Graph Theoretical Framework of Brain Networks in Multiple Sclerosis: A Review of Concepts

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INTRODUCTION

Multiple sclerosis (MS) is a chronic and heterogeneous autoimmune disease of the central nervous system leading to progressive clinical disability. The underlying pathology is characterized by inflammation and demyelination. Further processes of remyelination, repair, and functional and structural reorganization are important hallmarks of the disease (Filippi and Agosta, 2009). The sensitivity of magnetic resonance imaging (MRI) to acute and chronic white matter (WM) lesions has made this tool essential for diagnosis and treatment monitoring (Igra et al., 2017). However, conventional MRI techniques do not depict processes of brain reorganization and poorly reflect the clinical long-term course. Standard MRI protocols (i.e. T2-weighted lesion load) only weakly correlate with the emerging clinical disability (Li et al., 2006). Besides T2-visible lesions, the normal-appearing WM (NAWM) and gray matter (GM) are also diffusely affected in MS (Droby et al., 2015). This widespread pathology leads to altered connectivity between interacting brain regions and emerging functional impairment (e.g., motor and cognitive deficits, fatigue, psychiatric comorbidities such as depression or anxiety). Further adaptive processes of plasticity and metaplasticity may play an important role for the clinical course and disability progression. A holistic characterization of the focal lesions, WM and GM properties is of essential importance for forecasting the disease course and monitoring the efficacy of possible preventive or therapeutic interventions.

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Abbreviations: CIS, clinically isolated syndrome; DMN, default mode network; DTI, diffusion tensor imaging; EDSS, expanded disability status scale; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; GM, gray matter; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, multiple sclerosis functional composite; NAWM, normal-appearing white matter; PASAT, paced auditory serial addition test; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; TWMLL, total white matter lesion load; WM, white matter.

Focal demyelination is spread over the entire brain mainly involving WM, with predilection sites in the periventricular regions, while GM lesions are increasingly considered as significant hallmarks of the disease and play an important role for the long-term functional outcome (Seewann et al., 2011; Droby et al., 2015, 2016). It is entirely conceivable that WM and GM lesions have an essential effect on the interaction between brain regions. Despite predilection sites, the occurrence, location, shape and size of inflammatory lesions vary unpredictably. Furthermore, as of yet, no analytical strategies besides lesion counts or volume measurements have been adequately applied to quantify the lesion load to account for topographic, neuroanatomical particularities (De Stefano et al., 2002). Moreover, appropriate longitudinal analytical strategies for lesion mapping are needed.

Network-based approaches offer a possible solution to depict the topological organization of the brain of MS patients (Bullmore and Sporns, 2012). This not only allows to visualize the overall connectivity patterns, but also allows to quantitatively characterize the brain's global organization, further providing a framework to elucidate the relationship between brain structure and function.

Functional networks are commonly reconstructed based on the blood-oxygen-level-dependent (BOLD) signal, which is obtained from functional MRI (fMRI) (Logothetis, 2008). This approach has become vital to study the changes in blood oxygenation, which is closely linked to neural activity. Additionally, networks can be reconstructed from the electric potentials and magnetic fields generated by the brain, measured with electroencephalography (EEG) or magnetoencephalography (MEG) (Stam, 2004).

Structural networks can be reconstructed e.g., from T1-weighted MR images (He et al., 2007). Differences in image intensities arise from the latency, which is required by spinning protons to realign with an external magnetic field. As a result, the dominant signal intensities within the brain differ between GM, WM tissue and cerebrospinal fluid. Moreover, diffusion-tensor imaging (DTI) measures the diffusion of water molecules to generate contrast in MR images (Basser et al., 1994). For example, the DTI metric fractional anisotropy (FA) describes how probable it is that water diffusion is restricted to a specific orientation, and is thought to reflect fiber density, axonal diameter, and myelination in WM. This technique has the potential to map the WM integrity *in vivo* and non-invasively (Basser et al., 2000).

In recent years, graph theory has become an important approach to model brain networks as an interconnected and dynamic system (Bassett and Sporns, 2017). Current applications showed exceptional utility to characterize physiological and pathological cerebral processes and offer a more comprehensive model of neurological disorders. The graph theoretical analysis of brain networks in patients with MS has also introduced new avenues for the non-invasive characterization of disease-related structural and functional alterations that robustly mirror the disease course and clinical phenotypes (Hawellek et al., 2011). Given that most of the analyses on brain networks using graph theory have been conducted on clinically isolated syndrome (CIS) and relapsing-remitting MS (RRMS), in the present review we focus on these MS types, and discuss only selected findings in progressive types of MS. In this review, we present an introduction to graph theoretical metrics, review the latest functional and structural studies of MS, and discuss the clinical implications and future directions.

BASIC CONCEPT OF GRAPH THEORY AND PITFALLS IN MS

Modelling brain connectivity using graph theory

In graph theory, the brain is modeled in terms of nodes, as defined by distinct anatomical regions, and edges or connections, representing the existence or the strength of interactions between two regions (Fornito et al., 2016). The brain parcellation into nodes commonly follows a neuroanatomical scheme reflecting functional specialization. Strategies for node definition are emerging and are an active field of research, as the choice of parcellation scheme alters the resulting network structure (Zalesky et al., 2010). Moreover, it is important to keep in mind that while the nodes are considered in the geometrical representation, the anatomical distance between regions is not directly considered for the reconstruction of the network. The presentation of the general available software resources to reconstruct the brain networks is out of the scope of the present review. For more detailed information we invite the reader to consider recent reviews covering these topics (Bassett and Sporns, 2017; Liao et al., 2017). Only relevant aspects for MS imaging will be presented.

Possible connections between anatomical regions can be depicted through functional or structural imaging. Functional connectivity measures are obtained from time-dependent statistical associations between signals (e.g., from fMRI) (Friston, 2011). In this context, brain activity can be divided into task-directed or resting state (no-task) activity, each with specific activation profiles and different sets of involved regions. Analyses can be conducted in both the time and frequency domain, and based on that, numerous methods are applicable to construct brain functional networks. For example, analytical methods such as independent component analysis, seed-based and granger causality analyses have been widely applied (McKeown et al., 1998; Fox et al., 2005; Roebroeck et al., 2005), whereas graph theory has become increasingly important in the last years (Aerts et al., 2016).

Structural connectivity as reconstructed from diffusion imaging can be defined by the strength of anatomical connections between pairs of regions, mirroring properties of fiber bundles (Hagmann et al., 2008). In order to estimate WM fascicles and their projections, deterministic or probabilistic tractography analyses obtained from diffusion MRI are commonly performed, such that inferred structural connections can be fed into connectivity matrices (Behrens et al., 2007). A second possibility for the structural graph reconstruction is the use of structural covariance parameters, i.e. volume or cortical thickness

measurements, which allows for the calculation of inter-regional correlations (Lerch et al., 2006).

Regardless of whether structural or functional imaging is applied, the result is a connectivity matrix with a set of elements representing the implicit strength of the connections. This matrix can be thresholded and additionally binarized in order to reduce spurious or false positive connections.

The network's topological architecture is defined based on the relations of nodes and edges (Fig. 1). Different measures can be computed in order to quantify the global or local network organization. Global measures (e.g., path length and efficiency, see Table 1), provide an indication of the entire network's capability for information integration. Additionally, segregation measures, like clustering or modularity, are of particular interest for information processing at the local level, as they characterize the interactions of an individual node with its immediate neighbors (see Rubinov and Sporns, 2010 for a detailed description of network parameters). Moreover, measures of small-worldness can be used to assess the trade-off between local and global connectivity which enables efficient communication (Watts and Strogatz, 1998). An overview of selected network parameters, with description and related results is provided in Table 1. These network measures can be used to reveal fundamental aspects of normal and abnormal brain organization that are linked to underlying brain pathology.

