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Graph theory findings in the pathophysiology of temporal lobe epilepsy

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Abstract

Temporal lobe epilepsy (TLE) is the most common form of adult epilepsy. Accumulating evidence has shown that TLE is a disorder of abnormal epileptogenic networks, rather than focal sources. Graph theory allows for a network-based representation of TLE brain networks, and has potential to illuminate characteristics of brain topology conducive to TLE pathophysiology, including seizure initiation and spread. We review basic concepts which we believe will prove helpful in interpreting results rapidly emerging from graph theory research in TLE. In addition, we summarize the current state of graph theory findings in TLE as they pertain its pathophysiology. Several common findings have emerged from the many modalities which have been used to study TLE using graph theory, including structural MRI, diffusion tensor imaging, surface EEG, intracranial EEG, magnetoencephalography, functional MRI, cell cultures, simulated models, and mouse models, involving increased regularity of the interictal network configuration, altered local segregation and global integration of the TLE network, and network reorganization of temporal lobe and limbic structures. As different modalities provide different views of the same phenomenon, future studies integrating data from multiple modalities are needed to clarify findings and contribute to the formation of a coherent theory on the pathophysiology of TLE.

Keywords

Graph theory; Temporal lobe epilepsy; Pathophysiology; Functional connectivity; Diffusion tensor imaging; Small-world networks

1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of adult epilepsy (Engel, 2001; Williamson et al., 1993) and increasingly thought to be a disorder involving abnormal epileptogenic networks, rather than a single focal epileptogenic source (Bonilha et al., 2007;

Engel et al., 2013; Spencer, 2002). Several abnormalities in structural and functional network connectivity have been observed recently in TLE (Bartolomei et al., 2013; Bernhardt et al., 2011, 2013; Bonilha et al., 2007; Haneef et al., 2012). Links between structural/functional network structure with pathophysiology have been identified in Alzheimer's disease (Sanchez et al., 2011), traumatic brain injury (Sharp et al., 2011), and generalized epilepsy (Zhang et al., 2011), and may demonstrate utility with respect to TLE pathophysiology as well, potentially suggesting new diagnostic and therapeutic approaches.

The majority of seizures in TLE are associated with hippocampal sclerosis or other temporal lobe abnormalities (Margerison and Corsellis, 1966). However, in addition to the primary temporal epileptogenic focus in TLE, there is increasing evidence of additional extratemporal involvement, including the subcortical areas (Bonilha et al., 2005; Juhasz et al., 1999; Mueller et al., 2010) and neocortex (McDonald et al., 2008). Network changes in the interictal and ictal states of epilepsy are thought to result not only from dysregulation of extracellular ions and neurotransmitters (Engelborghs et al., 2000) and alterations in excitability at the single-neuron and local neuron population levels (Sloviter, 1996), but also from reconfiguration of long range connections between neuronal populations in different parts of the brain (Spencer, 2002). Graph theory is a promising mathematical approach to modeling interdependencies between random variables, which, applied to neurophysiological and neuroimaging data, has the capacity to illuminate aspects of brain network structure in TLE (Constable et al., 2013). A graph theoretical approach to understanding the pathophysiology of TLE provides a coherent model to examine structural and functional changes in connectivity, both at the single-neuron level based on cell cultures and simulated models, as well as at the population level based on neuroimaging and neurophysiological tests. It also allows for the quantification of various measures characterizing brain topology from both global and regional network perspectives, and provides a realistic model for the brain connectome, by modeling structural and functional connectivity through estimation of interregional dependencies. As such, a graph theory approach to TLE allows for the detection of changes in brain topology within, as well as external to, the temporal lobe, and provides a means of understanding brain environment changes contributing to altered neuron population excitability.

In this review, we examine basic concepts useful for interpreting rapidly emerging graph theory research on TLE, and discuss the current state of pathophysiological findings in TLE that have been identified based on graph theory models. This review is organized as follows: in Section 2, we provide an overview of the fundamental principles of graph theory as they pertain to characterizing normal and abnormal brain network topology; in Section 3, we review the current state of graph theory findings in the pathophysiology of TLE, summarized by modality; in Section 4, we synthesize and discuss consistent and inconsistent topological features that have been demonstrated thus far in TLE, as well as their relevance to ictogenesis, ictal propagation, and the interictal state.

2. Fundamentals of graph theoretic approach to brain connectivity

2.1. Historical derivations

The field of graph theory has its beginnings in 1735, when Leonhard Euler solved the historical Königsberg bridge problem. This mathematical problem asked whether the seven bridges in Königsberg, a city now called Kaliningrad, could be traversed in a single trip which crossed each bridge once and only once. By proving a solution in the negative after reformulating the landmasses as “nodes” and the bridges as “edges” (for formal definitions, see Section 2.2) (Euler, 1741), Euler’s proof has come to be regarded as the first theorem in graph theory (Chartrand, 1985). Since then, graph theory has spread to various fields (Kollar and Friedman, 2009): in statistical physics, beginning with representations of particle systems using undirected graphs (Gibbs, 1902); in statistics, with development of chain dependence theory for modeling dependent random variables (Markov, 1906); and in genetics, with use of directed graphs to model species inheritance (Wright, 1921, 1934).

2.2. Overview of common graphical model definitions

In graph theory, a graph G is defined by a set of vertices (nodes) and edges, i.e. $G = (V, E)$, where V denotes a finite set of vertices and E denotes the set of edges between them, with E a subset of the Cartesian product set $V \times V$ of pairs of distinct nodes. G is used to represent the conditional dependencies between the nodes; specifically, each edge represents a conditional dependence relationship. No edge is said to exist between nodes i and j if and only if nodes i and j are conditionally independent given all other nodes. A pair of nodes V_i, V_j is said to be connected by a directed edge if $V_i \rightarrow V_j$. The pair is said to be connected by an undirected edge if both $V_i \rightarrow V_j$ and $V_j \rightarrow V_i$. A subgraph of G is a graph whose set of vertices $A \subseteq G$ and including all edges ij such that $ij \in E$ (Lauritzen, 1996). For further details concerning mathematical properties and theory, we refer the reader to (Lauritzen, 1996; Pearl, 1988).

