

Review

Physiology of functional and effective networks in epilepsy



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HIGHLIGHTS

- The relationships between functional and structural networks provide insights into brain abnormalities that are observed in epilepsy.
- Functional and effective connectivity methods have been used to identify the ictal onset zone as well as to characterize the onset, spread, and termination of seizures.
- Studies of the dynamics of epileptic networks suggest mechanisms that may explain the sudden onset and termination of seizures.

ABSTRACT

Epilepsy is a network phenomenon characterized by atypical activity during seizure both at the level of single neurons and neural populations. The etiology of epilepsy is not completely understood but a common theme among proposed mechanisms is abnormal synchronization between neuronal populations. Recent advances in novel imaging and recording technologies have enabled the inference of comprehensive maps of both the anatomical and physiological inter-relationships between brain regions. Clinical protocols established for diagnosis and treatment of epilepsy utilize both advanced neuroimaging techniques and neurophysiological data. These growing clinical datasets can be further exploited to better understand the complex connectivity patterns in the epileptic brain. In this article, we review results and insights gained from the growing body of research focused on epilepsy from a network perspective. In particular, we put an emphasis on two different notions of network connectivity: functional and effective; and studies investigating these notions in epilepsy are highlighted. We also discuss limitations and opportunities in data collection and analyses that will further our understanding of epileptic networks and the mechanisms of seizures.

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1. Introduction

Epilepsy is a neurological disorder defined by recurrent episodes of aberrant neural dynamics in the central nervous system (Fisher et al., 2005). The particular clinical symptoms or impairments experienced during such seizures depend on the anatomical structures affected by the abnormal electrical brain activity and can range from asymptomatic electrographic seizures to constrained focal sensory or motor disturbances to generalized convulsions with loss of consciousness.

As one of the world's most common serious brain disorders, epilepsy affects over 70 million people worldwide of which an estimated 25–33% cannot be controlled by medical therapy alone (Duncan et al., 2006). Unless other neurological problems exist, patients with epilepsy typically have normal neurological function between seizures. The mechanisms underlying the transition from normal to epileptic neural activity in the brain remain uncertain. Better therapeutic strategies and medical management will therefore likely require an improved understanding of the neurophysiological basis underlying seizure initiation, spread, and termination.

Network based approaches provide novel techniques to understand the function and dynamics of neural activity in health and disease. Neurons form complex structural networks conveying their electrical signals on average to thousands of other neurons via dendrites, synapses and axons. The emergent functional neural dynamics are thus generally constrained by the underlying structural networks on which they unfold. Inspired by the effort to sequence the human genetic code to build a genome, recent efforts in brain research have aimed at developing a comprehensive map of global brain connectivity termed *the connectome* (Hagmann, 2005; Sporns et al., 2005; Sporns, 2013). These efforts have been fostered by the recent advent of novel imaging and recording technologies allowing the collection and analysis of high resolution functional and structural datasets leading to an enormous expansion of studies in this field in the last ten years. Alongside these developments, clinical protocols established for the diagnosis and treatment of epilepsy now also utilize many high resolution techniques, thereby providing a tremendous wealth of multimodal data to explore notions of brain connectivity in epilepsy.

In epilepsy research, conceptual insights paired with novel recording methods have led to unprecedented efforts to study networks underlying aberrant seizure activity. These studies are motivated by the intuition that epileptic brain activity emerges as a consequence of alterations in the associated brain networks and consequently posits epilepsy as a disease of aberrant network organization. From this viewpoint, the identification of an “Epilepsy Connectome”, i.e., a comprehensive mapping of all neural elements and the structural and functional interrelationships involved in the generation of a seizure, appears highly desirable since it delivers the underlying conditions giving rise to abnormal epileptic brain activity. Although a complete mapping of the epilepsy connectome is currently out of reach, the recent investigations attempting to

unlock pathological changes on the network level have provided valuable insights into the pathogenesis of seizures. Multidisciplinary approaches uniting clinical observations together with the inference and evaluation of cortical structural and functional networks using advanced neuroimaging and invasive electroencephalography and functional neuroimaging remains an active and promising research area (Lehnertz et al., 2009; Kramer and Cash, 2012).

Recent interest in brain epilepsy networks has motivated the application of graph theory concepts as well as modeling of brain connectivity using DTI, fMRI and EEG (Richardson, 2012; Bernhardt et al., 2013; Stefan and Lopes da Silva, 2013). Brain networks can be defined at multiple spatial and temporal scales, ranging from synapses to large brain regions, and microseconds to hours. We will therefore start out by reviewing the network terminology used here followed by three definitions of network connectivity that are commonly evaluated. The terminology and definitions adhered to and reviewed in this manuscript are widely used in neuroscience (Bullmore and Sporns, 2009; Sporns, 2011).

Next, we review and discuss the results and insights gained from the growing body of research focused on epilepsy from a network perspective. The research directed towards identifying network elements and connectivity in the context of epilepsy has included both structural and functional networks, i.e., networks constructed from coherent physiological activity emerging on multiple spatially distinct brain regions (Friston, 1994; Bullmore and Sporns, 2009). The relationships between structural and functional networks remain a topic of current research (Deco et al., 2012; Whalen et al., 2012). We will thus review the existing data on topological properties of both structural and functional brain networks and discuss the literature attending to the interdependence between these two types of networks in the context of epilepsy research. Furthermore, we will explore the notion of effective connectivity and discuss recent advances as they relate to epilepsy.

1.1. Networks: a primer

A network consists of nodes and edges. Depending on the spatial scale of interest, a network node can be an individual neuron, a population of neurons within a given structure, or an entire brain structure or region. Observations from each node may be obtained from micro-electrodes, macro-electrodes (e.g., from an electroencephalogram or multi-electrode array), and functional magnetic resonance imaging (fMRI), respectively. Consequently, the networks investigated can span very different spatial and temporal scales. The utility of this multi-scale character has been highlighted several times in the context of analyzing and describing brain dynamics (Breakspear and Stam, 2005; Honey et al., 2007; Deco et al., 2008; Richardson, 2011; Meisel and Kuehn, 2012). Edges or links represent the connectivity between nodes, which depends on how the network is defined: as structural, functional or effective.

Structural connectivity represents the underlying “wiring diagram” between nodes in a network. In neuroscience, structural connectivity describes the anatomical connections linking neural elements, i.e., dendrites, synapses, and axons between individual neurons or fiber tracts between brain regions. The structural connectivity can be regarded as relatively static, compared to the more rapid changes typically observed in neural dynamics. Depending on the modalities by which the connectivity is extracted or analyzed, the edges can be weighted or unweighted (i.e., each edge can have a distinct strength ascribed to the interaction, or not) and can be directed or undirected (i.e., describe a causal relation between two nodes, or not).

Functional connectivity is defined by dynamic interactions between nodes and captures patterns of deviations from statistical independence between spatially remote areas (Friston et al., 1993; Friston, 1994). As such it can be calculated from time series data as for example cellular activity, EEG, MEG or fMRI and is usually highly time dependent. Examples of functional connectivity measures used in neuroscience range widely, and include both linear and nonlinear measures in the time and frequency domains. The purely statistical relationships do not make explicit reference to causal effects between the network nodes.

Effective connectivity, in contrast, describes directed, causal interactions between the neural elements defined as nodes in the network (Friston, 1994; Buchel and Friston, 2000). It can be inferred through time series data analysis, statistical modeling or perturbation experiments. It is important to note that to infer causality, knowledge about the underlying network being perturbed is needed in addition to time-series data. This is discussed more below when we elaborate on effective connectivity.

In the following, we will summarize and review the work for functional and effective connectivity in the context of epilepsy research.

