Finding a Fragile Piece to End the Seizure War

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Neural Fragility as an EEG Marker of the Seizure Onset Zone
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Over 15 million patients with epilepsy worldwide do not respond to drugs. Successful surgical treatment requires complete removal or disconnection of the seizure onset zone (SOZ), brain region(s) where seizures originate. Unfortunately, surgical success rates vary between 30 and 70% because no clinically validated biological marker of the SOZ exists. We develop and retrospectively validate a new electroencephalogram (EEG) marker—neural fragility—in a retrospective analysis of 91 patients by using neural fragility of the annotated SOZ as a metric to predict surgical outcomes. Fragility predicts 43 out of 47 surgical failures, with an overall prediction accuracy of 76% compared with the accuracy of clinicians at 48% (successful outcomes). In failed outcomes, we identify fragile regions that were untreated. When compared to 20 EEG features proposed as SOZ markers, fragility outperformed in predictive power and interpretability, which suggests neural fragility as an EEG biomarker of the SOZ.

Commentary

Surgical resection of potentially epileptic brain tissue does not always result in seizure freedom in patients with drug-resistant epilepsy, pointing to the importance and difficulty of successfully identifying the brain regions responsible for initiating seizures (seizure onset zone; SOZ). This is why so much research continues to focus on identifying reliable biomarkers that can help clinicians optimally localize the SOZ. In addition to the standard clinical and radiographic signatures of epileptic tissue, candidate SOZ biomarkers include intracranial EEG (iEEG) patterns that are recorded from implanted electrodes and are localized to specific channels such as high-frequency oscillations and phase-amplitude coupling across frequency bands, as well as network properties such as inter-channel synchrony. In a recent study, Li et al. (2021) present an additional iEEG biomarker for the SOZ using a statistical method of estimating how much an individual channel contributes to the stability of the whole network. They call this metric “neural fragility.” As discussed below, this represents a useful addition to the arsenal of SOZ-detection methodologies, ideally one that is combined with other already existing approaches in the future.

What is neural fragility and how is it computed? The computation of neural fragility involves the automatic construction of an individually tailored model of the recorded tissue every 250 milliseconds. From this model, causal information can be inferred by calculating what would happen in response to changing connection strengths in the model, rather than simply describing patterns in the observed recordings. This approach is theoretically agnostic to the details of mechanisms that can contribute to seizures, not constraining itself to a particular electrophysiological pattern, but instead identifying the tendency of a channel to instigate network imbalance—and thus seizure initiation—in a more general sense. The algorithm particularly focuses on internally generated dynamics, efficiently building a model that estimates the rules by which the recorded network of regions evolves over time from any particular state. Applying the rich theoretical framework of dynamical systems to this model, it finds the minimum perturbation to each region’s influence on other regions that causes the whole model to become unstable. The transition to instability is a mathematically defined yet generic point at which a dynamical system can no longer recover from small, random disturbances to its resting state, as is characteristic of seizure onset. The size of this perturbation can then be used as a measure of how close each region is to setting off a network-wide destabilization, and thus a seizure, at each time point. This measure is the region’s neural fragility, the proposed new metric for deciding whether a particular location should be included in the SOZ.
How is the effectiveness of the neural fragility metric evaluated? This biomarker was assessed against other candidate iEEG metrics including various spectral band powers and graph theory-based measures of functional connectedness, in a head-to-head comparison of predictive value for 91 surgical resection outcomes. Predictive value was estimated by the performance of a machine learning classifier that uses the agreement of each metric’s values with clinically estimated SOZ labels to predict surgical outcomes, in comparison to actual outcomes. The authors found that neural fragility produced the most accurate predictions of surgical success (seizure-freedom) and failure by this measure. Importantly, however, it should be noted that most other metrics tested (such as oscillatory power in several bands) also produced statistically significant predictive power and up to 85% of the effect size in success-failure discrimination—despite the fact that these metrics did not benefit from a model-fitting procedure for their optimal estimation (as used for defining neural fragility).

