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Toward a Mechanistic Understanding of Epileptic Networks

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Abstract Focal epileptic seizures have long been considered to arise from a small susceptible brain area and spread through uninvolved regions. In the past decade, the idea that focal seizures instead arise from coordinated activity across large-scale epileptic networks has become widely accepted. Understanding the network model's applicability is critical, due to its increasing influence on clinical research and surgical treatment paradigms. In this review, we examine the origins of the concept of epileptic networks as the nidus for recurring seizures. We summarize analytical and methodological elements of epileptic network studies and discuss findings from recent detailed electrophysiological investigations. Our review highlights the strengths and limitations of the epileptic network theory as a metaphor for the complex interactions that occur during seizures. We present lines of investigation that may usefully probe these interactions and thus serve to advance our understanding of the long-range effects of epileptiform activity.

This article is part of the Topical Collection on *Epilepsy*

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Introduction

The process by which seizures initiate and spread has remained largely a mystery for nearly a century, prompting several incompatible hypotheses to explain clinical observations. Recently, the hypothesis that epilepsy is caused by aberrant neocortical large-scale connectivity, spanning regions on the scale of several centimeters, has become the dominant view [1]. A critical assessment of this concept is therefore appropriate, as this concept not only has permeated epilepsy research but also is starting to inform clinical practice. In this article, we will explore the foundations of the concept of the epileptic network in the neuroimaging and electrophysiology literature, and how it may be impacted by recent studies of seizure neurophysiology.

Origins of the Epileptic Network Hypothesis

The traditional focal-onset hypothesis is the underlying principle of surgical resection for the treatment of focal epilepsy, a procedure first employed successfully in the 19th century, with a large ($N = 55$) case series published in 1912 [2]. These early surgeries focused on "Jacksonian march" seizures, which are marked by slowly advancing activation of primary motor cortex, indicative of slow seizure propagation [3]. Focal resection of the tissue from which these seizures originate is effective in between 30 and 80 % of cases [4], with a recent trend toward smaller surgical volumes in selected cases [5, 6]. The success of these procedures provides strong evidence for the focal-onset hypothesis. Another piece of evidence comes from the extensive literature on high-frequency oscillations (HFOs), or transient bursts of activity in the high-frequency range of EEG, above what is typically reviewed in clinical EEG. These are typically limited to a smaller region than is usually spanned

by the seizure onset zone as it is clinically defined, and have been shown to arise from submillimeter areas in animal studies [7]. Resection of sites demonstrating high-frequency oscillations is associated with good surgical outcomes, for both ictal and interictal high-frequency oscillations [8, 9, 10•], while sparing sites free of high-frequency oscillations within the seizure onset zone does not adversely impact surgical outcome [9, 10•].

However, epilepsy surgery is not always effective despite complete removal of the putative seizure source [4, 10•, 11], and EEG recordings commonly give the impression of rapid seizure spread across large brain areas. In a marked departure from the traditional model, a seminal 2002 paper proposed the idea that "vulnerability to seizure activity in any one part of the network is influenced by activity everywhere else in the network, and that the network as a whole is responsible for the clinical and electrographic phenomena that we associate with human seizures" [12]. The evidence cited in support included examples of variation in seizure onset and spread in EEG recordings despite clinically stereotyped seizure semiologies, PET hypometabolism extending beyond the seizure onset zone and normalizing following successful focal resection, and similar surgical outcomes in temporal lobe epilepsy cases after resection of different non-overlapping areas, e.g., anterior temporal neocortex and mesial temporal structures.

It is not difficult to understand why the network explanation gained traction. Not only did the idea of an epileptic network provide a simple explanation for a complex array of clinical observations but it also held out the possibility of gaining a new understanding of focal epilepsy through an elegant paradigm shift. However, the epileptic network concept has a critical limitation: there is no corresponding physical entity. Rather, the use of the word "network" to describe the cerebral cortex is fundamentally metaphorical. The cerebral cortex is made up of billions of individual neurons that communicate with each other in a noisy, probabilistic fashion [13]. These neurons do not reciprocally relay information with a fixed delay as a network model assumes. Rather, each cell integrates and processes information and then communicates it to other cells with variable delay times [14]. In the face of this complexity, it is useful to simplify or analogize concepts. The classic adage "neurons that fire together wire together," for example, is a quick and intuitive way to say "it is currently our understanding that if a neuron fires an action potential after an adjacent cell fires an action potential, there is a higher probability these two neurons will fire with a similar pattern in the future." When applying the network metaphor, one must take care not to lose sight of these fundamental electrophysiology principles.

