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Functional brain network analysis using minimum spanning trees in Multiple Sclerosis: An MEG source-space study

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ABSTRACT

Cognitive dysfunction in Multiple Sclerosis (MS) is closely related to altered functional brain network topology. Conventional network analyses to compare groups are hampered by differences in network size, density and suffer from normalization problems. We therefore computed the Minimum Spanning Tree (MST), a sub-graph of the original network, to counter these problems. We hypothesize that functional network changes analysed with MSTs are important for understanding cognitive changes in MS and that changes in MST topology also represent changes in the critical backbone of the original brain networks. Here, resting-state magnetoencephalography (MEG) recordings from 21 early MS patients and 17 age-, gender-, and education-matched controls were projected onto atlas-based regions-of-interest (ROIs) using beamforming. The phase lag index was applied to compute functional connectivity between regions, from which a graph and subsequently the MST was constructed. Results showed lower global integration in the alpha2 (10–13 Hz) and beta (13–30 Hz) bands in MS patients, whereas higher global integration was found in the theta band. Changes were most pronounced in the alpha2 band where a loss of hierarchical structure was observed, which was associated with poorer cognitive performance. Finally, the MST in MS patients as well as in healthy controls may represent the critical backbone of the original network. Together, these findings indicate that MST network analyses are able to detect network changes in MS patients, which may correspond to changes in the core of functional brain networks. Moreover, these changes, such as a loss of hierarchical structure, are related to cognitive performance in MS.

Introduction

Multiple Sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease leading to both physical disability and cognitive dysfunction. It is still not fully elucidated how cognitive dysfunction and physical disability result from demyelination and neurodegeneration, given the large clinical and radiological variability of the disease. The brain is a complex network and it is widely claimed that normal cognitive function as well as cognitive dysfunction in neurological diseases cannot be fully understood without proper knowledge of the brain's topology, i.e. the spatial organisation of the network (Bullmore and Sporns, 2012; Stam and van Straaten, 2012). Therefore, analysing network topology in MS in relation to cognitive dysfunction and physical disability is highly relevant.

Graph theory provides a comprehensive and sophisticated framework to characterize network topology. By applying graph theory we have gained insight in how brain networks can display features of both integration and segregation of information processing, and how networks are organized to minimize economical costs and maximize efficiency (Bullmore and Sporns, 2012; Rubinov and Sporns, 2010; Stam and van Straaten, 2012; van Straaten and Stam, 2013). An optimal topology with local clustering and strategic long distance connections (i.e. short path length) has been called a small-world network (Watts and Strogatz, 1998). Moreover, brain networks are characterised by the presence of highly important nodes that lie central in the network's flow of information, i.e. hubs (Bullmore and Sporns, 2012).

Graph theoretical analyses applied to structural and functional networks in Relapsing Remitting MS (RRMS) are scarce (Hardmeier et al., 2012; Schoonheim et al., 2011, 2012a; Shu et al., 2011). Previous MEG studies revealed that functional networks in early RRMS patients

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display a more regular network, i.e. higher clustering and longer path length (Schoonheim et al., 2011) and, more specifically, temporal regions appear to lose "hubness", while parietal regions appear to become more hub-like in early RRMS patients (Hardmeier et al., 2012). Analyses in these MEG studies were performed at the sensor-level. This is difficult to interpret and may suffer from problems with functional connectivity estimation due to field spread and volume conduction. For this reason, more recent network studies have been based on analysis in source-space (Hipp et al., 2012; Palva et al., 2010), in particular using beamforming techniques (van Dellen et al., 2013; Douw et al., 2013; Hillebrand et al., 2012; Ponsen et al., 2013).

Although conventional graph theoretical analyses are helpful for understanding disease mechanisms (Bullmore and Sporns, 2012), they suffer from methodological difficulties when comparing different groups or conditions (Fornito et al., 2013; van Wijk et al., 2010). For instance, graph measures are influenced by the size of the network (i.e. the number of nodes), network sparsity (percentage links present) and the average degree (i.e. the number of connections per node). An often applied approach to correct for size or average degree dependence is to normalize graph metrics by random graphs. Even this normalization does not solve the dependence of size, degree and density effects and may even exuberate it. Fixing the number of nodes and average degree in the network does eliminate size effects but may introduce spurious connections or ignore strong connections in the network (van Wijk et al., 2010). Even the use of weighted graphs instead of un-weighted graphs does not provide an optimal solution since measures computed on these graphs are influenced by (the large number of) noisy connections and by the average functional connectivity strength.

