Epilepsy Currents
2020, Vol. 20(2) 80-82

DOI: 10.1177/1535759720904161
journals.sagepub.com/home/epi
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How Would You Like Your Epileptic Network? Linear, Nonlinear, Virtual?

Virtual Resection Predicts Surgical Outcome for Drug-Resistant Epilepsy

Kini LG, Bernabei JM, Mikhail F, et al. *Brain*. 2019;142(12):3892-3905. doi:10.1093/brain/awz303.

Patients with drug-resistant epilepsy often require surgery to become seizure-free. While laser ablation and implantable stimulation devices have lowered the morbidity of these procedures, seizure-free rates have not dramatically improved, particularly for patients without focal lesions. This is in part because it is often unclear where to intervene in these cases. To address this clinical need, several research groups have published methods to map epileptic networks but applying them to improve patient care remains a challenge. In this study, we advance clinical translation of these methods by: (1) presenting and sharing a robust pipeline to rigorously quantify the boundaries of the resection zone and determining which intracranial electroencephalographic (EEG) electrodes lie within it; (2) validating a brain network model on a retrospective cohort of 28 patients with drug-resistant epilepsy implanted with intracranial electrodes prior to surgical resection; and (3) sharing all neuroimaging, annotated electrophysiology, and clinical metadata to facilitate future collaboration. Our network methods accurately forecast whether patients are likely to benefit from surgical intervention based on synchronizability of intracranial EEG (area under the receiver operating characteristic curve of 0.89) and provide novel information that traditional electrographic features do not. We further report that removing synchronizing brain regions is associated with improved clinical outcome, and postulate that sparing desynchronizing regions may further be beneficial. Our findings suggest that data-driven network-based methods can identify patients likely to benefit from resective or ablative therapy, and perhaps prevent invasive interventions in those unlikely to do so.

Linear and Nonlinear Interrelations Show Fundamentally Distinct Network Structure in Preictal Intracranial EEG of Epilepsy Patients

Müller M, Caporro M, Gast H, et al. *Hum Brain Mapp*. 2020;41(2):467-483. doi:10.1002/hbm.24816.

Resection of the seizure-generating tissue can be highly beneficial in patients with drug-resistant epilepsy. However, only about half of all patients undergoing surgery get permanently and completely seizure-free. Investigating the dependences between intracranial electroencephalographic (EEG) signals adds a multivariate perspective largely unavailable to visual EEG analysis, which is the current clinical practice. We examined linear and nonlinear interrelations between intracranial EEG signals regarding their spatial distribution and network characteristics. The analyzed signals were recorded immediately before clinical seizure onset in epilepsy patients who received a standardized electrode implantation targeting the mesiotemporal structures. The linear interrelation networks were predominantly locally connected and highly reproducible between patients. In contrast, the nonlinear networks had a clearly centralized structure, which was specific for the individual pathology. The nonlinear interrelations were overrepresented in the focal hemisphere and in patients with no or only rare seizures after surgery specifically in the resected tissue. Connections to the outside were predominantly nonlinear. In all patients without worthwhile improvement after resective treatment, tissue producing strong nonlinear interrelations was left untouched by surgery. Our findings indicate that linear and nonlinear interrelations play fundamentally different roles in preictal intracranial EEG. Moreover, they suggest nonlinear signal interrelations to be a marker of epileptogenic tissue and not a characteristic of the mesiotemporal structures. Our results corroborate the network-based nature of epilepsy and suggest the application of network analysis to support the planning of resective epilepsy surgery.

Commentary

The study of electroencephalographic (EEG) synchronization during epileptic seizures recorded with intracerebral EEG dates back to the very early days of the application of computer analysis to the EEG, with the pioneering work of Mary Brazier.[1] Brazier's coherence-based method allowed propagation patterns to be traced between intracerebral sites; it was subsequently improved,[2] but a major step was made when nonlinear methods of association were introduced.[3] After falling out of favor for 25 years, these methods are now reappearing in the ubiquitous context of the study of epileptic networks, with more powerful analysis approaches. We discuss here 2 articles measuring interactions in intracerebral EEGs, constructing networks, and attempting to draw conclusions from network properties regarding epileptogenicity.