2. Functional connectivity

Signals can be measured non-invasively in many ways (e.g., using scalp EEG, MEG, or fMRI) or invasively using intracranial electrodes (iEEG). Furthermore, due to the clinical protocols for monitoring patients with epilepsy, there is a wealth of data available for functional connectivity analyses. For these reasons, many different functional connectivity methods have been well developed in the application to epilepsy. It is important to note that studies have compared the performance of different functional connectivity approaches (Ansari-Asl et al., 2006; Wendling et al., 2009). In general, these studies have found that there is no single best functional connectivity method and a tailored approach should be used for each specific application.

2.1. Relationship between structural and functional connectivity in epilepsy

Analysis of structural connectivity in human patients with epilepsy has benefited from the emergence of diffusion tensor imaging (DTI) technologies, which may reveal abnormalities in white matter fiber structure in disease. In particular, areas of abnormality in the brain have been identified surrounding the seizure onset zone in epilepsy (Le Bihan et al., 2001; Minati et al., 2006). However, while large fiber bundles are easier to identify, small bundles and fiber tracts that cross must rely on probabilistic tractography, which is dependent upon thresholds that are difficult to define objectively.

Despite the challenges, understanding structural connectivity is of great interest. Structural connectivity plays a pivotal role in governing functional connectivity, and perhaps ultimately in seizures.

Therefore, recent studies have investigated the interplay between structure and function (Deco et al., 2012; Whalen et al., 2012; Sritharan and Sarma, 2014).

A fairly recent study (van den Heuvel et al., 2009) combined 3 Tesla resting-state fMRI (RS-fMRI) time-series data with DTI scans on healthy subjects found that during rest, multiple cortical brain regions are functionally linked forming “resting-state networks,” and that direct neuroanatomical connections between these functionally linked brain regions underlie the ongoing inter-regional neuronal communication.

Zhang et al. (2010) aimed to understand the links between structure and function in epilepsy. They showed that idiopathic generalized epilepsy exhibits a *decoupling* between whole-brain functional and structural networks. Specifically, they applied network-based data analysis to DTI tractography and RS-fMRI to generate both structural and functional connectivity networks. Their graph theoretical analysis revealed that the patients lost optimal topological organization in both functional and structural connectivity, and showed significant increases in nodal topological characteristics in several cortical and subcortical regions, including mesial frontal cortex, putamen, thalamus and amygdala (regions thought to play important roles in the pathogenesis of epilepsy) relative to controls. These findings may suggest that the decoupling of functional and structural connectivity may reflect the progress of long-term impairment in idiopathic generalized epilepsy, and may be used as a potential biomarker to detect subtle brain abnormalities in epilepsy. Alternatively, this apparent decoupling may be related to intermittent pathophysiological disruptions by interictal discharges, and potential artifacts due to head motion (Power et al., 2012) should also be considered.

2.2. iEEG functional connectivity of epileptic networks

The analysis of how human brain activity couples during seizure has a long history (Brazier, 1972; Gotman, 1983; Lieb et al., 1987). A focal seizure with secondary generalization is believed to be a network phenomenon, which originates in a focal region and then spreads to other brain regions. Many recent works have applied ideas from network theory to study the relationship between functional connectivity and seizures in an epileptic brain. For more details and references, please see the review article by Kramer and Cash (2012). In general, identification of the network characteristics that support epileptic seizures remains an active research area, yet some prevailing results have emerged, including the importance of small-world topologies (Watts and Strogatz, 1998; Netoff et al., 2004; Percha et al., 2005) – although see (Bialonski et al., 2010) – and hubs (Kramer et al., 2008; Morgan and Soltesz, 2008). Perhaps the most robust finding has been the emergence of increased coupling of macroscopic brain voltage activity at seizure onset and termination in humans (Guye et al., 2006; Ponten et al., 2007; Schindler et al., 2007, 2008; Kramer et al., 2010) and in animal models (Netoff and Schiff, 2002; Topolnik et al., 2003; Timofeev and Steriade, 2004).

As an example of this approach to functional network analysis in epilepsy, Kramer et al. (2010) inferred a binary network representation from iEEG data during seizure. In these networks, an edge was assigned between two nodes (electrodes) if there was a statistically significant cross correlation between the iEEG signals observed at the two nodes. Fig. 1 illustrates some of the findings from this study. The density of the network increased at seizure onset and at seizure termination. During seizure, however, the density of the network returned to inter-ictal levels. These findings suggest that seizure maintenance is not characterized by hypersynchrony, and that brain regions decouple during the seizure. We note that, in this study, the seizure onset activities consisted of both low-amplitude, high-frequency discharges (as illustrated

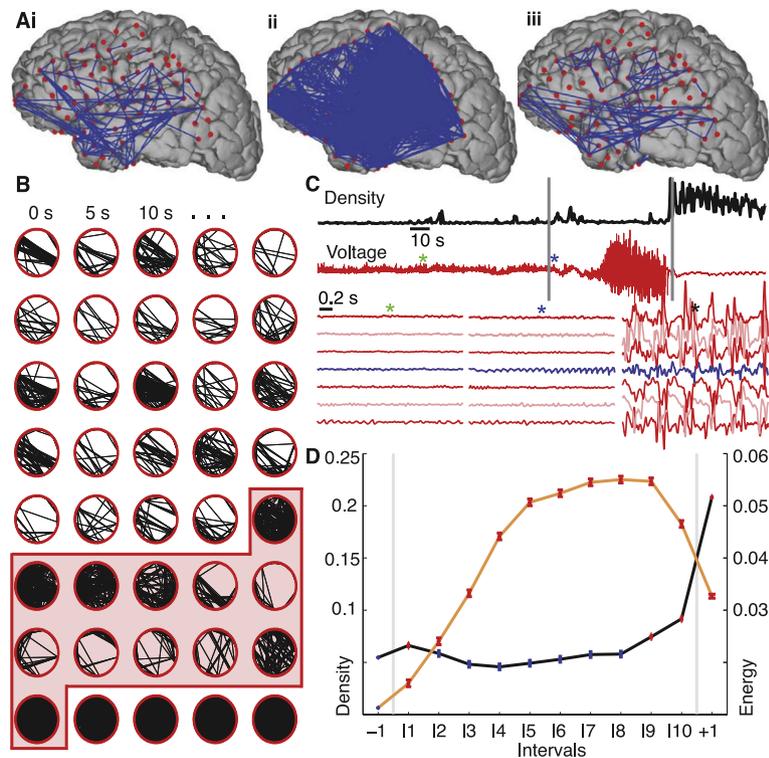


Fig. 1. Reprinted from [Kramer et al. \(2010\)](#) with permission from Society for Neuroscience (copyright 2010). Network synchronization increases at ictal onset and offset but falls to preictal values during the seizure. (A) Representative networks just before the seizure starts, (i) at seizure initiation, (ii) and in the middle of the seizure (iii) from a single seizure in a single patient. In this example, the electrode locations have been projected onto a reconstruction of this patient's cortical surface. Because some of the electrodes cannot be easily visualized in this two-dimensional representation, the data are displayed as circular networks containing all electrodes as individual nodes. (B) The networks progress from left to right, top to bottom, with a 5 s interval between networks. We arrange the electrodes in a circle (without reference to their physical locations) and indicate sufficiently strong coupling between electrode pairs with black lines. The shaded region denotes the ictal interval. Visual inspection of the evolving network topologies suggests increased network density (i.e., more edges) near ictal onset and termination. (C) The network density (black) and ECoG data from a single electrode (red, top) for the representative example. Signals were recorded using a common average reference. At ictal onset and termination, indicated with the vertical gray lines, the network density increases dramatically, whereas during the middle portion of the seizure, the ECoG data exhibits large-amplitude fluctuations. The colored asterisks indicate the location of three 2 s intervals plotted for representative grid and strip electrodes below, including the activity of the presumptive onset electrode as identified by the clinical team (blue trace). (D) The density (black curve), averaged across all subjects and seizures and adjusted for differences in subjects, for 12 time intervals: one preictal (−1), 10 ictal (I1, I2, . . . , I10), and one postictal (+1). In each interval, the circle indicates the mean density ($n = 9049$ networks preictal, $n = 939$ networks per ictal interval, and $n = 2817$ networks postictal) and the vertical lines the SE. Statistically significant increases in density compared with preictal values are indicated in red and occur at ictal onset (interval I1) and near ictal offset (intervals I9, I10, +1). We also plot the normalized signal energy (orange curve) for each interval averaged across all subjects and seizures ($n = 45,609$ preictal, $n = 3614$ per ictal interval, and $n = 10,842$ postictal). Unlike the density, the signal energy increases significantly above preictal values for all ictal and postictal intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in [Fig. 1](#)) as well as high-amplitude, low-frequency discharges. Many issues regarding functional network evolution during seizure require further investigation, including: (1) understanding how (or if) seizure onset-patterns ([Perucca et al., 2014](#)) impact the functional networks of seizure, and (2) how functional network evolution during seizure depends on other state changes in the brain (e.g., a sleep-to-wake at seizure onset).

