CRITICAL REVIEW AND INVITED COMMENTARY

Functional and structural brain networks in epilepsy: What have we learned?

*Eric van Diessen, *Sander J. H. Diederen, *Kees P. J. Braun, *Floor E. Jansen, and †Cornelis J. Stam

Epilepsia, **(*):1–11, 2013
doi: 10.1111/epi.12350

Summary

Brain functioning is increasingly seen as a complex interplay of dynamic neural systems that rely on the integrity of structural and functional networks. Recent studies that have investigated functional and structural networks in epilepsy have revealed specific disruptions in connectivity and network topology and, consequently, have led to a shift from "focus" to "networks" in modern epilepsy research. Disruptions in these networks may be associated with cognitive and behavioral impairments often seen in patients with chronic epilepsy. In this review, we aim to provide an overview that would introduce the clinical neurologist and epileptologist to this new theoretical paradigm. We focus on the application of a theory, called "network analysis," to characterize resting-state functional and structural networks and discuss current and future clinical applications of network analysis in patients with epilepsy.

KEY WORDS: **Network analysis, Graph theory, Functional and structural networks, Seizure generation, Cognition.**

Connectivity measures are used increasingly to investigate the integrity of brain networks in epilepsy. Based on the level of synchronous neural activity or structural correlates between different brain areas, studies revealed disease-specific patterns of increased or decreased connectivity. Although these studies provided useful information on how different brain areas are connected, they fail to clarify how these complex systems are organized and tell us little about the underlying mechanism that drives these changes in connectivity. In the study of epilepsy, network analysis (or network theory) is gaining more interest as it offers a framework to characterize the organization of brain networks (Ponten et al., 2007; Reijneveld et al., 2007; Bullmore & Sporns, 2009; Rubinov & Sporns, 2010; Stam, 2010; Stam & van Straaten, 2012). Network analysis reduces complex systems—such as the brain—to a collection of "nodes" and "edges." Nodes represent functional or structural elements of the network (recording sites or brain areas). Edges are any type of relation between brain areas, representing either a structural or functional connection. Together, these two building blocks enable characterization of the organization of brain networks.

The application of network analysis in epilepsy has provided valuable information on seizure onset, propagation, and termination (Ponten et al., 2007; Kramer et al., 2008; Schindler et al., 2008), on the interictal state of functional networks in epilepsy (van Dellen et al., 2009, 2012; Chavez et al., 2010; Horstmann et al., 2010; Liao et al., 2010), and on alterations in structural networks (Raj et al., 2010; Bernhardt et al., 2011). In addition, network analysis has been applied to improve our understanding of comorbidities of chronic epilepsy, such as behavioral problems and cognitive decline (Vlooswijk et al., 2011; Vaessen et al., 2012).

Because the literature on functional and structural networks in epilepsy expands rapidly (Kramer & Cash, 2012; Richardson, 2012; Engel et al., 2013) and the concepts involved are new to most clinicians, we aim to provide an overview to introduce modern network analysis, as applied to epilepsy, to the clinical epileptologist. To start, we introduce some basic concepts in network studies to put recent findings into perspective: What is functional and structural connectivity and how do we use these concepts for network construction? Then we summarize and interpret the results of functional and structural network studies in epilepsy, focusing on resting-state investigations to facilitate comparison between studies. Finally, we consider clinical implications of functional and structural network studies in

Accepted July 28, 2013.

*Department of Pediatric Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands; and †Department of Clinical Neurophysiology and MEG, VU University Medical Center, Amsterdam, The Netherlands

Address correspondence to Eric van Diessen, Department of Pediatric Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, KC 03.063.0; PO Box 85090, 3508 AB Utrecht, The Netherlands. E-mail: e.vandiessen-3@umcutrecht.nl

epilepsy that could bridge the gap between theoretical studies and the clinical need to understand epileptogenesis, and to more reliably predict its clinical outcomes.

Concepts in Functional and Structural Networks

Functional connectivity

A central concept to study the integrity of functional networks is functional connectivity. In clinical neuroscience, this concept denotes statistical associations between physiologic recordings of different brain areas (Aertsen et al., 1989). In a comprehensive review, Varela and colleagues stated that the extent to which different brain areas are functionally connected depends on the level of synchronous temporal activity, irrespective of signal amplitude (Varela et al., 2001), also called "synchronization." Functional connectivity can be studied in a task-related paradigm or in a so-called resting-state condition. During a resting-state condition, the subject is in a nonactive, awake state and task related activity is absent. This condition allows the detection of intrinsic activity of the brain (Greicius, 2008; van den Heuvel & Hulshoff Pol, 2010; Deco et al., 2011).

In the study of epilepsy, neurophysiologic techniques, such as (intracranial) electroencephalography (EEG) and magnetoencephalography (MEG), are widely used to localize epileptiform activity and to provide information on how brain areas are functionally connected. Over the last decades, different methods have been described to determine functional connectivity between brain areas (Pereda et al., 2005; Lemieux et al., 2011; Stefan & Lopes da Silva, 2013). Initially, connectivity studies focused on linear correlations between two signals as a function of the frequency during seizure propagation (Brazier, 1972; Gotman, 1983). Later, complex, nonlinear correlations were introduced to investigate functional coupling between different brain areas (Pijn et al., 1990; Bartolomei et al., 2001). Examples of nonlinear correlation measures currently used in epilepsy studies include the nonlinear correlation coefficient (Wendling et al., 2001); synchronization likelihood, that detects both linear and nonlinear interdependencies between two (time) signals (Stam & Van Dijk, 2002); phase lag index, that overcomes volume conduction as a confounding effect (Stam et al., 2007); granger causality, a method that denotes causality between interacting signals (Bressler & Seth, 2011) and partial directed coherence, an effective connectivity measure that is able to distinguish both direct and indirect causality flows (Baccala & Sameshima, 2001). All of these methods have their unique advantages and deal with specific limitations of neurophysiologic recordings (Pereda et al., 2005; Stam & van Straaten, 2012). Wendling and colleagues performed a modeling study that compared different connectivity measures, and concluded that the ideal method eventually depends on the studied model (Wendling et al., 2009). Furthermore, functional connectivity in neurophysiologic studies is usually analyzed in separate frequency bands: delta band (0–4 Hz), theta band (4–8 Hz), alpha band (8–13 Hz), beta band (13–30 Hz), and gamma band (>30 Hz), as each frequency band is associated with distinct networks and functions (Basar et al., 2001).

Using spontaneous low frequency fluctuations in the blood oxygenation level–dependent (BOLD) signal, functional MRI (fMRI) enables functional connectivity investigations with a higher spatial but lower temporal resolution compared to neurophysiologic recordings. Because BOLD signal changes relate to underlying neural activity, fMRI provides only an indirect measure of functional connectivity. The various methods used in this paradigm include a seed or region-of-interest (ROI) –based approach and the independent component analysis (ICA). The ROI-based approach is used to determine temporal correlations from a selected region (or multiple regions) with all other brain areas. Although this method is relatively easy to apply, it requires an a priori, investigator driven, definition of seed regions and has some statistical limitations (Fox & Raichle, 2007). In contrast to the ROI-based approach, the ICA is a data-driven method, which decomposes the BOLD signal into temporally correlated and spatially independent brain areas (Beckmann et al., 2005).

