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.

Key Words

Brain networks, Graph theory, minimum spanning tree, functional connectivity, EEG, MEG

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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 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 lead 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 bridges 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), that 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 C. 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, 2012). 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 x 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 the original matrix was symmetric, the corresponding graph will be undirected. If the original matrix was asymmetrical (which is the case if the synchronization measure has a direction, for instance, granger causality) the corresponding graph will be directed. This analysis can be done for one threshold, or for a range of thresholds. The number of nodes in the graph will always be N. The number of links or edges m will depend upon the combination of the original synchronization matrix and the selected threshold. Once a graph has been reconstructed various graph theoretical measures, such as the clustering coefficient or the average shortest path length or the degree distribution, can be computed.

The second option is to apply graph theoretical analysis directly to the original matrix. In this case the maximum number of edges m is (N-1)N /2 (self connections are disregarded). Each edge is assigned a weight that is derived from the synchronization strength in the original matrix. This procedure results in a weighted directed or undirected graph. Graph theoretical analysis of a weighted network requires the use of measures specifically adapted to this type of graph (Rubinov and Sporns, 2010). Finally, it is possible to combine both options: a binary graph is constructed based upon some threshold, and subsequently all supra-threshold edges are given a weight based upon the original synchronization matrix. We denote the sum of all edge weights in the graph by W.

We now describe how the scenario described above can give rise to problems when we want to compare different networks. The four important parameters to be considered are N, T, m and W. First we consider the comparison of unweighted graphs. If we compare two graphs G1 and G2 with the same N and T, there is no guarantee that they will have the same number of links m. The value of m will influence the value of measures such as the clustering coefficient C and the path length L computed from G1 and G2. For instance, it is likely that for increasing m the clustering coefficient will increase and the path length will decrease. In the limit of a complete graph, where all pairs of nodes are connected, the clustering coefficient and the path length will both be 1. The conclusion is that the comparison of G1 and G2 in terms of C and L is biased if they have different m. An additional problem is that the choice of T is essentially arbitrary. This could be addressed by considering a range of values of T, but then the choice of range is arbitrary and the comparisons for each value of T are still biased. Furthermore, an unfortunate choice of T could result in i) one or more of the nodes becoming disconnected (for T too high); ii) inclusion of noisy edges (for T too low). Consideration of a range of values of T also produces problems with the statistical analysis, since separate tests will have to be performed for each value of T, increasing the likelihood of type I errors.

Two solutions have been proposed so far: fixing m and comparison with random control networks (other solutions such as using the union of shortests paths are the topic of current research). In the first case we choose T for each graph to be compared such that all graphs have the same m. This disposes of the bias due to different m, but introduces the new problem of choosing a proper value of m for the comparison. Another strategy is to consider an ensemble of random graphs with the same N, T and m as the original graph. These random graphs are obtained by randomly reshuffling the edges of the original graph, with or without

preserving the original degree distribution. The graph theoretical measures of interest, for instance C and L, are computed for all random graphs and compared to C and L that were obtained for the original graph. In this way normalized measures can be computed: gamma = $C/<C_{random}>$ and lambda = $L/<L_{random}>$ ($<>$ indicates the ensemble average). Unfortunately this normalization approach still does not solve all the bias problems (van Wijk et al. 2010), and it also leaves open the choice of a proper m for comparing networks.

In the case of weighted networks there are also problems. In this case the total weight W will influence the value of the weighted clustering coefficient C_w and weighted path length L_w, both for the original graph as well as for the random control graphs. A higher W is likely to result in a higher C_w and higher L_w. Thus a comparison between two graphs will be biased if they have different values of W, which will typically be the case. Use of the normalized weighted gamma and lambda reduces the bias, but still does not solve it completely. Combining a threshold with weighted networks probably makes the problems worse since in this case one would have to compare graphs that have both the same m and the same W.

This brief analysis has illustrated some of the most basic problems involved in comparing graphs. It should be stressed that further problems can be expected if a wider range of scenarios is considered. For instance in the case of comparing networks with different N, a bias can be expected that cannot be completely solved with normalized measures (van Wijk et al., 2010; Zalesky et al., 2010). In addition, in the case of EEG and MEG synchronization measures that are sensitive to volume conduction are likely to influence the results of graph analysis (Peraza et al., 2012). In MRI studies of structural and functional networks many methodological factors may also influence the outcome of the analysis (Liang et al., 2012). With the rising interest in graph theoretical studies of brain networks these methodological issues become increasingly important since they complicate a comparison of results across different studies and different brain imaging techniques. Use of random exponential graph models, motif counts and the minimum spanning tree have been proposed as possible solutions (van Wijk et al., 2010). In the next section we will introduce the minimum spanning tree as an approach to obtain an unbiased representation of a weighted network.