Network analysis and pitfalls in MS

Distinct connectivity patterns have been increasingly linked to specific MS phenotypes using graph theory (Kocevar et al., 2016; Muthuraman et al., 2016). A preponderant pattern of decreased global connectivity due to acute neuroinflammation (Kocevar et al., 2016) or increased lesion load (He et al., 2009) can be attributed to the disease course. In addition, possible adaptation patterns with increased local and modular connectivity, reflecting compensatory mechanisms and network reorganization have been described (Fleischer et al., 2017). This complex interaction of long-range disconnection with a less efficient information transfer and a local reorganization might be of essential importance for the long-term outcome. The exact influence of these mechanisms on the interplay between focal demyelination and diffuse tissue damage for the entire network function and long-term disability is however still unclear.

The algorithms used to estimate the cortical thickness for structural network reconstruction are mainly based on T1-weighted sequences (Dale et al., 1999; Han et al., 2004; Kim et al., 2005), commonly assuming the absence of brain pathology (Shiee et al., 2014). However, morphometric measures like cortical thickness correlate with lesion load in MS (Charil et al., 2007). Hence, the cortical reconstruction may be biased by the presence of focal lesions, necessitating paradigms to quantify lesion load and topography. Nowadays, tools such as FreeSurfer (Dale et al., 1999) have integrated the possibility to use previously mapped lesions (cortical and juxtacortical) to correct the surface topology. This correction step has been shown to improve the surface reconstruction and further measures of cortical thickness (Shiee et al., 2014). The evaluation and appraisal of focal lesions on the network reconstruction is of great importance, since new lesions in specific regions could significantly influence structural (Droby et al., 2015) and functional brain networks (Droby et al., 2016). Due to the variety of network alterations seen in different MS populations, disease courses and disease durations, the value of longitudinal network studies to open new avenues for understanding MS pathophysiology is rising.

FUNCTIONAL NETWORK CONNECTIVITY IN MS

Important insights into cerebral reorganization processes due to acute and chronic inflammatory activity have become possible through fMRI studies. Functional connectivity alterations explain functional deficits and mirror the disease course (Rocca et al., 2017). Most of the performed studies analyzed brain networks during the resting-state. This task-free approach has the advantage of being independent from patients' disability levels and performance in the task-based MRI. Besides graph theoretical analyses, other methods such as independent component analysis or large-scale Granger causality (Abidin et al., 2017) have been previously used for the identification of the specific networks, typically in comparison to healthy controls (e.g., Gamboa et al., 2014; Faivre et al., 2016; Rocca et al., 2016). In this way, an increased functional activation of the basal ganglia and thalamus, as part of the motor network and relay centers for cortico-subcortical interactions, has been detected in comparison to healthy controls (Dogonowski et al., 2013). In a subsequent study, the authors found increased connectivity in primary and secondary motor regions after an acute relapse, while connectivity decreased following the recovery of motor functions (Dogonowski et al., 2016). In line with that, increased connectivity has been reported adjacent and contralateral to lesions, suggesting that functionally linked brain regions compensate for the focal structural damage (Droby et al., 2016).

Remarkably, not only a functional connectivity increase was detected as a possible compensatory mechanism in MS patients (Hawellek et al., 2011; Rocca et al., 2012; Basile et al., 2014), but also functional connectivity reductions were reported (Rocca et al., 2010b, 2012; Bonavita et al., 2011), potentially appearing as a consequence of reorganization or adaptation to acute or chronic inflammation. However, connectivity levels alone cannot differentiate between these mechanisms, and hence are not informative for ongoing pathological processes. The seemingly contradictory findings arise mainly because of the dynamical nature of connections, which is mostly disregarded. For instance, the connectivity levels calculated from the fMRI signal do not take into account that functional connectivity increases are evoked by activation of both inhibitory and excitatory neuron populations (Logothetis, 2008).

After highlighting the pitfalls of studying the connections between brain regions in an isolated manner, it becomes evident that addressing the entire brain network and its efficiency in MS patients using

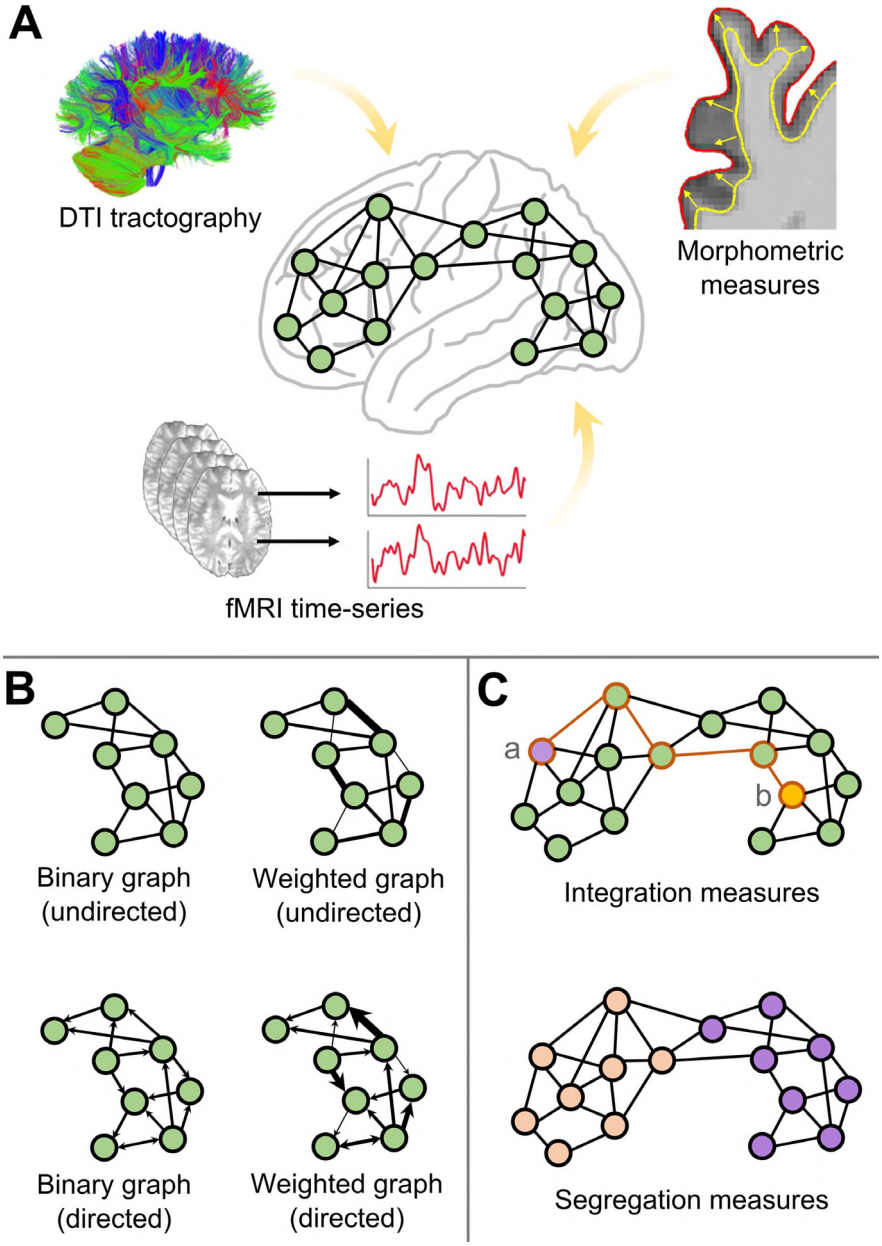

Fig. 1. (A) Brain networks are described as a graph, comprising a collection of nodes (representing brain anatomical regions) and edges (representing structural connections or functional relationships). (B) The network can be represented as binary (upper left) or weighted (upper right) graphs and can contain information about the direction of causal inference (lower row) between anatomical regions. (C) Graphical representation of some key graph theory metrics. Distance measures (upper row) like path length measure the average shortest distance between region a and region b; Segregation measures (lower row) like clustering coefficient represent the number of existing connections between a brain region and its nearest neighbors.

graph theory could provide a more integrative characterization of its connectivity dynamics and topological organization.