Structural connectivity

A pivotal question in studying functional connectivity is to what extent functional networks are constrained by structural connectivity (van den Heuvel & Hulshoff Pol, 2010). Where functional connectivity is considered as an on-going physiologic process of "communication" between different brain areas, structural networks can be considered as the supporting hardwire. This assumption is repeatedly confirmed by studies revealing a positive correlation between structural and functional connectivity (Damoiseaux & Greicius, 2009), although the exact relation between structural and functional connectivity is complex.

Most commonly, structural connectivity is inferred from diffusion tensor imaging (DTI). This imaging technique is based on the directionality of diffusion of water molecules in the brain. The diffusivity of water molecules is facilitated along the axons in the white matter, and is restricted in the direction perpendicular to axonal tracts (Basser & Jones, 2002). When carefully considering the pitfalls in the analysis of DTI (Jones & Cercignani, 2010), it offers the opportunity to reliably construct whole brain white matter networks from fiber tractography. To assess the integrity of axonal tracts, measures of diffusivity, tract volume, and fractional anisotropy are often used as markers to identify white matter connections between brain areas.

Alternatively, structural connectivity can be inferred from more standard anatomic MRI sequences. In a set of brain regions, either cortical thickness, or (sub) cortical gray matter volumes are quantified on three-dimensional

T1-weighted MR images. These brain regions are considered connected when they show morphologic correlations across subjects (He et al., 2007; Wen et al., 2011). The weakness of this approach is that it requires analysis of networks at the level of large groups. Recently, Tijms and others have proposed an alternative method to study structural networks based upon gray matter organization in individual subjects (Tijms et al., 2012).

Network organization

Whereas functional and structural connectivity answers the question if—and to what extent—different brain areas are connected, network analysis offers a framework to characterize the organization of functional and structural networks. As mentioned in the introduction, nodes (i.e., brain areas) and edges (i.e., structural connections or functional symmetric or asymmetric interactions between brain areas) form the most elementary building blocks of a network. These two building blocks are indispensable for further characterization of network organization (or topology). Network characteristics often used to describe global organization of whole brain networks are "clustering coefficient" and "average path length" (Fig. 1). The average clustering coefficient is a measure of segregation, which defines connection probability of nearest neighboring nodes and is therefore seen as a measure of the local connectedness within a network. A network characteristic to compute the global connectedness is the average path length. Path length refers to the number of edges that must be traversed to go from one node to another. The average path length is based on all possible pairs of nodes in a network and is inversely related to network integration (lower averaged path length means a better integration). Together, average clustering coefficient and averaged path length are frequently used to distinguish three basic network configurations: regular, small-world, and random (Watts & Strogatz, 1998). A regular (or ordered) network has many local connections (high clustering coefficient), but a limited number of distant connections (and thus a high average path length). The opposite is true for a random network, which has limited local connections and many distant connections. A small-world network combines the advantages of a regular network (good local connectedness) with the advantages of a random network (good global connectedness) and is considered to be the most efficient network topology (Fig. 2).

Apart from clustering coefficient and path length, various other network characteristics can be inferred from networks that could prove useful in further characterizing network organization (Rubinov & Sporns, 2010). Although a full overview on all network characteristics would go beyond the scope of this review, two networks characteristics are worthwhile mentioning as they are increasingly studied in relation to epilepsy: "hubs" and "modules" (Fig. 3). Hubs are nodes with many connections and with a central position within a network. Examples of network measures to quantify hub nodes are degree, strength, betweenness centrality, and eigenvector centrality. Hub nodes are crucial for efficient communication owing to their extensive connectivity and are, therefore, associated with an increased synchronized network. As will follow, studies have repeatedly identified a spatial association between pathologic hubs, or clusters of increased synchronization, and the epileptogenic zone (Schevon et al., 2007; Ortega et al., 2008; Wilke et al., 2011; Palmigiano et al., 2012). Otherwise, hub nodes have the ability to connect different modules within a network (connector hubs). Modules are subnetworks that can be defined as a group of nodes that are more connected to each other than to other parts of the network (Stam & van Straaten, 2012).

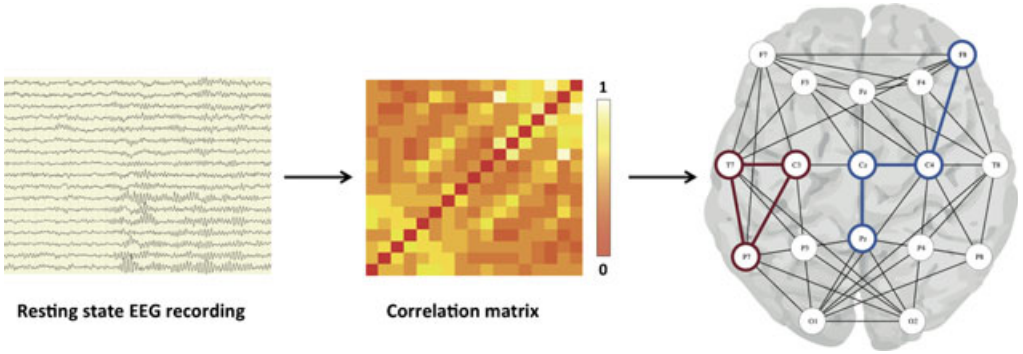

Figure 1.

Illustration of a network based on EEG data (average network based on children with idiopathic epilepsy [n = 25]; unpublished data). After selecting resting state EEG epochs, we computed a correlation matrix based on the linear and nonlinear interdependencies between two channels (in this case we used the synchronization likelihood [SL]). In the matrix, light-colored boxes indicate a high correlation. The diagonal was set on 0. After constructing a correlation matrix, various software programs allow the construction of visual graphs (figure on the right). For illustration purposes, we applied a threshold (k = 4) to obtain a binary network. Two elementary building blocks of the network are highlighted: clustering coefficient (in red) and shortest path length (in blue). Recording specifications: broadband frequency (0.5–45 Hz). Electrodes Fp1, Fp2, A1, and A2 were left out of the network due to myogenic and (eye) movement artifacts.