3. Construction and theoretical properties of minimum spanning trees

3.1. The concept of a minimum spanning tree

In graph theory a tree is defined as an acyclic connected graph (Estrada, 2011). Acyclic means that there are no loops (of any length) in the graph. A graph is connected if there exists a path between each pair of nodes in the graph. A tree with N nodes has exactly m = N-1 links or edges. A spanning tree is a subgraph that includes all nodes of the original graph (it has the same N) but only N-1 edges (it has no cycles). A minimum spanning tree (MST) of a connected weighted graph is the spanning tree of this graph that minimizes the sum of the weights of the edges included in the tree. If all the weights in the weighted graph are unique, its minimum spanning tree is also unique (Mares, 2008). In other words there is only one MST that corresponds to a weighted graph with unique weights.

Two major algorithms have been described to construct the MST of a weighted graph (Kruskal, 1956; Prim, 1957). Here, we will explain Kruskal's algorithm. Prim's method produces the same MST if the weights of the original graph are unique. To construct the MST of a weighted graph G_w with N nodes, we rank all the weights in the graph from lowest to

highest weight and we start with N disconnected nodes. The lowest weight link connects two nodes and forms the smallest possible tree. Next, we select the second lowest weight link, which either connects two new nodes or connects the two already included nodes to a third one. In the latter case, the original one-link tree has grown to two links. Each separate tree is a member of the forest. The third lowest weight link can join two separate trees in the forest. This procedure is repeated until the forest consists of one tree, which is a MST. If adding a new link would result in a cycle, this link is discarded, and the procedure continues with the next in order weight link. Another way of saying this is that all edges of G_w are sorted from the lowest to the highest weight. Edges are added to the tree working from the lowest weight edge upwards and avoiding cycles. From this description it is clear that non uniqueness of the edge weights of G_w causes problems in the construction of the MST. The MST will always have m = N-1 edges. Although the weights in G_w are used to construct the MST, the MST itself is considered to be binary. Its edges exist or do not exist, and do not have weights. Using the same procedure but starting with the highest edge weight and working downwards it is possible to construct the maximum spanning tree (MaST), studied in Wang et al. (2010). Whereas the minimum spanning tree minimizes the sum of the edge weights included, the maximum spanning tree maximizes this sum. Otherwise both spanning trees are equivalent. An example of a minimum spanning tree is shown in Fig. 2.

An MST constructed from a connected weighted graph with unique weights is unique. This implies that we can compare MSTs of different weighted graphs directly if they all have the same N, are connected and have unique weights. The uniqueness of the MST is important since it discards the need to choose an arbitrary threshold or value of m to reconstruct the graph. Compared to the analysis of the full weighted graph the MST has the advantage that it focuses on the most important subgraph and avoids bias due to differences in W between different graphs. A tree is also a much simpler structure than the original weighted graph. This simplifies the analysis, but the downside is that a tree does not reflect some properties, particularly those that depend upon cycles, such as clustering. As we will show, this is less of a disadvantage than is often assumed. First we will describe how the topology of a tree can be characterized with a set of relatively simple measures. Then we will refer to theoretical studies that highlight the importance of the MST in terms of traffic flow in a network, followed by a review of studies where the MST was reconstructed for brain networks in healthy subjects and patients.

3.2. Different configurations of trees

In terms of tree topology, two extreme shapes exist (Fig. 3). The first extreme is a path. In this case all nodes are connected to two other nodes, with the exception of the two nodes at either end, which have only one link. Nodes with only one link (i.e. degree 1 nodes) in a tree are referred to as "leaves" or leaf nodes. The number of such nodes in a tree is the leaf number. A path thus has a leaf number of two. The other extreme is a star. In a star there is one central node to which all other nodes are connected with one link. In a star with N nodes there are N-1 leaf nodes, the same number as the number of edges. Between the two extremes of a path and a star many different types of tree configuration are possible. These configurations can be characterized with various metrics in addition to the leaf number. The more important graph metrics are discussed in Van Mieghem (2014). The diameter of a tree is the longest distance (expressed in number of edges) between any two nodes of the tree. In the case of a path the diameter is equal to the number of edges m = N-1. In the case of a star the diameter is two. The degree of a node is defined as the number of edges connected to it. Between any two nodes in a tree exactly one path exists. This allows computation of the average path length