2.3. Application of mathematical definitions to brain connectivity

The theory of graphical models has been successfully adapted to represent brain connectivity networks. Based on graphical models, each node corresponds with a random variable (Lauritzen, 1996). Therefore, when using graphical models to represent the structural or functional connectome, the brain may be represented as a graph, where the set of nodes (V) may be composed of brain regions or voxels (on a macroscopic level) or individual neurons (on a cellular level). Depending on the data type, the edges (E) representing conditional dependencies between brain regions, voxels, or neurons are then estimated to represent either structural or functional connections.

Whether a network is modeled by directed and undirected edges depends on the neurological application. If a pair of regions/voxels/neurons are connected by a directed edge, then this indicates a causal relationship between the nodes. However, since most brain connections are reciprocal, many graphical models of brain networks utilize undirected edges (Felleman and Van Essen, 1991; Kaiser and Hilgetag, 2006; Sporns et al., 2004), which represent non-directional associations between regions. If edge directionality is desired, estimators such as Granger causality, structural equation modeling, or partial directed coherence are commonly

used (Bullmore and Bassett, 2011). In comparison, edges in undirected graphs may be estimated using simple correlation, partial correlation, mean phase coherence, synchronization likelihood, phase lag index (PLI), mutual information, Gaussian graphical models, and many other estimation methods (Table 1). These measures vary in their sensitivity to linear/nonlinear associations and nonstationarities in time-series data, and should be chosen based on the nature of data. Edges may be estimated to take on either binary values (unweighted), in which each edge exists or not, or weighted edges, in which weights for physical distance or the strength of functional or structural connectivity between nodes are provided.

2.4. What do node and edges represent?

As mentioned in Section 2.3 and Table 1, edges may be estimated using any of the range of association measures described to represent either structural or functional connectivity (Bullmore and Sporns, 2009). Structural (anatomic) connectivity is commonly based on structural MRI covariance or diffusion tensor imaging (DTI) (Alexander-Bloch et al., 2013; Bernhardt et al., 2013). Structural connectivity may also be studied at a synaptic level using cell cultures or simulated neuronal models. Functional connectivity reflects interregional neuronal interactions, and is commonly based on the temporal correlation between signals from different brain regions, including functional connectivity MRI (fcMRI), intracranial EEG (icEEG), surface EEG, or magnetoencephalography (MEG). In order to construct a brain graph, the nodes of the graph are typically defined first. In time-series data, such as EEG or fMRI, where each node is associated with multiple data values, graphs can be estimated on a subject-level basis. In other cases, if each node consists of a single attribute, only group-level graphs can be constructed. This is, for example, often the case in structural MRI, as studies to date have primarily considered cortical thickness or grey matter volume as the random variable at each node (Alexander-Bloch et al., 2013). DTI is a special case in that edges are not based on covariance estimation between data at the nodes. Rather, the edges themselves comprise the data; the probability of axonal connections between two regions may be estimated using probabilistic tractography, or the volume of the tract or any measure of anisotropy between two regions may be estimated using deterministic tractography.

Table 1 compares common nodes and edges specified by the various modalities employed in TLE graph theory research, and advantages and disadvantages of each modality. Although these are the most commonly encountered association measures in TLE graph theory research to date, they should not be interpreted as the only association measures that may be used. Rather, the choice of association measure is data-dependent. Exploratory data analysis is warranted to identify nonlinearity, the need to account for effects from other nodes, or whether the number of data samples allows for identification of stationary or nonstationary associations. For example, it has been recommended, in fMRI blood-oxygenation level dependent (BOLD) time-series data, that if the number of time points is about one order of magnitude greater than the number of nodes used, then stationary rather than non-stationary association measures should be used (Bullmore and Bassett, 2011).

2.5. Estimating brain topology based on graphs

After conducting statistical inference to estimate edges, a large number of topological network properties can be defined based on edge properties (the number of edges directly connected to a given region, the shortest distance between two regions, etc.). Based on the mathematical formulations of these quantities, each metric has an interpretation which characterizes a specific property of the brain network of interest. A summary of the interpretations of commonly utilized measures in TLE graph theory research, as well as a glossary of common graph theory terms, is provided in Table 2. Fig. 1 provides a schematic illustrating a basic approach to quantitating brain topology using these metrics, based on the nodes and edges described in Table 1.

Two basic metrics used to characterize brain networks are (1) the clustering coefficient (γ), which measures the local cliquishness between nodes as an index of network segregation, and (2) the characteristic path length (λ), which measures the global connectivity between nodes as an index of network integration. These two metrics are used together to distinguish between three classes of graphs: regular, small-world, and random (Watts and Strogatz, 1998) (Fig. 2). A random graph is defined by low local cliquishness and high global integration (i.e., small γ , short λ). A regular graph has the least amount of randomness, and has high local cliquishness with low global integration (i.e., large γ , long λ). A small-world graph falls between these two, defined by high local cliquishness as well as global integration (i.e., large γ , short λ) (Watts and Strogatz, 1998). A small-world network is considered to be the most efficient network topology, balancing both network integration and segregation (Bullmore and Bassett, 2011), and characterizes the normal human brain (Achard et al., 2006; Bernhardt et al., 2011; Sporns et al., 2004; Sporns and Zwi, 2004). However, different patient populations may tend towards more random or regular topologies within the range of small-worldness. Regular topologies have been associated with decreased global efficiency and vulnerability to targeted attack in comparison to small-world topologies, whereas random topologies have been associated with decreased local efficiency (Achard and Bullmore, 2007; Achard et al., 2006; Bernhardt et al., 2011). It has been noted that, in contrast to neurological conditions such as Alzheimer's disease and brain tumors that have a loss of small-world architecture (Stam et al., 2007), in epilepsy the more pathological (ictal) state is more small-world in nature than the less pathological (interictal) network configuration (Ponten et al., 2007).

3. Graph topology of epileptogenic networks using different modalities

Below, we summarize graph theoretic studies pertinent to elucidating the network structure of TLE, with an aim of synthesizing current understanding on topological changes associated with TLE pathophysiology. To provide a framework for which multi-modal findings can eventually be integrated, we review these studies by modality, and discuss their relevance toward TLE pathophysiology in the subsequent section.

