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Review

Graph theory and cognition: A complementary avenue for examining neuropsychological status in epilepsy

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ABSTRACT

The recent revision of the classification of the epilepsies released by the ILAE Commission on Classification and Terminology (2005–2009) has been a major development in the field. Papers in this section of the special issue explore the relevance of other techniques to examine, categorize, and classify cognitive and behavioral comorbidities in epilepsy. In this review, we investigate the applicability of graph theory to understand the impact of epilepsy on cognition compared with controls and, then, the patterns of cognitive development in normally developing children which would set the stage for prospective comparisons of children with epilepsy and controls. The overall goal is to examine the potential utility of this analytic tool and approach to conceptualize the cognitive comorbidities in epilepsy. Given that the major cognitive domains representing cognitive function are interdependent, the associations between neuropsychological abilities underlying these domains can be referred to as a cognitive network. Therefore, the architecture of this cognitive network can be quantified and assessed using graph theory methods, rendering a novel approach to the characterization of cognitive status. We first provide fundamental information about graph theory procedures, followed by application of these techniques to cross-sectional analysis of neuropsychological data in children with epilepsy compared with that of controls, concluding with prospective analysis of neuropsychological development in younger and older healthy controls.

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1. Introduction

There has been a spirited debate concerning the benefits and drawbacks of the approach to classifying the epilepsies recently released by the ILAE Commission on Classification and Terminology (2005–2009). While concerned with the classification of the epilepsies, this system and the classification systems before it have had significant implications for the way cognitive and behavioral comorbidities in epilepsy are conceptualized. This is because of the longstanding tradition of examining comorbidities in line with the contemporary classification of epilepsy syndromes. While a reasonable approach, there is growing appreciation that forces other than epilepsy syndrome may be important factors underlying the expression of cognitive and behavioral comorbidities.

In this review, we investigate a novel approach to characterizing the impact of childhood epilepsy on the global landscape of cognition, defined by the interaction of multiple cognitive domains. Given that different cognitive domains are interdependent with each other [1], the associations between the neuropsychological abilities underlying these domains could be referred to as a cognitive network. Thus, the architecture of the cognitive network can be quantified and assessed using formal methods to determine network conformation, i.e., graph theory.

Graph theory is a versatile tool that can be used to probe the topology of any system that can be identified as a network. This methodology has been applied to investigations of electrophysiological and imaging networks, as well as examination of brain structure, that have revealed global disruption in brain architecture and function in patients with epilepsy [2–7]. Large scale structural morphometrical brain changes have been correlated with specific cognitive deficits in epilepsy [8,9]; however, to date, there have been few examinations of neuropsychological measures considered as a cognitive network themselves using graph theory [10,11].

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Graph theory, in essence, can provide a measure of the architectural organization of cognitive function, as defined by the network formed by the interrelationships between multiple cognitive abilities and domains. As such, graph theory is an expansion on conventional statistical approaches such as factor or clustering analyses because it permits the evaluation not only of grouping of cognitive modules but also the participation of cognitive functions/domains within the entire cognitive architecture. For this reason, cognitive networks may provide novel insights into the cross-sectional status and longitudinal changes in cognitive structure, especially in regard to the abnormal conformation that may be driven by pathological. Even though cognitive networks are not individualized measures (i.e., they arise from group-wise correlations), they can be used to infer how individual test metrics may be related to the overall cognitive network under investigation. We wish to emphasize that the cognitive network we will be investigating is based on the specific tests that comprise a conventional neuropsychological battery; therefore, it should not be confused with well-known anatomical/functional cognitive-related brain regions.

Here, we will first provide some fundamental information about graph theory procedures, followed by application of these techniques to neuropsychological data in children with epilepsy compared with healthy controls, concluding with an examination of naturally occurring prospective changes in the cognitive networks of normally developing control participants.