between all node pairs. It is also possible to determine the betweenness centrality of any node as the fraction of all paths on the tree that include (but do not stop or end at) that node. Computation of betweenness centrality in the case of a tree is much easier and faster (and often analytically possible, see Wang et al. 2008) than in the case of a graph containing cycles. The eccentricity of a node is defined as the length of the longest path from this node to any other node. Degree, betweenness centrality and eccentricity can all be used to quantify the centrality of a node. A measure developed to characterize the hierarchical topology of a tree is the tree hierarchy T_h, defined as: T_h = leaf number / ($2\,m\,B_{max}$). In this formula m is the number of edges and B_{max} is the highest betweenness centrality of any node in the tree. The tree hierarchy is 2/m for a path, approaches 0.5 for a star (with large N), and can take values between 2/m and 1 for trees with an intermediate topology between path and star. The idea behind T_h is that it captures an optimal tree configuration characterized by a combination of short distances and prevention of overload of any node. With the exception of the leaf number and the T_h, the measures mentioned above are equivalent to measures defined for graphs with cycles. Some other measures defined for graphs with cycles such as degree correlations and kappa can also be applied to trees. Tree measures can be normalized by dividing them by the number of nodes N. MSTs of networks with the same N can be compared directly by the "survival rate" which is defined as the fraction of edges both MSTs have in common (Onnela et al., 2002). Finally, it is worth to mention that, for trees, some spectral metrics (see e.g. Van Mieghem, 2011) are useful. The effective graph resistance R_G equals N(N-1)/2 times the average hopcount and the spectrum (eigenvalues) of the tree's adjacency matrix is symmetric around zero.

3.3. The minimum spanning tree and traffic in weighted networks

While the minimum spanning tree is a simple subgraph of the original weighted network that facilitates direct comparison of networks with the same N and simplifies network characterization, it is not a priori given that it will still capture most of the important topological information in the original network. In view of this it is important that theoretical studies suggest the importance of the MST. A thorough review of the theoretical background of the MST is given in two papers by Jackson and Reid (Jackson and Reid, 2010a,b; Mares, 2008). A detailed discussion of this work is outside the scope of this review. Instead, here we will mention a few studies that relate the MST to traffic in weighted networks, since this relation may be relevant for interpretation of the significance of the MST of brain networks (since information processing is a fundamental objective of the brain). An important notion is that under certain conditions (as elaborated in Van Mieghem and van Langen, 2005; Van Mieghem and Magdalena, 2005; Van Mieghem and Wang, 2009) transport in weighted networks is dominated by the MST. Further analysis based upon node centrality has shown that the MST can be divided into two components, the "superhighways" or infinite incipient percolation cluster (IIPC) and the "roads" (Wu et al., 2006). Nodes of the superhighways have high centrality with a power law distribution, while nodes of the roads have low centrality. The implication is that small changes in the superhighways are likely to have a large impact on traffic flow in the system. In line with this, Wang et al. (2008) have shown that traffic in a weighted network is mainly limited to the MST in the strong disorder limit, with a high variability of link weights. They found a power law distribution for the betweenness centrality with an exponent related to the degree variance. The betweenness centrality distribution P(B) of the MST and infinite incipient percolation cluster (IIPC) of random and scale-free networks were also studied by Choi et al. (Choi et al., 2013). The exponent delta of the P(B) was 1.6 for MSTs close to criticality and 2.0 for supercritical MSTs. For the IIPC the exponent delta was 1.5, i.e. the superhighways are close to critical. This theoretical work

lends further support to the interpretation of the MST of empirical networks in terms of a subgraph that is responsible for most of the information flow in certain weighted networks. The relation of the MST to traffic flow has also been studied in a model of a spatial network where a cost was related to wiring length (Louf et al., 2013). Here, a model of a growing spatial network with topologies ranging from a star to a minimum spanning tree was introduced. They showed that a large number of interesting "global" properties, including a hierarchical organization, could emerge from a simple (local) cost assumption. Their new model was applied to the railway system to show how this network may be close to optimal. These results may be relevant for understanding brain networks, where connection cost has to be minimized in space and information transport has to be optimized at the same time (Bullmore and Sporns, 2012)

4. Applications to neuroscience data

As argued above, network comparison is a central problem in modern brain network analysis based upon graph theory. Weighted networks can be represented in a unique simplified way by the minimum spanning tree, which allows unbiased comparison in the case of networks with the same number of nodes. Furthermore, theoretical studies suggest that most of the traffic in a weighted network may flow through the MST. However, these considerations do not answer the question whether the MST is also a sensitive and practical tool for the comparison of empirical brain networks. Here we discuss in some detail experimental studies that have used the MST to characterize in one way or another functional brain networks. Since our focus at this stage is primarily on the methodological aspects we discuss the studies in three groups: (i) pioneering work; (ii) more extensive characterization of the MST in EEG studies; (iii) application of the MST to MEG source space data.