3.1. Structural MRI

Brain graphs constructed from structural MRI cortical thickness measurements are able to evaluate altered cortical reorganization by estimating cortical covariance. Using such

methods, increased path length and clustering coefficient (i.e., decreased global integration and increased local cliquishness) have been reported in TLE compared to controls, indicating a more regularized interictal configuration within the spectrum of small-world networks. An altered distribution of structural network hubs has also been identified. Hubs with greater than average betweenness centrality (a measure of “hub-ness”, see Table 2 for definition) were identified in the multimodal association areas and evenly distributed across all cerebral lobes in controls, but located primarily in the paralimbic and temporal association cortices in TLE (Bernhardt et al., 2011).

3.2. DTI

In contrast to structural MRI, graphs constructed from DTI tractography show increased path length and decreased clustering coefficient in frontal and temporal lobe epilepsy (Vaessen et al., 2012). Evidence of structural reorganization of the limbic system in mTLE has also been identified, with an overall reduction in limbic connectivity and increased limbic network cliquishness. The insula, superior temporal lobe, and thalamus were found to have increased clustering coefficient, as well as increased nodal efficiency and degree. In comparison, the hippocampus experiences decreased clustering coefficient and efficiency in TLE, although with an overall increased nodal degree (Bonilha et al., 2012).

3.3. FcMRI

FcMRI studies have shown that TLE retains small-world topology, although with decreased clustering coefficient compared to controls (Liao et al., 2010; Vlooswijk et al., 2011), implying sparser local brain connections and a decreased level of functional segregation in the brain. Meanwhile, characteristic path length has been reported to be both decreased (Liao et al., 2010) and increased (Vlooswijk et al., 2011) using fcMRI. Investigation of regional connectivity changes has revealed that, consistent with the known structural and functional connectivity between the default mode network (DMN) and temporal lobe (Buckner et al., 2008; Kobayashi and Amaral, 2003), many topological changes in TLE are present within the temporal lobe and DMN. Such changes include reduced functional connectivity between the posterior cingulate gyrus and bilateral hippocampi, as well as decreased intrinsic connectivity, measured through mean absolute correlation, within the ipsilateral hippocampus and parahippocampal gyrus (James et al., 2013). Evidence of both decreased and increased connectivity has been found throughout the TLE network, including decreased connectivity in several regions within the frontal, parietal, and occipital lobes, and increased connectivity in several regions within the medial temporal, frontal, and between the parietal and frontal lobes (Liao et al., 2010). Significant regional differences in local connectivity, measured through clustering coefficient, have also been identified which were not restricted to any particular lobe or network (Vlooswijk et al., 2011). Findings of both decreased and increased connectivity suggest that network level changes in TLE may be disruptive or compensatory, and confirm involvement of extratemporal structures in TLE. FcMRI has also identified an altered distribution of functional brain hubs in the DMN, with decreased nodal degree in several DMN regions including the posterior cingulate and precuneus, as well as the opercular inferior frontal gyrus and precentral gyrus, compared to controls (Liao et al., 2010). Overall, graph theory models of the functional connectome have demonstrated their ability to capture the altered TLE network structure, achieving about

84% classification accuracy in distinguishing TLE from controls using edge estimates and measures of hemispheric asymmetry (Zhang et al., 2011).

3.4. Surface EEG

The ability to perform subgraph analysis in graph theory can reveal network topology corresponding with regional differences in pathology. In left TLE, increased interictal clustering coefficient and small-world index, constituting a trend toward a more regular network, were observed in the θ -band of surface EEG recordings, primarily in the parietal and central electrodes. In comparison, the α -band showed a decreased clustering coefficient and small-world index, constituting a trend toward a more random network, in the frontal and occipital electrodes (Quraan et al., 2013). In patients with temporal or neocortical extratemporal epilepsy, interictal increases in clustering coefficient and characteristic path length were found (i.e., decreased global integration and increased local connectivity) compared with controls in all EEG frequency bands except the α -band (Horstmann et al., 2010). In another study on children with partial epilepsy, degree centrality, path length, clustering coefficient, betweenness centrality, closeness centrality, and eigenvector centrality were not found to significantly differ from controls. However, multivariate prediction models based on these variables were able to correctly distinguish partial epilepsy patients from controls with a high sensitivity and specificity (van Diessen et al., 2013).

3.5. IcEEG

In intra-operative electrocorticography (ECoG) recordings of TLE patients under propofol sedation, interictal PLI functional connectivity, clustering coefficient, and small world index were inversely correlated with TLE duration in the broad frequency range (0.5–48 Hz) (van Dellen et al., 2009). Network analysis of the presumed epileptogenic zone, as identified by high frequency oscillations (HFOs) in depth electrode recordings, showed a negative correlation of the amount of HFOs, particularly fast ripples, with a hub-measure (eigenvector centrality), suggesting a functional isolation of the epileptogenic zone in the interictal state (van Diessen et al., 2013). Interestingly, this association was not found for spikes. Betweenness centrality has also been found to reliably identify the epileptogenic zone in ECoG as confirmed by post-surgical seizure freedom (Wilke et al., 2011). Such studies are relevant in defining a role for graph theory based methods in localizing the epileptogenic zone during the epilepsy surgery workup. Graph theory measures of centrality may be of particular utility for localization, based on their ability to identify hubs central to the epileptic network (Table 2).

IcEEG studies in TLE have determined a further increase in regularity (higher clustering coefficient and characteristic path length) during the ictal compared to interictal phase (Kramer and Cash, 2012; Ponten et al., 2007). Studies have also found decreased synchronization interictally, followed by an ictally increased synchronization which culminates immediately prior to seizure termination (Ponten et al., 2007; Schindler et al., 2007).