Currently, only few studies have applied graph theory to fMRI data in MS, and these mostly investigated the brain's resting-state activity. Schoonheim et al. (2014) used eigenvector centrality mapping to select clusters of interest and reported an increase in centrality in the posterior cingulate gyrus and decreased centrality in the sensorimotor and ventral stream areas. Since the thalamus, an area exhibiting increased centrality, showed a higher connectivity to areas with decreased centrality, a rerouting of thalamic connections as a response to continuous inflammatory activity was proposed (Schoonheim et al., 2014). Furthermore, a recent study determined that network centrality abnormalities are related to the level of cognitive impairment (visuospatial and working memory, executive functioning, verbal memory and fluency, information processing speed and attention) in MS patients who were relapse-free for at least two months (Eijlers et al., 2017). The authors reported significantly decreased centrality in middle temporal regions and an increase in the default mode network (DMN) and frontal regions when comparing cognitively impaired patients with both cognitively preserved MS patients and healthy subjects. In comparison with the healthy group, further centrality decreases were observed in occipital, sensorimotor, hippocampal and caudate areas in the cognitively impaired MS patients, while centrality was increased in cerebellum and thalamus. The thalamus, among GM structures, is one of the earliest regions showing microstructural degeneration in MS (Deppe et al., 2016), hence its functional connectivity is of significant interest. Accordingly, one recent study found increased seed-based average thalamo-cortical connectivity in a heterogeneous sample of MS patients compared with healthy subjects, however, network parameters derived from graph theoretical analysis were not different between the groups (Tewarie et al., 2015). Liu et al. (2017) also investigated resting-state network alterations, reporting a decrease in local and global efficiency in RRMS patients. Nodal efficiency was decreased in the superior temporal gyrus, left rolandic operculum and left insula in both CIS and RRMS patients. Furthermore, the mean connectivity strength, which was related to disease duration, allowed the separation of RRMS and CIS patients from healthy controls with an accuracy of 77% for each group, but could not distinguish between the two groups of patients. In a dual structural and functional network approach, RRMS but not CIS patients demonstrated a significant decrease in local efficiency and clustering relative to

controls, while no differences emerged on the global level for either group (Shu et al., 2016). The lack of significant network changes in the CIS group was suggested to mirror subtle functional changes during the early stage of the disease (Shu et al., 2016).

In a further resting-state fMRI study including a heterogeneous sample of RRMS and CIS patients with no or only low disability status, indicated by Expanded Disability Status Scale (EDSS) scores lower than 3 and T2 lesion volume below 15 ml, network reorganization was found, as reflected by increased modularity (Gamboa et al., 2014). Since increased modularity is related to decreased long-range paths and increased local connectivity, the authors suggested that this may be the result of the disseminated focal lesions, leading to an adaptive rewiring of previously interconnected areas. The functional correlate of the modularity levels was demonstrated by better performance on neuropsychological testing (working memory, attention and speed of information processing) corresponding to lower modularity. Using a support vector machine classifier they were further able to differentiate patients from controls with an accuracy of 75% based on the modularity values (Gamboa et al., 2014). Rocca et al. (2016) showed that cognitively impaired MS patients, as determined with the paced auditory serial addition test (PASAT), can possibly be distinguished from cognitively preserved MS patients by a lower global network efficiency (Rocca et al., 2016). In this study, MS patients with cognitive impairment showed a reduction in centrality in the thalamus and left frontal lobes.

As previously discussed, most of these results point to a disruption of global information transfer in patients with MS, indicated mainly by abnormal network degree, global efficiency and path length, which is associated with the ongoing cognitive decline. However, on the local level the results are not always unequivocal. Recent evidence suggests local network efficiency disruption, however no differences in clustering coefficient or local efficiency compared to healthy individuals have been reported as well, indicating a preserved local network efficiency (Rocca et al., 2016). This controversy can result from the heterogeneity of the studied population, as different disease phenotypes were included in the specific studies. For example, Gamboa et al. (2014) specifically investigated network alterations in patients in the initial phase of MS (CIS and early RRMS) compared to healthy subjects, while Liu et al. (2017) and Shu et al. (2016) focused on comparisons between RRMS and CIS patients. Most other studies, however, included diverse disease subtypes including CIS, RRMS, primary progressive (PPMS) and secondary progressive MS (SPMS) (Schoonheim et al., 2014; Tewarie et al., 2015; Rocca et al., 2016; Eijlers et al., 2017). Furthermore, important clinical hallmarks such as acute relapses, disease duration or severity might be essential as well for dynamic changes of network properties.

Moreover, one further study focused on gender differences in MS, reporting a lower path length but normal clustering in male patients compared to male healthy controls, while no differences were detectable in females (Schoonheim et al., 2012). Yet, the interpretation is challenging as a decreased network efficiency in patients was inferred, while a lower path length along with preserved clustering usually suggests an efficiency increase (Watts and Strogatz, 1998).

Only one study used graph theoretical analyses on functional RRMS data obtained at different time points (Faivre et al., 2016). At baseline, nodal and local efficiency was higher in patients than healthy controls, while after two years efficiency values were decreased, and no longer differed from healthy controls. Patients were further stratified according to their baseline disability status, as assessed by the EDSS and Multiple Sclerosis Functional Composite (MSFC) scores. Thereby, the authors determined that the increase in nodal and local efficiency was related to the level of disability. The observed decrease in nodal and local efficiency after two years was detected for disabled MS patients, whereas patients with a less severe disease course showed an efficiency increase. In this study, differences in resting-state functional connectivity were most evident in the thalamus and the fronto-temporal and cingulate cortices, conferring those regions a pivotal role for the clinical progression. Early occurring, but progressively failing compensatory mechanisms were hypothesized to be responsible for this network change over time (Faivre et al., 2016).

In general, alterations of network parameters have been found predominantly in the sensorimotor cortex, cingulate and fronto-temporal regions, as well as in the thalamus (Schoonheim et al., 2014; Faivre et al., 2016; Rocca et al., 2016; Eijlers et al., 2017). The thalamus is known to transmit information between a number of cortical and subcortical structures and is involved in motor, integrative and higher cortical functions (Minagar et al., 2013), hence loss of connectivity of this region is very likely to translate into the clinical disability observed in MS patients. Indeed, thalamic degeneration has been shown to correlate with the functional decline even at early stages of MS (Benedict et al., 2013). Similarly, fronto-temporal and cingulate cortical atrophy has been associated with clinical disability and WM lesion load (Charil et al., 2007) and directly related to neuropsychological dysfunction in MS (Morgen et al., 2006). Moreover, the presence of focal lesions and atrophy in these regions is correlated with fatigue in MS patients (Rocca et al., 2014).

However, combining all the reported findings to define one clear network setup is elusive, as there is heterogeneity of the results due to several influencing factors differing across the studies. For example, by creating the connectivity matrix neglecting all negative correlations, a loss of information is provoked (Shu et al., 2016). Additionally, patient characteristics strongly differ between studies regarding disease duration, disability level, age, gender, disease course and further demographic and disease-specific variables. Also, most studies have been performed with data acquired cross-sectionally, which do not allow inferences to be made about the dynamics of brain networks in MS. Jack et al.