Using a different approach, [Burns et al. \(2012\)](#) and [Yaffe et al. \(2012\)](#) studied the temporal evolution of the functional connectivity network structure during seizures in iEEG and stereotactic EEG (sEEG), respectively. Both studies examined the eigenvalue centrality of adjacency matrices computed using coherence in a particular frequency band. The centrality of a node in a network is a notion of that node's importance or influence in the network ([Newman, 2010](#)). The first eigenvector of an adjacency matrix is equivalent to the centrality vector. Each entry in the centrality vector represents the relative centrality, or importance, of the corresponding node in the network. These studies tracked the evolution of the first eigenvector of the adjacency matrix over time during pre-ictal, ictal, and post-ictal periods. It was found that within a given patient, seizures progressed through a consistent set of distinct states with clear state transitions. Furthermore, the states were relatively stable during interictal periods showing only small

fluctuations in the first eigenvector during non-seizure periods. This suggests that the functional connectivity of an epileptic network has a finite set of states through which it progresses. The results of these studies are illustrated in [Fig. 2](#).

There are many challenges that still remain for iEEG based functional connectivity research. These include: the determination and application of appropriate coupling measures to iEEG data, the transformation from a coupling statistic to an edge, the impact of iEEG reference montage on network features ([Lepage et al., 2014](#)), the development of rigorous tools for the assessment of network statistics, and the development of data analysis tools to assess dynamic network evolution. One tool that can be of great use in furthering this line of research is the International Epilepsy Electrophysiology Portal, which has been developed to “advance research towards the understanding of epilepsy by providing a platform for sharing data, tools, and expertise between researchers” (www.ieeg.org).

2.3. fMRI functional connectivity of epileptic networks

[Biswal et al.'s \(1995\)](#) description of brain functional connectivity using fMRI has resulted in an expansion of interest and studies of fMRI based brain connectivity. This approach relies upon

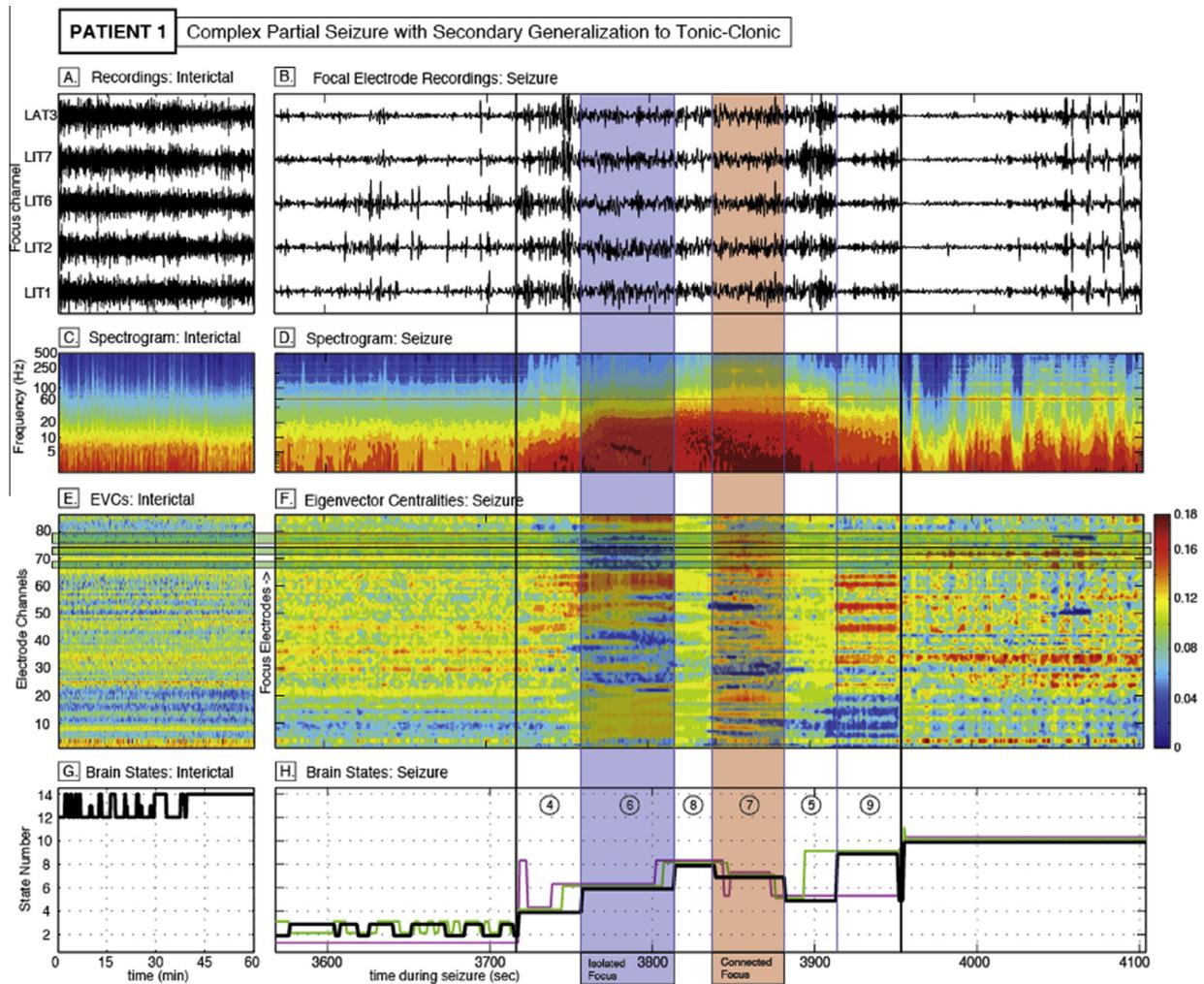


Fig. 2. Reprinted from Burns et al. (2013) with permission from the American Society of Mechanical Engineers (copyright 2013). Analysis of a complex partial seizure with generalization to tonic-clonic recorded from Patient 1. (A) An example of one hour of interictal recordings from a subset of the focal electrodes. Signals were recorded using a common reference. (B) Peri-ictal recording of about a seizure from same electrodes shown in A with 2.5 min before (preictal) and after (postictal) and seizure onset and suppression marked by solid black vertical lines (note the difference in time scale (sec) from that in A (min)). (C) Interictal average spectrogram over the electrodes shown in A and B from the time period shown in A. (D) Peri-ictal average spectrogram over the electrodes shown in A and B from the time period shown in B. (E) Eigenvector centralities (EVCs) of all electrodes during the interictal time period plotted in A. (F) EVCs of all electrodes during the peri-ictal time period plotted in B. (G) States fitted to the interictal EVCs plotted in E. (H) States fitted to the peri-ictal EVCs plotted in F in black with vertical blue lines indicating the state transitions across the simultaneous times in B, D, and F states fitted to all other seizures recorded in Patient 1, scaled to the length of the seizure plotted in B, are also plotted in H in non-black colors. State corresponding to the isolated focus state shaded in blue, state corresponding to the connected focus state shaded in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

correlation of spontaneous low frequency (<0.1 Hz) fluctuations in the blood oxygen level-dependent (BOLD) response and has been termed resting functional connectivity MRI (rfc-MRI). Accordingly, areas exhibiting spontaneous BOLD correlations are said to be functionally connected. Advances in this field include the description of the default mode network (DMN) (Raichle et al., 2001), the presence of anti-correlated networks (Greicius et al., 2003), a combination of multi-institutional databases to provide normative data on connectivity (Biswal et al., 2010), and the description of multiple brain networks that may be extracted by data-driven methods (Craddock et al., 2012).

