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Review

The trees and the forest: Characterization of complex brain networks with minimum spanning trees

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ABSTRACT

In recent years there has been a shift in focus from the study of local, mostly task-related activation to the exploration of the organization and functioning of large-scale structural and functional complex brain networks. Progress in the interdisciplinary field of modern network science has introduced many new concepts, analytical tools and models which allow a systematic interpretation of multivariate data obtained from structural and functional MRI, EEG and MEG. However, progress in this field has been hampered by the absence of a simple, unbiased method to represent the essential features of brain networks, and to compare these across different conditions, behavioural states and neuropsychiatric/neurological diseases. One promising solution to this problem is to represent brain networks by a minimum spanning tree (MST), a unique acyclic subgraph that connects all nodes and maximizes a property of interest such as synchronization between brain areas. We explain how the global and local properties of an MST can be characterized. We then review early and more recent applications of the MST to EEG and MEG in epilepsy, development, schizophrenia, brain tumours, multiple sclerosis and Parkinson's disease, and show how MST characterization performs compared to more conventional graph analysis. Finally, we illustrate how MST characterization allows representation of observed brain networks in a space of all possible tree configurations and discuss how this may simplify the construction of simple generative models of normal and abnormal brain network organization.

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1. Introduction: modern brain network analysis

In the history of neuroscience two concepts for understanding the function of the brain have played a major role. The first idea is that the brain consists of many different parts or components and that each of these subdivisions is likely to be responsible for a very specific function. One example of this approach is the work by Franz Joseph Gall, who assigned very specific functions to different regions of the cortex based upon measurements of the overlying skull. This concept of “phrenology” was heavily criticized, but later studies based upon the correlation between brain lesions and cognitive deficits gave a more scientific basis to the notion of functional localization in the brain. In particular, Broca and Wernicke identified brain regions responsible for motor and sensory aspects of language, and Penfield confirmed with intraoperative stimulation experiments a highly specific topographic cortical representation of motor and sensory functions. To a large extent, modern brain imaging studies have been directed at localizing different cognitive functions by identifying the specific brain regions activated during cognitive tasks.

The second idea emphasizes the unitary, integrated nature of brain function, and assumes that higher cognitive functions cannot be meaningfully assigned to any specific part of the brain. This approach is reflected by the criticisms by Flourens on the phrenological work by Gall. Karl Lashley proposed a holistic view of brain function based upon his discovery that memory failure in animal experiments depended on the amount of tissue removed rather than on damage to any specific area. Somewhat similar holistic ideas about brain function were advocated by Karl Pribram. Donald Hebb proposed that the elementary functional units of the central nervous system are cell assemblies. Attempts at strict localization of brain function have been criticized by Uttal, who referred to this type of work as “neophrenology” (Uttal, 2001).

In recent years the controversy between strict localization and holistic views of brain function has resulted in attempts to integrate both aspects in a single framework. Many neuroscientists now think of the brain as a complex network which reflects an optimal balance between “segregation” and “integration” (Sporns, 2013). In addition, it

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has become clear that the complex architecture of brain networks can be studied successfully even in a no-task resting-state (Gusnard et al., 2001). This has led to an increased interest in the study of resting-state functional or effective connectivity, especially with fMRI. However, the complexity of the data obtained in such studies poses new problems for proper analysis and understanding.

An important breakthrough was achieved when graph theory was applied to neuroscience data. Graph theory is a branch of mathematics that describes networks at the most elementary level, as sets of nodes ("vertices") and links ("edges"). Graph theory originated when Euler solved the seven bridge problem of Konigsberg in 1736. Initially, graph theory was mainly used to study relatively small, deterministic networks as a branch of combinatorics. This situation changed and extended to stochastic networks, when social scientists became interested in the study of large networks, and Erdős and Rényi developed the mathematical theory of random networks (Erdős and Rényi, 1960). The latest decisive development was the introduction of the "small-world network" by Watts and Strogatz (Watts and Strogatz, 1998) and the "scale-free network" by Barabasi and Albert (Barabasi and Albert, 1999), which initiated the new field of "network science", the theory of complex networks. The small-world network is a simple model that combines both local connectedness (segregation) and global integration. The scale-free network is a model of a growing network, where a new node connects to existing nodes with probability proportional to their degree. This type of growth, called preferential attachment, results in a scale-free degree distribution, where the probability that a randomly chosen nodal degree D equals k, is a power-law in k, $\Pr[D = k] = c\,k^{-\gamma}$, where c is a normalization constant and the power exponent $\gamma = 3$ (in Barabasi–Albert graphs). Importantly, such networks have a relatively large number of highly connected nodes or hubs. The introduction of small-world and scale-free models gave rise to an explosive growth of modern network studies in a large range of fields, ranging from molecular and genetic networks all the way up to economic and social systems (Estrada, 2011; Van Mieghem, 2014).