An alternative approach is to construct and compare the minimum spanning tree (MST) of the original weighted graphs (Jackson and Read, 2010a,b; Wang et al., 2008). A spanning tree is a sub-graph of the original graph that does not contain circles or loops and connects all nodes in the original graph. The MST is a tree which has the minimum total weight of all possible spanning trees of the original graph (Van Mieghem and Magdalena, 2005). If the original graph contains N nodes then the MST always has N nodes and $M = N - 1$ links, therefore enabling direct comparison of MSTs between groups and avoiding aforementioned methodological difficulties such as setting arbitrary thresholds. Furthermore, if the original network can be interpreted as a kind of transport network, and if edge weights in the original graph possess strong fluctuations, also called *the strong disorder limit*, all transport in the original graph flows over the MST (Van Mieghem and van Langen, 2005). If the *strong disorder limit* condition holds, then the union of all shortest paths coincides with the MST and the MST forms the critical backbone of the original graph (Van Mieghem and Magdalena, 2005; Wang et al., 2008).

Network analyses of functional brain networks after constructing MSTs in neurological diseases are limited (Alexander-Bloch et al., 2010; Lee et al., 2006; Schoen et al., 2011). In epilepsy, MST network analyses allowed identification of critical nodes in a temporal network associated with seizures (Ortega et al., 2008) and characterization of different network topologies in different epilepsy types (Lee et al., 2006). In addition, default mode network changes in Alzheimer's disease were captured by constructing MSTs based on part of the original graph (Ciftci, 2011). A recent study on functional network changes during brain maturation in children revealed that MST network analyses were sensitive for detecting changes in network topology and were related to conventional graph theoretical outcome measures on the same data (Boersma et al., 2012).

The aim of our study was three-fold. Firstly, the main question was to investigate if we could detect functional network changes in MSTs of early RRMS patients. Secondly, to what extent these changes were associated with cognitive dysfunction. Thirdly, if these changes in MST topology between MS patients and healthy controls were present, could these correspond to changes in the critical backbone of functional brain networks in RRMS?

Methods

General study design

In this cross-sectional study, MS patients and healthy controls underwent MEG, MRI, neuropsychological assessment and neurological examination on the same day. As outcome measures we used MST metrics, cognition and neurological status. An overview of the applied methods is given in Fig. 1.

Participants

Subjects from a previous study were included (Meer et al., 2013; Tewarie et al., 2013): 21 MS patients (mean age 41.9 ± 7.7, disease duration 6.8 ± 0.9 years) and 17 controls (mean age 39.8 ± 9.8) and were gender-, education- and age-matched. All patients were diagnosed with clinically-definite Multiple Sclerosis (Polman et al., 2005), specifically RRMS (Lublin and Reingold, 1996). Patients were recruited from the VU University Medical Center. All patients were part of the six-year follow-up of an early inception cohort, in which patients were included at diagnosis and subsequently followed annually (Schoonheim et al., 2012b). Physical disability was measured using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) and found to be relatively mild (median 2, range 0–4.5). The study was approved by the institutional ethics review board of the VUmc and all subjects gave written informed consent prior to participation. All subjects underwent a set of neuropsychological tests as described earlier (Schoonheim et al., 2011; Tewarie et al., 2013). In summary, the brief repeatable battery for neurological disease (BRB-N), consisting of the selective reminding test (SRT), the 10/36 spatial recall test (SPART), the symbol digit modalities test (SDMT), the word list generation test (WLG), the concept shifting test (CST), the stroop colour word test and the memory comparison test (MCT) were administered. An overall cognitive Z-score was calculated and used in further analyses.

Magnetic Resonance Imaging

An MRI scan was obtained from all subjects, using a 3 T-MRI system (GE Signa HDXT V15m). A 2D dual-echo T2-weighted sequence (TR 9680 ms, TE 22/112 ms) and T1-weighted sequence (TR 475 ms, TE 9 ms) were obtained with 48 slices of 3 mm and 3D-T1 heavily T1-weighted sequence (FSPGR, TR 7.8 ms, TE 3.0 ms, TI 450 ms) with 1 mm, slices covering the entire brain. All scans were inspected by an experienced rater (MMS). Subsequently, lesion volumes were quantified. All lesion volumetric analyses were performed using Alice (Perceptive informatics Inc.) applying a local thresholding technique. Total gray matter (NGMV), total white matter (NWMV), and whole brain volumes (NBV), corrected for head size, were measured using the FSPGR images and SIENAX (Smith et al., 2002) version 2.5 (part of FSL 4.1, FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl).

Magnetoencephalography

As described previously (Meer et al., 2013; Tewarie et al., 2013), MEG data were recorded using a 151-channel whole-head MEG system (CTF systems; Port Coquitlam, BC, Canada) while participants were in a supine position in a magnetically shielded room (Vacuumschmelze, Hanau, Germany). A third-order software gradient (Vrba et al., 1999) was used with a recording passband of 0–150 Hz and a sample frequency of 625 Hz. Participants had to be free of any metal objects. Magnetic fields were recorded during a no-task, eyes-open condition for three minutes and eyes-closed condition for five consecutive minutes. At the beginning and end of each recording, the head position relative to the coordinate system of the helmet was determined by leading small alternating currents through three head position coils attached to the left and right preauricular points and the nasion.