3.6. MEG

In patients with temporal or neocortical extratemporal epilepsy, MEG has demonstrated a more regular interictal network in the δ -band (Horstmann et al., 2010). Increased θ -band edge weight correlation was associated with a higher total number of lifetime seizures based on a study of patients with frontal or temporal lobe epilepsy secondary to glioma (Douw et al., 2010), suggesting an association of increased synchronizability with seizure frequency and supporting the association of hypersynchronizability with axonal sprouting in TLE (Sutula et al., 1989).

3.7. Mouse models

In a mouse model of neocortical epilepsy, serial fcMRI and DTI at one, three, and seven weeks following seizure induced by tetanus toxin injection showed an increase in clustering coefficient and path length compared to controls over time, which returned to baseline at ten weeks along with improvement in seizures. These findings suggest a more regular epileptic network topology compared to that found in non-epileptic networks. Changes were associated with increased intra-hemispheric and reduced interhemispheric functional connectivity, identified by fcMRI, as well as a distributed reduction in white matter connectivity not restricted to the epileptic focus, identified by DTI (Otte et al., 2012).

3.8. Simulated neuronal models

Simulated neuronal models can be used to examine network changes in connectivity on an individual neuron level, in order to understand the significance of topological results found from large-scale modalities such as neuroimaging and neurophysiology. Using small-world neuronal models of excitatory neurons, a change in the neuronal firing pattern from normal to seizure-like to bursting behavior has been observed as neuronal network configurations change from regular to small-world to random. In these small-world networks, long-range connections were found to carry the wave of neuronal activity to distant parts similar to a seizure spread. However, over time, these waves tended to annihilate each other due to local cliquishness. In more random, locally disconnected networks, characterized by a drop in the clustering coefficient, spread of neuronal activity was found to occur faster than the waves could self-annihilate, leading to bursting behavior. Based on these findings, the authors have argued that, as opposed to the generally held viewpoint, a hypersynchronous network may not lead to seizures, but rather to bursting behavior (Netoff et al., 2004). In another simulated neuronal model, simulations of addition/removal of mossy fibers and hilar neurons has allowed for evaluation of the effect of different degrees of sclerosis on network topology. Such simulations on rat dentate gyrus sclerosis have found that, initially and during the majority of the sclerotic process (<90% of hilar neurons removed), there is an increase in small-world index due to a decrease in path length (enhancement of long-range connectivity) and increase in clustering coefficient (enhancement of local connectivity). The major topological determinant during submaximal sclerosis was mossy fiber sprouting, which compensates for hilar neuron loss and leads to the decrease in path length (increase in global connectivity), despite the loss of many long-range hilar connections. Only in the last stages of sclerosis does path length sharply increase, due to the loss of the last hilar neurons, while clustering coefficient decreases, leading to a decrease in small-world index.

Examination of isolated excitatory and inhibitory networks revealed that the decrease in path length during submaximal sclerosis is primarily responsible for the increase in network hyperexcitability during the initial stages of sclerosis, while the increase in path length in the final stages of sclerosis is responsible for the decline in network hyperexcitability (Dyhrfeld-Johnsen et al., 2007).

Using a two-dimensional small-world lattice of Hindmarsh-Rose thalamocortical neurons, another study has also shown that a larger number of long-range connections in small-world networks is conducive to seizures. Increases in the relative number of long-range compared to local connections caused synchronization to change from a local phase model, where synchrony decreases with larger neuronal distances, to a global model where phase synchrony is not dependent on neuronal distance. The authors have theorized that the shift in balance to a global phase synchrony model conducive to seizures may be attributable to axonal sprouting, in which spurious glutamatergic connections are created in reaction to brain injury. These new glutamatergic connections cause the chance of seizures to increase, due to hyperexcitability in addition to increased long-range connections (Percha et al., 2005).

3.9. Cell cultures

Brief exposure of hippocampal neuronal cultures to glutamate has been found to cause epileptic activity (Sun et al., 2001) through hypersynchrony and more frequent bursting of neurons that survive glutamate injury (Srinivas et al., 2007). A loss of small-worldness, caused by a decrease in clustering coefficient but no change in path length, was found in glutamate-injured hippocampal networks (Srinivas et al., 2007). This change in clustering coefficient is supported by findings from simulated neuron models that a drop in clustering coefficient corresponds with the neuronal bursting associated with epileptic discharges (Netoff et al., 2004).

4. Discussion

4.1. Study similarities and dissimilarities

Several consistent aspects of abnormal network reorganization have been elucidated using a graph theory approach to TLE. First, small-world topology is maintained in TLE (Bernhardt et al., 2011; Liao et al., 2010; Vlooswijk et al., 2011). This indicates that small-world topological characteristics are preserved in TLE networks, including high prevalence of cliques and a majority of nodes being inter-connected by short paths. Second, within the range of small-world topologies, a more regularized interictal network topology is present (Bernhardt et al., 2011; Horstmann et al., 2010). Consequently, although small-world topological characteristics are preserved in TLE, a fewer number of nodes are connected by short paths than in healthy control brain networks. Based on subgraph analysis of surface EEG data, these levels of regularity may differ across lobes, as well as across different functional networks represented by different EEG frequency bands (Quraan et al., 2013). Third, the interictal state in TLE is characterized by increased characteristic path length, indicating decreased global integration. This is supported by both structural (Bernhardt et al., 2011; Vaessen et al., 2012) and functional (Horstmann et al., 2010; Otte et al., 2012;

Vlooswijk et al., 2011) neuroimaging and neurophysiological modalities. Fourth, both structural MRI and fMRI have identified a redistribution of hubs in TLE, with structural MRI finding that hubs become less evenly distributed across all four cerebral lobes and more concentrated in paralimbic and temporal lobe regions (Bernhardt et al., 2011), and fMRI showing that several hubs, including the opercular inferior frontal gyrus and precentral gyrus, as well as the DMN posterior cingulate and precuneus, become much less prominent in TLE (Liao et al., 2010). Finally, seizure propagation is regulated by the relative contributions of long-range neuronal connections and local segregation to seizure spread and annihilation, respectively (Dyhrfjeld-Johnsen et al., 2007; Netoff et al., 2004; Percha et al., 2005).