Modern network theory has been applied to the study of the brain as well. Both structural and functional networks have been studied in a range of organisms, from *Caenorhabditis elegans* to macaque, cat and human, during development and in health and disease (Bullmore and Sporns, 2009, 2012; Stam, 2010; Stam and van Straaten, 2012; van den Heuvel and Hulshoff Pol, 2010; van Straaten and Stam, 2013). Several important conclusions that have emerged from this rapidly growing field are the following. First, all studies have confirmed that both structural as well as functional brain networks display the typical features of a small-world network. A high level of clustering (connectedness of the neighbours of a node) is combined with a short average shortest path length (number of links in the shortest path from one node to another node). Second, the degree distribution of brain networks is approximately scale-free, which reflects the presence of a large number of highly connected nodes or hubs. Third, these hubs are preferentially connected to each other, forming a so-called "rich club" (van den Heuvel and Sporns, 2011). Fourth, brain networks display a hierarchical modular structure (Alexander-Bloch et al., 2010). Each module is a subnetwork that consists of nodes that are strongly connected to each other, but only weakly to nodes outside the module. Hierarchy is reflected by that fact that modules can often be divided into submodules, and these again into sub-submodules over several levels. Importantly, modules typically correspond to functional systems of the brain. Finally, brain networks display the property of mixing or degree correlations. At the macroscopic level high degree nodes are preferentially attached to other high degree nodes, and low degree nodes to other low degree nodes (assortative mixing). There is some evidence that mixing at the neuronal level is disassortative (Bettencourt et al., 2007). The rich club is a high-degree subgraph with high assortativity.

The topological properties of structural and functional brain networks discovered by modern network science are relevant for understanding the development, normal functioning and pathology of the brain. During normal development the topology changes from random to a more small-world-like organization, and this process is strongly related to genetic factors (Boersma et al., 2011; Schutte et al., 2013; Smit et al., 2008). Brain network organization is different in males and females, possibly due to the influence of sex hormones on brain development (Douw et al., 2011; Gong et al., 2009b). Brain network organization is also related to cognitive performance. In particular, short average path length has been associated with higher intelligence (Li et al., 2009; van den Heuvel et al., 2009). Functional brain networks may also change during the performance of cognitive tasks, during sleep and in coma (Crossley et al., 2013; Uehara et al., 2013). The optimal architecture of structural brain networks becomes disrupted in various neurological and psychiatric disorders. Abnormalities have been reported in Alzheimer's disease, frontal lobe dementia, Parkinson's disease, multiple sclerosis, brain tumours, epilepsy, schizophrenia, depression, autism and ADHD (Bassett and Bullmore, 2009; Stam and van Straaten, 2012). In several of these studies, network changes correlated with cognitive deficits and disease severity.

However, in several cases there is considerable controversy concerning the nature of the network changes. In a recent review of graph theoretical studies in Alzheimer's disease, Tijms et al. (2013) showed that different studies have reported either an increase or a decrease of the clustering coefficient or the path length. Only the loss of important hub nodes, especially in the posterior part of the default mode network, seems to be a consistent finding across studies. Similar controversies can be found for epilepsy (Kramer and Cash, 2012; van Diessen et al., 2013). While most studies agree that functional brain networks become more regular (higher clustering and longer path length) during seizures, in the interictal state both increased randomness (reflected by a lower clustering coefficient and shorter path length) as well as increased regularity have been reported (Kramer and Cash, 2012; van Diessen et al., 2013). With respect to the significance of hubs in epilepsy there is more agreement: several studies suggest that pathological hubs are more prevalent in epilepsy and that the removal of these hub nodes is associated with a more favourable outcome of epilepsy surgery (Ortega et al., 2008; van Diessen et al., 2013; Wilke et al., 2011). The application of modern network theory to brain neuroscience has thus improved our understanding of the development and organization of brain networks and their relation to cognition. At the same time these studies have shown conflicting results, in particular in the case of brain disease. At least some of these problems may be due to methodological issues. We will first discuss some of these methodological factors in Section 2 and then propose the minimum spanning tree as a possible solution in Section 3.

2. Problems with network comparison

To understand the influence of methodological issues on the outcome of a graph theoretical analysis we will first discuss an example in some detail. The basic steps are shown schematically in Fig. 1. Suppose we have a resting-state EEG or MEG recording with N channels. From this recording we select a number of artefact-free epochs. The data are filtered in a frequency band of interest, and subsequently the correlations between all possible pairs of EEG time series are determined with a suitable measure of functional or effective connectivity. The results can be averaged over all epochs and represented in a single $N \times N$ matrix, where each element contains the strength of synchronization between a pair of channels. We can do a graph theoretical analysis of this matrix in two different ways.

The first option is to consider a threshold T. The nodes in the graph correspond to the EEG channels. Two nodes are connected in the graph if the synchronization strength between the corresponding EEG time series exceeds the threshold T; otherwise they are not connected. This procedure results in a binary graph, where connections (edges) either exist or do not exist; no weights are assigned to the edges. If

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