Table 1. Selected graph theoretical parameters and their description as well as related findings in studies which investigated alterations in structural and functional networks. Unless otherwise indicated, Cohen's *d* is stated in brackets (in some cases, it was averaged over regions or densities). From each study and group, sample sizes are specified. ↑ increase, ↓ decrease, ≈ no alteration in graph theoretical parameter. √ Studies supporting our hypothetical model of early network compensation. MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; CIS, clinically isolated syndrome; HC, healthy controls; CI, cognitively impaired; CP, cognitively preserved; WM, white matter; DMN, default mode network

Measures	Description & interpretation	Alterations in structural networks	Alterations in functional networks
Measures of centrality			
Degree centrality (Freeman, 1977, 1979)	Quantification of the importance of a node in the network based on the number of connections that it exhibits to others, thus a measure of the extent to which a graph is connected. Nodes termed 'hubs' have a higher degree than other nodes in the network. → An increase indicates a higher influence of the corresponding region in the network		Eijlers et al. (2017) 87 CI MS, 180 CP MS, 96 HC ↑ CI MS vs. CP MS (0.51; 0.41) and HC (0.82; 0.42) in DMN and frontal regions ↑ CI MS vs. HC in cerebellum (0.48) and thalamus (0.48) ↓ CI MS vs. CP MS (0.49) and HC (0.73) in middle temporal areas ↓ CI MS vs. HC in occipital (0.97) and sensorimotor areas (0.58), hippocampus (0.67) and caudate nucleus (0.65)
Eigenvector centrality (Bonacich, 1972; Newman, 2006a)	Nodes are weighted considering not only their number, but also quality of connections. → Brain regions with higher eigenvector centrality are connected to regions that themselves are central in the network		Schoonheim et al. (2014) 128 MS, 50 HC ↑ MS vs. HC in thalamus (0.44), posterior cingulate gyrus (0.68) ↓ MS vs. HC in sensorimotor (0.71) and ventral stream areas (0.74)
Nodal efficiency (Freeman, 1977; Achard and Bullmore, 2007)	The minimum shortest path length between a particular node and all other nodes in the network. → An increase represents a higher ability of a region to propagate information with the other nodes		Liu et al. (2017) 34 MS, 34 CIS, 36 HC ↓ MS and CIS vs. HC in superior temporal gyrus, left rolandic operculum and insula Faivre et al. (2016) 8 CI RRMS, 16 CP RRMS, 38 RRMS, 24 HC ↑ Early RRMS vs. HC at baseline (0.34) ↓ CI RRMS after two years vs. CI RRMS at baseline in thalamus and fronto-temporal regions (0.832)
Measures of segregation			
Clustering coefficient (Watts and Strogatz, 1998; Onnela et al., 2005)	The fraction of a node's neighbors that also neighbor each other. A measure of cluster formation, resulting in dense interconnection with neighboring regions in order to maintain local information flow. → An increase represents a cost-efficient organization principle of the brain with increased local cliquishness	Tewarie et al. (2014b) 102 MS, 42 HC ↑ MS vs. HC √ Muthuraman et al. (2016) 33 RRMS, 20 CIS, 40 HC ↑ RRMS vs. CIS (0.60) and HC (0.92) ↑ CIS vs. HC (1.00) Shu et al. (2016) 32 RRMS, 41 CIS, 35 HC ↓ RRMS and CIS vs. HC √ Fleischer et al. (2017) 33 early RRMS, 32 HC ↑ RRMS vs. HC (1.00) √ Kocevar et al. (2016) 24 RRMS, 17 PPMS, 24 SPMS, 64 CIS, 26 HC ↓ HC vs. RRMS and SPMS	Shu et al. (2016) 32 RRMS, 41 CIS, 35 HC ↓ RRMS and CIS vs. HC ≈ CIS vs. HC Tewarie et al. (2015) 86 MS, 21 HC ≈ MS vs. HC Rocca et al. (2016) 246 MS, 55 HC ≈ MS vs. HC Schoonheim et al. (2012) 30 MS, 30 HC (each 15 female) ≈ male MS vs. male HC ≈ female MS vs. female HC
Transitivity (Newman and Park, 2003)	The probability that two nodes neighbor each other based on the relative number of triangles in the graph, compared to the total number of connected triples of nodes. A variant of the clustering coefficient.		

Table 1 (*continued*)

Measures	Description & interpretation	Alterations in structural networks	Alterations in functional networks
	→ An increase represents a cost-efficient organization principle of the brain with increased local cliquishness	Llufriu et al. (2017) 72 MS, 38 HC ↑ MS vs. HC (0.50)	
Local efficiency (Latora and Marchiori, 2001; Vragovic et al., 2005)	The average of the inverse shortest path length between all neighbors of a given node, but considering that the node is taken out from the network. → An increase shows that the network capacity for local information transfer between neighboring regions is strengthened	√ He et al. (2009) 330 RRMS ↓ RRMS with increasing WM lesion load Shu et al. (2011) 39 MS, 39 HC ↓ RRMS vs. HC (0.86) ↓ RRMS with increasing EDSS score (0.63) and WM lesion load (0.66) √ Fleischer et al. (2017) 33 early RRMS, 32 HC ↑ RRMS vs. HC (3.39) Shu et al. (2016) 32 RRMS, 41 CIS, 35 HC ↓ RRMS and CIS vs. HC ↓ RRMS vs. CIS	Liu et al. (2017) 34 MS, 34 CIS, 36 HC ↓ RRMS vs. HC ≈ CIS vs. HC Shu et al. (2016) 32 RRMS, 41 CIS, 35 HC ↓ RRMS vs. HC ≈ CIS vs. HC Rocca et al. (2016) 246 MS, 55 HC ≈ MS vs. HC √ Faivre et al. (2016) 8 CI RRMS, 16 CP RRMS, 38 RRMS, 24 HC ↑ RRMS vs. HC at baseline (0.88) ↑ CI RRMS vs. HC after two years (0.68) ↓ CI RRMS after two years vs. CI RRMS at baseline (0.81) ↑ CP RRMS vs. HC after two years (0.78) ↑ CP RRMS after two years vs. CP RRMS at baseline (0.41)
Modularity (Girvan and Newman, 2002; Newman, 2006b)	A module is a set of densely connected nodes that are sparsely connected to the rest of the network. Higher modularity implies a stronger subdivision into segregated groups of nodes. → An increase in modularity indicates an optimized network organization principle of the brain in response to changing environments	√ Muthuraman et al. (2016) 33 RRMS, 20 CIS, 40 HC ↑ RRMS vs. CIS (0.56) and HC (1.03) ↑ CIS vs. HC (0.99) √ Fleischer et al. (2017) 33 early RRMS, 32 HC ↑ RRMS vs. HC (0.68) √ Kocevar et al. (2016) 24 RRMS, 17 PPMS, 24 SPMS, 64 CIS, 26 HC ↓ HC vs. RRMS (1.18) ↓ CIS vs. RRMS (2.00), SPMS (1.33) and PPMS (1.18) ↑ RRMS vs. SPMS (0.67) and PPMS (1.18)	√ Gamboa et al. (2014) 16 early RRMS, 20 HC ↑ MS vs. HC (3.54)
Measures of integration			
Global efficiency (Latora and Marchiori, 2001)	The average of the inverse shortest path length between all nodes in the network. A network integration parameter to describe information flow over the entire network. → An increase indicates that brain units are well integrated and that information transfer across the whole brain is more efficient	He et al. (2009) 330 RRMS ↓ RRMS with increasing WM lesion load Shu et al. (2011) 39 MS, 39 HC ↓ RRMS vs. HC (0.99) ↓ RRMS with increasing EDSS score (0.66) and	Liu et al. (2017) 34 MS, 34 CIS, 36 HC ↓ RRMS vs. HC ≈ CIS vs. HC Shu et al. (2016) 32 RRMS, 41 CIS, 35 HC ≈ MS and CIS vs. HC Rocca et al. (2016) 246 MS, 55 HC

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Table 1 (*continued*)

