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Review

Graph theory findings in the pathophysiology of temporal lobe epilepsy

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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.

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.

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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).