While representing another option to help identify the tissue from which seizures may originate, neural fragility and its potential predictive value should be interpreted with some caveats concerning the generality of the conditions in which they were obtained. The computation of neural fragility is restricted to a certain kind of perturbation (“column perturbations”) that may not be biologically plausible in relation to seizure initiation in epilepsy. This model of a perturbation considers regions as functional nodes such as neurons that directly influence each other, yet iEEG signals are rather thought to reflect synaptic input more than local neuronal activity. As far as local neural activity can be decoupled from synaptic input to a region such as through cell-intrinsic dynamics, this interpretation breaks down and fragility may not be as predictive of the SOZ in distinct etiologies involving intrinsic cell properties. Another biological constraint against the generality of this biomarker is that the cortex is not strictly an autonomous dynamical system as assumed for simplicity here. Instead, the cortex has external inputs that affect the evolution of its state trajectory, such as inputs from thalamus and non-recorded cortical regions, that are not well-expressed within an evolution rule using only internal state. Neural fragility would not be expected to work as well when such inputs are involved in a seizure etiology. Thus, the fragility metric is also inherently sensitive to the choice of all other electrode locations beyond the putative SOZ.

Furthermore, nearness-to-instability is called “fragility” here, with negative connotation, but this phenomenon is also often called “criticality,” something thought to be essential for normal neurophysiology with a large body of empirical support. Being close to a point of instability, called a bifurcation or critical point, allows ready switching between qualitatively different states, neither of which need be pathological, at any given time. For example, neurons near a membrane potential bifurcation can readily switch between a resting state and a burst-firing state to mediate the rapid transitions needed between active inspiration and passive expiration in breathing rhythm-generating circuits. Similar dynamics are thought to be at work in cortical circuits and would be flagged as seizure-promoting by the neural fragility metric. Therefore, neural fragility may encourage removing precisely those regions of particular functional importance, not just pathological ones. Interestingly, for patients where surgery was not performed because the clinically estimated SOZ was near eloquent cortex, mean neural fragility appears to be even higher (their Extended Data Fig. 2 [note that the caption mistakenly appears in Extended Data Fig. 3]), which could be explained by eloquent cortex using criticality for normal function. Surgical success is defined here by lack of seizure recurrence, but the potential bias toward removing functional regions that use critical dynamics suggests including other measures of post-operative functionality and cognitive side-effects for a more holistic evaluation of fragility. Such considerations do not take away from the potential utility of this metric, but similar to considering how radiation therapy for cancer aims at cell division with many off-target effects on normal tissues, understanding the risks and benefits of using neural fragility will help facilitate more effective clinical decision-making about resection treatment.

Another important caveat is in interpreting the predictive value estimated for each candidate metric, which can only be assessed indirectly through the performance of a machine learning-based classifier. The results thus depend on the intelligence and fairness of the classifier. The low interpretability of most metrics other than neural fragility (Extended Data Fig. 9) suggests the classifier is making decisions that are difficult to interpret biologically, based on patterns that we would otherwise recognize only as noise. This raises the possibility of overfitting particularly for these metrics and thus the question of whether the relatively higher performance of neural fragility in comparison will persist if repeated for the wide variety of epilepsy etiologies not seen during training. Nevertheless, this work has converted the previously-established insight that dynamical instability captures a major cause of seizures into a quantitative, heat-map form for facile use by clinicians, benchmarking it with a powerful machine learning classifier albeit with the caveats highlighted here. Using neural fragility in conjunction with (rather than in comparison to) more biologically grounded metrics such as those capturing the abnormal timing of high-frequency rhythms (e.g., abnormal phase-amplitude coupling) could help explain other etiologies and increase specificity toward pathological regions without losing regions that use critical dynamics for normal function. The individually tailored computational algorithms utilized in fragility calculations, like those used for phase-amplitude coupling analyses, can potentially be assembled into well-designed software packages, and thus may have practical utility for relatively rapid individually tailored analyses within a clinical setting. However, such algorithms would need to first be tested on considerably larger datasets spanning a broad range of seizure etiologies before any such adoption was considered. Thus, neural fragility represents an additional way to potentially...
help clinicians identify the SOZ and, in combination with existing approaches, may eventually help to improve surgical resection treatment outcomes.

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