Measures	Description & interpretation	Alterations in structural networks	Alterations in functional networks
		WM lesion load (0.99) Muthuraman et al. (2016)	↓ CI MS vs. CP MS (0.51)
		33 RRMS, 20 CIS, 40 HC ↑ RRMS vs. CIS (0.84) ↑ CIS vs. HC (0.98) ≈ MS vs. HC Shu et al. (2016)	
		32 RRMS, 41 CIS, 35 HC ↓ RRMS and CIS vs. HC ↓ (RRMS vs. CIS) Fleischer et al. (2017)	
		33 early RRMS, 32 HC ≈ RRMS vs. HC Llufriu et al. (2017)	
		72 MS, 38 HC ↓ MS vs. HC (1.00) Kocevar et al. (2016)	
		24 RRMS, 17 PPMS, 24 SPMS, 64 CIS, 26 HC ↑ HC vs. CIS, RRMS, SPMS and PPMS Tewarie et al. (2014b)	
Path length (Watts and Strogatz, 1998)	The shortest distance between pairs of nodes. A measure of the efficiency of information transfer within a network. → An increase reflects an impaired global integration and a lower ability of the brain network to propagate information in parallel	102 MS, 42 HC ↑ MS vs. HC Llufriu et al. (2017)	Shu et al. (2016) 32 RRMS, 41 CIS, 35 HC ≈ MS and CIS vs. HC Schoonheim et al. (2012)
		72 MS, 38 HC ↑ MS vs. HC (0.81) Kocevar et al. (2016)	30 MS, 30 HC (each 15 female) ↓ male MS vs. male HC (0.95) ≈ female MS vs. female HC Tewarie et al. (2015)
		24 RRMS, 17 PPMS, 24 SPMS, 64 CIS, 26 HC ↓ HC vs. CIS (2.00), RRMS (1.00) and SPMS (2.00)	86 MS, 21 HC ≈ MS vs. HC Rocca et al. (2016)
			246 MS, 55 HC ↑ CI MS vs. CP MS (0.47)
Communicability (Estrada and Hatano, 2008)	The count of the total number of walks between two nodes, considering that the longer walks have less influence than the shorter walks. A measure of the efficiency with which information can spread across a network by taking indirect connections into account. → An increase indicates a protective mechanism of the brain from errors in transmission (and thus is presumably sensitive to reorganizational changes after a lesion)	Li et al. (2013) 24 RRMS, 30 HC ↑ HC vs. RRMS in frontal regions ↓ HC vs. RRMS in the deep gray matter	
Measures of network resilience			
Assortativity (Newman, 2002)	The tendency of a network's node to attach to nodes with the same degree. A measure of resilience of a network. → An increase describes the improved ability of the network brain to maintain functioning as response to continuous damage	Llufriu et al. (2017) 72 MS, 38 HC ≈ MS vs. HC (0.50) Kocevar et al. (2016)	Rocca et al. (2016) 246 MS, 55 HC ↑ CI MS vs. CP MS (0.21)
		24 RRMS, 17 PPMS, 24 SPMS, 64 CIS, 26 HC ↓ HC vs. SPMS (1.61) and PPMS (1.98) ↓ CIS vs. SPMS (1.00) ↓ RRMS vs. SPMS (1.28) and PPMS (1.76)	

(2010) linked potential imaging, biological and clinical markers to depict their alterations over the time course of Alzheimer's disease. This theoretical model has been adapted to MS, relating ongoing structural damage to changes in network efficiency that ultimately cause cognitive dysfunction (Schoonheim et al., 2015). From the current perspective of network analysis over time, we propose a modification of this model by including network compensation mechanisms in addition to clinical impairment and tissue damage (Fig. 2). Our model is based on evidence suggesting that an increased or maintained modular and local connectivity may represent an important hallmark of the network reorganization that is thought to mediate robustness and efficiency instead of functional deterioration (Gamboa et al., 2014; Faivre et al., 2016; Rocca et al., 2016). As soon as this network adaption cannot be sustained due to ongoing tissue damage, the network collapses and clinical impairment occurs.

STRUCTURAL NETWORK CONNECTIVITY IN MS

Analysis of structural networks through graph theory could indeed offer new tools that mirror ongoing pathological processes at different anatomical sites more precisely (Stam, 2014). For the exact characterization of tissue phenomena such as demyelination, remyelination and neurodegeneration, it is imperative to model GM (He et al., 2009) and WM properties (Shu et al., 2011). For the description of GM networks, correlations of cortical thicknesses or GM intensities as derived from voxel-based morphometry across brain areas at the group level are used. Regions with similar microstructural properties have a higher probability to show structural connections (Mechelli et al., 2005; Lerch et al., 2006). This is, however, an indirect degree of inter-regional interactions that cannot be directly applied to measure connectivity at the single-subject level. Several procedures have been proposed to overcome methodological drawbacks and quantify structural connectivity at the single-subject level (Tijms et al., 2012; Kim et al., 2016; Wang et al., 2016). One additional problem is the implication of semi-quantitative measures (i.e. GM intensity analysis of T1-weighted images) for the structural covariance. The use of direct quantitative measures (e.g., proton density or magnetization transfer ratio) could offer a more reliable assessment of tissue properties; however the specificity to biological changes is still a matter of debate. Moreover, because of longer scanning times and the still existing need to establish the exact link between the measured values and histological properties (e.g., to axon density or myelin concentration), these techniques have not yet found entrance into the network analysis or clinical practice.

An impressive step toward the development of biologically meaningful network reconstruction methods has been achieved by the use of diffusion imaging (van den Heuvel et al., 2010). WM structural connectivity can be reconstructed from diffusion tensor imaging (DTI) with either deterministic or probabilistic tractography (Khalsa et al., 2014). The significant advantage of WM network reconstruction is the ability to assess connectivity properties at the single-subject level (Filippi et al., 2011).

MS as a disconnection syndrome

One of the first graph theoretical studies in patients with RRMS reconstructed the GM networks from cortical thickness correlation measures, showing specific network properties with increased lesion load (He et al., 2009). MS patients exhibited significantly decreased local and global efficiency in cortical thickness covariance networks with increasing total T2-hyperintensive WM lesion load (TWMLL). Several regional correlation strengths (measuring the average correlation extent by which a node is connected to the rest of the network) also showed significant decreases with increasing TWMLL. This inverse correlation was particularly observed in the insula, precentral gyrus, prefrontal and temporal association cortices. Due to previous findings having shown pronounced cortical thinning (Charil et al., 2007) and cortical lesions (Kutzelnigg and Lassmann, 2006) in these regions, the authors suggested that the cortical regions with decreased local efficiency might be more vulnerable to cortical or adjacent WM lesions (He et al., 2009).

In a further analysis of the structural covariance networks reconstructed from T1-weighted images supplied by functional networks analysis reconstructed from MEG, Tewarie et al. (2014b) tested the disruption hypothesis on both network types. The group of MS patients displayed a higher clustering coefficient and a higher shortest path length compared to healthy controls in the structural covariance network, both indicative of a network architecture that is preferentially locally clustered.

To account for the possibility that connections between two adjacent regions may be disrupted by MS lesions, a new network parameter called communicability, depicting both direct and indirect connections between two regions, was recently applied in a DTI-based network analysis within MS patients (Li et al., 2013). The comparison between RRMS patients and healthy controls revealed a decrease in communicability, predominantly within frontal lobe regions.

Moreover, it was recently shown that the disruption of structural networks is associated with impaired cognitive performance, especially involving attention and executive functions (Llufriu et al., 2017). In the analysis of structural networks reconstructed through probabilistic tractography, a decline of structural connectivity was depicted by decreased global efficiency and nodal strength in a mixed group of RRMS and SPMS patients. The repeatedly observed network disruption and the loss of network efficiency have led to the notion of MS as a so-called disconnection syndrome (Rocca et al., 2015) – a network pattern that was also seen in other brain diseases like dementia and schizophrenia (Filippi et al., 2013).