Epileptic Networks in the Literature

As part of our review, we conducted a meta-analysis of the literature. A PubMed search (12/29/1994–3/6/2016) for the terms "epileptic network(s)" and "seizure network(s)" yielded 191 original research articles and 60 review articles. After excluding the reviews, we classified the methodology from each article according to which organism was studied, data modality (e.g., fMRI, EEG), and whether the study utilized methods designed to characterize large-scale metaphorical networks. These are functional and effective connectivity studies, whose methodology will be further described below.

We noted a large increase in publication rate of network studies since the seminal 2002 paper (Fig. 1a). The majority of these studies utilized data from humans (Fig. 1b). The variety of methodologies used for all classifications of studies is striking (Fig. 1c). However, 52 % of human studies and 8 % of animal studies exclusively addressed metaphorical large-scale networks, and relied on neuroimaging or electrophysiological correlation techniques that assume network structure based on functional correlation measurements applied to data reflecting a mixture of brain activity (Fig. 1b). The remaining articles, particularly in the animal literature, studied networks that were closely aligned with known physiology. For example, articles investigating the spread effects of audiogenic seizures in rats [15, 16] used the term "seizure network" to describe the auditory system through which audiogenic seizures spread.

Network Methodology

To understand the limitations of methods focusing on metaphorical large-scale networks, we describe them in detail here. These techniques rely on the network-based understanding of the cerebral cortex, which is common in the human neuroimaging literature [17–19]. Networks can be based on structural, functional, or effective connectivity [20]. Structural connectivity elucidates anatomical connections, functional connectivity imposes connections based on correlations in functional measures, and effective connectivity adds directional influences to functional networks. Since the vast majority of the epilepsy studies examine functional connectivity, this review focuses on that category.

The prototypical epileptic network study uses graph theoretic analyses to infer connectivity patterns in large cortical regions of cortex, and how these connectivity patterns are modulated by seizures [21]. To create a network, one uses a measure relating each pair of sensors, which may be voxels, scalp or intracranial EEG electrodes, or MEG sensors. The data then takes the form of an N by N adjacency matrix, X, where N is the number of sensors being examined, and X_{ij} is a measure relating the ith and jth sensors. The most commonly used measure is pairwise correlation of the time series between sensors [22, 23], but can also be constructed from cross spectral measurements [24], cross spectra in a specific frequency band [25], pairwise phase correlations [22, 26], or any pairwise measure among sensors [27]. The measure
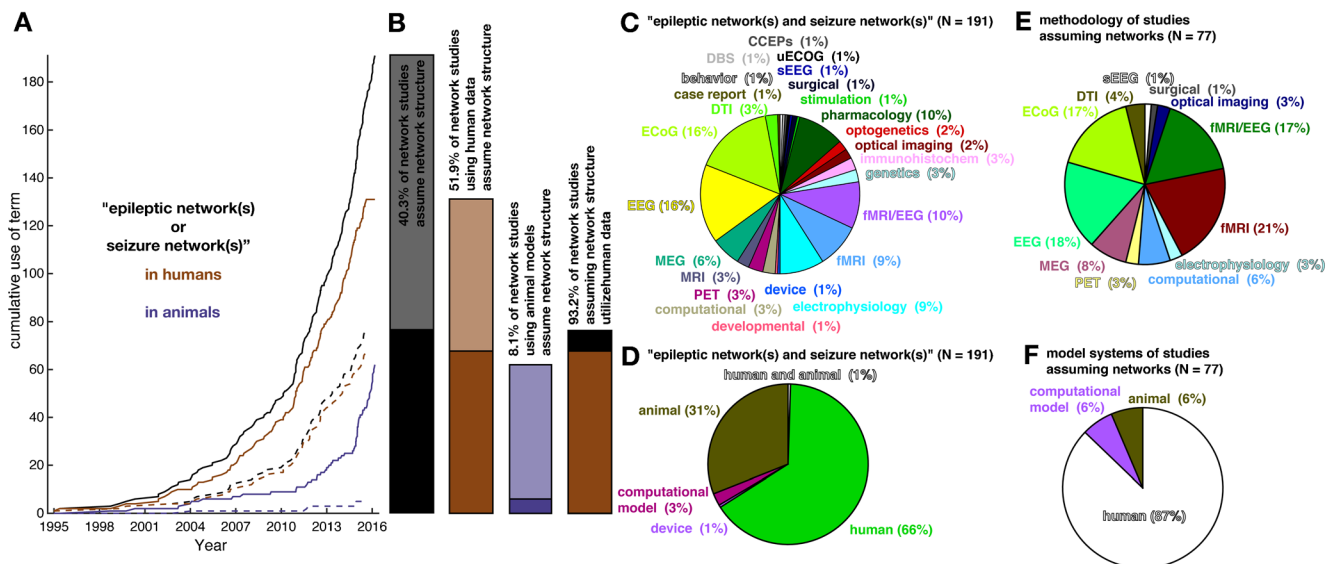
Fig. 1 Trends in usage of the terms "epileptic network" and "seizure network." **a** Cumulative usage of the terms in question (*solid lines*) and usage for a subset of the terms for studies assuming network structure (*dotted lines*), for all studies (*black*), human studies (*brown*), and animal studies (*purple*). **b** Stacked bar chart showing proportions of network studies that utilize methods that assume network structure. Stacked bar charts for human studies and animal studies are colored in *brown* and *purple*, respectively. **c** Pie charts for categories of methodologies used in network studies. **d** Pie charts for categories of model organisms used in network studies. **e** Pie charts for categories of model organisms used in both network studies that utilize methodologies that assume network structure. **f** Pie charts for categories of methodologies used in network studies that assume network structure. Label colors correspond to their respective pie wedges