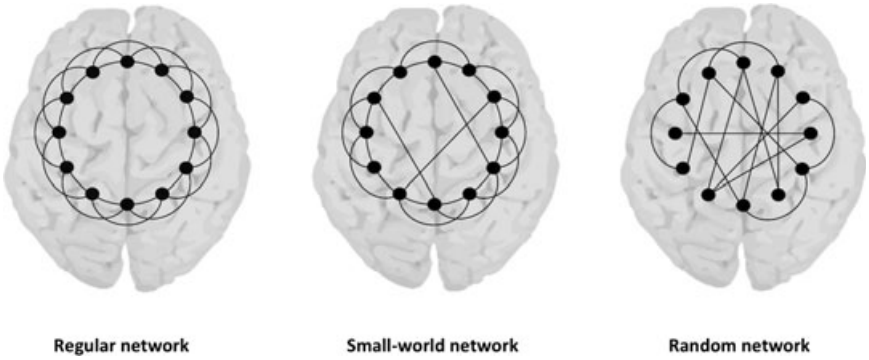

Figure 2.
Three basic network topologies: regular, small-world, and random. A regular network (left figure) has a characteristic high average clustering coefficient (on average, there is a high connection probability of nearest neighboring nodes) and a long average path length (on average, many connections must be traversed to travel from one node to another) resulting in a good local connectedness. The opposite is true for a random network (right figure) (low average clustering coefficient and short average path length). In a small-world network configuration (middle figure), the advantages of a regular and random network are combined into an efficient network topology.

however, we focus on studies using a network analytical

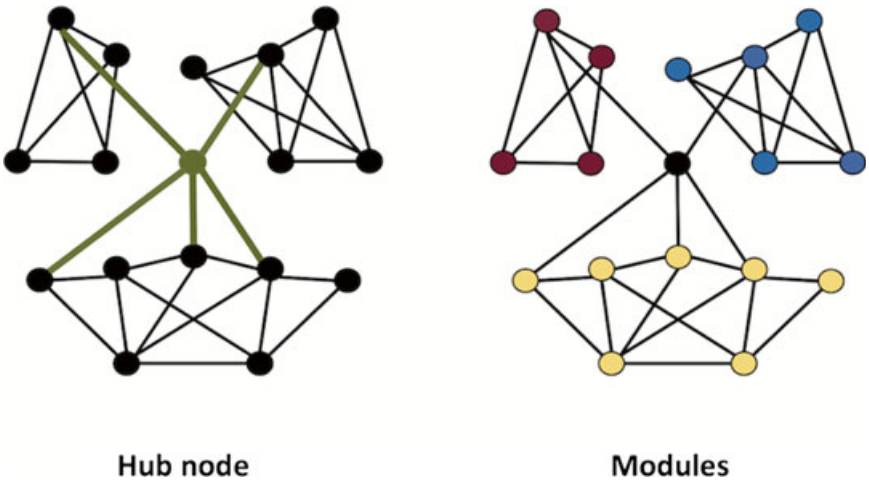

Figure 3.
Two schematic illustrations of networks. In the left figure, an example of hub node is highlighted in green: it has a central position in the network, has many connections with other nodes, and connects different modules. Several network measures exist to quantify this hub node. The simplest form is "degree," which simply counts the number of connections of a node. "Strength" also takes into account the weight of the connections (in this figure, all connections have the same weight). More advanced calculations include betweenness centrality and eigenvector centrality. Betweenness centrality takes into account the fraction of all shortest path length that needs to pass through a specific node. Eigenvector centrality determines the importance of a node on the basis of the number and weight of connections to other nodes and how those other nodes are connected. In the right figure, three groups of nodes (red, yellow, and blue) represent so-called modules. Modules are groups of nodes that are more strongly connected with each other than with nodes from different modules.

Ictal Networks: Seizure Generation and Network Topology

The study of seizure dynamics based on intrinsic neurophysiologic activity in epilepsy has a long history. In the past, many studies have focused on seizure propagation and localization of the epileptogenic zone. In this section, approach. Preictal, ictal, and postictal network topology have been studied with (intracranial) EEG recordings to gain insight into the temporal evolution of epileptic networks. More specifically, we will focus on how seizures influence network organization.

Intracranial recordings during the ictal period revealed a network shift towards a more regular topology (with increased clustering coefficient and path length) compared

to the preictal period in partial seizures (Ponten et al., 2007; Kramer et al., 2008; Schindler et al., 2008). Network analysis based on surface EEG recordings during generalized seizures also found an ictal network with a more regular topography compared to the interictal state (Ponten et al., 2009). Having zoomed in on the ictal period (ictal onset, midictal, and ictal termination) in patients with temporal lobe epilepsy (TLE), variations were seen as functional connectivity fluctuates over time (Ponten et al., 2007). An increased average clustering coefficient and path length, reflecting a more regular network configuration of the epileptic brain, characterizes the ictal onset. During the midictal period, the number of connections drops to preictal values, resulting in a less synchronizable network, and eventually a normalization of network configuration occurs after ictal termination (Fig. 4) (Ponten et al., 2007; Schindler et al., 2008).

Kramer and others described changes in functional network configuration during a focal seizure in terms of formation and dissolution of subnetworks (or modules). At seizure onset, one dominant and highly regular subnetwork is formed from highly connected nodes. Toward seizure termination this dominant subnetwork disintegrates into smaller subnetworks and network topology again becomes more random (Kramer et al., 2010). Both the formation of one dominant subnetwork and the shift, during a seizure, toward a more regular network topology could rely on decreased centrality of hubs and an altered synchronizability during the ictal state (Ponten et al., 2007; Schindler et al., 2008; Wilke et al., 2011).

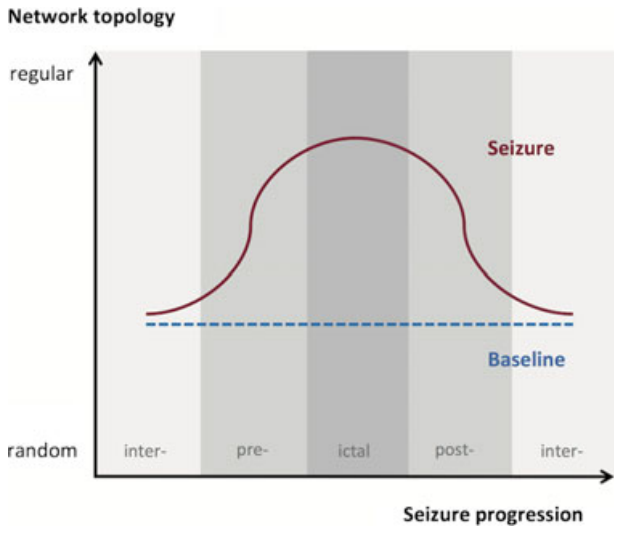

Figure 4.
Schematic representation of network changes in the ictal state. An increase in ordered network topology (red line) is observed during a seizure, compared with baseline (blue dashed line), with a gradual increase during the preictal state and a gradual decrease in the postictal state.
Epilepsia © ILAE

Interictal Networks

Neurophysiologic studies

In patients with epilepsy, comorbid cognitive and behavioral deficits are often found. Explanations are sought and investigated in terms of altered neural synchrony, differentiating pathologic interictal networks from healthy brains (Uhlhaas & Singer, 2006). Studies using EEG or MEG recordings in patients with partial epilepsy repeatedly revealed an increased functional connectivity and a subsequent loss in network efficiency, particular in the theta frequency band (Bartolomei et al., 2006; Bettus et al., 2008; Bosma et al., 2009; Douw et al., 2010a,b; Horstmann et al., 2010; van Dellen et al., 2012). Different studies, however, reported conflicting results with respect to changes in network efficiency. Where some studies reported a decreased clustering coefficient and/or path length in patients with partial seizures due to brain tumors (Bartolomei et al., 2006; van Dellen et al., 2012), others found an increased clustering coefficient and path length in patients with partial epilepsy (Horstmann et al., 2010). These contradicting findings could reflect differences in methodology, etiology, or duration of disease (see section "Potential modifiers and methodological considerations in functional and structural network studies"). In addition, network characteristics such as clustering coefficient and path length might be insufficient to fully understand the relation between network organization and brain functioning in epilepsy. Studies are therefore increasingly focusing on other network characteristics to yield additional information on the interictal network organization. For example, van Dellen and others found that a less modular organization, decreased clustering coefficient, and a lower synchronizability (i.e., a measure for the stability of the synchronous state in a network) were associated with an increased seizure occurrence and with cognitive decline in patients with brain tumor patients who had clinical seizures (van Dellen et al., 2012).