2. Graph theory

Graphs are mathematical representations of complex networks in the form of nodes (e.g., brain regions, cognitive tests) and edges or links (connections or correlations between nodes). Therefore, graph theory is the study of such graphs. There are different kinds of graphs that can be constructed; however, the most common ones in the field of neuroscience are binary and weighted graphs, either undirected (symmetric) or directed (nonsymmetric). Directed graphs are those that convey causality or directionality of effect. For example, directed graphs could be constructed to investigate temporal causality in functional connectivity studies in order to understand the origin and propagation of a temporal signal [12]; therefore, such graphs are nonsymmetric (the *value* of the link or edge from node A to B is not the same as the one from B to A). Undirected graphs are those that reflect the relationship between different nodes or regions without any regard to direction (e.g., covariance analyses of brain structure or function); therefore, these graphs are said to be symmetric (the *value* of the link from node A to B is the same as the one from B to A). When the type of graph is chosen, it can then be investigated using the natural weights of the connections (i.e., correlation coefficient in a fMRI analysis) or by binarizing the matrix (1 if there is a connection; 0 if there is no connection between a pair of nodes) at a given threshold or range of thresholds (see below). The type of graph to use is based on the data and hypotheses of the study under consideration.

The nodes in a graph in the neurosciences could be anatomical regions based on various brain atlases (e.g., AAL, Freesurfer's Desikan Killiany, or Destrieux atlases) or functionally defined areas [13]. The connections between nodes in functional MRI, DTI, or high-resolution structural MRI could convey a network of functional associations, white matter connectivity, or regional covariance (i.e., volumetric analyses), respectively. The nodes and edges form a *NxN* matrix or network, in which *N* is the number of defined nodes. Once nodes are defined and a graph is obtained, thresholding should be performed in order to remove spurious connections. The main types of thresholding are statistical or topological. Statistical thresholding is based on the significance of the connections between nodes, while topological thresholding is based on the strength of the connections between nodes. There are two main ways of performing topological thresholding: absolute thresholding and proportional thresholding. In the former, every connection is included in the graph if it is greater than the specified correlation value, while in the latter, only the strongest links (higher weight) within the chosen percentage value would be included in the graph. For example, in an undirected network (symmetric matrix) of *N* number of nodes, the total possible number of edges or connections would be $N(N\text{-}1)/2$. This means that, for a network of 100 nodes, a proportional threshold of 10% would show 495 edges out of the 4950 possible connections in the fully connected network. Since proportional thresholding provides the same number of links given the same number of nodes under study, group analyses can be possible. For the remainder of this discussion, we will be referring to topological thresholding by performing proportional thresholding, unless stated otherwise. Graph theory measures can be acquired at a certain threshold or over a range of threshold values also known as the sparsity value, density, or cost.

2.1. Graph theory measures

Once a graph is calculated, different measures can be obtained in order to investigate its properties, which include metrics of segregation, integration, and centrality. A graph that shows segregation is one that allows for subgraphs to exist, which might represent specialized processes taking place within the network. An integrated graph is one that is capable of interchanging information between regions in an efficient manner. Centrality measures explain those nodes that play an important role in the configuration of the graph [14]. Some of the most common graph measures that investigate such properties are described below.

2.1.1. Characteristic path length

The characteristic path length is a measure that reflects the average separation between two nodes in the network [15]; therefore, it is a measure that provides information about the level of integration in the graph. However, this measure diverges when nodes in the network are disconnected (have no neighbors), which usually happens at low graph densities. Given that global measures (i.e., global measures of integration) should be acquired over a range of graph densities in order to be certain that the results are not driven by the chosen threshold, results from this metric could be introducing confounding information (if nodes are disconnected). Therefore, for this work, we are using the harmonic mean instead (see below).

2.1.2. Harmonic mean and global efficiency

Harmonic mean, H_m, is a measure of global integration in the graph. It is defined as the inverse of the global efficiency, *E*, which is the average of the inverse of each of the shortest paths (direct connections between nodes) in the network [16]. The lower the values of H_m, the higher the integration of the network; therefore, the higher the graph efficiency. Given that H_m is calculated as the inverse of the global efficiency, which only considers connected nodes, this measure does not suffer from divergence as does the characteristic path length.

2.1.3. Local clustering coefficient and local efficiency

The local clustering coefficient is a measure of local segregation in the network. It is defined as the ratio of the number of connections between each node's neighbors to the total number of connections that would exist between them [15]; therefore, it lies between 0 and 1, with 0 representing no connections between a node's neighbors and 1 having all possible connections. However, local efficiency is a measure based on the shortest paths between each node's neighbors, which reflects how efficient is the communication between the immediate neighbors of a node [16].

2.1.4. Average clustering coefficient and transitivity

The average clustering coefficient is defined as the sum of the local clustering coefficient of each node divided by the total number of nodes in the network. Nodes with a lower number of connections