Along with these consistent findings, we identify one main discrepancy in current TLE graph theory literature. There has been a large amount of variation in conclusions regarding the direction of alteration in clustering coefficient for the TLE network, with both increases (Bartolomei et al., 2013; Bernhardt et al., 2011; Bonilha et al., 2012; Horstmann et al., 2010) and decreases (Liao et al., 2010; Vaessen et al., 2012; Vlooswijk et al., 2011) identified. Neuronal graph theory models have shown that clustering coefficient increases during the majority of the sclerotic process, and decreases in the final stages of sclerosis (Dyhrfjeld-Johnsen et al., 2007). Although such pathological differences may partially account for inter-study differences in clustering coefficient, heterogeneity in sample size, study population, and anti-epileptic drug (AED) regimens must also be considered. The impact of these factors on network topology remains relatively unexplored. Intermodality differences in spatial resolution should also be considered. For example, given the higher microstructural sensitivity of DTI compared to structural MRI, findings of decreased/increased clustering coefficient in DTI/structural MRI, respectively, may reflect chronological differences in microstructural and macrostructural changes. Additionally, mean estimates of clustering coefficient have been shown to possess a high positive correlation with the sample variance of the clustering coefficient (Cardanobile et al., 2012), leading studies based on networks with high clustering coefficient sample variance to have higher mean clustering coefficient estimates. Thus, inter-study differences in mean clustering coefficient may also be partially attributable to differences in the variance of the clustering coefficient, and future work is needed to separate these effects.

Additionally, although characteristic path length has quite consistently been observed to be interictally increased in TLE based on fMRI, DTI, icEEG, surface EEG, MEG, and structural MRI, one fMRI study (Liao et al., 2010) has observed an interictal decrease in characteristic path length. The particular TLE subpopulation examined in the discrepant fMRI study may play a role in the difference in the direction of altered path length identified. In particular, this study was based solely on bilateral mTLE patients, whose network topology may differ from that of lateralized TLE patients primarily considered in the other studies.

4.2. Relationships of current knowledge to TLE pathophysiology

By providing a consistent model for network structure whose properties may be quantitated and compared independent of modality, graph theory has demonstrated its ability to provide

a unifying analytical technique across multiple modalities (neuroimaging, neurophysiology, neuronal/simulated models), scales (cellular, microstructural, macroscopic), and network types (structural or functional). Below, we discuss the relevance of graph theory findings across the various modalities utilized to study TLE for pathophysiology, including ictogenesis, ictal propagation, and the interictal state.

4.2.1. Ictogenesis—The major contribution of TLE graph theory research to ictogenesis is consistent demonstration of network reconfiguration, associated with decreased network robustness against pathological attack or neuronal dysfunction. This suggests a mechanism for the kindling model of ictogenesis, in which repeated focal stimulation by recurrent seizures is thought to lead to increased predisposition to epilepsy. Specifically, graph theory has consistently revealed an interictal network configuration which, while still small-world, bears a more regular configuration compared to healthy controls (Bernhardt et al., 2011; Horstmann et al., 2010; Liao et al., 2010; Quraan et al., 2013; Vlooswijk et al., 2011). In addition to a more regularized network configuration, redistribution of network hubs toward the temporal lobe and paralimbic association cortices in TLE (Bernhardt et al., 2011) may also provide an environment conducive to ictogenesis. In graph theory, robustness of a network to attack is typically assessed by measuring the ability of the graph not to fragment into subgraphs when nodes are removed either randomly (“random attack”) or based on degree centrality (“targeted attack”). Based on this method of assessing robustness, an association between network regularity and reduced network tolerance to pathological attack has been shown (Achard et al., 2006; Bernhardt et al., 2011). Computational modeling has also shown that hyperconnected hubs are involved in epilepsy pathophysiology (Case and Soltesz, 2011). Networks with hyperconnected, high-degree hubs such as the temporal lobe and paralimbic cortices (Bernhardt et al., 2011) are less robust to attack, since these networks are less able to remain connected when a large number of nodes are removed (Cabral et al., 2012). In the context of epileptogenicity, increased likelihood of graph fragmentation in the event of attack, such as stroke or excitotoxicity, would lead to the loss of the normally traveled routes of neuronal neurotransmission and the forcing of abnormal synaptic reorganization. It is interesting to speculate that this finding of increased network regularization, composed of increased clustering coefficient and characteristic path length, may arise in the latent period, possibly initially as a compensatory increase in local connections in response to an elimination of long-range connections in early injury. The decreased network robustness to attack induced by this network configuration may then predispose patients to go on to develop epilepsy, due to abnormal synaptic reorganization induced by graph fragmentation.

A second main contribution of current graph theory research to ictogenesis is from a machine learning perspective, in demonstrating the potential utility of network topology to predict the epileptogenic zone and interictal to ictal transition. Redistribution of network hubs, identified through structural MRI and fMRI, has identified that regions in the paralimbic and temporal cortices undergo connectivity changes to become part of the epileptogenic zone (Bernhardt et al., 2011), with the DMN becoming less central as a hub region (Liao et al., 2010). The relevance of hubs as a reliable biomarker of the epileptogenic zone has been shown using electrocorticography (Wilke et al., 2011), implicating their

potential clinical relevance in pre-surgical assessment. Topological network parameters, such as regularity and synchronizability, have also shown possible utility as feature inputs into machine learning algorithms to predict the interictal to ictal transition. Specifically, icEEG findings during the ictal period have demonstrated increased regularity during the ictal phase (Kramer and Cash, 2012; Ponten et al., 2007), as well as a change from low interictal to high ictal spatial synchronization, which reaches a maximum immediately prior to seizure termination (Ponten et al., 2007; Schindler et al., 2007). Further ictal reduction in network robustness to targeted attacks (Achard et al., 2006; Bernhardt et al., 2011) due to ictally increased regularity may induce vulnerability to network fragmentation, and consequently global dysfunction, during the seizure. With the development and approval of implantable responsive neurostimulation (RNS) devices, improved prediction algorithms capitalizing on graph analytic techniques can theoretically result in better seizure control.

