Wheels Within Wheels: Theory and Practice of Epileptic Networks

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Introduction

The concept of an epileptic network is based on the long-standing clinical observation that ictal electroencephalography (EEG) patterns cannot be easily explained by the traditional model of a single seizure focus triggering activity that spreads to uninvolved brain regions.[1] Accumulating evidence suggests that the pathophysiological underpinnings of focal seizure generation and propagation may involve large-scale networks, which are characterized by 1- and 2-way communication (often undergoing time delays via signal transmission[2]) across sites in multiple lobes of the brain. Focal seizures evolve over multiple cortical and subcortical structures often with remarkable reproducibility from one seizure to the other in a given patient; however, even when stereotyped, seizures commonly evolve in a distributed fashion with delayed secondary discharges and complex propagation patterns.[3-8] In such cases, the traditional model of the epileptogenic focus is too simplistic to capture the spatiotemporal organization of the epileptic network, which has spurred many to start applying complex system approaches used in data and network to understand the underlying neurophysiological mechanisms in epilepsy.

Epileptic networks are mapped onto a network defined by nodes (brain regions) and edges (connections between the nodes). These connections can be defined for each patient structurally (ie, nerve fiber tracts) or functionally (ie, examining the coupling of different brain regions during activity recorded with different modalities, such as EEG or functional MRI (fMRI)). In some cases, directionality of the edges may also be assessed. Together, the defined nodes and edges comprise a complete set of structural or functional links, the so-called connectome, that can then be subject to network analysis. This conceptual framework has been used extensively to characterize epileptic networks in terms of structural and dynamic, state-dependent properties.[9-12] When the connectome is linked to a dynamic model, it represents a large-scale brain network model, which can be used for data analysis or the simulation of patient-specific brain activation data. The organizational scale of the network model determines its applicability to data and may cover wide ranges, spatially from the subcellular to the full-brain scale and temporally from milliseconds for action potentials to days/years for modeling seizure occurrence.[13,14] Despite its simplicity, connectome-based analyses have yielded potentially important observations, such as elucidating the role of widespread pathological excitation, clarifying the loss of inhibition in modulating seizure severity and extent of spread,[15-18] and quantifying the degree of connectome patient-specificity for the prediction of seizure propagation.[19,20] Microelectrode recordings in small cell populations in the human are well-situated to address questions on

pathophysiology and mechanisms of localized seizure spread and interaction between different seizure territories, whereas intracranial macroelectrode recordings sample large-scale network organizational features used in clinical decision-making. This field bears promise, especially when shifting its focus from simply identifying generic large-scale networks toward characterizing such connections across temporal and spatial scales. We discuss this progress in the following for macroscopic and micro-/mesoscopic networks.

Networks Across Scales: Macroscale EEG and Imaging

Complex system theory provides a fundamental organizing principle of seizure dynamics, capturing characteristics in electrophysiological recordings comprising seizure onset and termination. The set of a seizure's dynamic properties is called the dynamotype, which leads naturally to a Taxonomy of Seizure Dynamics providing practical, objective metrics for classification into 16 theoretically possible classes.[21] This taxonomy coupled with the underlying connectome of the brain is the basis for computational brain network models simulating the range of possible seizure propagation profiles.[14] Recognizing that different biological processes might have similar outcomes, as well as the fact that the same (nonlinear) systems may produce a range of different behaviors, the connectome-based brain model presents a strategy to identify what those processes might be experimentally. The capacity to individualize the brain model opens up the possibilities for a personalization of diagnostic and curative approaches. Personalized network modeling is currently being studied by multiple investigators to predict outcome in patients undergoing epilepsy surgery.[20,22-24]

Currently, when evaluating a patient for epilepsy surgery, the seizure-onset zone region is defined qualitatively based on clinical, EEG, and imaging features. For surgeries outside the temporal lobe, even when there is a clear hypothesis for the area of seizure origin, less than half of patients achieve complete seizure freedom.[25] A third of these candidates have a complex pattern of remission or relapse.[25] Often this is attributed to an error in identifying the seizure focus. It is also not uncommon for the focus to be incompletely resected,[26] or for seizures to be multifocal, with some seizure foci going undetected. Personalized brain network models address these issues as they allow a large number of clinical hypotheses to be tested and may help overcome sampling limitations as they are not limited by the number of intracranial electrodes that can be implanted. Initial retrospective studies indicate good precision in detecting the epileptogenic networks using this approach, underlying the importance of ongoing prospective multicenter trials to estimate the impact of virtual epileptic patient models on improving surgical prognosis. The analysis of factors limiting prospective model performance is critical for future clinical application outside of clinical trials.

Another intriguing possibility for surgical failure is a reorganization of the large-scale pathological network postsurgically to produce seizures from sites that were previously dormant. In the current clinical state, physicians do not know if they selected the optimal resection or ablation size and location even in patients who are seizure free after surgery. Could a better understanding of the patient-specific brain network improve care?[27] This question has spurred multiple studies of novel biomarkers or computational models of personalized networks with the goal of improving the outcomes of epilepsy surgery and exploring minimally invasive interventions. For example, using data collected from intracranial monitoring done for presurgical evaluation, and a network analysis approach, a computational model for neocortical focal seizures was generated that categorized the observed networks of individuals into 3 discrete network types.[28] The classification, if verified, could be clinically relevant, as it also suggested 3 different treatment approaches based on the network classification (pharmaceutical, surgical, or neurostimulation). This concept of network analysis having predictive value for surgery has been also studied in other computational models derived from electrocorticographic patient data to reconstruct networks.[7,23,24] Computational modeling has also been applied in other whole-brain imaging modalities such as fMRI functional networks, which suggest network changes over the course of disease progression.[5,29,30] Aberrant structural networks based upon diffusion tractography have been shown to predict outcome and structural node-based abnormalities in unresected brain region have been associated with poor surgical outcomes.[31,32] In addition, seizure spread as measured by intracranial EEG has been shown to be constrained by the underlying white matter networks as measured by diffusion tractography.[33] These network changes in the different models suggest that there may be dynamic network biomarkers for predicting surgical treatment outcome. A caveat to this work is that it has all been done retrospectively, and the true test of computational models will be in whether they can inform clinicians prospectively.