values can then be subjected to a statistically defined threshold test [24], where a measure exceeding threshold is interpreted as a "connection" between the two sensors, while a value under the threshold implies a disconnection [23].

A graph can then be constructed with sensors as nodes, and pairwise connections (i.e., each X_{ij}) as edges [28]. Mathematical investigations can then be applied to identify properties of this graph. For example, networks can be described as "regular" (i.e., exhibiting high local connectivity and low global connectivity), "random" (i.e., exhibiting low local connectivity and high global connectivity), or "complex" (i.e., balanced connectivity) [29]. Another type of network commonly mentioned in epilepsy studies is a "small-world network," which is a category of highly clustered networks [30].

These network models lend themselves to qualitative descriptions of regional connectivity among nodes, providing, for example, a high-level network view of seizure spread [31]. However, the binary view of site-to-site connectivity oversimplifies the underlying neural physiology, and could therefore result in over-interpretation. For example, two independent studies demonstrated increasing synchronization toward the end of seizures, which led to the conclusion that increased synchronization might cause seizure termination [31]. However, a recent study focusing on details of human seizure electrophysiology presented results that are inconsistent with the idea of large-scale synchronization mediating seizure termination [32••]. Additionally, certain types of connectivity are associated with increased post-surgical success [22]. Though, as Kramer and Cash discuss [1], not only are the findings from

network study of epilepsy nonspecific, the results are disparate and at times contradictory.

This lack of reproducibility in network studies could be due to some salient caveats to network methodology that must be considered. One of the most severe is that there is no validated, or even agreed upon technique for determining what constitutes coupling between nodes. Studies either look for reproducibility in their networks [31], or develop a theoretical or statistical basis for setting a threshold for connectivity [24]. These processes have the potential to render the fundamental assumption of network structure unfalsifiable. That is, methods for understanding network structure assume network structure inherently. Few studies have taken the initial step to interrogate whether a network exists in the first place. Additionally, many studies assume that data are stationary or have Gaussian (normal) distributions. These assumptions have been shown to result in alarmingly high false positive rates (60–90 %) in resting fMRI studies including those used to study epileptic networks [33••]. These issues can be avoided by using statistical resampling or "bootstrap" methods to set statistically defined thresholds for coupling [34], and as discussed below, studying the mechanistic substrates that might or might not underlie network structure.

