# The minimum spanning tree: An unbiased method for brain network analysis

P. Tewarie [a,*,1], E. van Dellen [b,c,d,1], A. Hillebrand [c], C.J. Stam [c]

[a] Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands
[b] Alzheimer Center and Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands
[c] Department of Clinical Neurophysiology and MEG Center, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[d] Department of Psychiatry, BrainCenter Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

## ARTICLE INFO

## ABSTRACT

The brain is increasingly studied with graph theoretical approaches, which can be used to characterize network topology. However, studies on brain networks have reported contradictory findings, and do not easily converge to a clear concept of the structural and functional network organization of the brain. It has recently been suggested that the minimum spanning tree (MST) may help to increase comparability between studies. The MST is an acyclic sub-network that connects all nodes and may solve several methodological limitations of previous work, such as sensitivity to alterations in connection strength (for weighted networks) or link density (for unweighted networks), which may occur concomitantly with alterations in network topology under empirical conditions. If analysis of MSTs avoids these methodological limitations, understanding the relationship between MST characteristics and conventional network measures is crucial for interpreting MST brain network studies. Here, we firstly demonstrated that the MST is insensitive to alterations in connection strength or link density. We then explored the behavior of MST and conventional network-characteristics for simulated regular and scale-free networks that were gradually rewired to random networks. Surprisingly, although most connections are discarded during construction of the MST, MST characteristics were equally sensitive to alterations in network topology as the conventional graph theoretical measures. The MST characteristics diameter and leaf fraction were very strongly related to changes in the characteristic path length when the network changed from a regular to a random configuration. Similarly, MST degree, diameter, and leaf fraction were very strongly related to the degree of scale-free networks that were rewired to random networks. Analysis of the MST is especially suitable for the comparison of brain networks, as it avoids methodological biases. Even though the MST does not utilize all the connections in the network, it still provides a, mathematically defined and unbiased, sub-network with characteristics that can provide similar information about network topology as conventional graph measures.

© 2014 Elsevier Inc. All rights reserved.

## Introduction

### General introduction

Brain functioning requires both specialization and global integration of information (Tononi et al., 1998). The brain is organized as a complex network, and neural functioning can only be fully understood when activity is studied in the context of this network (Bullmore and Sporns, 2009; Stam and van Straaten, 2012; Park and Friston 2013). Major graph theoretical advances have provided elegant tools for systems neuroscience (Rubinov and Sporns, 2010). Graph theory makes it possible to fully characterize structural and functional brain networks, which

provides insights in fundamental properties of the structural and dynamical organization of neural communication (Bullmore and Sporns, 2009, 2012).

Early studies used the small-world and scale-free model to describe structural and functional networks (Sporns and Zwi 2004; Bullmore and Sporns, 2009). A small-world topology efficiently combines local specialization and global integration (Watts and Strogatz, 1998). A scale-free topology is characterized by a power law degree[2] distribution with an important role for hub nodes (Barabasi and Albert, 1999). Human structural and functional networks have both small-world and scale-free characteristics that have often been correlated to optimal cognitive functioning (Bullmore and Sporns, 2012; van den Heuvel et al., 2009). Importantly, a deviation from this optimal topology has been linked to cognitive and clinical symptoms in neuropsychiatric diseases

* Corresponding author at: VU University Medical Center, Department of Neurology, PO Box 7057, 1007 MB Amsterdam, The Netherlands. Fax: +31 20 4440715.
*E-mail address:* p.tewarie@vumc.nl (P. Tewarie).
[1] Equal contribution.

[2] Degree refers to the number of connections to a node. A node with a high number of connections is considered to be a hub.

(Stam and van Straaten, 2012; Stam, 2014). In recent years, other aspects of complex brain networks have also attracted attention, such as modularity, hierarchy, and mixing properties such as degree correlations and the 'rich-club' of strongly interconnected hub nodes (Bullmore and Sporns, 2009, 2012; van den Heuvel et al., 2012).

*Problem definition*

Although findings obtained with conventional graph metrics such as the clustering coefficient, shortest path length and degree distribution (see Network characteristics) have increased our understanding of the complexity of the brain's architecture, methodological issues have limited comparability between experimental conditions, cohorts and studies. Brain network studies are typically based on neuroimaging data (such as functional MRI (fMRI), similarity in cortical structure or Diffusion Tensor Imaging) or neurophysiological recordings (such as electroencephalography (EEG), magnetoencephalography (MEG), or corticography) (Bullmore and Sporns, 2012). Especially for this type of empirical data, the underlying network topology is often topic of interest and a priori unknown. A connectivity matrix containing information on all possible structural or functional connections can be converted into a network, which can then be analyzed with graph theoretical approaches. For this purpose, connections can be either unweighted (i.e. they either exist or do not exist) or weighted (i.e. they have a weight that characterizes its strength). Both the comparison of unweighted and weighted networks based on neuroimaging data is accompanied by methodological hurdles. For thorough studies on this topic we refer to Fornito et al. (2013) and van Wijk et al. (2010). Here we will briefly discuss this topic.