There has been a recent acceleration of studies investigating rfc-MRI in epilepsy. Contingent upon the goals of the study, a given MRI volume serves as a network node or region of interest (ROI). Termed the “seed” region, it can either be correlated with all voxels in the brain (ROI-to-whole-brain) to explore global connectivity (Pereira et al., 2010; Negishi et al., 2011), or correlated with another ROI (ROI-to-ROI) to ascertain connectivity between areas of interest in a network (Bettus et al., 2010). Additional methods

of analyzing rfc-MRI as it relates to epilepsy and/or functional connectivity include independent component analysis (Zhang et al., 2010), graph theory (Constable et al., 2013), temporal clustering analysis, regional homogeneity, and amplitude of low frequency fluctuation measures (Wurina et al., 2012).

2.4. RS-fMRI, temporal lobe epilepsy, and the default mode network

The DMN is likely the most studied network by rfc-MRI. The DMN is characterized by regions of enhanced activity while the brain is at rest, and consists of the posterior cingulate cortex (PCC)/precuneus (PC), ventral anterior cingulate cortex/mesial prefrontal cortex (mPFC), angular gyrus, inferior temporal cortex (ITC), and mesial temporal lobe (mTL) (Raichle et al., 2007; Buckner et al., 2008; Zhang et al., 2010). Zhang et al. (2010) found that in patients with mTLE that presented with hippocampal sclerosis (HS), there were significant alterations in functional connectivity throughout the DMN, including decreased connectivity in the MTL, ITC, and dorsal mPFC bilaterally, and increased connectivity in the PCC. In

contrast, McCormick et al. (2013) found functional connectivity between the hippocampus and PCC was decreased in the epileptogenic hemisphere, while connectivity to the contralateral PCC was increased. However, it is hard to directly compare these opposing trends since the McCormick group used ROI-to-ROI for analysis, while Zhang et al. (2010) used ICA. Nonetheless, these studies together suggest that physiological impairment to one node of the DMN can lead to network-wide alterations, including a possible compensatory response in the PCC in the case of HS. In another study, increases in connectivity in mTLE were observed in the hippocampus and amygdala that were contralateral to the epileptogenic hemisphere, while decreased connectivity between the entorhinal cortex and anterior hippocampus was seen in the affected hemisphere (Bettus et al., 2010). This paradoxical trend in hippocampal connectivity contradicts findings by Pereira et al. (2010), who determined that mTLE patients with left HS display bilateral decreases in hippocampal functional connectivity. However, the latter study was exclusive to subjects with HS, while the prior included subjects without cortical abnormalities and with non-HS malformations. In addition, these studies determined connectivity through different methods, using ROI-to-ROI and ROI-to-whole-brain measures, respectively. Another study that was not exclusive to patients with HS, and evaluated functional connectivity with ROI-to-whole-brain methodology found that in patients with right or left TLE there is decreased connectivity between the hippocampus and PC in the DMN (Haneef et al., 2014). Thus, changes in DMN hippocampal connectivity in patients with TLE seem to vary, with possible causes being differences in histopathological abnormalities, analytical methodology, and individual patient brain dynamics.

The studies defined above provide a rough sketch of what is possible to derive regarding the network physiology of epilepsy using rfc-MRI. There has been great interest in characterizing the connectivity of the IOZ. Whole-brain analyses that are possible with noninvasive fMRI provide one potential advantage over invasive electrode analyses that may be subject to a sampling problem. Rfc-MRI studies show evidence for both increased and decreased connectivity in the IOZ (Bettus et al., 2010; Stufflebeam et al., 2011). This mirrors the electrophysiological literature, showing hypersynchrony (Schevon et al., 2007), and fragmentation (Truccolo et al., 2011) of the IOZ as well as for its isolation from areas outside the IOZ (Warren et al., 2010). While rfc-MRI studies derive larger scale networks, their correspondence with electrophysiological measures of connectivity suggests that this line of research may be an important one to explore (He and Liu, 2008; Keller et al., 2011, 2013).

Great strides have been made in analyzing the functional connectivity of epileptic networks, yet ultimately we would like to apply this understanding to improve treatment of epilepsy, and efforts to achieve this are being explored. Negishi et al. (2011) showed patients with reduced contralateral connectivity in pathological regions to have better seizure freedom rates after unilateral resection. The above-mentioned rfc-MRI IOZ abnormalities suggest that rfc-MRI can be developed into a useful biomarker for the IOZ, which can guide surgical treatment by selecting the site for resection as well as neurostimulation. Alternatively, insights into functional connectivity may suggest novel treatment strategies to stop seizures by partially isolating rather than removing (Ching et al., 2012) pathological brain areas responsible for seizure.

While currently there is no generally accepted clinical use for rfc-MRI as applied to epilepsy, the studies outlined above demonstrate the possible potential for identifying the ictal onset zone. In addition, proof of concept has been shown for defining functional zones as may be also required for epilepsy surgery. In patients with brain tumors, Zhang et al. (2009) showed electrical stimulation mapping of sensorimotor cortex to better correlate with rfc-MRI

than task-based MRI, and Kokkonen et al. (2009) used an ICA-based analysis to show good correspondence between task based and resting fMRI. Mitchell et al. (2013) have recently showed in surgical patients implanted with electrodes that a classifier approach for defining language and resting networks correlates with results of electrical stimulation mapping. Finally, the aforementioned study by McCormick et al. (2013) showed rfc-MRI between hippocampus and precuneus better predicted post-surgical memory deficits than Wada testing. The growing body of such results strongly suggests that functional connectivity analyses – most likely integrated with anatomical and effective connectivity – will provide useful clinical tools to aid both surgical and non-surgical treatment of epilepsy.

3. Effective connectivity

While functional connectivity aims to assess connectivity based on statistical dependencies in neuronal activity, effective connectivity aims to establish causal relationships between distinct regions. In other words, functional connectivity relies on disproving the null hypothesis that separate brain areas function independently of one another, while effective connectivity seeks to model these relationships by adding weighted directionality to them (Friston, 2011). This can be achieved by two approaches: interventional and non-interventional. Non-interventional methodologies rely on recordings of brain dynamic activity (e.g., fMRI or ECoG), and employ methods such as Granger causality and dynamic causal modeling to derive causal interactions (Brovelli et al., 2004; Kiebel et al., 2009).

In contrast, interventional approaches measure evoked responses to stimulation applied directly to the human brain to achieve the same end (Matsumoto et al., 2004; David et al., 2010; Entz et al., 2014; Keller et al., 2014a,b). Here we will focus on the latter, as it facilitates direct evaluation of connectivity in the human brain in patients with epilepsy, and is thus a powerful tool in studying both connectivity and seizure electrophysiology. This is highlighted by studies that have shown correspondence between connectivity measures using interventional effective connectivity measures and noninvasive MRI-based measures, including anatomic connectivity using DTI (Conner et al., 2011) and functional connectivity using resting fMRI (Keller et al., 2011).

