibility may be easier for physicians to understand and use but they may not generalize well. In contrast, some deep-learning models might generalize well on new data but could be challenging to interpret. Indeed, many of the best tools for seizure prediction apply machine learning to quantitative iEEG features rather than model underlying electrophysiologic phenomena. On the other hand, mechanistic studies of epilepsy may reveal novel approaches to treating seizures including with drugs and neuromodulation. As our understanding of epilepsy grows, it is critical to advance predictive and explanatory studies together.

### Challenge 3: data and code sharing

Data and code sharing is fundamental to moving computational epilepsy studies towards clinical translation. We advocate for proper de-identification of protected health information, unified formatting of datasets, long-term public storage of the data, and the release of open-source code (Fig. 3C). Many groups choose to not share raw data due to institutional regulations, privacy laws, or burdensome data wrangling. However, misaligned incentives against data-sharing exist such as competition for publications, grants and potential for monetization.[130,131] We propose that sufficiently de-identifying iEEG datasets and including complementary imaging and clinical metadata is feasible, such that quality data sharing should be required by funding agencies and academic journals. Many software packages exist that facilitate removing identifying information in common recording formats, such as EDF.[132-134] For neuroimaging, defacing software[135] can automatically remove the face part of the images and storage of Nifti (.nii) files facilitates anonymization. With these advances, it is possible to share EEG-recording and imaging data along with non-identifiable metadata to facilitate community-driven solutions for epileptogenic network localization.

However, it is not enough simply to 'share' the data as many formats for both raw EEG data and metadata are difficult for outside users to effectively parse. The Brain Imaging Data Structure (BIDS) is a community-driven format for storing and sharing de-identified data,[135-137] supports all common EEG recording formats and has an open-source specification for metadata storage. Open-source web portals, such as OpenNeuro, can automatically check data to determine BIDS-compliance. Other platforms such as Pennsieve, which is developing an Epilepsy Data Ecosystem to integrate with other platforms, does similar data aggregation and data sharing for the NIH SPARC program.[138] Finally, sharing high-quality code and documentation (such as on GitHub) can allow researchers to easily benchmark their proposed algorithms against prior work.

## Introduction of a diverse, multicentre dataset

One of the primary barriers to appropriately developing and testing robust methods of EZ localization which can handle the vast clinical heterogeneity that exists among patients with epilepsy is a lack of enough high-quality data. To address this need, we document a publicly available dataset including recordings from 122 patients who underwent iEEG implantation and subsequent surgery for drug resistant epilepsy (Fig. 4). The data are organized in the standardized BIDS format on OpenNeuro, in projects ds003029, ds003876, and ds004100. Each dataset includes clinical metadata, such as implant type, surgery type, surgical outcome, electrode labels and standardized coordinates, as well as which electrode contacts were targeted by surgery. The electrophysiologic data is recorded and stored in referential montages and is unprocessed. Seizures were identified by board-certified epileptologists, and interictal clips were selected to minimize the presence of artefacts. Project ds003029 contains seizure recordings (mean per patient 3 ± 1.3), ds003876 contains interictal recordings (one to four clips per patient), while ds004100 contains both (mean seizures per patient 5.6 ± 1.5 with one interictal clip each). Full descriptions are present in the ReadMe files contained on OpenNeuro. Our datasets do not include clips where stimulation-based mapping was performed. Portions of each dataset have been used and published as part of previous studies[58,63,65,79]; however, we release additional subjects, recordings, electrode localizations, and metadata that were previously unpublished.