The study of Müller et al[4] evaluates the linear relationships measured by coherence and the nonlinear relationships measured by mutual information during a 3-minute preictal period in 20 patients with bilateral temporal electrode implantations. Nonlinear measures usually reflect *both* linear and nonlinear relationships but in this study the nonlinear relationships represent the *excess* part of the relationship which cannot be explained by linear relationships.

The study finds that linear relationships are equally present across patients in the more abnormal, and subsequently resected, mesial structures, and in the less abnormal contralateral structures. In contrast, the excess nonlinear relationships were less uniformly distributed across patients and were predominant on the more abnormal side and also in interhemispheric interactions. The study also found that, in patients with successful surgery, the nonlinear relationships were mostly present in regions subsequently resected. The authors interpreted these findings as indicating that linear relationships may represent physiological interactions driven by mesial temporal anatomy whereas nonlinear relationships could reflect pathological activity.

Indeed, one could envisage as an explanation for these findings that the frequent interictal spikes present in epileptic mesial temporal structures lead to nonlinear interactions whereas the physiological background EEG may interact through linear relationships. It would have been interesting to relate the findings from this network analysis to the more traditional markers of epileptic regions, interictal spikes.

In the paper of Kini et al,[5] the epileptic network of 28 patients with subdural electrodes is investigated in an effort to determine whether its properties can have predictive value for surgical outcome. The epileptic network is defined by a linear method only, defining a network link by the value of coherence between 2 electrodes during preictal and ictal periods. A high coherence defines a high level of synchronization between 2 electrodes. The synchronizability of the whole network (the set of interactions between all the electrodes) can be viewed as how easily the network can support oscillatory dynamics given the connection strengths that are calculated using coherence.

One can then calculate the change in synchronizability of the network when removing the contacts of one region. If the network synchronizability increases after removing the contacts of one region, that region has a desynchronizing effect on the network. Conversely, if the network synchronizability decreases after the removal, the region has a synchronizing effect on the network. Removing a set of contacts and recalculating the network characteristics can be termed a "virtual resection" since it allows assessing how a network reacts when a part of it is removed. The concept of virtual resection is currently applied by a French multicenter study in a clinical trial using a very complex whole brain model, which integrates anatomical and tractography information as well as seizure propagation information from intracerebral electrodes.[6]

Kini et al found that synchronizability decreased from preseizure to seizure and decreased significantly more during the early part of the seizure in patients who became seizure-free. Remarkably, this difference allowed discriminating patients with good outcome from patients with poor outcome with an accuracy of 86%. This difference represents a characteristic of the global network; it does not provide guidance regarding which regions should be resected. When the authors compute the change in synchronizability of the epileptic network resulting from virtually resecting the subsequently resected region (trying to assess if the subsequently resected region had a synchronizing or desynchronizing effect on the epileptic network), they did not find statistically significant differences that predicted outcome. They found interesting differences in specific frequency bands (β in one patient subgroup and γ in another subgroup) but these were not significant after the necessary correction for multiple comparisons; these changes are encouraging however, and may point to a potential use of the virtual resection method after validation in a larger patient group. One could speculate that the inclusion of nonlinear measures of interaction, not used in this study, could increase the statistical power of the analysis, particularly if, as speculated by Müller et al, such nonlinear relationships reflect the interactions of epileptic activity.

The study of epileptic networks recorded with intracranial electrodes, with linear or nonlinear methods, is not a new concept but new approaches may allow a better understanding of which are the regions critical for seizure generation and maintenance. Whereas early studies analyzed seizures only, recent studies analyze seizures as well as interictal epochs and both provide valuable information. One must remember, however, that no study will free us from the fundamental weakness of intracranial recordings, that of spatial undersampling. Maybe more effort could be made toward determining the characteristics of the network specific to the situation when we are not recording from the epileptogenic zone: the properties of the epileptic network in patients who fail surgery may not reflect an intrinsic property of the seizures of such patients, but the fact that we have an incomplete and poorly representative image of the seizure.

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