4.1. Pioneering work

The first application of the minimum spanning tree as a tool to analyse complex functional brain networks on the basis of EEG recordings was published in 2006 (Lee et al., 2006). Lee et al. investigated 11 epilepsy patients, 6 with left temporal lobe epilepsy (LTLE) en 5 with right temporal lobe epilepsy (RTLE). In their study five epochs, each containing 43 EEG channels and of 1 minute duration, and separated from other epochs by five minutes, were studied. The last epoch was chosen just before seizure onset. Connectivity matrices were derived from broadband (0.5-70 Hz) EEG signals by computing correlation coefficients between all possible pairs of channels for overlapping 10 second windows in the 1 minute epochs. For each of these windows an MST was derived from the correlation matrix with Kruskal's algorithm. Differences between MSTs of subsequent windows were quantified with a distance or dissimilarity measure $D_{x,y}$ of the MST (derived from the simpler survival rate described by Onnela et al., 2002). In addition, hierarchical clustering and a dendrogram were used to characterize the MSTs. The raw correlation matrix did not show a significant effect of time, nor did it reveal differences between the LTLE or RTLE groups. In contrast, using the MST the LTLE and RTLE patients could be separated (at a time scale of 1 minute, but also for the 10 second windows) in the epoch preceding seizure onset. Lee et al. suggested that this might reflect recruitment of surrounding ipsilateral regions by a seizure focus, which is not reflected by an increase or decrease in connectivity per se, but rather by a re-organization of the network. These results indicate that MST analysis can be sensitive in picking up these subtle changes in topology that precede the emergence of an epileptic seizure.

The same group applied a slightly modified version of the MST EEG analysis in a later study concerning network changes in states of altered consciousness (Lee et al., 2010). Ten healthy male volunteers were investigated before, during and after Propofol-induced anesthesia. MST's were based upon correlation matrices derived from moving windows of 7 seconds of 21 channel EEG data, either broad band or filtered in the delta, theta, alpha or beta band. In addition, the complexity of the spatial temporal data was quantified by computing a connection entropy based upon the survival rates of all possible connections. Results were compared with those obtained from random control datasets. MST analysis was able to distinguish between the three states of consciousness (before, during and after anesthesia). During anesthesia loss of network connections, alteration in connection duration, and lower connection entropy were found, especially in the delta band. Furthermore, connection entropy of the empirically observed networks was always lower than for the random data. The distribution of connection survival times showed a power law, but did not change during the three different states, which was interpreted as reflecting adaptive reconfiguration of functional brain networks. Of particular interest, as can be seen in Fig.3 in (Lee et al., 2010), a subgroup of connections was much more stable over time. This subset could correspond to a stable backbone, and perhaps to the superhighways reported in theoretical work (Wu et al., 2006).

The same approach based upon the connection entropy of the MST was applied in a more recent study in schizophrenia (Schoen et al., 2011). In this study 30 patients with acute schizophrenia and 30 matched controls were investigated with 18 channel EEG 1 and 6 weeks after the start of treatment with antipsychotics in the patient group. MSTs were determined from Pearson correlation matrices of 5 minutes of EEG segmented in moving windows of 8 seconds. Untreated schizophrenics, and schizophrenics after 6 weeks treatment had greater connection entropy in the gamma band. Only before treatment PANSS (positive and negative symptoms scale) and negative symptoms were negatively correlated with connection entropy (as defined in Lee et al., 2006). One problem with this study is that results in the gamma band derived from scalp EEG may be severely affected by muscle artefact (Whitham et al., 2007). Of note, this was explicitly considered in the study of Lee et al. (2010) where the gamma band was left out of the analysis.

The first application of MST analysis to EEG by Lee et al. in 2006 suggested its usefulness for epilepsy research. This idea was taken up by another group who applied MST analysis to intra operative EEG recordings in five patients with epilepsy (Ortega et al., 2008). In this study the focus was different however, since the authors used the MST derived from Pearson correlation matrices of 28 channels to identify electrodes of special significance for the epileptic network. They distinguished between three different types of nodes characterized by: (i) the highest local synchronization power (weighted node strength); (ii) the highest MST degree; (iii) the highest interactions load (MST node betweenness). Ortega et al. investigated whether removal of any of these three node types (or combinations of node types) correlated with surgical outcome (as defined with the Engel scale). They found that removal of nodes with high local synchronization strength was a sufficient but not necessary condition for a good outcome. Outcome did not depend on the number of nodes removed. In this study epilepsy originated in the mesial temporal lobe in 4 of 5 patients; network analysis however revealed critical nodes in lateral temporal cortex in five patients. Thus network analysis shows that the epileptic network may extend beyond the epileptic focus, and this could have implications for epilepsy surgery: removal of a critical node, even if it is not in or near the focus, could abort the seizures. A similar result, obtained with more conventional network analysis, has been reported more recently by another group (Wilke et al., 2011).