In MS, diffuse changes in WM tissue have been confirmed adjacent to but also distant from the lesion site (Kutzelnigg et al., 2005; Droby et al., 2015). To depict changes within the WM, DTI has been repeatedly used to describe impaired microstructural integrity of WM tracts in the course of MS (Rovaris et al., 2009). Comparative analyses between MS patients and healthy controls have

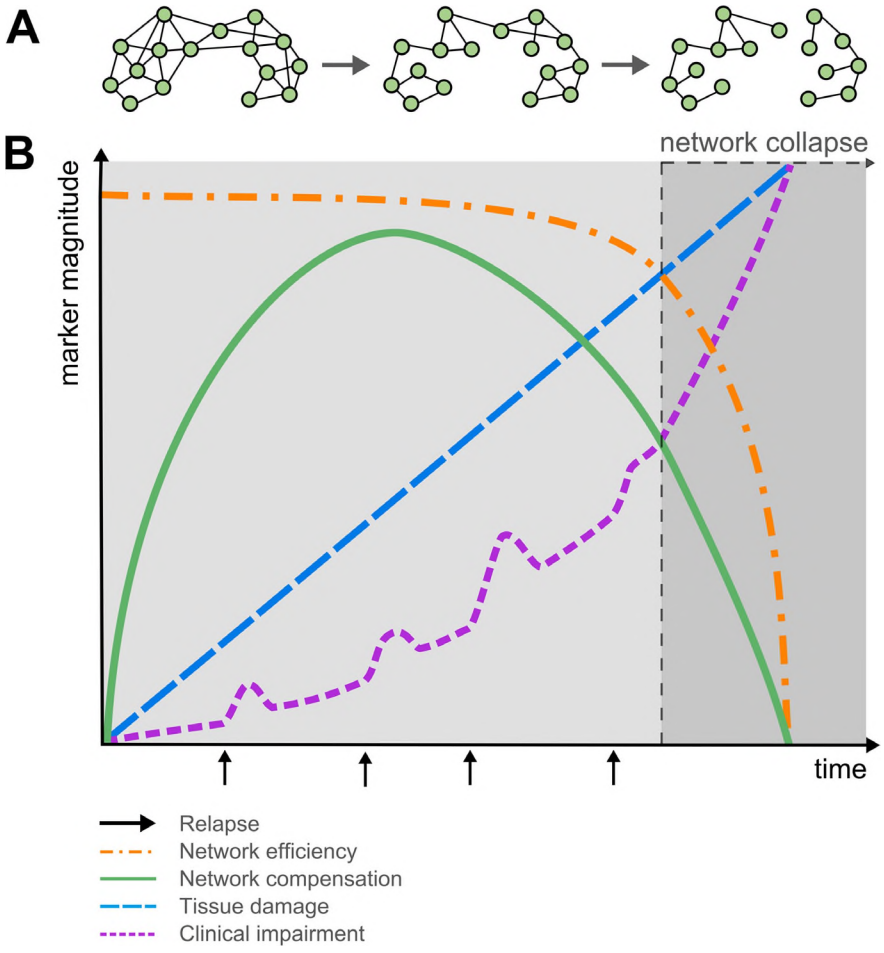

Fig. 2. (A) Exemplified altered network behavior with an initial increase in local and modular processing, which cannot be maintained over time and is followed by a 'network collapse'. (B) Model of network reorganization processes over the disease course including clinical impairment, network efficiency and network compensation as well as tissue damage. Modified from Schoonheim et al. (2015).

shown a reduction in fractional anisotropy and increased diffusivity within WM fiber tracts in NAWM (Roosendaal et al., 2009). Several attempts have been made to model WM connectivity in MS (Shu et al., 2011; Zhou et al., 2014). Using deterministic tractography, Shu and colleagues revealed significant associations between decreased global and local network efficiencies and clinical disability measured by EDSS scores as well as T2 lesion burden in patients with RRMS (Shu et al., 2011). The most pronounced efficiency reduction was observed in regions belonging to the DMN, sensorimotor, visual, and language networks.

Early structural compensation processes

In addition to showing disruption patterns, network analyses have also suggested increased connectivity, which might be of great interest, potentially mirroring aspects of compensation and adaptive reorganization in early MS phases (Rocca et al., 2010a; Muthuraman et al., 2016; Shu et al., 2016; Fleischer et al., 2017). Indeed, specific topology patterns have been linked to adaptability in the normal brain (Fan et al., 2011), and some parameters are closely related to the disease course and clinical progression, as recently shown in Alzheimer's (de Haan et al., 2012), and in Parkinson's diseases (Baggio et al., 2014).

Structural network alterations in the initial phase of MS were observed by our group in the earliest disease stages (CIS and RRMS patients with a disease onset of less than 6 months) (Muthuraman et al., 2016). A combined GM and WM structural network analysis in subjects with CIS in comparison to patients with early RRMS revealed distinguishable network deviations already in the initial scan after the first demyelinating event (Muthuraman et al., 2016). The structural network reorganization at the very beginning of the disease implied an increased local and modular connectivity and a concomitant decrease in long-range paths (Muthuraman et al., 2016). These findings suggest that the networks in patients with early definite RRMS undergo continuous reorganization processes that either do not or have not yet occurred in those with CIS. Furthermore, by reconstructing structural networks based on DTI, Shu et al. found reduced global and local efficiency as well as decreased clustering in RRMS and CIS in comparison to healthy controls (Shu et al., 2016). In these patients, all of the network properties exhibited intermediate values between healthy controls and MS patients; likely depicting a transition stage before passing over to the relapsing-remitting state of the disease.

Although a loss of communicability in an early MS cohort was seen in comparison to controls in frontal regions (see section 'MS as a disconnection syndrome'), Li et al. (2013) also identified increased communicability between deep GM structures with major inter- and intra-hemispheric WM tracts. These foci of increased communicability were thought to demonstrate early compensatory effects.

Recently, we evaluated the reorganization of structural networks in 138 RRMS patients grouped by their disease duration (Fleischer et al., 2017 and see Fig. 3). We could show that both WM and GM reconstructed networks presented a breakdown of long-range connectivity, but also an increased clustering and modular connectivity pattern, in particular 6 and 12 months after the first clinical event. Cluster formation and brain modularization occurred, although neither lesion load nor brain

volume was significantly altered between the disease duration groups.

Since a relationship between modularity and adaptability of brain was proposed (Kashtan and Alon, 2005; Meunier et al., 2010), these processes of network reorganization presumably represent mechanisms to compensate for ongoing focal damage and are essential to maintain network functioning. Indeed, several studies have presented evidence that community structure properties of the brain (e.g., modularity increase) can be linked to maintenance of function despite continuous damage as shown in neurodegenerative disorders (Meunier et al., 2010, 2014). The observations emphasize that the network architecture changes are not merely a consequence of diffuse tissue damage, but should be seen as integrative processes for optimal network functioning.

Longitudinal approaches

Longitudinal network approaches afford an opportunity to appropriately investigate whether network alterations constitute processes that partially or entirely compensate for tissue damage so that no clinical decline occurs. Since adaptive mechanisms likely emerge in the first year after disease onset (Fleischer et al., 2017), while no other quantifiable differences exist, it is imperative to gain information on the network behavior of MS patients followed-up over months and years. Thereby, it can be determined whether changes in graph theoretical metrics in comparison to healthy controls or to other MS subtypes are consistent over time. For longitudinal analyses, the robust reproducibility over time and low variability of network properties as derived from DTI (Bassett et al., 2011) or fMRI (Deuker et al., 2009) are essential.

One functional connectivity study in CIS patients with no cognitive impairment found increased synchronization at rest in specific brain networks suggestive of early reorganization (Roosendaal et al., 2010). This functional reorganization was observed in the absence of detectable atrophy, but was not (or no longer) detectable in patients with definite RRMS and increased brain damage, indicating that cortical reorganization is an early and probably finite phenomenon in MS. This may suggest that different processes (i.e. atrophy and network alterations) do not completely share an identical temporal pattern. Thus, longitudinal multimodal approaches measuring adaptive or degenerative aspects of the disease are highly warranted.

