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Resting But Not Idle: Insights Into Epilepsy Network Suppression From Intracranial EEG

The Interictal Suppression Hypothesis in Focal Epilepsy: Network-Level Supporting Evidence

Johnson GW, Doss DJ, Morgan VL, Paulo DL, Cai LY, Shless JS, Negi AS, Gummadavelli A, Kang H, Reddy SB, Naftel RP, Bick SK, Williams Roberson S, Dawant BM, Wallace MT, Englot DJ. *Brain*. 2023;146(7):2828-2845. doi:10.1093/brain/awad016

Why are people with focal epilepsy not continuously having seizures? Previous neuronal signalling work has implicated gamma-aminobutyric acid balance as integral to seizure generation and termination, but is a high-level distributed brain network involved in suppressing seizures? Recent intracranial electrographic evidence has suggested that seizure-onset zones have increased inward connectivity that could be associated with interictal suppression of seizure activity. Accordingly, we hypothesize that seizure-onset zones are actively suppressed by the rest of the brain network during interictal states. Full testing of this hypothesis would require collaboration across multiple domains of neuroscience. We focused on partially testing this hypothesis at the electrographic network level within 81 individuals with drug-resistant focal epilepsy undergoing presurgical evaluation. We used intracranial electrographic resting-state and neurostimulation recordings to evaluate the network connectivity of seizure onset, early propagation and non-involved zones. We then used diffusion imaging to acquire estimates of white-matter connectivity to evaluate structure–function coupling effects on connectivity findings. Finally, we generated a resting-state classification model to assist clinicians in detecting seizure-onset and propagation zones without the need for multiple ictal recordings. Our findings indicate that seizure onset and early propagation zones demonstrate markedly increased inwards connectivity and decreased outwards connectivity using both resting-state (one-way ANOVA, *P*-value $= 3.13 \times 10^{-13}$) and neurostimulation analyses to evaluate evoked responses (one-way ANOVA, *P*-value $= 2.5 \times 10^{-3}$). When controlling for the distance between regions, the difference between inwards and outwards connectivity remained stable up to 80 mm between brain connections (two-way repeated measures ANOVA, group effect *P*-value of 2.6×10^{-12}). Structure–function coupling analyses revealed that seizure-onset zones exhibit abnormally enhanced coupling (hypercoupling) of surrounding regions compared to presumably healthy tissue (two-way repeated measures ANOVA, interaction effect *P*-value of 9.76×10^{-21}). Using these observations, our support vector classification models achieved a maximum held-out testing set accuracy of $92.0 \pm 2.2\%$ to classify early propagation and seizure-onset zones. These results suggest that seizure-onset zones are actively segregated and suppressed by a widespread brain network. Furthermore, this electrographically observed functional suppression is disproportionate to any observed structural connectivity alterations of the seizure-onset zones. These findings have implications for the identification of seizure-onset zones using only brief electrographic recordings to reduce patient morbidity and augment the presurgical evaluation of drug-resistant epilepsy. Further testing of the interictal suppression hypothesis can provide insight into potential new resective, ablative and neuromodulation approaches to improve surgical success rates in those suffering from drug-resistant focal epilepsy.

Commentary

The resting state is the background neural activity in the absence of a specific task, or indeed in the absence of a seizure. Resting state EEG is recorded with the person in a relaxed awake state without external stimuli. While we focus our time on interictal epileptiform discharges and ictal EEG patterns, might this somewhat neglected portion of the EEG be actively suppressing seizures, so perhaps is not really "resting" at all? Johnson et al call this the interictal suppression hypothesis (ISH) in the article at the center of this commentary.[1]

The resting state can be studied functionally by analysis of EEG coherence, as a measure of connectivity, with or without evoked responses. Coherence is the degree of synchronicity of a given frequency band between 2 regions of the brain. Corresponding structural connectivity can be studied by methods such as diffusion tensor imaging (DTI).

The authors hypothesis that in the resting state, the seizure onset zone (SOZ), and its early propagation zone (PZ), maintain abnormal connectivity to surrounding normal brain, as detected by connectivity measures. This builds on their previous work,[2] showing increased functional connectivity between epileptogenic regions and other structures. They propose that identifying the SOZ from interictal data accurately could reduce the need for ictal recordings.

The authors used intracranial EEG (iEEG) data from 81 patients with medication-resistant focal epilepsy at one center undergoing stereo-electroencephalography (SEEG), over 60% with a form of temporal lobe epilepsy (TLE). Most went on to have some form of resection (43%), laser ablation (5%), or neuromodulation (30%). Coverage was extensive with a mean of 123 ($\pm$31) electrodes in each patient.

As per usual clinical course, designations were assigned to each SEEG contact by epileptologists. Seizure onset zone was defined as the first EEG changes for clinically significant ictal events, while PZ was the iEEG spread within 10 seconds. Other contacts were defined as noninvolved zones (NIZ).

Understanding SEEG and network lingo is useful here—"nodes" are pairs of EEG contacts. In SEEG, each depth inserted is denoted by a letter. The most mesial contacts start at 1 and increase in number in an outward direction. For example, H1-2 is the most mesial 2 contacts or "node" of the H depth, with location depending on placement decided preoperatively. Lines of connection between nodes (structural or functional) are the "edges."

Twenty-minute SEEG samples during the Resting state were analyzed in all patients for connectivity, as well as after single pulse electrical stimulation (SPES) in 23 patients, which allowed for analysis of directionality and relative attenuation or elevation of power bands. Coherence values for the edges between nodes were used as the measure of functional connectivity, and compared between the assigned regions (SOZ, PZ, and NIZ). A variation in coherence analysis called partial directed coherence determined information flow to be outward or inward.