Two studies have used the MST for the investigation of functional brain networks derived from fMRI. In the first study resting-state fMRI was performed in 13 patients with childhood onset schizophrenia (COS) and 19 healthy controls (Alexander-Bloch et al., 2010). The focus of this study was on modularity, and the MST and the k nearest neighbour graph were used only to force connectedness of the graphs to guarantee unbiased comparison between groups. Modularity and local clustering and small-worldness were reduced and global efficiency and robustness were increased in the COS group. These results were taken to support the concept of "dysmodularity" in schizophrenia. It should be noted that results of this study, in contrast to the three studies mentioned above, were not based upon an analysis of the MST proper. Although Alexander-Bloch et al. stress the importance of forcing connectedness of the graphs, and having the same edge density when comparing graphs, the analysis is performed for a large range of edge densities. It is unclear whether a hierarchical clustering analysis of the MST itself, as described by Lee et al. (2006) would also have revealed the dysmodularity in the COS group. Recent work has shown that trees can be used to reveal the modular structure of complex networks (Bagrow, 2012).

The first fMRI study that analysed the MST itself was performed on a data set set (#2-2000-1118W) from an international repository of raw fMRI data (www.fmridc.org) (Ciftçi, 2011). This data set consists of fMRI recordings in 14 healthy young subjects, 14 healthy elderly controls and 13 patients with "clinical dementia" during a simple sensory motor task. The network was defined as 32 nodes, all regions from the AAL atlas belonging to the default mode network. MSTs were derived, both at the individual level as well as the group level from correlation matrices of fMRI BOLD signals. The analysis involved the MST degree distribution and agglomerative hierarchical clustering of the group level MSTs. The mean level of connectivity was highest in the young controls, and lower in both elderly controls and Alzheimer patients. The degree distributions of the empirical data showed a peak at degree 2, reflecting a more chainlike MST, while random surrogate data showed a maximum at degree 1, reflecting a more starlike topology. No differences in degree distribution were found between the three groups. Ciftçi (2011) noted a distinction between highly persistant and less consistent edges, somewhat in line with the results of Lee et al. (Lee et al., 2010). Hierarchical clustering analysis of the MST showed that the connection between the hippocampus/parahippocampal gyrus on the one hand to the precuneus and posterior cingulate gyrus on the other hand, that is normally mediated by the angular gyrus and the inferior temporal gyrus, was disrupted in Alzheimer patients. Ciftçi (2011) concluded that the MST carries information about the clustering of the network.

4.2. More extensive characterization of the MST in EEG studies

The pioneering studies described above revealed two important points. Firstly, they showed that MST analysis could indeed be used for an unbiased comparison of brain networks between groups and conditions. Secondly, they demonstrated that MST analysis could reveal significant effects that were not always evident from an analysis of the raw connectivity matrices. However, in all the studies described above the actual analysis of the MST itself was rather limited: the focus was either on quantifying the overlap between different MSTs, the degree distribution, or the hierarchical structure. While these approaches to MST characterization are certainly promising, it is possible to extract more topological information from the MST than has been done in these earlier studies. In fact, almost all measures that are normally applied to unweighted graphs can be used for the analysis of MSTs as well. The most important exceptions are those measures, such as for instance the clustering coefficient,

that depend upon the presence of cycles of any length. In contrast, there is at least one measure that is especially useful in the case of trees: the leaf number. This measure is particularly useful to quantify the extent to which a tree is more chainlike or more starlike. A more extensive description of tree measures can be found in section 3. Here we discuss briefly two EEG studies that have implemented a more extensive characterization of the MST. In the next section we show how such an extensive characterization can be combined with MEG source space networks.