Functional MRI studies

A considerable number of fMRI studies have used a resting-state paradigm to investigate functional connectivity in generalized and partial epilepsies. In patients with TLE, studies have repeatedly identified a general decrease of functional connectivity (Laufs et al., 2007; Liao et al., 2010; Luo et al., 2011), most prominently in the ipsilateral hemisphere (Bettus et al., 2009; Pittau et al., 2012) and already visible at an early stage of TLE (Mankinen et al., 2011). Furthermore, TLE is associated with a disrupted interhemispheric connectivity in subcortical structures (Pereira et al., 2010; Morgan et al., 2011). A reduced functional connectivity (Luo et al., 2012; Masterton et al., 2012; McGill et al., 2012; Yang et al., 2012) and an increased interhemispheric connectivity (Bai et al., 2011) were found in patients with generalized epilepsies.

Few of these fMRI studies further explored network organization by means of network analysis. In a pioneering study, Liao and others investigated how changes in functional connectivity were related to network organization in patients with TLE. In addition to widespread decreased connectivity in—and between—occipital, temporal, parietal, and frontal lobes, increased connectivity was found within the temporal lobe. Network analysis revealed a decreased clustering coefficient and path length and a lower number of hub nodes, primarily within the default mode network (Liao et al., 2010). Together, these findings illustrate the widespread alterations in network topology in partial epilepsy. Similarly, Vlooswijk and others investigated whole brain network organization and its relation to cognitive decline in patients with cryptogenic epilepsy. In contrast to Liao and others, a decreased clustering coefficient and a trend toward an increased average path length was found in patients. These network alterations were associated with cognitive decline (Vlooswijk et al., 2011). Possibly, the differences between both fMRI studies are related to differences in patient population and duration of disease.

Structural networks in epilepsy

Cortical thickness analysis has been applied to explore structural networks in patients with TLE, and was found to be useful in distinguishing patients from controls (Raj et al., 2010). Bernhardt and others investigated whether structural network alterations— based on cortical thickness—progressively increase over time in patients with TLE. Although small-world topology was largely preserved in patients, an increased clustering coefficient and path length were observed. To further explore network organization in TLE, the authors investigated the distribution of hub nodes. In contrast to controls, in whom hub nodes were distributed evenly over the different lobes, hub nodes in patients with TLE were found primarily in the limbic and temporal association cortices. The authors speculate that this pathologic distribution of hub nodes in patients with TLE could be related to the disturbed connectivity between temporolimbic and extratemporal neocortical structures (Bernhardt et al., 2011). These speculations were partly verified in a recent DTI study that revealed structural reorganization of the limbic areas, leading to aberrant connections and epileptogenicity (Bonilha et al., 2012).

To date, only one study has investigated whole brain structural networks in epilepsy by means of DTI. Vaessen and others investigated network integrity of patients with nonsymptomatic partial epilepsy. Of interest, a decreased clustering coefficient and increased path length were observed only in patients with cognitive decline. Network organization in patients with epilepsy without cognitive decline did not differ from that in healthy controls (Vaessen et al., 2012). This study convincingly illustrates how network alterations can be related to cognitive profiles of patients with epilepsy.

Potential Modifiers and Methodologic Considerations in Functional and Structural Network Studies

Various studies have identified potential modifiers that could influence results from functional and structural networks, irrespective of the underlying disease. In addition to general modifiers, such as age (Micheloyannis et al., 2009; Khundrakpam et al., 2012; Smit et al., 2012), gender (Boersma et al., 2011), state of vigilance (Kuhnert et al., 2010), and intellectual performance (Li et al., 2009; van den Heuvel et al., 2009), more specific modifiers in epilepsy include, for example, antiepileptic drug (AED) use (Fig. 5). It remains unclear to what extent AEDs influence global functional networks properties (Horstmann et al., 2010) and whether cognitive impairments associated with disrupted functional networks in partial epilepsies are related to chronic use of AEDs (Vlooswijk et al., 2011). In addition, in epilepsy patients with underlying structural brain lesions, it is unknown whether alterations in networks arise from epilepsy per se, or from the associated structural lesions, as investigated in patients with brain tumors (Douw et al., 2010b, 2013; van Dellen et al., 2012). Other potential modifiers when studying network organization in epilepsy include duration of epilepsy (van Dellen et al., 2009; Liao et al., 2010) and seizure frequency (Douw et al., 2010b; van Dellen et al., 2012). To avoid heterogeneity of patients or lesion type and the possible effects of AEDs, animal models may help to further understand how disease duration

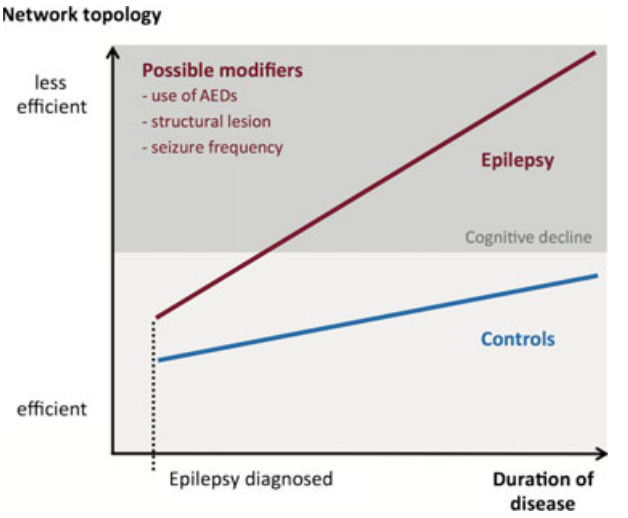

Figure 5.
Schematic representation of interictal network topology changes. As time progresses, network topology in epilepsy (red line) becomes less efficient, as compared to healthy controls (blue line), which may be associated with cognitive decline. Possible modifiers of this effect are reported in the figure: use of antiepileptic drugs (AEDs), structural lesions, and/or seizure frequency.
Epilepsia © ILAE

and seizure frequency affect overall brain network topology. In a model of focal neocortical epilepsy induced in previously healthy rats that have no significant structural cortical brain lesions, whole brain resting-state fMRI network analysis revealed an increased clustering coefficient and decreased path length, suggesting a more regular functional topology compared to healthy control animals (Otte et al., 2012).

As mentioned, results from interictal studies have often been contradictive. In general, neurophysiologic studies show an increased connectivity, whereas fMRI studies often report an opposite, decreased connectivity. These differences might reflect possible alterations in neurovascular coupling secondary to epilepsy (Bettus et al., 2011). Otherwise, differences in spatial and temporal resolution between neurophysiologic and fMRI studies make it difficult to compare results. More simultaneous EEG and fMRI studies are therefore needed to further explore the relation between neurophysiologic and BOLD-associated connectivity. Furthermore, it can be challenging to compare studies using a network analytical approach. Studies have consistently identified a less efficient network organization in epilepsy, albeit either a more regular or a more random network topology. In a comprehensive review, several methodologic considerations were raised that could be accountable for these opposite results (van Wijk et al., 2010). Size of networks (i.e., number of nodes) or edge-density, connectivity measures used, thresholding of unweighted networks, and normalization of network characteristics all influence the eventual network topology and should be considered when comparing different network studies.