In the context of reorganization toward a more locally organized network, two studies that analyzed age-related modularity changes of brain networks reported a decrease in the modular structure with increasing age in healthy controls (Meunier et al., 2009; Song et al., 2014). On the one hand, this not only underlines the importance of longitudinal approaches, it also stresses that brain networks studies including MS patients unavoidably need to be accompanied by a matched healthy control group. On the other hand, the decrease in modularity with increasing age in the normal brain supports the concept that the increased modular brain structure observed in MS patients is not related to early degeneration or tissue damage, but rather to an early adaptive response. Hence, the focus on network changes in the initial disease stages should be specifically considered as this phase of the disease is of essential relevance for the long-term prognosis and the development of functional impairment, and thus, an optimal characterization of the underlying processes will help to better forecast the disease course.

Network analyses in Alzheimer's disease presented the first hints of adaptive mechanisms, as mirrored by modularity increases, which are limited to the initial phase of the disease (de Haan et al., 2012). Later, when the network's integrity can no longer be maintained, these adaptive processes abate, resulting in functional impairment.

The above-mentioned studies (see section 'MS as a disconnection syndrome') observed that clinical worsening in MS patients with longer disease duration is accompanied by a decrease in network efficiency. These findings, together with the reported differences between CIS and early RRMS patients as well as the association between disease duration and network parameters, indicate a dynamic rather than immutable nature of the network parameters during the disease course (Figs. 2 and 3).

CLINICAL UTILITY

It is an essential issue to explore and validate potential clinical applications of brain network analyses. Despite the important value of conventional MRI measures (e.g., focal inflammatory lesions, lesion load or brain atrophy) for the diagnostic setup and therapeutic monitoring, the poor-to-moderate correlation between MRI lesion load and patients' clinical disability ("clinical-radiological paradox") remains a pending issue for future studies (Barkhof, 2002; Davis, 2014).

Addressing structural networks properties (e.g., local and global efficiency) instead of lesion load could be implemented to track the long-term disease burden (He et al., 2009). Albeit the efficient small-world properties are maintained in patients with MS, significant disruptions of the global and local network topology could be considered as breaking points for disease progression and clinical decline (Shu et al., 2016). However, clinical decline cannot be explained solely by aberrant cortical GM properties (Tewarie et al., 2014b). Besides changes in GM networks, the topological organization of WM networks based on DTI tractography was shown to be linked to the clinical status – decrease in global efficiency significantly correlated with EDSS scores, disease duration and TWMLL (Shu et al., 2011). Regions which displayed decreased nodal efficiency – precentral gyrus, posterior cingulate gyrus, precuneus, rolandic operculum – also showed significant correlations with the above-mentioned clinical variables (EDSS, disease duration and TWMLL), implying that these areas play a pivotal role in the clinical phenotype of MS patients.

In early disease stages, increased modularity, cluster formation and local efficiency within both GM and WM likely mirror adaptive features of brain networks,

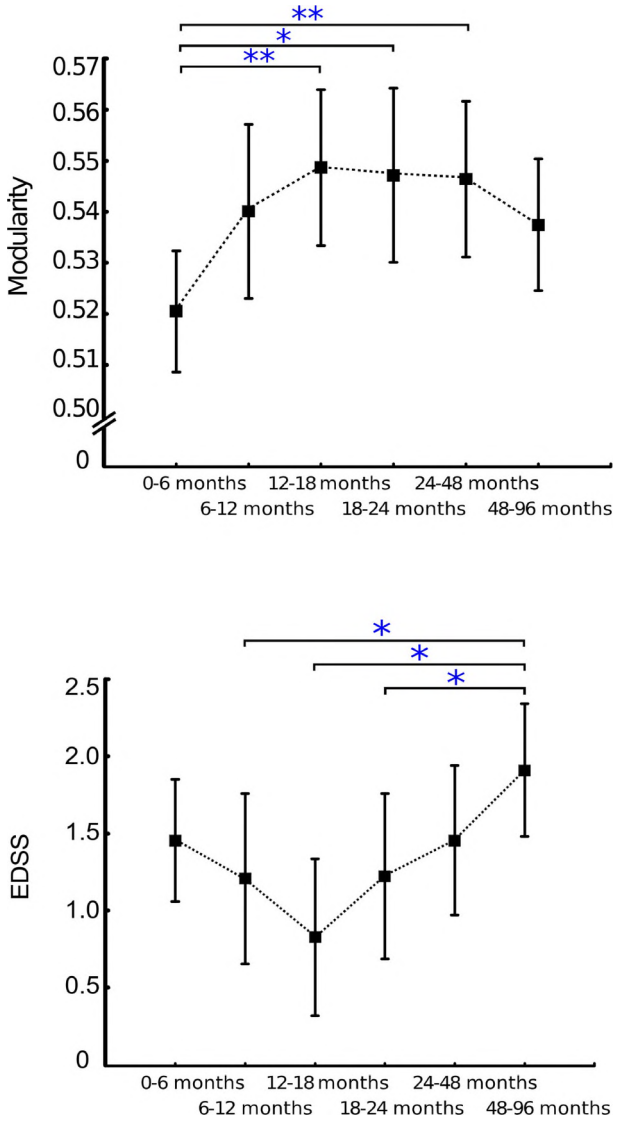

Fig. 3. EDSS scores (lower plot) and the DTI-derived network parameter modularity (upper plot) for the six disease duration groups. * = $p < 0.05$; ** = $p < 0.001$. Modified from Fleischer et al. (2017). Mean values and standard deviations are shown.

counteracting clinical decline (Fleischer et al., 2017). With disease progression, continuous disruption of network efficiency is accompanied by clinical impairment (Fleischer et al., 2017). These observations suggest a mutual evolution of network reorganization and disease deterioration, as presented in our hypothetical model of network compensation (Fig. 2). Although the WM structural reorganization evolved with disease onset, the increased network parameters reached a plateau one year later. Interestingly, EDSS follows a u-shaped curve over the disease stages whereas modularity, clustering coefficient and local efficiency follow an inverse u-shaped curve (Fig. 3).

After the first clinical demyelinating event, patients as well as clinicians are faced with the uncertainty of whether this was an isolated, monophasic syndrome or the first relapse of a chronic neuroinflammatory disease. This differentiation is challenging and clinically highly relevant, because early treatment could delay disease progression (Comi et al., 2009). Based on initial MRI abnormalities of patients presenting with such a first demyelinating event, a clear distinction between CIS and RRMS cannot always be reliably achieved (Montalban et al., 2010), even using the revised McDonald criteria (Polman et al., 2011; Milo and Miller, 2014). Therefore, the characterization of network topology properties could impressively improve the classification of MS clinical subtypes and track the further course or help clinicians to precisely adapt immune modulatory treatment. Few studies aiming to differentiate clinical entities on the basis of structural connectivity have been conducted, applying algorithms for automatized discrimination between CIS and RRMS patients (Kocevar et al., 2016; Muthuraman et al., 2016). In one of our recent studies, we achieved a group classification accuracy of 97% based on clustering coefficient derived from cortical thickness and single-subject performance of 65% based on modularity obtained from probabilistic tractography (Muthuraman et al., 2016). By focusing on the precision of network metrics in early MS, the best performance using a binary classification task was achieved using modularity (*F*-measure (precision and recall) 88.9%) in discriminating CIS from RRMS patients, while assortativity (*F*-measure 70.6%) allowed the differentiation between CIS, RRMS and SPMS patients (Kocevar et al., 2016). Based on T1-weighted and diffusion tensor imaging to reconstruct structural connectivity matrices, the authors showed that modularity was lower in patients with CIS compared to RRMS, SPMS and PPMS, and higher in RRMS compared to SPMS and PPMS patients. These findings suggest that we will likely make use of graph theory network analysis in differentiating clinical subtypes. Network-derived metrics from patients at initial stages of MS, based merely on one structural MRI scan and without a priori knowledge of clinical data or disease history, can be used to feed data into this machine-learning-based classification tool with the potential to be incorporated into routine clinical practice.