In the study of Boersma et al., eyes-closed resting state 14 channel EEGs recorded in 227 children at age 5, with a second recording two years later, were analysed with the synchronization likelihood, a measure of generalized synchronization (Boersma et al., 2013). In the alpha band a number of significant changes in MST measures was found. At age 7 the MST showed a larger diameter, higher eccentricity, a lower leaf number and a lower tree hierarchy. A detailed explanation of these measures can be found in section 3. Here, the important thing to note is that a larger diameter, higher eccentricity and lower leaf number all point to a more chainlike, elongated shape of the MST at age 7. In addition, this study showed a remarkable difference between boys and girls. Compared to girls, boys had a higher leaf number, betweenness centrality, maximum degree and a smaller diameter and eccentricity in the theta band. This suggests that the MST topology of boys was more starlike, and the MST topology of girls more chainlike. If we compare this pattern to the change observed between age 5 and age 7, one could argue that brain networks in girls show a more mature pattern. The same EEG dataset has been analysed before with more classical graph theoretical techniques (Boersma et al., 2011), showing that the clustering coefficient increased in the alpha band, and the path length in all bands, between age 5 and 7. Clustering was higher in girls compared to girls in the alpha and beta bands. These two studies allow us to compare the patterns obtained with more classical graph theoretical analysis and MST analysis. Higher clustering and longer path length, characteristic of girls and maturation, seem to be the equivalent of a more elongated, chainlike MST topology with large diameter, high eccentricity and low leaf number. Tentatively, one might also argue that a more regular network topology corresponds to more chainlike trees, whereas more random networks correspond to more starlike trees.

A similar type of more extensive MST analysis was applied in the study of Demuru et al. (2013). Demuru et al analysed a publicly available dataset ((http://physionet.org/pn4/eegmmidb/) of 64 channel EEG recording of 109 subjects. EEG was recorded under three conditions: imagined right hand movement, imagined left hand movement and rest. Functional connectivity, assessed with the phase lag index (Stam et al., 2007), increased in both imagined hand movement conditions compared to the rest condition, and regional analysis showed that this effect was different for both hemispheres depending on the side of imagined hand movement. The normalized clustering coefficient and path length did not reveal significant condition effects. In the beta band significant effects of condition and side were found for MST eccentricity and diameter, and a significant effect of condition for MST hierarchy. In this particular study both the raw functional connectivity as well as the beta band MST measures were more sensitive than the weighted normalised clustering coefficient and path length. Compared to the study of Boersma et al. (Boersma et al., 2013), a strength was the use of the PLI, which is less sensitive to confounding effects of volume conduction and active reference electrodes compared to the synchronization likelihood. This study suggests that network analysis based upon the MST might be a candidate for the development of brain computer interfaces.

4.3. Application of the MST to MEG source space data.

A limitation of the EEG studies reported above is the fact that the relation between the recording electrodes and the location of the underlying sources is not a priori known. In addition, in the case of scalp recordings considerable blurring of the signal could occur due to current spread in intervening tissues. These problems can be addressed by the use of MEG source space as a starting point of the network analysis (Hillebrand et al., 2012). Compared to EEG, MEG is hardly affected by the conductivity of the skull and does not require the use of a reference electrode. With beamformer methods recorded MEG signals can be projected to sources based upon an anatomical atlas fitted to the MRI of the experimental subjects (Hillebrand et al., 2005). It is important to note that source space analysis does not completely solve the problem of field spread, and still requires the use of a functional connectivity estimator, such as the phase lag index, that reduces the resulting biases in estimated connectivity. Three recent studies applied minimum spanning tree analysis to connectivity matrices based upon MEG source space and the PLI. In all cases 78 cortical regions of the AAL atlas were used as nodes of the network (Gong et al., 2009).

   The first study investigated MEG source space functional networks in 20 patients with lesional epilepsy at baseline and at two time points postoperatively (van Dellen et al., 2013). Higher PLI in the alpha band correlated with higher seizure burden. In seizure free patients an increase in leaf number, decrease in eccentricity and decrease in betweenness centrality were observed between baseline and follow up. Connectivity and network measures also showed a relation to the location of the lesion. This study showed that MST analysis is sensitive to patterns of plasticity and brain network reorganization that are related to clinical outcome.

   Tewarie et al. (2013) investigated the MST of MEG source space brain networks in 21 early MS patients and 17 matched healthy controls. They used the tree dissimilarity measure introduced by Lee et al. to compare controls and patients with a reference MST based upon the average PLI matrix of the control group (Lee et al., 2006). When the MSTs were dissimilar, then the MSTs were further characterized and compared. This revealed a loss of network integration in alpha2 and beta bands, and an increase in the theta band. Alpha 2 MST characteristics, in particular the tree hierarchy, correlated with impaired cognition in the MS patients. This study confirms that cognitive problems in MS may be correlated with changes in global network organization. In addition it was shown that the distribution of PLI values was close to a strong disorder state. This is important since it suggests that the MST is likely to reflect most of the traffic in the underlying network (Wang et al., 2008).