3.1. CCEPs and the ictal onset zone

Cortico-cortical evoked potential (CCEP) mapping involves brief (<10 ms) electrical stimulation at a given location and recording an evoked potential at another site. CCEPs are typified by an early deflection (N1) that occurs before 50 ms, and a later one (N2) after 50 ms (Matsumoto et al., 2004; Keller et al., 2011). CCEPs provide a unique opportunity to directly study differences in electrophysiology between normal and epileptogenic cortex in the human brain, and have shown potential as a diagnostic tool in epilepsy. Valentin et al. (2002) used single pulse electrical stimulation to stimulate the IOZ and recorded responses within and outside of it. They identified both early (<100 ms) and late evoked responses, and determined that while early responses showed a similar distribution in normal and pathological tissue, late responses, which presented like after-discharges, were linked to the IOZ in patients with temporal lobe epilepsy (TLE). Notably, in TLE the distribution of delayed responses was nearly as reliable as studying seizure onset in localization of the IOZ. This suggests CCEPs may not only allow identification of seizure networks, but could also be clinically useful in corroborating the suspected IOZ.

Stimulation of the IOZ results in larger N1 responses than when normal cortex is perturbed (Iwasaki et al., 2010; Enatsu et al., 2012b). Additionally, ictal onset patterns characterized by

repetitive spiking show larger CCEPs amplitudes than those by focal paroxysmal fast activity. These results seem to contradict the conclusion by [Lacruz et al. \(2007\)](#) that ipsilateral and contralateral connections between normal and epileptogenic hemispheres were similar. These findings may be reconciled by considering that the latter study only looked for the presence or absence of CCEPs responses, while those that found differences between ictal and normal cortex assessed the amplitude of evoked potentials.

In addition to ictal onset, ictal propagation has also been explored using CCEPs. The topography of brain networks as determined by CCEPs is often partially inconsistent with seizure spread. For example, CCEPs carried out on the posterior cingulate gyrus in patients with posterior cingulate epilepsy revealed effective connections that did not completely correlate with seizure spread ([Enatsu et al., 2014](#)). Furthermore, in cases where focal epilepsy was associated with secondary generalization, the discrepancy between CCEPs distribution and ictal propagation patterns was larger than in those without secondary generalization. Ictal propagation to regions not generating evoked potentials after stimulation of the IOZ supports the notion of step-wise seizure propagation to regions that are not under the direct influence of the electrographically identified IOZ. At the same time, regions that respond to CCEPs but do not display ictal activity lend credence to the presence of inhibitory mechanisms that prevent ictal activity from spreading throughout entire neural networks ([Enatsu et al., 2012a](#)).

3.2. Limitations and future directions

CCEP investigations have limitations, the most apparent being their invasiveness and restricted sampling ([Lacruz et al., 2007](#); [David et al., 2013](#); [Keller et al., 2014b](#)). Additionally, extrapolation of findings to healthy subjects falls into question since measurements are being obtained from epileptogenic cortex. However,

coverage of the brain by intracranial electrodes generally allows dense sampling of most or all lobes of at least one hemisphere (see [Figs. 1 and 3](#) for examples), because uncertainty regarding the location of seizure-producing regions is precisely what warrants invasive EEG monitoring in the first place ([Entz et al., 2014](#); [Keller et al., 2014a,b](#)). Furthermore, only a minority of intracranial electrodes record epileptic activity (be it interictal discharges or ictal onsets), so that most of the sampled cortex is not pathological. In fact, it is quite important to ensure normal regions are being recorded not only to define the limits of resection, but for the stimulation mapping that is performed in language, sensory and motor cortex to avoid neurological deficits. Additionally, surgical candidates are chosen when there is an absence of generalized dysfunction save for possible focal neuropsychological weaknesses pointing to the location of the epilepsy-producing brain regions.

Another weakness of CCEP studies is the lack of standardization of protocols, a weakness revealed by the expansion of centers performing these studies. Indeed, stimulation parameters can vary widely both within and between studies. For example, studies focused upon defining connectivity ([Matsumoto et al., 2004](#); [Entz et al., 2014](#); [Keller et al., 2014a](#)) use 1 Hz stimulation frequencies, whereas studies focusing ([Valentin et al., 2002](#); [Lacruz et al., 2007](#)) use much longer intervals (8–10 s). Stimulation intensity also varies considerably across the above-mentioned studies, with an application of current that ranges from 4 to 10 mA. There are data to suggest that stimulation intensity may differentially activate feedforward versus feedback connections ([Lacruz et al., 2007](#); [Matsuzaki et al., 2013](#)). A further consideration of standardization includes the choice of monopolar versus bipolar stimulation. Finally, dynamics should be considered, as it is likely that connectivity may change spontaneously over time, sleep and cognitive states and in the transition from the interictal to ictal states. This latter consideration should be explored further and may hold

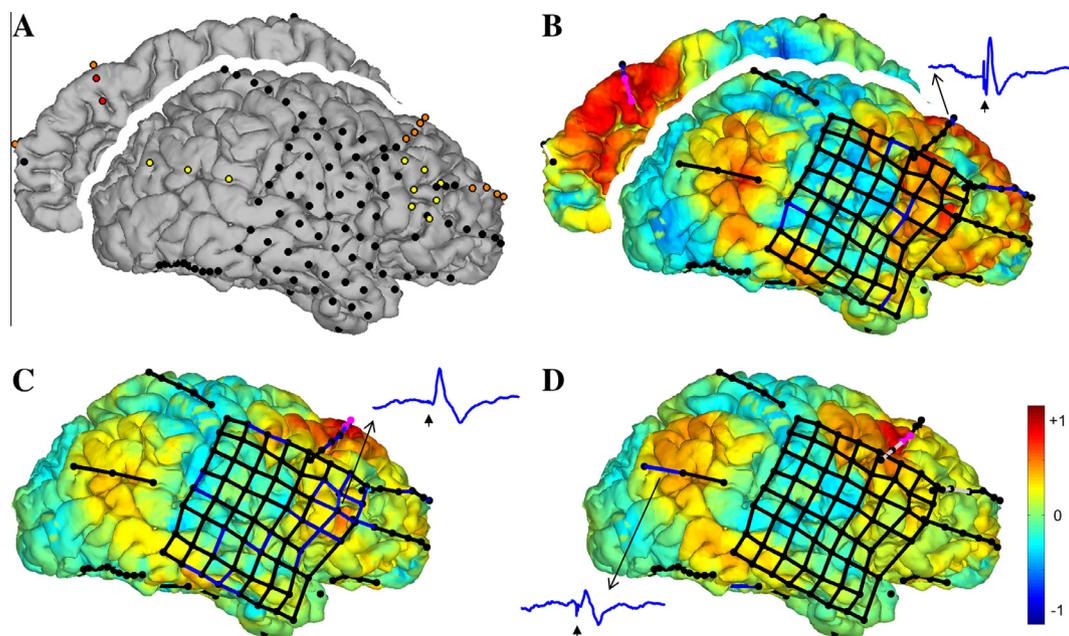


Fig. 3. Resting fMRI connectivity and effective connectivity assessed by CCEPs both correlate with the seizure network defined by the zones of seizure onset and spread. (A) The electrodes are color-coded according to their involvement in the seizure: red, seizure onset zone; orange, early spread; yellow, later spread. (B–D) Bipolar stimulation of electrode pairs in the seizure onset zone (B) and early spread zone (C, D) yield CCEP responses in distributed brain areas that show similarities to the seizure network. CCEP responses are depicted as lines linking bipolar electrode pairs. Signals are recorded using a bipolar montage. Significant CCEP responses are coded in progressively lighter shades of blue; light gray lines indicate missing (e.g., artifacted) data; black lines, absence of supra-threshold CCEP responses. The color overlay on the brain surface in B–D represents the correlation of slow (<0.1 Hz) fluctuations in resting-state BOLD fMRI signal for all brain areas related to a seed placed at the site of each CCEP stimulation. Warmer colors indicate positive correlations, colder colors negative correlations. The insets in B–D show exemplary CCEP waveforms from 200 ms before to 400 ms after stimulation; the arrow denotes the time of stimulation. Observe for instance that the inferior parietal lobule, which is implicated by seizure spread, shows positive resting-state fMRI correlations with the superior frontal gyrus, the locus of the seizure onset and early spread, and also exhibits significant CCEP responses to stimulation of the same area (D). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

an important key to unraveling the pathogenesis of seizure onset and spread.

