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Targeted Review

Network analysis for a network disorder: The emerging role of graph theory in the study of epilepsy

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ABSTRACT

Recent years have witnessed a paradigm shift in the study and conceptualization of epilepsy, which is increasingly understood as a network-level disorder. An emblematic case is temporal lobe epilepsy (TLE), the most common drug-resistant epilepsy that is electroclinically defined as a *focal* epilepsy and pathologically associated with hippocampal sclerosis. In this review, we will summarize histopathological, electrophysiological, and neuroimaging evidence supporting the concept that the substrate of TLE is not limited to the hippocampus alone, but rather is broadly distributed across multiple brain regions and interconnecting white matter pathways. We will introduce basic concepts of graph theory, a formalism to quantify topological properties of complex systems that has recently been widely applied to study networks derived from brain imaging and electrophysiology. We will discuss converging graph theoretical evidence indicating that networks in TLE show marked shifts in their overall topology, providing insight into the neurobiology of TLE as a network-level disorder. Our review will conclude by discussing methodological challenges and future clinical applications of this powerful analytical approach.
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Key questions

1. What is graph theory?
2. What are the main graph theoretical findings in the healthy brain connectome?
3. Is there a consistent pattern of topological alterations in TLE?
4. What are other potential applications for graph theoretical analysis in epilepsy?
5. What are ongoing developments in graph theoretical connectome analysis?

1. Introduction

Epilepsy is one of the most prevalent chronic neurological disorders worldwide, affecting about 1% of the general population. More than one-third of patients with epilepsy present with seizures that are resistant to antiepileptic drugs [1,2], with the majority of them having temporal lobe epilepsy (TLE).

Temporal lobe epilepsy is electroclinically defined as a *focal* epilepsy and has been classically associated with hippocampal sclerosis (HS) [3], a lesion defined by cell loss and gliosis in the hippocampal formation. Magnetic resonance imaging (MRI) investigations of the hippocampus and adjacent mesiotemporal regions have revolutionized the evaluation of patients with TLE, since MRI permits the identification of signs associated with HS in vivo. While surgery can lead to seizure freedom in patients with drug-resistant epilepsy, up to 40% may continue to have postoperative seizures.

Although reasons for seizure recurrence are incompletely understood, it has been increasingly recognized that the pathological substrate in TLE may extend beyond the hippocampus to an interconnected network of multiple limbic and extralimbic brain regions in a considerable patient subgroup. Indeed, consistent evidence from electrophysiology, histopathology, and neuroimaging has suggested a widespread and rarely purely focal pattern of alterations. These results have contributed to an evolving shift in the understanding of focal epilepsy, moving from being caused by focal pathology to being the result of a dysfunction in localized circuits. In fact, the revised 2010 Seizure and Epilepsy Classification by the International League Against Epilepsy defines focal seizures as those originating within limited networks [4].

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In recent years, the hypothesis that TLE may be more adequately described as a network disorder has been fostered by the introduction of graph theory, a mathematical framework to quantify topological properties of complex interconnected systems. A rapidly increasing body of graph theoretical analyses of structural and functional data has provided compelling evidence that not only TLE but also other focal epilepsies show marked alterations in the topology of large-scale networks; moreover, shifts in network topology have been associated with clinically relevant parameters, including disease duration and postsurgical seizure outcome, suggesting a possible utility of topological markers in the diagnostics and management of TLE.

Taking TLE as an example, the current *targeted review* will briefly outline convergent evidence suggesting that prevalent focal epilepsies likely represent system-level disorders of functional and structural networks. We aim to provide our readers an introduction into the most common concepts and parameters of graph theoretical analysis and highlight several noninvasive techniques that offer the possibility of *connectome* analysis. After summarizing main findings in TLE, we will conclude by outlining not only potential challenges but also promises of graph theoretical net assessments in clinical settings.

2. Evidence justifying the study of TLE as a network disorder

The hallmark of drug-resistant TLE is hippocampal sclerosis, a highly epileptogenic lesion characterized by variable degrees of neuronal loss and gliosis in the hippocampus [5]. Concomitant abnormalities include granule cell dispersion [6,7], selective loss of inhibitory neurons [8], and axonal sprouting [9], which may collectively reflect an intense reorganization of neuronal networks. Despite most studies focusing on the hippocampus, postmortem and ex vivo tissue analyses have reported a high prevalence of histological changes in the adjacent amygdala, entorhinal, parahippocampal, and temporopolar cortices [10–12]. Moreover, classic [13] and more recent work has shown histological and architectural changes in several neocortical [14,15] and thalamic divisions [16,17].