Clinical Implications of Functional and Structural Networks in Epilepsy

Network studies in patients with epilepsy can have multiple clinical implications. First, they can be used to investigate the mechanisms underlying comorbid cognitive decline. Both structural and functional network studies have shown that cognitive decline in epilepsy patients is associated with a loss of network efficiency (Vlooswijk et al., 2011; Vaessen et al., 2012). As a result, the authors speculated that network studies could potentially identify patients at risk for developing cognitive impairment. Other studies have explored the diagnostic use of the network analytical approach. The predictive value of conventional EEG reports was compared with functional connectivity analysis of the same EEG recording in a univariate model to distinguish patients from those in whom the diagnosis epilepsy was eventually rejected after a first suspected seizure. Particularly in the theta frequency band, increased functional connectivity was found to be useful as a diagnostic tool with a superior sensitivity and specificity compared to conventional EEG report (Douw et al., 2010a). Similarly, we showed that by combining several network characteristics into a sophisticated model, we were able to predict the diagnosis of epilepsy more reliable than based upon the presence of epileptiform transients (van Diessen et al., 2013b). More recently, expression of epilepsy-related proteins in brain tumor patients with clinical seizures was found to be related with specific network alterations, such as the connectivity between brain modules (Douw et al., 2013). The authors therefore suggested that network analysis could be used as a noninvasive diagnostic biomarker for microscopic tumor characteristics.

The development of functional network biomarkers (Zhang et al., 2012) to predict the risk of seizure recurrence is another possible clinical application of functional network analysis. Although network properties fail to reliably predict seizure onset (Takahashi et al., 2012), they may improve prediction of outcome (seizure recurrence) after epilepsy surgery (Negishi et al., 2011). Ortega and others retrospectively analyzed intracranial corticography data in patients with TLE and found that resection of cortical areas with clusters of highly synchronized activity was related to an increased seizure control (Ortega et al., 2008; Palmigiano et al., 2012). Similarly, Wilke and others revealed that resection of hub nodes that were active during a seizure was associated with seizure freedom in patients with neocortical epilepsy (Wilke et al., 2011). Together, these studies indicate the potential use of network analysis to improve the outcome of epilepsy surgery.

Conclusions and Future Directions

Functional and structural network studies have thus far provided valuable insights into ictal and interictal network alterations in epilepsy. Ictal studies have repeatedly identified a more regular network topology and changes in modularity when the epileptic brain goes into a seizure. Toward the end of a seizure, network topology returns to its baseline configuration. In contrast, results from interictal studies are more contradictive. We have summarized different potential modifiers and methodologic consideration that could turn helpful when interpreting contradicting results from ictal and interictal functional and structural network studies. Throughout the review, we discussed the strengths and weaknesses of each modality used in network analytical studies and summarized them in Table 1. In addition, "conventional" network characteristics such as clustering coefficient and path length might be insufficient to clearly pinpoint epilepsy specific changes in the interictal network topology. Advanced network characteristics, such as measures of hub-nodes, modules, and synchronization could turn out to be useful. Of interest, studies using these measures have already revealed disease-specific changes in hub distribution and/or modularity of the epileptic network (Ortega et al., 2008; Bernhardt et al., 2011; Wilke et al.,

Table 1. Overview on strengths and weaknesses of different modalities used in network analytic studies

Modality	Strengths	Weaknesses
Functional networks		
EEG	Widely used in clinical practice	Low spatial resolution (less for high-definition EEG)
	High temporal resolution	Sensitive to volume conduction artifacts
	Suitable to study ictal networks	
Intracranial recordings	Direct electrical recordings of neuronal activity	Only available in a surgical setting
	High temporal and spatial resolution	No whole brain network analysis possible
	No myogenic artifacts	
MEG	High temporal and spatial resolution	Sensitive to movement artifacts
	Source space analysis allows identification of anatomic network specification	Not widely available
fMRI	High spatial resolution	Low temporal resolution
	Allows the study of subcortical networks separately	Assumption of BOLD changes in respect to electrophysiologic changes in the epileptic brain
	Widely available	
Structural networks		
Cortical thickness	Inferred from standard MRI sequences	Analysis of individual networks complicated
	High spatial resolution	Analysis of subcortical structures not possible
DTI	Physical network connections can be studied	Several technical pitfalls when analyzing DTI data
	Both cortical and subcortical structures and their interconnectedness can be studied	Many arbitrary choices in the process of data extraction

2011; van Dellen et al., 2012; Douw et al., 2013; van Diessen et al., 2013a). Otherwise, recent network analytic studies are using novel approaches to overcome methodologic shortcomings, such as the minimum spanning tree (MST). The MST approach considers the smallest possible subnetwork, which still connects all the nodes in a network without forming cycles, and reduces the connection costs in a network. This approach might be particularly valuable when comparing patients with controls (or different types of epilepsy); MST networks have the unique advantage that networks from different groups contain the same number of nodes and connections, thereby facilitating comparisons between groups, particularly in neurophysiologic studies. Several neuropsychiatric studies have already successfully applied this technique (Lee et al., 2006, 2010; Ortega et al., 2008; Alexander-Bloch et al., 2010; Schoen et al., 2011; Boersma et al., 2013). Studies using more advanced network characteristics and/or the MST approach are needed to further explore their potential in the study of epileptogenic networks. In addition, these novel measures can be used with different neurophysiologic and neuroimaging techniques; this allows the construction of more detailed networks on different temporal and spatial scales that could potentially result in a more accurate visualization and quantification of epileptogenic networks.

Another question that remains unanswered is to what extent functional networks are constrained by structural networks (Otte et al., 2012; Voets et al., 2012; Wang et al., 2012). Longitudinal studies combining both functional (fMRI, MEG) and structural networks (based on cortical thickness associations or DTI) simultaneously are crucial to understand the integration of these networks and their implication for clinical outcome of patients with epilepsy. The combination of these modalities could potentially elucidate specific network alterations in epilepsy and possibly clarify why in some patients behavioral and cognitive deficits arise (Vlooswijk et al., 2011; Vaessen et al., 2012).

Finally, despite the contradictive results as described earlier, characterization of networks in the dynamic process of seizure generation and in the interictal state has advanced our understanding of epilepsy as a network disease. In addition, a network analytical approach could become valuable in the diagnostic process. Standard EEG recordings performed in the initial diagnostic work-up have proven that a network analytic approach can be used to differentiate patients from controls (Douw et al., 2010a; van Diessen et al., 2013b). Larger EEG studies with external validation are needed to fully explore the true diagnostic value of functional networks. Furthermore, invasive neurophysiologic recordings and neuroimaging studies in the presurgical work-up have already shown the potential value of a network approach (Ortega et al., 2008; Wilke et al., 2011; Morgan et al., 2012; Varotto et al., 2012; Bartolomei et al., 2013) and should be further exploited. Earlier identification of network alterations may lead to an accelerated and improved intervention in (refractory) epilepsy to reduce future burdens, such as cognitive decline or behavioral impairments.