Another important consideration involves the use of intraparenchymal depth electrodes (David et al., 2013) versus epicortical contacts (Matsumoto et al., 2004; Entz et al., 2014; Keller et al., 2014a,b). While CCEP studies may be carried out using both surgical approaches, there are expected differences in physiological changes induced by electrical stimulation related to difference in location of stimulation, charge density, and spread. The need to reconcile these differences is important as these two techniques offer different windows into brain physiology. Epicortical surface arrays tend to be broader and sample more areas while SEEG studies provide recordings of the deep sulci that may be missed by grid and strip electrodes. Combining results obtained from these different types of studies would provide complementary information that would yield a more complete picture of effective connectivity and its relationship to seizure pathology.

Although findings on effective connections are limited thus far, efforts have begun to establish collaborative databases that could potentially combine CCEP data from thousands of patients across institutions. Ideally this will lead to a cohesive probabilistic atlas of effective connectivity, or ‘functional tractography,’ throughout the human brain. Such an atlas has the potential to facilitate the study of differences in connectivity in different types of epilepsy, and also to probe brain connectivity in general (David et al., 2013).

Also conducive to this goal is a systematic stimulation of complete electrode arrays in implanted patients, as CCEPs studies to date have been characterized by stimulation to specific cortical areas (i.e., the IOZ and regions involved in eloquent function such as speech), while neglecting to study those that are not of immediate interest but do have electrographic coverage. Efforts that utilize this strategy are now underway (Fig. 3).

4. Dynamics on networks

In general, understanding the impact of network structure on dynamics remains an active and challenging research area (Watts and Strogatz, 1998; Strogatz, 2001; Boccaletti et al., 2006). In the specific context of neuroscience, a variety of techniques exist for modeling the emergence of collective neuronal activity, including for example “neuronal avalanches” (Zapperi et al., 1995; Beggs and Plenz, 2003, 2004; Vogels et al., 2005). In general, these models focus on a critical state of activity characterized by power laws (Bak et al., 1987; Bak and Paczuski, 1995), and avalanche propagation typically occurs without oscillations or synchrony. In the specific context of seizures, it has been shown that seizure activity deviates from normal dynamics characterized by these power laws suggesting a deviation from criticality (Hobbs et al., 2010; Meisel et al., 2012). The impact of network structure on node dynamics continues to be explored. Simulation studies suggest that the pathological organization of seizing activity is supported by small-world topologies (Netoff et al., 2004; Percha et al., 2005), although the interaction of network structure and intrinsic neuronal properties are also crucial (Bogaard et al., 2009).

Recent results have shown that the sudden emergence of organized dynamic activity (e.g., “explosive synchronization”) depends on the relationship between the structural network and dynamical properties of the nodes (specifically, when the natural frequency of the oscillators are positively correlated with their connectivity) (Gomez-Gardenes et al., 2011). Research into explosive synchronization has typically focused on simple (Kuramoto) oscillators (Aoki and Aoyagi, 2011; Gomez-Gardenes et al., 2011) a fundamental dynamic model but without a direct connection to neuronal physiology. For example, these oscillator models possess a unique well-defined phase (while brain activity is typically much more

complicated), and the typical coupling is continuous, rather than pulse-like. Extending these notions of explosive synchronization to the context of neural systems – and the sudden emergence and termination of seizures – may provide new insights.

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References

- Ansari-Asl K, Senhadji L, Bellanger JJ, Wendling F. Quantitative evaluation of linear and nonlinear methods characterizing interdependencies between brain signals. *Phys Rev E Stat Nonlin Soft Matter Phys* 2006;74:031916.
- Aoki T, Aoyagi T. Self-organized network of phase oscillators coupled by activity-dependent interactions. *Phys Rev E Stat Nonlin Soft Matter Phys* 2011;84:066109.
- Bak P, Paczuski M. Complexity, contingency, and criticality. *Proc Natl Acad Sci USA* 1995;92:6689–96.
- Bak P, Tang C, Wiesenfeld K. Self-organized criticality: an explanation of the 1/f noise. *Phys Rev Lett* 1987;59:381–4.
- Beggs JM, Plenz D. Neuronal avalanches in neocortical circuits. *J Neurosci* 2003;23:11167–77.
- Beggs JM, Plenz D. Neuronal avalanches are diverse and precise activity patterns that are stable for many hours in cortical slice cultures. *J Neurosci* 2004;24:5216–29.
- Bernhardt BC, Hong S, Bernasconi A, Bernasconi N. Imaging structural and functional brain networks in temporal lobe epilepsy. *Front Hum Neurosci* 2013;7:624.
- Bettus G, Bartolomei F, Confort-Gouny S, Guedj E, Chauvel P, Cozzone PJ, et al. Role of resting state functional connectivity MRI in presurgical investigation of mesial temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry* 2010;81:1147–54.
- Bialonski S, Horstmann MT, Lehnertz K. From brain to earth and climate systems: small-world interaction networks or not? *Chaos* 2010;20:013134.
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 1995;34:537–41.
- Biswal BB, Mennes M, Zuo XN, Gohel S, Kelly C, Smith SM, et al. Toward discovery science of human brain function. *Proc Natl Acad Sci USA* 2010;107:4734–9.
- Boccaletti S, Latora V, Moreno Y, Chavez M, Hwang DU. Complex networks: structure and dynamics. *Phys Rep* 2006;424:175–308.
- Bogaard A, Parent J, Zochowski M, Booth V. Interaction of cellular and network mechanisms in spatiotemporal pattern formation in neuronal networks. *J Neurosci* 2009;29:1677–87.
- Brazier MA. Spread of seizure discharges in epilepsy: anatomical and electrophysiological considerations. *Exp Neurol* 1972;36:263–72.
- Breakspear M, Stam CJ. Dynamics of a neural system with a multiscale architecture. *Philos Trans R Soc Lond B Biol Sci* 2005;360:1051–74.
- Brovelli A, Ding M, Ledberg A, Chen Y, Nakamura R, Bressler SL. Beta oscillations in a large-scale sensorimotor cortical network: directional influences revealed by Granger causality. *Proc Natl Acad Sci USA* 2004;101:9849–54.
- Buchel C, Friston K. Assessing interactions among neuronal systems using functional neuroimaging. *Neural Netw* 2000;13:871–82.
- Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008;1124:1–38.
- Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 2009;10:186–98.
- Burns SP, Santaniello S, Anderson WS, Sarma SV. State dynamics of the epileptic brain. In: Proceedings of the 6th ASME annual dynamic systems and control conference (DSCC), Palo Alto, CA; 2013. p. V002T22A001.
- Burns SP, Sriharan D, Jouy C, Bergey G, Crone N, Anderson WS, et al. A network analysis of the dynamics of seizure. *Conf Proc IEEE Eng Med Biol Soc* 2012;2012:4684–7.
- Ching S, Brown EN, Kramer MA. Distributed control in a mean-field cortical network model: implications for seizure suppression. *Phys Rev E Stat Nonlin Soft Matter Phys* 2012;86:021920.
- Conner CR, Ellmore TM, DiSano MA, Pieters TA, Potter AW, Tandon N. Anatomic and electro-physiologic connectivity of the language system: a combined DTI–CCEP study. *Comput Biol Med* 2011;41:1100–9.