Limitations of Data Used to Infer Network Structure

Human studies of functional networks employing electrophysiology data, i.e., EEG, ECoG, or MEG, are limited to

the areas sampled by electrodes or sensors. These are determined by clinical considerations as well as the technical limitations of the study modalities. EEG and MEG have limited sensitivity in some cortical regions [35, 36], while ECoG studies are focused in the areas of clinical interest, or are broad surveys with very sparse sampling. None of these studies include subcortical structures, which may play a significant role in seizure propagation. The involvement of the thalamus in absence seizures is well documented [37, 38], and recent studies show that the thalamus participates in the initiation of focal neocortical seizures in a chronic rat model [39••, 40]. Loss of awareness during focal seizures has been attributed to ictal inhibition of key thalamic and brainstem structures in a rat hippocampal seizure model [41]. A recent study also showed normal and epileptiform activity from subcortical structures induced nonlinearly transformed effects in diffuse cortical structures, without causing seizures [42]. Such widespread cortical changes may be misinterpreted as evidence of large-scale cortical networks.

Perhaps most importantly, EEG, ECoG, and MEG predominantly detect postsynaptic currents, with little or no contribution from action potentials or multiunit activity. It is often assumed that multiunit firing is congruent with postsynaptic activity, but this assumption breaks down dramatically during seizures due to enhanced effects of surround inhibition [14, 43••, 44]. In surround inhibition, powerful excitatory barrages spreading ahead of the seizure induce strong inhibitory currents that suppress pyramidal cell firing [45]. As EEG cannot distinguish excitatory from inhibitory potentials, a high amplitude waveform may or may not be associated with excitatory population firing, depending on its location relative to the seizure. Thus, EEG as it is typically used in network studies can overestimate the cortical territory that is actively seizing [46].

A number of human studies using EEG [47], ECoG [48, 49], and microelectrode array recordings [32••] have shown small and progressive delays in the appearance of epileptiform discharges across disparate cortical areas. This is consistent with a "traveling wave" effect, similar to the outward travel of water ripples produced when a stone is dropped into a pond. A few studies have identified directional relationships during seizures or interictal discharges that were consistent with clinical assessments of seizure origin [48, 50, 51]. A study of causality relationships in high gamma activity during the period immediately preceding seizure onset identified source/sink patterns that were used to support carrying out limited surgical resections in two cases [52•].

These delays can be highly informative about the structure of the seizure in the underlying cortex, and yet are unaccounted for in many studies of epileptic networks. This is due to the use of sliding windows with lengthy durations, which have the effect of blurring together small temporal differences across recording sites. Thus, the appearance of "synchrony" may simply be due to the rapid speed at which these waves travel. Local differences in multiunit behavior can still exist at each site, despite the apparent EEG synchrony. As we mentioned above, an epileptiform discharge can rapidly propagate from seizing brain to an area outside the seizure proper that is subject to enhanced feedforward inhibitory effects. This results in the near-simultaneous appearance of a waveform at two sites with markedly different neuronal firing patterns. One cannot, then, assume that a high EEG synchrony measurement translates to correlated neuronal behavior.

The Physiological Basis of Seizure Initiation and Spread

The idea that seizures activate large brain areas simultaneously is derived from clinical observations of seizures as wide-area phenomena on EEG as it is traditionally interpreted. The known effects of surround inhibition and the distance potentially traveled by seizure-induced excitatory barrages, however, imply that seizures can influence a large brain area while remaining restricted to a small cortical region. This is supported by evidence that neuronal firing patterns in seizing brain are markedly different than that in the larger area of influence, paralleling more detailed analyses of these differences in animal models [10•, 44, 46]. This is a critical observation, as it undermines a fundamental assumption of the epileptic network theory: that a functional correlation between two brain areas implies mutually coordinated neural activity. Thus, the most commonly used methods of identifying functional correlation are incapable of determining which areas are driving the seizure, and which are passively responding to it.

It is important to understand how small groups of hyperexcitable neurons can have widespread effects. On smaller scales, on the order of millimeters or less, network remodeling via the sprouting of reciprocal connections in hyperexcitable populations of neurons has been hypothesized as a key element of epileptogenesis [7]. During epileptogenesis, a positive feedback loop develops in which neurons become increasingly interconnected as they are increasingly activated, via cellular changes associated with Hebbian learning [53]. Increased reciprocal connections have been observed in animal models [7] and in human medial temporal lobe (MTL) neurons [54]. Additionally, there is substantial support from computational models of MTL neurons that hyperexcitability and recurrent connectivity are sufficient conditions for epileptogenesis [55]. These studies suggest that the network metaphor may still be useful when individual neurons make up the nodes, and recurrent connectivity is considered.