Funding

Eric van Diessen and Kees Braun were supported by the Dutch National Epilepsy Fund (NEF 09-93 and 08-10, respectively).

Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those

guidelines. None of the authors has any conflict of interest in relation to this work to disclose.

References

Aertsen AM, Gerstein GL, Habib MK, Palm G. (1989) Dynamics of neuronal firing correlation: modulation of "effective connectivity". *J Neurophysiol* 61:900–917.

Alexander-Bloch AF, Gogtay N, Meunier D, Birn R, Clasen L, Lalonde F, Lenroot R, Giedd J, Bullmore ET. (2010) Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia. *Front Syst Neurosci* 4:147.

Baccala LA, Sameshima K. (2001) Partial directed coherence: a new concept in neural structure determination. *Biol Cybern* 84:463–474.

Bai X, Guo J, Killory B, Vestal M, Berman R, Negishi M, Danielson N, Novotny EJ, Constable RT, Blumenfeld H. (2011) Resting functional connectivity between the hemispheres in childhood absence epilepsy. *Neurology* 76:1960–1967.

Bartolomei F, Wendling F, Bellanger JJ, Regis J, Chauvel P. (2001) Neural networks involving the medial temporal structures in temporal lobe epilepsy. *Clin Neurophysiol* 112:1746–1760.

Bartolomei F, Bosma I, Klein M, Baayen JC, Reijneveld JC, Postma TJ, Heimans JJ, van Dijk BW, de Munck JC, de Jongh A, Cover KS, Stam CJ. (2006) Disturbed functional connectivity in brain tumour patients: evaluation by graph analysis of synchronization matrices. *Clin Neurophysiol* 117:2039–2049.

Bartolomei F, Bettus G, Stam CJ, Guye M. (2013) Interictal network properties in mesial temporal lobe epilepsy: a graph theoretical study from intracerebral recordings. *Clin Neurophysiol* Clin Neurophysiol: Jun 28 [Epub ahead of print]. doi: 10.1016/j.clinph.2013.06.003.

Basar E, Basar-Eroglu C, Karakas S, Schurmann M. (2001) Gamma, alpha, delta, and theta oscillations govern cognitive processes. *Int J Psychophysiol* 39:241–248.

Basser PJ, Jones DK. (2002) Diffusion-tensor MRI: theory, experimental design and data analysis – a technical review. *NMR Biomed* 15: 456–467.

Beckmann CF, DeLuca M, Devlin JT, Smith SM. (2005) Investigations into resting-state connectivity using independent component analysis. *Philos Trans R Soc Lond B Biol Sci* 360:1001–1013.

Bernhardt BC, Chen Z, He Y, Evans AC, Bernasconi N. (2011) Graph-theoretical analysis reveals disrupted small-world organization of cortical thickness correlation networks in temporal lobe epilepsy. *Cereb Cortex* 21:2147–2157.

Bettus G, Wendling F, Guye M, Valton L, Regis J, Chauvel P, Bartolomei F. (2008) Enhanced EEG functional connectivity in mesial temporal lobe epilepsy. *Epilepsy Res* 81:58–68.

Bettus G, Guedj E, Joyeux F, Confort-Gouny S, Soulier E, Laguitton V, Cozzone PJ, Chauvel P, Ranjeva JP, Bartolomei F, Guye M. (2009) Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. *Hum Brain Mapp* 30:1580–1591.

Bettus G, Ranjeva JP, Wendling F, Benar CG, Confort-Gouny S, Regis J, Chauvel P, Cozzone PJ, Lemieux L, Bartolomei F, Guye M. (2011) Interictal functional connectivity of human epileptic networks assessed by intracerebral EEG and BOLD signal fluctuations. *PLoS ONE* 6: e20071.

Boersma M, Smit DJ, de Bie HM, Van Baal GC, Boomsma DI, de Geus EJ, Delemarre-van de Waal HA, Stam CJ. (2011) Network analysis of resting state EEG in the developing young brain: structure comes with maturation. *Hum Brain Mapp* 32:413–425.

Boersma M, Smit DJ, Boomsma DI, De Geus EJ, Delemarre-van de Waal HA, Stam CJ. (2013) Growing trees in child brains: graph theoretical analysis of electroencephalography-derived minimum spanning tree in 5- and 7-year-old children reflects brain maturation. *Brain Connect* 3:50–60.

Bonilha L, Nesland T, Martz GU, Joseph JE, Spampinato MV, Edwards JC, Tabesh A. (2012) Medial temporal lobe epilepsy is associated with neuronal fibre loss and paradoxical increase in structural connectivity of limbic structures. *J Neurol Neurosurg Psychiatry* 83:903–909.

Bosma I, Reijneveld JC, Klein M, Douw L, van Dijk BW, Heimans JJ, Stam CJ. (2009) Disturbed functional brain networks and neurocognitive function in low-grade glioma patients: a graph theoretical analysis of resting-state MEG. *Nonlinear Biomed Phys* 3:9.

Brazier MA. (1972) Spread of seizure discharges in epilepsy: anatomical and electrophysiological considerations. *Exp Neurol* 36:263–272.

Bressler SL, Seth AK. (2011) Wiener-Granger causality: a well established methodology. *Neuroimage* 58:323–329.

Bullmore E, Sporns O. (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 10: 186–198.

Chavez M, Valencia M, Navarro V, Latora V, Martinerie J. (2010) Functional modularity of background activities in normal and epileptic brain networks. *Phys Rev Lett* 104:118701.

Damoiseaux JS, Greicius MD. (2009) Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Struct Funct* 213:525–533.

Deco G, Jirsa VK, McIntosh AR. (2011) Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat Rev Neurosci* 12:43–56.

Douw L, de Groot M, van Dellen E, Heimans JJ, Ronner HE, Stam CJ, Reijneveld JC. (2010a) 'Functional connectivity' is a sensitive predictor of epilepsy diagnosis after the first seizure. *PLoS ONE* 5: e10839.

Douw L, van Dellen E, de Groot M, Heimans JJ, Klein M, Stam CJ, Reijneveld JC. (2010b) Epilepsy is related to theta band brain connectivity and network topology in brain tumor patients. *BMC Neurosci* 11:103.

Douw L, de Groot M, van Dellen E, Aronica E, Heimans JJ, Klein M, Stam CJ, Reijneveld JC, Hillebrand A. (2013) Local MEG networks: the missing link between protein expression and epilepsy in glioma patients? *Neuroimage* 75C:203–211.

Engel J Jr, Thompson PM, Stern JM, Staba RJ, Bragin A, Mody I. (2013) Connectomics and epilepsy. *Curr Opin Neurol* 26:186–194.

Fox MD, Raichle ME. (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8:700–711.

Gotman J. (1983) Measurement of small time differences between EEG channels: method and application to epileptic seizure propagation. *Electroencephalogr Clin Neurophysiol* 56:501–514.

Greicius M. (2008) Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol* 21:424–430.

He Y, Chen ZJ, Evans AC. (2007) Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* 17:2407–2419.