   In a longitudinal study of resting-state functional brain network organization in Parkinson patients and healthy controls conventional graph analysis based upon weighted normalised clustering coefficient and path length showed for the Parkinson patients a loss of clustering which progressed over time, and a shorter path length at later stages (Olde Dubbelink et al., 2013). Minimum spanning tree analysis revealed a shift from more integrated ("star like") to more disintegrated ("path like") networks in Parkinson patients, and these changes also progressed over time. Importantly, changes in network organization in the PD group were correlated with motor and cognitive impairment. This study is again a good illustration of the ability of network analysis to pick up clinically relevant changes in brain network organization, even in early stage disease.

5.Conclusion and future prospects

We have shown that modern network analysis is a rapidly growing field in neuroscience, but the lack of a proper methodology for network comparison between studies, and between conditions within studies, is increasingly becoming an important obstacle to further progress. This is especially clear for diseases such as dementia, schizophrenia and epilepsy, where many network studies have already been performed. Contradictory results such as either increased randomness or excessive regularity of functional networks have been reported in Alzheimer's disease and epilepsy (Tijms et al., 2013; van Diessen et al., 2013). In this review, we investigated whether the minimum spanning tree could be useful to overcome some of these problems. The minimum spanning tree allows a unique, simplified representation of a weighted network, provided all the weights are unique. Theoretical studies suggest that the MST represents most of the traffic in a weighted network, and can be used to detect the hierarchical structure. A detailed investigation of empirical studies employing the MST showed that the MST was often effective in detecting group differences and condition effects, and even rapid network changes over time. In most studies, the MST analyses were at least as sensitive as, or more sensitive than, analyses of raw connectivity data or analyses using more a conventional graph theoretical approach. These findings suggest that the minimum spanning tree is a promising approach for network comparison and characterization.

Several studies have already employed both MST analysis and analysis of raw connectivity data and conventional graph measures, often the clustering coefficient and the average shortest path length. In those studies where connectivity data or conventional graph analysis showed an effect, an effect was always present in the MST analysis as well (Boersma et al., 2011; 2013; Olde Dubbelink et al., 2013; van Dellen et al., 2013). In other studies MST analyses succeed in demonstrating an experimental effect while other methods were less successful (Demuru et al., 2013; Lee et al., 2006). The empirical evidence so far suggests that changes in the clustering coefficient and average shortest path length cannot be translated in a simple way into MST measures. The studies of Boersma et al. suggested that more regular networks with higher clustering and longer path length correspond with more line like MSTs with longer diameter and smaller leaf number, while more random networks show low clustering and short path length and the corresponding MSTs shorter diameters and higher leaf numbers. However, an opposite pattern was shown in the study of Olde Dubbelink et al. (2013). In this study, a lower clustering coefficient and shorter path length were associated with a more line like MST with large diameter and lower leaf number. These studies differ in a number of methodological aspects, such as the use of EEG versus MEG, synchronization likelihood versus phase lag index and signal space versus source space analysis. It is important to note however that in both cases, given the connectivity matrix, the MST was unique while the clustering coefficient and path length could have been computed in many different ways as discussed in detail in section 3. Of interest, even when changes in the clustering coefficient were a prominent part of the conventional graph analysis the MST, which does not measure clustering, still showed significant effects. What is needed here is a systematic comparison of the most important conventional as well as MST-based measures in a model study using various types of typical complex networks.

In recent years there has been a proliferation of new measures for the characterization of complex networks (Rubinov and Sporns, 2010). In a similar way it is also possible to use a large variety of different measures to characterize minimum spanning trees. It is very likely however, that these measures are highly correlated and can be replaced by a smaller number of more independent measures. A simulation study showed that most graph measures can be clustered into 2 to 4 groups, depending upon the topology of the underlying network (Li et al., 2011). For example, in the case of Erdős Rényi random graphs a strong correlation between

the clustering coefficient and the average shortest path length can be expected. While a systematic study of MSTs from this point of view is currently lacking, many correlations between MST measures can be understood relatively easily by considering the two extreme forms of a tree: either a path or a star (Fig. 3). If an MST is more similar to a path, it will have a longer diameter, higher eccentricity, lower leaf number and lower maximum betweenness centrality. If an MST is more similar to a star it will have a shorter diameter, lower eccentricity, large leaf number and higher maximum betweenness centrality. Thus MST analysis of network changes usually allow an interpretation in terms of a shift toward a more line like ("less integrated") or a more star like ("more integrated") configuration. A challenge for the future is to find a minimum set of MST measures that captures most of the relevant changes in MST morphology.