Let us first consider unweighted networks, where the problem is to decide whether a connection is present or absent; this decision involves arbitrary choices that influence the network properties of interest. To construct unweighted networks one has to apply a threshold on the connectivity values of the original weighted network of interest. This results in scaling of the network properties as a function of the threshold (Fornito et al., 2010). Moreover, the threshold can be chosen in a variety of ways, for example based on an arbitrary choice, or using statistical criteria of connectivity strength, based on the average degree, or based on the density of the network. The main problem with choosing a threshold based on connectivity strength is that a difference in the distribution of connectivity values in two connectivity matrices may result in two unweighted networks having different densities. Subsequently, these differences in densities affect the estimated network characteristics even when the actual underlying network topology is the same. This problem cannot be solved by simply using different threshold values for each network (van Wijk et al., 2010). When the threshold is based on a fixed average degree or average density, the number of connections in the network is fixed. However, this may result in either inclusion of spurious or noisy connections in networks (for too high density values or too high average degree) or the exclusion of relevant connection in networks (for too low density values or too low average degree) (van Wijk et al., 2010).

The analysis of weighted networks is similarly accompanied by methodological problems, despite the fact that it does not suffer from threshold problems. Graph measures on these networks are influenced by average connection strength, the range of connectivity values and by the noisy and spurious connections contained in these weighted networks.

Proposed normalization procedures to correct for these biases in both unweighted and weighted network analyses do not provide an adequate solution (van Wijk et al., 2010). Normalization typically involves comparison of estimated network characteristics to those for a reference network with the same density, and sometimes also the same degree distribution. This normalization step may reduce the bias but does not solve it completely. Furthermore, the choice for a specific random network as surrogate data is arbitrary as one could use a random network obtained by reshuffling the original link weights, either with or without preserving the degree distribution, or by using the configuration model (Maslov and Sneppen, 2002; Newman et al., 2001). Therefore, analyses of both unweighted and weighted networks involve arbitrary choices that in itself affect the network properties. This may partly explain why studies on network alterations in brain diseases describe contradictory findings for specific patient populations, as has been reported for Alzheimer's disease and epilepsy (Diessen et al., 2013; Tijms et al., 2013).

*The minimum spanning tree*

Analysis of the minimum spanning tree (MST) may be helpful as it avoids methodological biases when comparing networks. The MST is mathematically defined as the sub-network that connects all nodes while minimizing the link weights and without forming loops (Kruskal, 1956; Prim, 1957). The link weights in neuroimaging data typically represent the connectivity strength (which can be considered as an inverse distance; an MST based on connectivity strength formally is a maximum spanning tree). Two assumptions underlying the MST analysis are that all nodes in the original weighted network are connected, and that all link weights are unique. Theoretically, the MST is insensitive to scaling effects since its topology only depends on the ordering of the weights in the original network and not on the absolute values or the distribution of these weights (Jackson and Read, 2010). Furthermore, every transformation of the weights which preserves weight ordering does not affect the MST (Dobrin and Duxbury, 2001). Apart from being insensitive to scaling effects, the MST may also efficiently capture the essential properties of complex networks, as found for many fields of science. The MST has been used as dimension reduction method in genetic linkage maps, as a method to partition highways and roads in transport networks, or as way to find the state with the lowest energy or disorder in physical systems (Dussert et al., 1986; Jackson and Read, 2010; King and Tidor, 2009; Wu et al., 2006, 2008).

MST analysis was first applied to brain networks by Lee et al. (2006), and has been used in several recent studies on development and neuropsychiatric diseases (Boersma et al., 2012; Demuru et al., 2013; Olde Dubbelink et al., 2014; Ortega et al., 2008; Tewarie et al., 2013a; van Dellen et al., 2014; Stam et al., 2014). However, it is unclear how the MST relates to conventional measures of network organization such as clustering and path length. Furthermore, it has been stated that the MST is biologically unlikely to be a realistic representation of brain networks because the MST, in contrast to real brain networks, contains no loops (Meunier et al., 2009). Here, we use simulations to demonstrate 1) how analysis of the MST overcomes scaling effects; and 2) how topological changes of the MST relate to topological changes of the original graph in terms of the measures that describe its small-worldness and scale-freeness. Indeed, we show that several MST characteristics are very strongly related to the conventional graph theoretical measures, such as the path length and node degree. Finally, we discuss how these insights can be used to interpret data from empirical MST studies.

**Simulations**

*Network characteristics*

Formal definitions and explanations of all network characteristics used in this paper are given in Table 1. Empirical networks often display non-random organization, characterized by local specialization (i.e. local clusters of connections) and global integration (through relatively sparse long range connections). This local specialization is usually quantified by computing the clustering coefficient $C$, which is the fraction of triangles in the network (Rubinov and Sporns, 2010). The average shortest path length $L$ is often considered as a measure for global integration and is defined as the average number of links in the shortest path between any two nodes, subsequently just referred to as path