Horstmann MT, Bialonski S, Noennig N, Mai H, Prusseit J, Wellmer J, Hinrichs H, Lehnertz K. (2010) State dependent properties of epileptic brain networks: comparative graph-theoretical analyses of simultaneously recorded EEG and MEG. *Clin Neurophysiol* 121:172–185.

Jones DK, Cercignani M. (2010) Twenty-five pitfalls in the analysis of diffusion MRI data. *NMR Biomed* 23:803–820.

Khundrakpam BS, Reid A, Brauer J, Carbonell F, Lewis J, Ameis S, Karama S, Lee J, Chen Z, Das S, Evans AC. (2013) Developmental changes in organization of structural brain networks. *Cereb Cortex* 23:2072–2085.

Kramer MA, Cash SS. (2012) Epilepsy as a disorder of cortical network organization. *Neuroscientist* 18:360–372.

Kramer MA, Kolaczyk ED, Kirsch HE. (2008) Emergent network topology at seizure onset in humans. *Epilepsy Res* 79:173–186.

Kramer MA, Eden UT, Kolaczyk ED, Zepeda R, Eskandar EN, Cash SS. (2010) Coalescence and fragmentation of cortical networks during focal seizures. *J Neurosci* 30:10076–10085.

Kuhnert MT, Elger CE, Lehnertz K. (2010) Long-term variability of global statistical properties of epileptic brain networks. *Chaos* 20:043126.

Laufs H, Hamandi K, Salek-Haddadi A, Kleinschmidt AK, Duncan JS, Lemieux L. (2007) Temporal lobe interictal epileptic discharges affect cerebral activity in "default mode" brain regions. *Hum Brain Mapp* 28:1023–1032.

Lee U, Kim S, Jung KY. (2006) Classification of epilepsy types through global network analysis of scalp electroencephalograms. *Phys Rev E Stat Nonlin Soft Matter Phys* 73:041920.

Lee U, Oh G, Kim S, Noh G, Choi B, Mashour GA. (2010) Brain networks maintain a scale-free organization across consciousness, anesthesia, and recovery: evidence for adaptive reconfiguration. *Anesthesiology* 113:1081–1091.

Lemieux L, Daunizeau J, Walker MC. (2011) Concepts of connectivity and human epileptic activity. *Front Syst Neurosci* 5:12.

Li Y, Liu Y, Li J, Qin W, Li K, Yu C, Jiang T. (2009) Brain anatomical network and intelligence. *PLoS Comput Biol* 5:e1000395.

Liao W, Zhang Z, Pan Z, Mantini D, Ding J, Duan X, Luo C, Lu G, Chen H. (2010) Altered functional connectivity and small-world in mesial temporal lobe epilepsy. *PLoS ONE* 5:e8525.

Luo C, Qiu C, Guo Z, Fang J, Li Q, Lei X, Xia Y, Lai Y, Gong Q, Zhou D, Yao D. (2011) Disrupted functional brain connectivity in partial epilepsy: a resting-state fMRI study. *PLoS ONE* 7:e28196.

Luo C, Li Q, Xia Y, Lei X, Xue K, Yao Z, Lai Y, Martinez-Montes E, Liao W, Zhou D, Valdes-Sosa PA, Gong Q, Yao D. (2012) Resting state basal ganglia network in idiopathic generalized epilepsy. *Hum Brain Mapp* 33:1279–1294.

Mankinen K, Long XY, Paakki JJ, Harila M, Rytky S, Tervonen O, Nikkinen J, Starck T, Remes J, Rantala H, Zang YF, Kiviniemi V. (2011) Alterations in regional homogeneity of baseline brain activity in pediatric temporal lobe epilepsy. *Brain Res* 1373:221–229.

Masterton RA, Carney PW, Jackson GD. (2012) Cortical and thalamic resting-state functional connectivity is altered in childhood absence epilepsy. *Epilepsy Res* 99:327–334.

McGill ML, Devinsky O, Kelly C, Milham M, Castellanos FX, Quinn BT, DuBois J, Young JR, Carlson C, French J, Kuzniecky R, Halgren E, Thesen T. (2012) Default mode network abnormalities in idiopathic generalized epilepsy. *Epilepsy Behav* 23:353–359.

Micheloyannis S, Vourkas M, Tsirka V, Karakonstantaki E, Kanatsouli K, Stam CJ. (2009) The influence of ageing on complex brain networks: a graph theoretical analysis. *Hum Brain Mapp* 30:200–208.

Morgan VL, Rogers BP, Sonmezturk HH, Gore JC, Abou-Khalil B. (2011) Cross hippocampal influence in mesial temporal lobe epilepsy measured with high temporal resolution functional magnetic resonance imaging. *Epilepsia* 52:1741–1749.

Morgan VL, Sonmezturk HH, Gore JC, Abou-Khalil B. (2012) Lateralization of temporal lobe epilepsy using resting functional magnetic resonance imaging connectivity of hippocampal networks. *Epilepsia* 53:1628–1635.

Negishi M, Martuzzi R, Novotny EJ, Spencer DD, Constable RT. (2011) Functional MRI connectivity as a predictor of the surgical outcome of epilepsy. *Epilepsia* 52:1733–1740.

Ortega GJ, Menendez de la Prida L, Sola RG, Pastor J. (2008) Synchronization clusters of interictal activity in the lateral temporal cortex of epileptic patients: intraoperative electrocorticographic analysis. *Epilepsia* 49:269–280.

Otte WM, Dijkhuizen RM, van Meer MP, van der Hel WS, Verlinde SA, van Nieuwenhuizen O, Viergever MA, Stam CJ, Braun KP. (2012) Characterization of functional and structural integrity in experimental focal epilepsy: reduced network efficiency coincides with white matter changes. *PLoS ONE* 7:e39078.

Palmigiano A, Pastor J, Garcia de Sola R, Ortega GJ. (2012) Stability of synchronization clusters and seizurability in temporal lobe epilepsy. *PLoS ONE* 7:e41799.

Pereda E, Quiroga RQ, Bhattacharya J. (2005) Nonlinear multivariate analysis of neurophysiological signals. *Prog Neurobiol* 77:1–37.

Pereira FR, Alessio A, Sercheli MS, Pedro T, Bilevicius E, Rondina JM, Ozelo HF, Castellano G, Covolan RJ, Damasceno BP, Cendes F. (2010) Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. *BMC Neurosci* 11:66.

Pijn JP, Vijn PC, Lopes da Silva FH, Van Ende Boas W, Blanes W. (1990) Localization of epileptogenic foci using a new signal analytical approach. *Neurophysiol Clin* 20:1–11.

Pittau F, Grova C, Moeller F, Dubeau F, Gotman J. (2012) Patterns of altered functional connectivity in mesial temporal lobe epilepsy. *Epilepsia* 53:1013–1023.

Ponten SC, Bartolomei F, Stam CJ. (2007) Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures. *Clin Neurophysiol* 118:918–927.

Ponten SC, Douw L, Bartolomei F, Reijneveld JC, Stam CJ. (2009) Indications for network regularization during absence seizures: weighted and unweighted graph theoretical analyses. *Exp Neurol* 217:197–204.