Networks Across Scales: Micro and Mesoscale

Although microelectrodes provide highly specific data for small cell populations, any investigations into large-scale network activity in humans proposing to take advantage of these data must take into account their limited spatial coverage, as well as the relatively limited number of such recordings available. Current microelectrode systems approved for human use cover a few square mm (the "Utah" microelectrode array, Blackrock Microsystems Inc) or a small number of cells sampled at a limited number of brain sites (Behnke-Fried microwire depth arrays, Ad-tech Medical Instrument Corp). Due to these limitations, such recordings are perhaps best used to test specific hypotheses or to validate animal experiments or computational models. Animal studies have several noted advantages, for example, the ability to employ widefield calcium or GCaMP imaging, perturbation techniques such as optogenetics or pharmacological intervention, and the ability

to conduct longitudinal and well-powered studies in a homogeneous data set. Unfortunately, there are few established epilepsy models that have been shown to reproduce the large-scale network effects seen in humans, particularly for focal neocortical syndromes. Existing work includes a focal brain tumor model explored during spontaneous epileptiform activity and seizures using widefield GCaMP imaging,[34] a post-stroke epilepsy model in which thalamic connectivity with the seizure focus site in primary somatosensory cortex was demonstrated to have an important role in seizure generation,[35] and studies of the effects of optogenetic cell-type specific activation on pilocarpine-induced seizures,[36,37] with stimulation of interneurons in the fastigial nucleus of the cerebellum preventing seizures in a mouse pilocarpine model.[38] As these models all have important limitations in terms of relevance for patients with chronic focal epilepsy syndromes, there is an urgent need for further work in this area.

Returning to human recordings, there remains considerable controversy regarding such basic issues as the cellular signature of seizures, or indeed how to determine whether a given brain site is actively seizing. Two contrasting models have been put forward. One proposes that seizure activity across the brain is driven from a relatively small, migrating cortical region exhibiting a well-defined seizure signature analogous to those seen in animal models,[18,39-42] with a predominantly inhibitory response in brain sites outside of this area,[39,43,44] and the second proposes that heterogenous firing activity across large brain regions operate in synchrony to produce seizures, through an as yet unexplained mechanism.[45,46]

If it is the case that seizures are driven from small cortical regions, a large gap in knowledge remains: how does this localized activity translate to the large-scale seizure effects that have been well documented in EEG studies? The focal-seizure hypothesis was recently extended to account for this effect, due to the dual role for inhibition inherent in this model. At the seizing brain site, inhibition has failed and a runaway excitation effect emerges.[18,39] Outside of this region, inhibition is not only intact but is driven to high levels due to the strong excitatory synaptic currents generated from the seizing brain area. This results in weakly synchronized or possibly asynchronous oscillatory activity which may be interpreted as ictal spread.[41,43,44] Another possibility is the recruitment of disparate seizure sites, which may potentiate overall epileptic network effects and severity. This is clinically a well-recognized phenomenon,[47] but has been only minimally explored in animal studies[17] and computational models.[20] Capturing this effect in human microscale recordings is an important goal that could help to elucidate the cellular mechanisms and effects of such a scenario and provide crucial validation for high level network analyses.

Conclusion

Once a computational model has been created, predictions can be formulated and validated on new data sets that were not used to train the initial model. This approach allows researchers to glean new mechanistic insights and create models which can then be tested prospectively. There are many different types of mathematical approaches that can be applied to modeling a dynamic nonlinear network such as the brain, which is constantly plastic. However, mathematical modeling of epilepsy network topology is still an emerging field. The field would benefit from an influx of new mathematical perspectives on analyzing network topologies that could be applied to modeling seizure spread across the brain. For example, one could consider symmetries within the network topology or emerging theories on control principles of complex systems.[48,49] An interdisciplinary group including neuroscientists, computer scientists, and mathematicians assembled in late 2018 at the Epilepsy Foundation My Brain Map Innovation Institute Workshop intended to facilitate bringing together different perspectives in these early days of network modeling. Major conclusions from this workshop included (1) large curated data sets from multiple institutions are required to validate computational network models, (2) interdisciplinary approaches will facilitate advancing the field, and (3) for clinicians to understand and incorporate network analyses as clinical decision-making tools (for surgery, neurostimulation, or other activities) we need visualization tools that are ergonomic, intuitive to clinicians, and recommend an action for the clinician to take. Therefore, clinical tools to visualize the results of network based analyses will be key for successful clinical implementation.

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Summary

- Focal epilepsy syndromes prominently feature network interactions between sites in multiple lobes of the brain.
- Multiscale analyses conducted simultaneously at the cellular, local and brain network level are essential for the discovery of seizure origination, spread, and termination mechanisms.
- Network models guide development of patient-specific surgical interventions.

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