The investigation and treatment of TLE have been revolutionized by the advent of MRI, which has become essential in detecting hippocampal sclerosis in vivo. Commonly evaluated MRI markers include quantitative volumetry and T2 signal analysis, which can be used to accurately lateralize structural abnormalities in most patients [18]. Corroborating histopathological reports, atrophy and signal change have been described in adjacent mesiotemporal and temporopolar structures, as well as the thalamus [19–24]. More recently, whole-brain quantitative gray matter assessments, such as voxel-based morphometry and cortical thickness mapping, have shown atrophy in large portions of lateral temporal, frontal, and frontocentral neocortical regions [25–37]. A series of cross-sectional and longitudinal studies have revealed that mesiotemporal thalamic and neocortical atrophy intensify over time [26,37–40]; moreover, patterns of damage may, in part, relate to postsurgical outcome [24,27].

The study of regional gray matter changes has been complemented by assessments targeting interregional *structural connectivity*. In particular, modeling of diffusion-weighted MRI data lends parameters, such as the fractional diffusion anisotropy and mean diffusivity, which are scalar markers of tissue microstructure and architecture at a given voxel. Diffusion tractography – the identification of continuous paths following the preferred diffusion direction through the white matter – furthermore provides an approximate delineation of anatomical white matter pathways. Several diffusion MRI studies have shown altered fractional anisotropy and mean diffusivity in TLE across major bundles, both within and beyond temporolimbic regions, suggestive of a diffuse disorganization in fiber arrangement as well as alterations in axonal membranes [41–46]. Structural networks may also be derived from covariance patterns of morphological MRI markers, such as cortical thickness or regional gray matter volume [25,47–51]. Structural covariance analysis may detect manifestations of persistent functional–trophic crosstalk, maturational interchange, as well as common developmental and pathological influences [48,52–57]. In TLE, several covariance analyses have mapped abnormal structural correlations between mesiotemporal and neocortical regions [25,32,58], between thalamic and neocortical regions [30,59], and within corticocortical networks [59].

In line with pathological and structural data, electrophysiological studies have consistently emphasized the importance of an epileptogenic network, rather than a single region, in understanding focal epilepsies [60–65]. In TLE, while most seizures originate in the hippocampus [66], the epileptogenic network has been shown to often extend to entorhinal, lateral temporal, and inferior frontal cortices as well, together with subcortical nuclei, such as the amygdala and medial thalamus [61,62]. Offering a synoptic view on brain dynamics at a millisecond scale, electrophysiological studies employing electroencephalography (EEG) and magnetoencephalography (MEG) not only have been of high utility in characterizing changes at seizure onset but also could reveal chronic changes in local and distributed activity [67,68]. Notably, studying statistical relationships between time series has been used to evaluate dynamic changes in interregional connectivity; moreover, electrophysiological techniques provide a range of spectral (i.e., frequency-dependent) markers that have the potential to probe tissue epileptogenicity in vivo.

While of a lower spatial resolution than electrophysiological techniques, functional magnetic resonance imaging (fMRI) based on the measurement of blood oxygenation level-dependent alterations in MRI signal (BOLD) offers a high spatial resolution with whole-brain coverage. In recent years, *functional connectivity* has been increasingly studied through the analysis of task-free (also known as *resting-state*) paradigms, a 5- to 10-min long functional MRI acquisition during which the subject does not perform any explicit task [69,70]. In healthy individuals, resting-state networks have been shown to be highly reproducible across subjects [71] and correspond closely to brain systems engaging in specific tasks [72].

In TLE, several resting-state fMRI studies have reported connectivity alterations in multiple intrinsic networks [73]. Decreases in connectivity have been reported within ipsilateral mesiotemporal networks [74,75] between ipsilateral and contralateral hippocampi [76–78] and between mesial and lateral temporal regions [76,77]. Ipsilateral disruptions may co-occur with connectivity increases in contralateral mesiotemporal networks [74,75], suggesting functional reorganization of the less-affected hemisphere. Addressing functional connectivity beyond the temporal lobes, several studies have identified abnormal interactions between mesiotemporal seeds and targets in posterior cingulate, precuneus, inferior parietal, and medial prefrontal cortices [79–82]. Connectivity disruptions in these regions comprising the so-called *default mode network* (DMN) have been confirmed by studies using data-driven network parcellation techniques [83–86] and those placing seeds in nontemporal areas [87]. Default mode network connectivity alterations in TLE likely relate to the important role of the hippocampus in this network [88]; they may relate to reorganization of memory circuits in this condition [89,90]. Complementing these findings, several EEG–fMRI analyses have shown functional changes in DMN regions associated with epileptic spikes [91,92]. Beyond mesiotemporal and DMN networks, resting-state functional connectivity disruptions in TLE have been reported in regions known to be involved in sensory processing [82,85,93] and attention [94], together with subcortical and cerebellar areas [76,79,80,82]. Several studies have suggested an effect of connectivity disruptions on cognition, particularly with respect to memory impairments [95,96]. Furthermore, connectivity disruptions may also be associated with socioaffective difficulties seen in some patient subgroups with TLE [97–99].

Collectively, converging evidence from histology, electrophysiology, and neuroimaging suggests that the pathological substrate of TLE is rarely localized to the mesiotemporal lobe structures. Instead,

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