Raj A, Mueller SG, Young K, Laxer KD, Weiner M. (2010) Network-level analysis of cortical thickness of the epileptic brain. *Neuroimage* 52:1302–1313.

Reijneveld JC, Ponten SC, Berendse HW, Stam CJ. (2007) The application of graph theoretical analysis to complex networks in the brain. *Clin Neurophysiol* 118:2317–2331.

Richardson MP. (2012) Large scale brain models of epilepsy: dynamics meets connectomics. *J Neurol Neurosurg Psychiatry* 83:1238–1248.

Rubinov M, Sporns O. (2010) Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 52:1059–1069.

Schevon CA, Cappell J, Emerson R, Isler J, Grieve P, Goodman R, McKhann G Jr, Weiner H, Doyle W, Kuzniecky R, Devinsky O, Gilliam F. (2007) Cortical abnormalities in epilepsy revealed by local EEG synchrony. *Neuroimage* 35:140–148.

Schindler KA, Bialonski S, Horstmann MT, Elger CE, Lehnertz K. (2008) Evolving functional network properties and synchronizability during human epileptic seizures. *Chaos* 18:033119.

Schoen W, Chang JS, Lee U, Bob P, Mashour GA. (2011) The temporal organization of functional brain connectivity is abnormal in schizophrenia but does not correlate with symptomatology. *Conscious Cogn* 20:1050–1054.

Smit DJ, Boersma M, Schnack HG, Micheloyannis S, Boomsma DI, Hulshoff Pol HE, Stam CJ, de Geus EJ. (2012) The brain matures with stronger functional connectivity and decreased randomness of its network. *PLoS ONE* 7:e36896.

Stam CJ. (2010) Characterization of anatomical and functional connectivity in the brain: a complex networks perspective. *Int J Psychophysiol* 77:186–194.

Stam CJ, Van Dijk BW. (2002) Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets. *Physica D* 163:236–251.

Stam CJ, van Straaten EC. (2012) The organization of physiological brain networks. *Clin Neurophysiol* 123:1067–1087.

Stam CJ, Nolte G, Daffertshofer A. (2007) Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. *Hum Brain Mapp* 28:1178–1193.

Stefan H, Lopes da Silva FH. (2013) Epileptic neuronal networks: methods of identification and clinical relevance. *Front Neurol* 4:8.

Takahashi H, Takahashi S, Kanzaki R, Kawai K. (2012) State-dependent precursors of seizures in correlation-based functional networks of electrocorticograms of patients with temporal lobe epilepsy. *Neurol Sci* 33:1355–1364.

Tijms BM, Series P, Willshaw DJ, Lawrie SM. (2012) Similarity-based extraction of individual networks from gray matter MRI scans. *Cereb Cortex* 22:1530–1541.

Uhlhaas PJ, Singer W. (2006) Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron* 52:155–168.

Vaessen MJ, Jansen JF, Vlooswijk MC, Hofman PA, Majoie HJ, Aldenkamp AP, Backes WH. (2012) White matter network abnormalities are associated with cognitive decline in chronic epilepsy. *Cereb Cortex* 22:2139–2147.

van Dellen E, Douw L, Baayen JC, Heimans JJ, Ponten SC, Vandertop WP, Velis DN, Stam CJ, Reijneveld JC. (2009) Long-term effects of temporal lobe epilepsy on local neural networks: a graph theoretical analysis of corticography recordings. *PLoS ONE* 4:e8081.

van Dellen E, Douw L, Hillebrand A, Ris-Hilgersom IH, Schoonheim MM, Baayen JC, De Witt Hamer PC, Velis DN, Klein M, Heimans JJ, Stam CJ, Reijneveld JC. (2012) MEG network differences between low- and high-grade glioma related to epilepsy and cognition. *PLoS ONE* 7: e50122.

van den Heuvel MP, Hulshoff Pol HE. (2010) Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharmacol* 20:519–534.

van den Heuvel MP, Stam CJ, Kahn RS, Hulshoff Pol HE. (2009) Efficiency of functional brain networks and intellectual performance. *J Neurosci* 29:7619–7624.

van Diessen E, Hanemaaijer JI, Otte WM, Zelmann R, Jacobs J, Jansen FE, Dubeau F, Stam CJ, Gotman J, Zijlmans M. (2013a) Are high frequency oscillations associated with altered network topology in partial epilepsy? *Neuroimage* 82C:564–573.

van Diessen E, Otte WM, Braun KP, Stam CJ, Jansen FE. (2013b) Improved diagnosis in children with partial epilepsy using a multivariable prediction model based on EEG network characteristics. *PLoS ONE* 8:e59764.

van Wijk BC, Stam CJ, Daffertshofer A. (2010) Comparing brain networks of different size and connectivity density using graph theory. *PLoS ONE* 5:e13701.

Varela F, Lachaux JP, Rodriguez E, Martinerie J. (2001) The brainweb: phase synchronization and large-scale integration. *Nat Rev Neurosci* 2:229–239.

Varotto G, Tassi L, Franceschetti S, Spreafico R, Panzica F. (2012) Epileptogenic networks of type II focal cortical dysplasia: a stereo-EEG study. *Neuroimage* 61:591–598.

Vlooswijk MC, Vaessen MJ, Jansen JF, de Krom MC, Majoie HJ, Hofman PA, Aldenkamp AP, Backes WH. (2011) Loss of network efficiency associated with cognitive decline in chronic epilepsy. *Neurology* 77:938–944.

Voets NL, Beckmann CF, Cole DM, Hong S, Bernasconi A, Bernasconi N. (2012) Structural substrates for resting network disruption in temporal lobe epilepsy. *Brain* 135:2350–2357.

Wang Z, Zhang Z, Jiao Q, Liao W, Chen G, Sun K, Shen L, Wang M, Li K, Liu Y, Lu G. (2012) Impairments of thalamic nuclei in idiopathic generalized epilepsy revealed by a study combining morphological and functional connectivity MRI. *PLoS ONE* 7:e39701.

Watts DJ, Strogatz SH. (1998) Collective dynamics of 'small-world' networks. *Nature* 393:440–442.

Wen W, He Y, Sachdev P. (2011) Structural brain networks and neuropsychiatric disorders. *Curr Opin Psychiatry* 24:219–225.

Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. (2001) Interpretation of interdependencies in epileptic signals using a macroscopic physiological model of the EEG. *Clin Neurophysiol* 112: 1201–1218.

Wendling F, Ansari-Asl K, Bartolomei F, Senhadji L. (2009) From EEG signals to brain connectivity: a model-based evaluation of interdependence measures. *J Neurosci Methods* 183:9–18.

Wilke C, Worrell G, He B. (2011) Graph analysis of epileptogenic networks in human partial epilepsy. *Epilepsia* 52:84–93.

Yang T, Luo C, Li Q, Guo Z, Liu L, Gong Q, Yao D, Zhou D. (2012) Altered resting-state connectivity during interictal generalized spike-wave discharges in drug-naive childhood absence epilepsy. *Hum Brain Mapp* 34:1761–1767.

Zhang J, Cheng W, Wang Z, Zhang Z, Lu W, Lu G, Feng J. (2012) Pattern classification of large-scale functional brain networks: identification of informative neuroimaging markers for epilepsy. *PLoS ONE* 7:e36733.