Once these excitable and recurrently connected neurons initiate a focal seizure, the seizure then spreads. Recent evidence from human microelectrode array recordings of seizures indicates that seizures propagate slowly to adjacent brain areas, via slow, modular recruitment of small groups of cells, and simultaneously influence activity well outside the seizing brain area [44, 46]. This group of actively seizing cells was termed the "ictal core." At the core's leading edge, termed the "ictal wavefront," the seizure advances via the sudden collapse of inhibition in small groups of cells, in a stepwise fashion [44, 56]. The slow pace of seizure propagation, e.g., the Jacksonian March, has been observed behaviorally for centuries as the "evolution" of seizures [57].

Despite its limited spatial extent, the ictal wavefront is the source of the epileptiform discharges that constitute the well-recognized EEG appearance of a seizure [32••, 58]. The synaptic currents associated with these discharges distribute outward very rapidly, at speeds as high as a meter per second. Synaptic current distribution occurs under normal conditions [59], but the effect is amplified during seizures due to the intense excitatory population activity and the failure of feedforward inhibition at the ictal wavefront. The result is an epileptiform discharge that travels rapidly across large distances. When epileptiform discharges are viewed in recordings with limited temporal resolution, they can appear to occur simultaneously in large regions [44, 56]. Thus, analysis of EEG recordings typically makes seizures appear to spread faster and expand farther than is actually the case [32••, 46]. This difference between population firing and EEG activity also explains the opposing results from network studies on high and low frequency field potentials [1].

Long-Range Effects of Epileptiform Activity

While the above description of localized seizure onset and spread behavior has been shown to be applicable to humans [44], it is conceivable, and in fact likely, that many epilepsy cases involve multiple, disparate seizure foci. Under this scenario, seizures may arise independently in disparate brain areas [60], or a focal seizure can trigger an independent, coexisting seizure in a new area. The original and new seizures can then stop at different times [61]. However, it is not clear that even these situations constitute evidence of a pre-existing, pathological network. It is more straightforward to explain these multifocal seizures as an emergent phenomenon that develops when a spreading seizure broadcasting excitatory barrages triggers a new seizure in a susceptible area. Thus, the apparent network structure arises in a manner analogous to how hurricanes form from localized atmospheric

dynamics, or how flying geese arrange themselves in a "V" formation. Further investigation is needed to detail these distant spread mechanisms, and how the resulting seizures manifest in clinical EEG recordings.

Focal epileptiform activity can have long-range effects that are not necessarily epileptic (reviewed in [62]). Mesial temporal seizures can induce delta rhythms in the prefrontal cortex that have been associated with loss of awareness [63], and seizure-induced effects in subcortical structures, specifically in the thalamus and hypothalamus, have correlated with suppression of higher brain functions in a rodent epilepsy model [64••]. A recent study found that a single interictal discharge in the hippocampus reliably induces a spindle in the prefrontal cortex in both rats and humans [42]. Importantly, both of these types of long-range effects are not necessarily epileptic yet are salient and coincident with epileptic events. These correlations could be another potential source of false positives in a topographical network analysis.

Conclusions

The theory of epileptic networks is a metaphor for describing the complex brain interactions that occur during focal seizures that has spurred investigation into long-range effects of seizures. There is evidence of a process operating on large spatial scales, by which seizures influence brain areas at a distance from their generators, populating the spectrum between focal and generalized seizures. Current methods of identifying epileptic networks, however, are agnostic to any specific normal or pathologic physiological entity, and cannot provide the information needed to advance the field. Investigating the neurophysiological underpinnings of large-scale epileptic activity is likely to yield new insights into seizures that may well translate into new therapeutic approaches. For example, the possibility of identifying "choke points" that can be targeted to interrupt the transmission of seizure activity to disparate brain regions may become the basis for new invasive interventions to control recurrent seizures, or to block their clinical effects [65].

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