Using our dataset as well as other high-quality iEEG cohorts,[139,140] future studies may effectively develop, validate, and

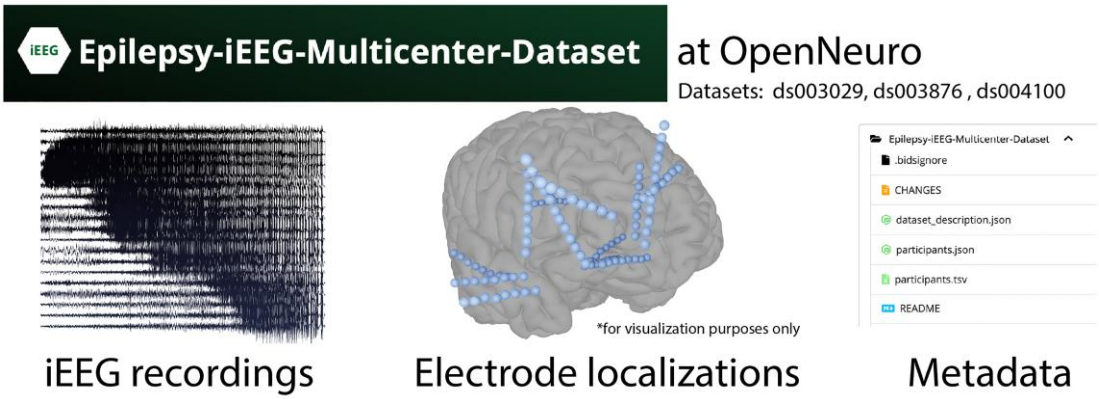


**Figure 4 Multicentre open-source iEEG datasets.** We have released our data on OpenNeuro to aid in development, validation, and testing of new methods of seizure onset zone localization.

test a wide variety of methods to quantitatively localize the EZ. For example, subsets of our dataset can be used to study more clinically homogeneous populations, such as those which were only implanted with sEEG, or only underwent MTL laser ablations. Alternatively, our dataset could serve as a 'test set' to quantify performance of algorithms developed on private cohorts. Finally, we encourage others to release de-identified data from their centre in the iEEG BIDS format so that further studies may achieve even better statistical rigor, and our group currently has NIH funding to help aggregate more data across epilepsy centres to accelerate research.

## Prospective studies

We posit that multiple methods, each which offer complementary information, may be integrated into a single software package that provides spatially-localized probabilities of epileptogenicity.[70] Ideally, these tools may reach a high level of accuracy using only interictal recording or stimulation data alone, reducing the lengthy and costly stays in epilepsy monitoring units for recording seizures. While we foresee that some proprietary algorithms may arise, we believe that it is critical to keep scientific discovery in this field open-source so that all centres may have equitable access to tools which can improve care. We further expect that clinical quantitative iEEG models will complement insights from neuroimaging-based EZ localization tools leveraging structural, diffusion-weighted, and functional MRI. Ultimately, we foresee that the quantitative insight that these tools provide will augment, rather than replace, the expertise of clinicians in surgical planning.

Incorporating retrospectively validated computational models in prospective clinical trials will require careful study design. Decision making at the patient level could include predictions from quantitative models in an unblinded, randomized fashion to help clinicians decide between two equally probable clinical hypotheses (e.g. medial temporal versus medial + temporal neocortical onsets), decide between therapeutic options in very specific epilepsy surgery decisions (e.g. standard temporal lobectomy versus medial temporal ablation), or to advise surgical teams regarding the extent of intervention in cases where several options are present. While there are precedents for all of these types of trials, a careful, multicentre approach will likely be necessary to establish protocols, standards for data collection, annotation, analysis and interpretation, with sufficient power to assess the value of these methods. Certainly non-destructive therapies, such as neuromodulation, which can be tested in different portions of the epileptic network in the same patient, provide an interesting alternative to larger surgical trials, but current hardware limitations in the number of contacts and leads make this somewhat invasive, as switching between different implanted leads currently requires repeat surgery and changing connections to implanted devices.

With our description and consolidation of a high-quality multicentre dataset, we hope that researchers will benchmark their proposed algorithms using this cohort in a sound statistical fashion, similar to our prior efforts to benchmark seizure detection and prediction.[11,141] We encourage researchers to de-identify their data using the tools described and release their data in an open access and easily shareable format. These collective efforts will continue to move the field towards a robust epileptogenic network localization algorithm.

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## Competing interests

The authors have no conflicts of interest to disclose.

## Supplementary material

Supplementary material is available at *Brain* online.

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