- Constable RT, Scheinost D, Finn ES, Shen X, Hampson M, Winstanley FS, et al. Potential use and challenges of functional connectivity mapping in intractable epilepsy. *Front Neurol* 2013;4:39.
- Craddock RC, James GA, Holtzheimer 3rd PE, Hu XP, Mayberg HS. A whole brain fMRI atlas generated via spatially constrained spectral clustering. *Hum Brain Mapp* 2012;33:1914–28.
- David O, Bastin J, Chabardes S, Minotti L, Kahane P. Studying network mechanisms using intracranial stimulation in epileptic patients. *Front Syst Neurosci* 2010;4:148.
- David O, Job AS, De Palma L, Hoffmann D, Minotti L, Kahane P. Probabilistic functional tractography of the human cortex. *Neuroimage* 2013;80:307–17.
- Deco G, Jirsa VK, Robinson PA, Breakspear M, Friston K. The dynamic brain: from spiking neurons to neural masses and cortical fields. *PLoS Comput Biol* 2008;4:e1000092.
- Deco G, Senden M, Jirsa V. How anatomy shapes dynamics: a semi-analytical study of the brain at rest by a simple spin model. *Front Comput Neurosci* 2012;6:68.
- Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. *Lancet* 2006;367:1087–100.
- Enatsu R, Bulacio J, Nair DR, Bingaman W, Najm I, Gonzalez-Martinez J. Posterior cingulate epilepsy: clinical and neurophysiological analysis. *J Neurol Neurosurg Psychiatry* 2014;85:44–50.
- Enatsu R, Jin K, Elwan S, Kubota Y, Piao Z, O'Connor T, et al. Correlations between ictal propagation and response to electrical cortical stimulation: a cortico-cortical evoked potential study. *Epilepsy Res* 2012a;101:76–87.
- Enatsu R, Piao Z, O'Connor T, Horning K, Mosher J, Burgess R, et al. Cortical excitability varies upon ictal onset patterns in neocortical epilepsy: a cortico-cortical evoked potential study. *Clin Neurophysiol* 2012b;123:252–60.
- Entz L, Toth E, Keller CJ, Bickel S, Groppe DM, Fabo D, et al. Evoked effective connectivity of the human neocortex. *Hum Brain Mapp* 2014. <http://dx.doi.org/10.1002/hbm.22581>.
- Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470–2.
- Friston KJ. Functional and effective connectivity in neuroimaging: a synthesis. *Hum Brain Mapp* 1994;2:56–78.
- Friston KJ. Functional and effective connectivity: a review. *Brain Connect* 2011;1:13–36.
- Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab* 1993;13:5–14.
- Gomez-Gardenes J, Gomez S, Arenas A, Moreno Y. Explosive synchronization transitions in scale-free networks. *Phys Rev Lett* 2011;106:128701.
- Gotman J. Measurement of small time differences between EEG channels: method and application to epileptic seizure propagation. *Electroencephalogr Clin Neurophysiol* 1983;56:501–14.
- Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci USA* 2003;100:253–8.
- Guye M, Regis J, Tamura M, Wendling F, McGonigal A, Chauvel P, et al. The role of corticothalamic coupling in human temporal lobe epilepsy. *Brain* 2006;129:1917–28.
- Hagmann P. From diffusion MRI to brain connectomics [Ph.D. dissertation]. Lausanne, CH: EPFL; 2005.
- Haneef Z, Lenartowicz A, Yeh HJ, Levin HS, Engel Jr J, Stern JM. Functional connectivity of hippocampal networks in temporal lobe epilepsy. *Epilepsia* 2014;55:137–45.
- He B, Liu Z. Multimodal functional neuroimaging: integrating functional MRI and EEG/MEG. *IEEE Rev Biomed Eng* 2008;1:23–40.
- Hobbs JP, Smith JL, Beggs JM. Aberrant neuronal avalanches in cortical tissue removed from juvenile epilepsy patients. *J Clin Neurophysiol* 2010;27:380–6.
- Honey CJ, Kotter R, Breakspear M, Sporns O. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proc Natl Acad Sci USA* 2007;104:10240–5.
- Iwasaki M, Enatsu R, Matsumoto R, Novak E, Thankappan B, Piao Z, et al. Accentuated cortico-cortical evoked potentials in neocortical epilepsy in areas of ictal onset. *Epileptic Disord* 2010;12:292–302.
- Keller CJ, Bickel S, Entz L, Ulbert I, Milham MP, Kelly C, et al. Intrinsic functional architecture predicts electrically evoked responses in the human brain. *Proc Natl Acad Sci USA* 2011;108:10308–13.
- Keller CJ, Bickel S, Honey CJ, Groppe DM, Entz L, Craddock RC, et al. Neurophysiological investigation of spontaneous correlated and anticorrelated fluctuations of the BOLD signal. *J Neurosci* 2013;33:6333–42.
- Keller CJ, Honey CJ, Entz L, Bickel S, Groppe DM, Toth E, et al. Corticocortical evoked potentials reveal projectors and integrators in human brain networks. *J Neurosci* 2014a;34:9152–63.
- Keller CJ, Honey CJ, Mégevand P, Entz L, Ulbert I, Mehta AD. Mapping human brain networks with cortico-cortical evoked potentials. *Philos Trans R Soc B* 2014. <http://dx.doi.org/10.1098/rstb.2013.0528>.
- Kiebel SJ, Garrido MI, Moran R, Chen CC, Friston KJ. Dynamic causal modeling for EEG and MEG. *Hum Brain Mapp* 2009;30:1866–76.
- Kokkonen SM, Nikkinen J, Remes J, Kantola J, Starck T, Haapea M, et al. Preoperative localization of the sensorimotor area using independent component analysis of resting-state fMRI. *Magn Reson Imaging* 2009;27:733–40.
- Kramer MA, Cash SS. Epilepsy as a disorder of cortical network organization. *Neuroscientist* 2012;18:360–72.
- Kramer MA, Eden UT, Kolaczky ED, Zepeda R, Eskandar EN, Cash SS. Coalescence and fragmentation of cortical networks during focal seizures. *J Neurosci* 2010;30:10076–85.
- Kramer MA, Kolaczky ED, Kirsch HE. Emergent network topology at seizure onset in humans. *Epilepsy Res* 2008;79:173–86.
- Lacruz ME, Garcia Seoane JJ, Valentin A, Selway R, Alarcon G. Frontal and temporal functional connections of the living human brain. *Eur J Neurosci* 2007;26:1357–70.
- Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, et al. Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging* 2001;13:534–46.
- Lehnertz K, Bialonski S, Horstmann MT, Krug D, Rothkegel A, Staniek M, et al. Synchronization phenomena in human epileptic brain networks. *J Neurosci Methods* 2009;183:42–8.
- Lepage KQ, Kramer MA, Chu CJ. A statistically robust EEG re-referencing procedure to mitigate reference effect. *J Neurosci Methods* 2014;235c:101–16.
- Lieb JP, Hoque K, Skomer CE, Song XW. Inter-hemispheric propagation of human mesial temporal lobe seizures: a coherence/phase analysis. *Electroencephalogr Clin Neurophysiol* 1987;67:101–19.
- Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibusaki H, et al. Functional connectivity in the human language system: a cortico-cortical evoked potential study. *Brain* 2004;127:2316–30.
- Matsuzaki N, Juhasz C, Asano E. Cortico-cortical evoked potentials and stimulation-elicited gamma activity preferentially propagate from lower- to higher-order visual areas. *Clin Neurophysiol* 2013;124:1290–6.
- McCormick C, Quraan M, Cohn M, Valiante TA, McAndrews MP. Default mode network connectivity indicates episodic memory capacity in mesial temporal lobe epilepsy. *Epilepsia* 2013;54:809–18.
- Meisel C, Kuehn C. Scaling effects and spatio-temporal multilevel dynamics in epileptic seizures. *PLoS One* 2012;7:e30371.
- Meisel C, Storch A, Hallmeyer-Elgner S, Bullmore E, Gross T. Failure of adaptive self-organized criticality during epileptic seizure attacks. *PLoS Comput Biol* 2012;8:e1002312.
- Minati L, Aquino D. Probing neural connectivity through diffusion tensor imaging DTI. In: Trapp R, editor. *Cybernetics and systems 2006*. Austrian Society for Cybernetics Studies; 2006. p. 263–8.
- Mitchell TJ, Hacker CD, Breshears JD, Szrama NP, Sharma M, Bundy DT, et al. A novel data-driven approach to preoperative mapping of functional cortex using resting-state functional magnetic resonance imaging. *Neurosurgery* 2013;73:969–82. discussion 982–3.
- Morgan RJ, Soltesz I. Nonrandom connectivity of the epileptic dentate gyrus predicts a major role for neuronal hubs in seizures. *Proc Natl Acad Sci USA* 2008;105:6179–84.
- Negishi M, Martuzzi R, Novotny EJ, Spencer DD, Constable RT. Functional MRI connectivity as a predictor of the surgical outcome of epilepsy. *Epilepsia* 2011;52:1733–40.
- Netoff TI, Clewley R, Arno S, Keck T, White JA. Epilepsy in small-world networks. *J Neurosci* 2004;24:8075–83.
- Netoff TI, Schiff SJ. Decreased neuronal synchronization during experimental seizures. *J Neurosci* 2002;22:7297–307.
- Newman MEJ. *Networks: an introduction*. Oxford, New York: Oxford University Press; 2010.
- Percha B, Dzakpasu R, Zochowski M, Parent J. Transition from local to global phase synchrony in small world neural network and its possible implications for epilepsy. *Phys Rev E Stat Nonlin Soft Matter Phys* 2005;72:031909.
- Pereira FR, Alessio A, Sercheli MS, Pedro T, Bilevicius E, Rondina JM, et al. Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. *BMC Neurosci* 2010;11:66.
- Perucca P, Dubeau F, Gotman J. Intracranial electroencephalographic seizure-onset patterns: effect of underlying pathology. *Brain* 2014;137:183–96.
- Ponten SC, Bartolomei F, Stam CJ. Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. *Clin Neurophysiol* 2007;118:918–27.
- Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 2012;59:2142–54.
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci USA* 2001;98:676–82.
- Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. *Neuroimage* 2007;37:1083–90. discussion 1097–9.
- Richardson MP. New observations may inform seizure models: very fast and very slow oscillations. *Prog Biophys Mol Biol* 2011;105:5–13.
- Richardson MP. Large scale brain models of epilepsy: dynamics meets connectomics. *J Neurol Neurosurg Psychiatry* 2012;83:1238–48.
- Schevon CA, Cappell J, Emerson R, Isler J, Grieve P, Goodman R, et al. Cortical abnormalities in epilepsy revealed by local EEG synchrony. *Neuroimage* 2007;35:140–8.
- Schindler K, Leung H, Elger CE, Lehnertz K. Assessing seizure dynamics by analysing the correlation structure of multichannel intracranial EEG. *Brain* 2007;130:65–77.
- Schindler KA, Bialonski S, Horstmann MT, Elger CE, Lehnertz K. Evolving functional network properties and synchronizability during human epileptic seizures. *Chaos* 2008;18:033119.
- Sporns O. *Networks of the brain*. Cambridge, MA: MIT Press; 2011.
- Sporns O. The human connectome: origins and challenges. *Neuroimage* 2013;80:53–61.