4.2.2. Ictal propagation—Graph theory research has suggested that seizure propagation may be regulated by the the balance between local cliquishness, which tends to annihilate epileptogenic waves, versus global connections, which tend to carry waves to distant parts of the network (Netoff et al., 2004; Percha et al., 2005). Mossy fiber sprouting, associated with hypersynchronizability in TLE (Sutula et al., 1989) and found using graph theory to lead to an increase in long-range connections (Dyhrfeld-Johnsen et al., 2007), are potentially responsible for the shift in balance to a global phase synchrony model conducive to seizure propagation. Regional differences in the balance between local cliquishness and global connections may provide the environment responsible for the observed common mode of seizure propagation from the initiating temporal lobe → ipsilateral frontal lobe → contralateral frontal lobe → contralateral temporal lobe. However, individual variations in seizure propagation have been observed, including cases in which seizure activity does not involve the contralateral temporal lobe, or involves the contralateral temporal lobe prior to involving the frontal lobes (Lieb et al., 1991). One hypothesis for understanding these individual variations, which arises from graph theory, is that of different spatial patterns of local cliquishness and longrange connections, which would be expected to lead to different modes of seizure propagation. A graph theoretical approach is particularly useful for investigating individual variations in seizure propagation, by providing a non-invasive method of quantifying regional differences in hypersynchrony, as well as a consistent analytical platform for combining cross-modality findings with different spatiotemporal resolution. Relative levels of local cliquishness and global connectivity also demonstrate their relevance to ictal propagation by predicting development of hyperexcitability: during initial stages of sclerosis, when network hyperexcitability increases, both characteristic path length and clustering coefficient are increased, whereas the final stages of sclerosis, when network hyperexcitability decreases, are characterized by a sharp increase in characteristic path length with simultaneous decrease in clustering coefficient (Dyhrfeld-Johnsen et al., 2007).

4.2.3. Interictal state—Exposure to glutamate and other excitatory amino acids during prolonged seizures is thought to mediate seizure-induced cell death (Choi, 1988; Sun et al., 2001). Graph theory studies of hippocampal cell cultures indicate that, from a network perspective, glutamate-induced changes to connectivity are characterized by a drop in

clustering coefficient but no change in characteristic path length (Srinivas et al., 2007), indicating that local but not global connectivity is affected by glutamate injury. By affecting the balance between local cliquishness and long-range connections, these networks would be expected, based on contributions of these factors to seizure annihilation and spread, to experience increased seizure activity. This is supported by *in vitro* models of epileptogenesis induced by glutamate exposure to hippocampal neurons, which found that glutamate exposure causes the remaining surviving neurons to develop an epileptogenic phenotype, characterized by high-frequency spike firing and spontaneous epileptiform discharges (Sun et al., 2001). The local effect of glutamate excitotoxicity on hippocampal connectivity also supports histological evidence that electrical stimulation of the perforant pathway to the hippocampus produces only local injury to dentate hilar cells (Sloviter, 1983), in addition to endfolium sclerosis being the only pathology apparent in some TLE cases (Margerison and Corsellis, 1966).

Longer epilepsy duration has been found to be associated with network randomization, involving a gradual decrease in clustering coefficient. This change in network configuration is thought to result from randomization of local connections over time (van Dellen et al., 2009). This may be a result of cell loss, as has been described in brain tumor patients (Bartolomei et al., 2006), or increasing sclerosis, which causes similar decreases in clustering coefficient (Dyhrfjeld-Johnsen et al., 2007). Given the vulnerability of regularized networks toward fragmentation, we speculate that randomization over time may also be a compensatory response to the regularized TLE network. In general, however, more random network topology leads to decreased local efficiency (Achard and Bullmore, 2007), which may contribute to the more pronounced cognitive decline observed in TLE patients with more severely decreased levels of clustering coefficient (Vaessen et al., 2012; Vlooswijk et al., 2011).

Previous non-graph theoretical volumetric research has identified an association between hippocampal atrophy in TLE with limbic system atrophy, including the parahippocampal region, cingulate gyrus, basal forebrain, thalamus, medial orbitofrontal areas, and insula (Duzel et al., 2006). From DTI graph theory models, increased limbic network cliquishness, indicating increased structural segregation within the limbic system, has been identified along with overall decreased intra-limbic network connectivity (Bonilha et al., 2012). This suggests that limbic system atrophy (decreased connectivity) in TLE may be accompanied by increased local fragmentation (increased clustering coefficient). In comparison, DTI findings of decreased hippocampal clustering coefficient, along with overall increased hippocampal nodal degree (Bonilha et al., 2012), suggests decreased structural segregation of the hippocampus from the rest of the network, due to a decrease in local white matter connections in conjunction with increased, possibly compensatory, non-local connections. This restructuring was shown to result in an overall functional decrease in local efficiency. We postulate that the primary mechanism of dentate hilar cell loss in TLE (Margerison and Corsellis, 1966) may be responsible for compensatory formation of abnormal connections in areas such as the insula, superior temporal lobe, and thalamus. These abnormal connections may lead to higher local connectivity between adjacent structures, and consequently increased epileptogenic excitation.

5. Limitations of graph-theoretical approach

There are certain limitations particular to graph theory analysis. Although a graph theory approach allows for examination of changes in network, regional, and neuronal connectivity, it does not evaluate certain aspects of TLE pathophysiology, including changes in neuronal membrane or metabolic properties, or changes in ion or neurotransmitter concentration. Corroboration of graph-theoretic with more traditional analytic methods remains to be better clarified. For instance, increased intra-temporal functional connectivity has been described based on graph-theoretic analysis of fcMRI (Liao et al., 2010), whereas reduced intra-temporal functional connectivity has been found using seed-based fcMRI analysis (Bettus et al., 2010; Pereira et al., 2010). In comparing results between modalities, differences in spatial and temporal resolution should be taken into account. Due to limitations in electrode placement for icEEG, graphs constructed from icEEG should be considered as regional rather than whole-brain networks. However, EEG has higher temporal resolution than other modalities such as fMRI, which have high spatial but low temporal resolution, and may provide more accurate estimates of temporal quantities such as hypersynchronizability. Another caution in interpreting graph theory findings is in evaluating whether network changes detected are the cause or consequence of seizures.