   From the point of view of neuroscience an important question is whether MST changes can be interpreted in a meaningful way in terms of the structure and function of the underlying neural networks. Theoretical studies suggest that in the strong disorder limit the MST may reflect most of the traffic in the underlying network (Wang et al., 2008). Furthermore the MST might be divided into a core, the superhighways, and more peripheral roads (Wu et al., 2006). In the study of Tewarie et al. (2013) it was shown that brain network data might indeed correspond to the strong disorder state, in which case the MST would represent most of the shortest paths in the network. This could explain why a simple subgraph of a weighted network can still capture relevant changes in the case of disease or disturbed consciousness. It might also explain why MST changes correlate with cognition and motor function (Demuru et al., 2013; Olde Dubbelink et al., 2013). One very interesting empirical observation is that the MST seems to consist of a stable core and more variable periphery (Lee et al., 2006). It would be very interesting to study whether these component are somehow related to the superhighways and roads described in theoretical work. Another important question for future studies is to what extent the MST, and in particular its more stable core, corresponds to the default mode network and/or the rich club of highly interconnected hubs. The MST also provides a good starting point for hierarchical clustering of complex networks. This approach has already been proven useful for distinguishing between sub groups of epilepsy patients and identification of disconnected clusters in Alzheimer's disease (Ciftçi, 2011; Lee et al., 2006). A more systematic use of hierarchical clustering in combination with the MST could show whether clusters identified in this way correspond to different cognitive domains.

   Modern network analysis provides a natural general framework for the integration of data obtained with different techniques and across different spatial and temporal scales. As we have shown MST analysis has already been applied to different techniques such as EEG, electrocorticography, MEG and fMRI. An important question for future research is whether the MST could be helpful for cross modal comparison of networks. Another important issue in network analysis is the temporal evolution of network organization. The studies of Lee et al. have shown that the MST can be used for this type of analysis (Lee et al., 2006; 2010). Perhaps the most interesting challenge of all is to find a good generative model of complex brain networks. Many studies have attempted to explain properties of structural and functional brain networks, as well as their relation, in terms of a few underlying principles such as optimization in the face of connection cost and speed of information processing (Bullmore and Sporns, 2011; Goñi et al., 2014; Vértes et al., 2012). Since the minimum spanning tree allows a highly simplified, but still meaningful representation of a complex network, it might also facilitate the task of finding a generative model of complex brain networks.

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Fig. 1. Schematic illustration of graph theoretical analysis of multi channel MEG data.

(A) The starting point is a multi channel recording of brain activity, either EEG or MEG, filtered in a frequency band of interest. The same approach can be used for fMRI BOLD time series. (B) A measure of correlation or synchronization is computed between all possible pairs of channels. The results are shown in a N by N matrix, where each entry contains the correlation or synchronization strength of a particular pair of channels. In this case the magnitude of the synchronization is shown on a colour scale from 0 (blue) to 1 (red). (C) After application of a threshold T all cells with a value larger than T are given a value of 1, and all other cells a value of 0. This step converts the weighted complete graph to a binary graph. In this case the original matrix is symmetrical and the resulting graph is undirected. (D) the binary graph is shown in a glass brain representation. Each node corresponds to a recording site or MEG source, and nodes are connected by an edge if the synchronization strength exceeds the threshold T. From this graph various graph theoretical measures such as the clustering coefficient and the average shortest path length can be computed.

Fig. 2 Comparison of binary graph and minimum spanning tree

(A) Binary graph constructed from a weighted synchronization matrix after application of a threshold T. Edges correspond to node pairs with a synchronization strength above the threshold T. (B) Minimum spanning tree constructed from the same weighted synchronization matrix as used for the binary graph shown in (A). The color of the nodes depict the betweenness centrality (blue = 0; red = 1). The minimum spanning tree is an acyclic connected subgraph that maximizes the synchronization strength between all node pairs.

Fig. 3. Schematic illustration of trees and tree measures

Different configurations of a tree consisting of N = 9 nodes and m = 8 edges. The plot in the middle shows the diameter (maximum distance between any two edges of the tree) as a function of the leaf number (number of nodes with only one edge). Leaf nodes are shown in red. All other nodes are blue. D max represents the highest possible diameter for a tree with a given leaf number L. Dmax = N-L+1. D min represents the lowest possible diameter for a tree with a given leaf number L: Dmin = 2(N-1)/L. (A) tree with L = 2 and Dmax = Dmin = 8. This type of tree is called a path. (B) Tree with the longest possible diameter (6) for a leaf number of 4. (C) Tree with the lowest possible diameter (4) for a leaf number of 4. (D) Tree with diameter of 2 and leaf number of 8. This type of tree is called a star. The path and the tree represent two extreme configurations of a tree. The area between the lines corresponding to Dmax and Dmin represent a space of different possible tree configurations, bounded by maximum and minimum possible diameter for each leaf number.