The authors found that the SOZ and PZ showed increased undirected and inward functional connectivity compared to the NIZ, in both mesial TLE (mTLE) and non-mTLE, as evidence of organized network suppression at rest by surrounding nodes. When the non-SOZ network was stimulated by SPES, low-frequency power attenuated and high-frequency power was augmented in the SOZ, suggestive of an inhibitory influence: high-frequency power is associated with gamma-aminobutyric acid (GABA).

In 26 patients with available DTI, the ratio of structural to functional connectivity for each SEEG edge was calculated in each patient as a measure of structure-function coupling. The SOZ exhibited local structure-function *hypercoupling* within 5 to 20 mm of edge connections—the functional connectivity by iEEG exceeded the expected structural connectivity by DTI, and suggests a functional local reorganization seen around the SOZ. The authors adjusted whole brain tractography of the brain to focus on connectivity only around the implanted contacts, using an elegant novel technique called SWiNDL (subsampling whole-brain tractography with iEEG near-field dynamic localization) in order to correlate with the local functional connectivity.

When they looked at resective or ablative surgical outcome, PZ connectivity in seizure-free patients (Engel 1) was higher and closer to the SOZ. Propagation zone connectivity in patients with persistent disabling seizures (Engel 2-4) was lower and indistinguishable from the NIZ, suggesting that the network was not well-defined, and thus surgical intervention was less effective.

The authors designed a support vector machine (SVM) model trained with the resting state iEEG functional connectivity data to classify SEEG nodes as being in the SOZ, PZ, or NIZ. SVM is a type of artificial intelligence (AI) algorithm that is used to classify elements of a dataset. The model had a good overall accuracy for the SOZ of 92%, but less accurate for the PZ and NIZ, with some additional improvement if structural connectivity data was incorporated.

Have the authors answered their question of why people with focal epilepsy are not always seizing? The large increase in inwards inhibitory connectivity of the SOZ as well as structure function hypercoupling, in the resting state, might reduce the ability of the network to generate seizures. The increased inward gamma band power (thought to represent local GABA inhibitory interneuron activity) to the SOZ supports this. Perhaps in an epileptic encephalopathy, there is a more profound breakdown of this resting interictal inhibitory state, resulting in semicontinuous epileptiform activity.

They suggest they have found a useful AI iEEG model to classify the SOZ and PZ with practical implications to aid clinical decision-making, or even reduce the need for ictal recordings. However, the study sample size is small limiting the ability to draw robust conclusions on validity and generalizability of the findings, and such models require validation across multiple varied datasets using open-source code and data before becoming clinically useful. This model may be complementary but not replace analysis of interictal and ictal epileptiform discharges. More accurate prediction of the epilepsy network including the SOZ and its immediate PZ should allow a more precise surgical resection or modulation and improve outcomes. More data correlating surgical outcomes with network-defining tools is necessary. Potential for bias exists based on the allocation of SOZ, PZ, and NIZ by the treating epileptologist, and implantation bias, with an increased density of SEEG electrodes around the suspected SOZ.

A major limitation of SEEG is spatial coverage—we can only infer about a small volume of brain 3 mm in diameter recorded by each electrode, so we are not testing the whole network. There is a lack of control groups for iEEG data, so more difficult to know what is truly "normal." One could argue whether the recordings taken on the first day post-implant are a true reflection of a resting state. The definition of PZ as within 10 seconds of ictal onset may be oversimplified, was based on data from anteromedial temporal lobe cases, and does not consider individual propagation patterns from SOZ locations.[3]

We still only know a fraction about cerebral neuronal networks, and more work is needed to confirm the ISH. The findings are consistent with other groups showing resting state inhibition of nodes in the SOZ.[4]

Where does this inward inhibition come from? Evidence supports that subcortical–cortical interactions contribute to inhibitory control of epileptic brain regions.[5-7] Enhancing this inward inhibitory connectivity to the SOZ may be partly the mechanism by which neuromodulation works, such as deep brain stimulation of the anterior and centromedian nuclei of the thalamus. Exploration of optimal sites and parameters for stimulation could be facilitated by similar iEEG connectivity analysis. The usefulness of SEEG then expands to include identifying optimal sites and parameters for neuromodulation or ablative targets, in addition to defining a resection. Guidelines are needed for these and other analyses tools for iEEG interpretation and practical application.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Johnson GW, Doss DJ, Morgan VL, et al. The interictal suppression hypothesis in focal epilepsy: network-level supporting evidence. *Brain*. 2023;146(7):2828-2845. doi:10.1093/brain/awad016
2. Goodale SE, González HFJ, Johnson GW, et al. Resting-state SEEG may help localize epileptogenic brain regions. *Neurosurgery*. 2020;86(6):792-801.
3. Andrews JP, Gummadavelli A, Farooque P, et al. Association of seizure spread with surgical failure in epilepsy. *JAMA Neurol*. 2019;76(4):462-469.
4. Gunnarsdottir KM, Li A, Smith RJ, et al. Source-sink connectivity: a novel interictal EEG marker for seizure localization. *Brain*. 2022;145(11):3901-3915.
5. Norden AD, Blumenfeld H. The role of subcortical structures in human epilepsy. *Epilepsy Behav*. 2002;3(3):219-231.
6. Englot DJ. When the brakes fail: basal ganglia and seizure generalization. *Epilepsy Curr*. 2020;20(3):130-131.
7. Bae S, Lim HK, Jeong Y, et al. Deep brain stimulation of the anterior nuclei of the thalamus can alleviate seizure severity and induce hippocampal GABAergic neuronal changes in a pilocarpine-induced epileptic mouse brain. *Cereb Cortex*. 2022;32(24):5530-5543.