There are also some statistical issues worth considering. Due to the large number of hypotheses typically tested in these studies attributable to the large number of edges and graph theory metrics, use of commonly employed multiple comparison procedures may be overly conservative, leading to a potentially high number of Type II errors. One method of dealing with this is use of a two-stage approach, in which the number of tests is restricted *a priori* based on clinical hypotheses or through mean or variance filters (Bourgon et al., 2010). Such filters can decrease the Type II error, although, if not carefully chosen, can cause loss of Type I error control. Therefore, studies should be interpreted in the context of the multiple testing correction procedure utilized, as well as the relative possibility of false negatives or positives. Another issue lies in the utilized method of region delineation if a region-of-interest (ROI) based approach is chosen for defining nodes. If defined regions are composed of multiple voxels, then often the average time course across all voxels is used to represent the time course of the region, which may not necessarily be most representative of the region. ROI delineation is also potentially problematic if based on anatomic boundaries, as there are particular regions for which clear boundaries do not exist (Constable et al., 2013; Scheinost et al., 2012). Other methods of ROI delineation have been proposed, including independent component analysis (ICA)-based ROI delineation (James et al., 2013; Luo et al., 2011; Mankinen et al., 2012); whole-brain functional parcellation based on the time courses themselves (Craddock et al., 2012; Shen et al., 2010, 2013; van den Heuvel et al., 2008), and task-based ROI delineation, in which nodes are defined based on voxel activation in response to a task (Bonelli et al., 2012; Frings et al., 2009). Each of these methods however, has its own disadvantages, including limitations in the number of independent components which can be mathematically identified, difficulty resolving how to apply functional parcellations to groups of patients, and limited numbers of task-activated ROIs, respectively (Constable et al., 2013). Differences in graph construction rules, including choices with respect to binary/weighted networks or thresholding, may also have a

strong impact on the results (Horstmann et al., 2010). One approach is to report only results identified robustly across different construction rules. An alternative approach, called the intrinsic connectivity distribution, has been recently proposed, which requires neither *a priori* region delineation nor the need for arbitrary threshold choices (Scheinost et al., 2012). Statistical methods for enforcing sparsity in the estimated edges, such as the graphical lasso, offer an additional avenue (Friedman et al., 2008; Meinshausen and Bühlmann, 2006).

Another limitation of a graph theory approach relates to the robustness of graph property estimates to the choice of number of nodes. Although N nodes may be chosen to represent the network, the true number of nodes in the network may be greater or less than N , affecting estimates of graph properties. Commonly used models in epilepsy research, such as the Watts-Strogatz small-world model, have been found to retain high correlation in estimated values of graph properties, when evaluated across different numbers of nodes. However, this and many other models, including the Barabási–Albert scale-free model, also have low variability with respect to feature entropy, so that estimation of graph properties may be highly affected by the choice of construction (Cardanobile et al., 2012). Thus, choice of node and graph construction must be considered when evaluating inter-study discrepancies.

6. Conclusions and future directions

One particular need in graph theory applied to TLE research is for additional cell culture studies and simulated neuron models to clarify the significance of topological changes, especially in regards to understanding how identified changes in topology affect vulnerability to seizures, and in order to reconcile with findings from neuroimaging and neurophysiological testing. Correlation with currently existing methods, such histology and immunohistochemistry, is also needed to understand how changes in network topology facilitate or reflect changes in cellular composition. However, even in its current state, graph theory offers a powerful analytical method in characterizing pathophysiological changes of brain topology in TLE.

Overall, a rapidly growing body of evidence highlights the potential role of graph theoretic methods in understanding the network and regional changes contributing to the pathophysiology of TLE. Neuronal plasticity, compensatory restructuring, and alternative neural transmission routes point to the need to consider the entire network when understanding underlying pathophysiology and in considering possible therapies. Graph theory allows for a network perspective on pathophysiology, which complements currently existing methods that consider pathophysiology from a more individual level, such as histology, immunohistochemistry, and electrophysiology. In particular, a graph theoretic approach to pathophysiology provides a method of quantifying both local and global alterations in synchrony and connectivity, taking into account network interdependencies. As we illustrate in this review, it can be applied on a regional or cellular level to any investigational method for which conditional dependence between elements of the brain exist. The altered balance of network integration and segregation in TLE highlights the need for a network perspective in pathophysiology, as well as AED development, as altered interregional neuronal interactions may lead to particular patterns of compensatory

restructuring in response to AEDs. These changes corroborate the increasing evidence that TLE is a network, rather than focal, temporal lobe disorder, and one for which graph theory is of great potential utility.

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HIGHLIGHTS

- Graph theory models of brain connectivity can illuminate aspects of temporal lobe epilepsy (TLE) pathophysiology pertaining to ictogenesis, ictal propagation, and the interictal state from a network perspective.
- A more regular interictal brain network, increased characteristic path length, and redistribution of hubs in TLE, associated with reduced neuronal tolerance to pathological attack, have been consistently identified.
- Integration of multimodal findings calls for additional cell culture and simulated neuron models to highlight the significance of topological changes.

Fig. 1.

Schematic of typical graph theory approach to estimating brain topology. Using the nodes and edges defined in Table 1, an adjacency matrix is constructed based on measures of association between nodes (A and B). The values of the adjacency matrix are used to form a graph of the brain network nodes and edges (C). Using the set of estimated edges, estimates of brain topology characteristics can then be calculated (D–F). To illustrate, in (D), the square node has a clustering coefficient of $1/3$, which is calculated as the ratio of the number of existing (two) to possible (six) connections between its direct neighbors. In (E), the characteristic path length between the square and triangle nodes is the length of the shortest path between them (two). In (F), we show an example of two sets of interconnected nodes, or modules, which are connected by the square hub.

Fig. 2.

(a) Regular, (b) small-world, and (c) random network configurations. These are defined by the ratio of local to global connections. Characteristic path length, shown as a dotted line, between the two square nodes is longest (three edges) in (a) and shortest (one edge) in (b) and (c). γ = clustering coefficient, λ = characteristic path length.

Table 1

Common nodes used and relative advantages and disadvantages of various modalities analyzed by graph theory.