- Sporns O, Tononi G, Kotter R. The human connectome: a structural description of the human brain. *PLoS Comput Biol* 2005;1:e42.
- Sritharan D, Sarma SV. Fragility in dynamic networks: application to neural networks in the epileptic cortex. *Neural Comput* 2014. http://dx.doi.org/10.1162/NECO_a_00644.1-34.
- Stefan H, Lopes da Silva FH. Epileptic neuronal networks: methods of identification and clinical relevance. *Front Neurol* 2013;4:8.
- Strogatz SH. Exploring complex networks. *Nature* 2001;410:268–76.
- Stufflebeam SM, Liu H, Sepulcre J, Tanaka N, Buckner RL, Madsen JR. Localization of focal epileptic discharges using functional connectivity magnetic resonance imaging. *J Neurosurg* 2011;114:1693–7.
- Timofeev I, Steriade M. Neocortical seizures: initiation, development and cessation. *Neuroscience* 2004;123:299–336.
- Topolnik L, Steriade M, Timofeev I. Hyperexcitability of intact neurons underlies acute development of trauma-related electrographic seizures in cats in vivo. *Eur J Neurosci* 2003;18:486–96.
- Truccolo W, Donoghue JA, Hochberg LR, Eskandar EN, Madsen JR, Anderson WS, et al. Single-neuron dynamics in human focal epilepsy. *Nat Neurosci* 2011;14:635–41.
- Valentin A, Anderson M, Alarcon G, Seoane JJ, Selway R, Binnie CD, et al. Responses to single pulse electrical stimulation identify epileptogenesis in the human brain in vivo. *Brain* 2002;125:1709–18.
- van den Heuvel MP, Mandl RC, Kahn RS, Hulshoff Pol HE. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Hum Brain Mapp* 2009;30:3127–41.
- Vogels TP, Rajan K, Abbott LF. Neural network dynamics. *Annu Rev Neurosci* 2005;28:357–76.
- Warren CP, Hu S, Stead M, Brinkmann BH, Bower MR, Worrell GA. Synchrony in normal and focal epileptic brain: the seizure onset zone is functionally disconnected. *J Neurophysiol* 2010;104:3530–9.
- Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. *Nature* 1998;393:440–2.
- Wendling F, Ansari-Asl K, Bartolomei F, Senhadji L. From EEG signals to brain connectivity: a model-based evaluation of interdependence measures. *J Neurosci Methods* 2009;183:9–18.
- Whalen AJ, Brennan SN, Sauer TD, Schiff SJ. Observability of neuronal network motifs. In: 46th annual conference on information sciences and systems (CISS); 2012. p. 1–5.
- Wurina, Zang YF, Zhao SG. Resting-state fMRI studies in epilepsy. *Neurosci Bull* 2012;28:449–55.
- Yaffe R, Burns S, Gale J, Park HJ, Bulacio J, Gonzalez-Martinez J, et al. Brain state evolution during seizure and under anesthesia: a network-based analysis of stereotaxic eeg activity in drug-resistant epilepsy patients. *Conf Proc IEEE Eng Med Biol Soc* 2012;2012:5158–61.
- Zapperi S, Baekgaard Lauritsen K, Stanley HE. Self-organized branching processes: mean-field theory for avalanches. *Phys Rev Lett* 1995;75:4071–4.
- Zhang D, Johnston JM, Fox MD, Leuthardt EC, Grubb RL, Chicoine MR, et al. Preoperative sensorimotor mapping in brain tumor patients using spontaneous fluctuations in neuronal activity imaged with functional magnetic resonance imaging: initial experience. *Neurosurgery* 2009;65:226–36.
- Zhang Z, Lu G, Zhong Y, Tan Q, Liao W, Wang Z, et al. Altered spontaneous neuronal activity of the default-mode network in mesial temporal lobe epilepsy. *Brain Res* 2010;1323:152–60.