	Common nodes used		Commonly used association measures for edges	Advantages		Disadvantages	
Structural MRI	1	Cortical thickness	Co-variance	Grey or white matter		For approaches (1) and (2), correlation matrices can only be constructed on the group level, and are therefore unable to assess single patients for diagnostic or predictive utility	
	2	Subcortical grey matter volumes					
	3	Voxel cubes					
DTI	Voxels or regions		Volume of voxels in tracts connecting regions, fiber density	1	Deep white matter tracts	1	Unreliable tracing of corticocortical white matter tracts due to low diffusion anisotropy
				2	Provides structural correlations which can be constructed on the single subject level	2	Underestimates probability of connections between regions that are far apart in the brain
FcMRI	Resting state BOLD time series		Correlation	High spatial resolution		1	Low temporal resolution
						2	Possible physiological artifacts
						3	Assumes hemodynamic response as a proxy for neuronal activity
Surface EEG	Resting state electrode recordings for different frequency bands		Synchronization likelihood, phase lag index, mean phase coherence	1	High temporal resolution	1	Low spatial resolution
				2	Able to study ictal networks	2	Spurious correlations may be introduced by active reference electrode
						3	Non-cerebral artifacts due to volume conduction
IcEEG	Electrode recordings for different frequency bands		Synchronization likelihood, phase lag index, directed transfer function	1	Directly measures neuronal activity	1	Ethical limitations – lack of healthy controls for comparison, due to the need for invasive electrodes implanted in the brain
				2	High temporal and spatial resolution		
				3	Able to study ictal networks	2	Unable to perform whole brain network analysis
MEG	MEG channels for different frequency bands		Phase lag index, cross-correlation, mean phase coherence	1	High temporal and spatial resolution	Movement artifacts	
				2	Less susceptible to brain inhomogeneities		

	Common nodes used	Commonly used association measures for edges	Advantages	Disadvantages
Cell cultures	Electrode spike timing recordings	Cross-covariance	Able to simulate experimental conditions	Does not replicate complete connectivity of the biological network
Simulated models	Neurons	Number of connections to a postsynaptic population from a single presynaptic neuron	Able to simulate experimental conditions	Does not replicate complete connectivity of the biological network

Table 2

Common graph theory definitions in TLE graph theory research.

Definition	
Assortative network	Network in which hubs tend to connect to each other. Assortativity is most commonly measured using the <i>assortativity coefficient</i> or <i>neighbor connectivity</i>
Assortativity coefficient	Calculated as the Pearson correlation coefficient of degree between pairs of linked nodes. Positive values indicate nodes with similar degree; negative values indicate nodes with dissimilar degree. Measures the propensity of nodes to connect to others with similar degree
Betweenness centrality	Calculated as the number of all geodesics (shortest paths) in a network that pass through a given node, divided by the total number of geodesics in the network. Provides a measure of the node's importance. Nodes with high betweenness centrality are located on highly traveled paths
Characteristic path length	Calculated as the average number of edges along the shortest distances between all possible pair of network nodes. Lower characteristic path length indicates higher level of global network integration. Measure of long-distance connectivity, as well as network's ability for serial information transfer
Clique Closeness centrality	A subset of nodes such that an edge exists between each pair of nodes in the subset Calculated as the inverse of the sum of the distance of a node <i>i</i> to all other nodes. Measure of how long it takes for information to spread from a given node to others in the network
Clustering coefficient (local)	Calculated as the number of edges between the nodes within the neighborhood of a given node, divided by the total number of possible edges between the nodes in the neighborhood. Measure of how close a given node's neighbors are to forming a clique
Clustering coefficient (network)	Calculated as the mean local clustering coefficient, averaged over all nodes in the network. Measure of the degree to which regions cluster, providing measure of local connectivity
Degree centrality (degree)	Calculated as the number of edges directly linking a node to other nodes in the network. Higher degree centrality indicates regions that are more connected to the rest of the network
Degree distribution	The probability distribution of the degrees in a network
Disassortative network	Network in which hubs tend to avoid connecting to each other (see "assortative network")
Edge weight correlation	Similarity of the weighted connections to one region. High edge weight correlation increases efficiency of information processing, although excessively high edge weight correlations increase epileptogenicity
Eigenvector centrality	The eigenvector centrality of node <i>i</i> is calculated from the <i>i</i> th element of the first eigenvector of the adjacency matrix. Identifies nodes that are connected to highly connected nodes (i.e. nodes that are connected to nodes that are central within the network)
Global efficiency	Calculated as the average of the inverse of the shortest path lengths in a network. Measure of network's ability for parallel information transfer
Indegree	A directed graph measure; calculated as the number of nodes that point to a particular node. Reflects the number of incoming connections to a node
Leverage centrality	Calculated as the ratio of a node's degree relative to the degree of neighboring nodes. Provides a measure of the node's importance, by estimating the extent to which a node's neighbors rely on it for information. Positive leverage centrality indicates that a node is more central to the network than its neighbors and is a "hub," whereas negative leverage centrality indicates that the node is less central than its neighbors
Local efficiency	Calculated as the inverse of the average shortest path connecting the given node with all other nodes. Provides a measure of the efficiency of a given node in communicating with the rest of the brain
Module	A subgraph of nodes which are more strongly connected to each other than the rest of the network. Modules often correspond to different functional aspects of the network
Network hub	Node with degree centrality greater than the average degree of the network. Identifies nodes which mediate many of the short path lengths between other nodes
n-to-1 connectivity	Calculated as the sum of the connectivity degrees between a given node with all other nodes in the network. Measures the amount of information that the given node receives from the rest of the network
Outdegree	A directed graph measure; calculated as the number of edges pointing out of a given node, reflecting the number of outgoing connections. High outdegree identifies nodes that act as sources of information flow
Small world index	Calculated as the normalized ratio of the clustering coefficient to the characteristic path length. Networks with small-world architecture have small-world index >1 , along with clustering coefficient >1 and characteristic path length ≈ 1
Strength (mean absolute correlation)	Calculated as the average of the absolute value of the correlations between a node and all other nodes