Cognitive impairment is common in patients with MS, with a prevalence ranging from 43% to 70%, at earlier or later stages of the disease, affecting various aspects of cognitive functioning, including sustained attention, visuospatial perception, executive functioning, verbal fluency and long-term memory (Chiaravalloti and DeLuca, 2008; Patti, 2009). The origins and mechanisms underlying cognitive impairment in MS are partly explained by WM injury (Sanfilipo et al., 2006) and possibly to a greater extent by GM pathology (Nocentini et al., 2014). However, from a network point of view, cognitive decline in MS patients can also be explained through the disconnection phenomena (see section 'Structural network connectivity in MS') within cortico-cortical and cortico-subcortical disconnection patterns (Dineen et al., 2009; Van Schependom et al., 2014). Patients with cognitive impairment show lower mean network degree and global efficiency but higher path length and assortativity as shown by functional connectivity analysis (Rocca et al., 2016). Since cognition depends on long-range connec-

tions between brain regions (Abad et al., 2015), impaired wiring efficiency resulting from decreased global efficiency and increased assortativity contribute to cognitive impairment. Regional network dysfunction – significantly lower nodal degree in the thalamus, caudate nucleus, cingulate cortex and precuneus – was also shown to be associated with alterations of working memory and information processing speed performance (Bonnet et al., 2010; Rocca et al., 2016). Overall, graph theory studies interpret worsening of cognitive performance in MS to be related to a modification of network properties (Rocca et al., 2016). Precisely, cognitive decline was attributed to decreased modularity (Gamboa et al., 2014), decreased network centrality (Schoonheim et al., 2014), impaired clustering (Helekar et al., 2010) and changes in path length (Schoonheim et al., 2012).

From a conceptual point of view, at disease onset, focal structural damage to the brain might be compensated by functional reorganization of networks (Schoonheim et al., 2015). At some point of disease, pronounced structural damage limits adaptive reconfiguration resulting in network collapse and cognitive impairment (Tewarie et al., 2015). Further explanations could be that (i) cerebral networks respond to diffuse tissue damage and focal lesions by a reorganization of WM and GM compartments with strengthening of local connectivity (Fleischer et al., 2017); (ii) cognitive impairment is associated with exhaustion of network compensation manifested in divergent patterns of WM and GM connectivity or a failure of functional reorganization phenomena and subsequent breakdown of network compensation patterns; (iii) the lesion pattern could have a large impact on specific network responses (e.g., via affecting densely interconnected nodes) and thus on inter-individual disease courses (Droby et al., 2016).

By mapping malfunctioning network assemblies relevant for cognitive performance, MRI-derived connectivity fingerprints could represent important surrogate markers of cognitive reserve or specific deficits for clinicians and their patients, and thus also permit monitoring cognitive rehabilitation.

Studies of brain network organization in MS that address network-based treatment interventions will be essential in facing upcoming challenges. Development of new pharmacological and non-pharmacological approaches to MS treatment relies on the understanding of network changes that are critical for MS progression and long-term disability (Guye et al., 2010). For instance, future studies might use network fingerprints for therapeutic interventional trials in MS to evaluate the effectiveness of disease- or symptom-modifying treatments and monitor disease progression (Bullmore and Sporns, 2009). Alternatively, more advanced therapeutic approaches could be designed to reroute the information flow from overloaded hubs (He and Evans, 2010; Schoonheim et al., 2014). Graph theoretical network approaches can be of emerging utility to sensibly track network modifications under medical treatment, although network-tailored treatment modalities are still far from their practical use.

FUTURE PERSPECTIVES

Despite remarkable advances in the last years, network analysis using graph theory in MS is still in its infancy, and several issues need to be addressed before venturing into broad clinical assessment. First, the topological description of the brain networks modelled by graph theory is constructed upon a set of mathematical definitions based on the covariance of functional or structural measures between brain regions. Hence, one of the major challenges is to understand the exact physiological and pathophysiological mechanisms underlying the signals extracted by imaging methods. Beyond that, we need to determine how these graph theoretical measures mirror neuronal processes, i.e. interregional communications.

From a methodological aspect, differences in the connectivity matrix generation lead to difficulties in rendering studies comparable. Standardized methods are needed to facilitate the reproducibility of results among studies. In this sense, connectivity matrices should be generated – if possible – with a data-driven approach as long as well-defined models are lacking. Furthermore, a variable amount and divergent types of network parameters are reported in different studies (see e.g., Gamboa et al., 2014; Rocca et al., 2016). As for fMRI studies (Poldrack et al., 2008; Nichols et al., 2017), a guideline or recommendation on how to present graph theory results is needed.

Reporting network parameters including measures of integration and segregation, as well as stressing a particular brain region's importance would be worthwhile for future studies. Thereby, a complete overview of network measures characterizing several aspects of global and local brain connectivity is offered (Rubinov and Sporns, 2010).

Graph theory provides modality invariant information on brain networks, and thus offers the opportunity to quantify and relate different data types to each other. Hence, signals acquired at different spatial levels, from molecules to the whole brain and organism, and with various temporal resolutions, from milliseconds to months and years, become comparable (Bassett and Sporns, 2017). Applying data mining (Mwangi et al., 2014) within graph theoretical analyses, predictions can be made by combining information captured from several network parameters.

A promising imaging method to which graph theory can be applied in the future is quantitative MRI (qMRI) that is well suited for estimating the macromolecular tissue volume as a measure of brain anatomy (Mezer et al., 2013). For instance, the quantitative parameter magnetization transfer ratio was found to differ between MS subtypes, indicating distinct intensities of pathological changes in lesional and extra-lesional GM (Yaldizli et al., 2016). In line with this, the qMRI measures T1 relaxation time and proton density were tested in a recent study, thereby providing a robust framework for longitudinal tissue characterization in MS (Gracien et al., 2017).

It is known that the increases in the measured signals likely arise from an increased proportion of free water and

thereby reflect loss of neurons among other microstructural changes (Gracien et al., 2016).

Consistency of the qMRI measures after modification of parameters like field strength and coils are of major concern, given that they have an effect on image accuracy (Mezer et al., 2013). This point is of relevance especially for multicenter studies, which enable more advanced and comprehensive investigation of disease pathophysiology by allowing the acquisition of larger amounts of data. However, full compliance across centers is difficult and requires the use of standardized approaches for qMRI data acquisition (Ashton, 2010).

Moreover, it is important to consider how (i) the kind of focal disseminated damage (either acute inflammatory or chronic lesions), (ii) their location (either in the GM or within the WM) and (iii) their size and amount influence connectivity matrices and the resulting estimated network efficiency (He et al., 2009). A longitudinal investigation in MS patients with relapses to monitor reorganization fingerprints with acute inflammatory activity has been of major importance to gain insights into network behavior in phases of clinical remission as well as during relapses (Droby et al., 2016). In order to track network efficiency alterations over time (Faivre et al., 2016) and provide predictors of the disease course at the individual patient level, there is an inevitable need for more longitudinal studies with analyses of network reorganization processes, ideally accompanied by histological examinations (Kilsdonk et al., 2016). The latter will, for instance, help in identifying whether imaging methods reliably capture the pathology taking place in the damaged tissue compartments.

Alterations of functional networks due to the disease do not reveal fully conclusive results (see section 'Functional network connectivity in MS'). Thus, the issue whether structural or functional reorganization mirrors an adaptive or maladaptive response to damage is still a matter of debate (Penner and Aktas, 2017; Rocca and Filippi, 2017; Schoonheim, 2017). Some MS studies have connected increases in brain connectivity, primarily seen in the early disease stages, to beneficial reorganization processes (Audoin et al., 2003), while decreases were associated with maladaptation as detected in progressive MS (Rocca et al., 2010b). However, this apparent causality between connectivity strength and clinical or cognitive disability is an oversimplification, as some studies in MS argue the converse, e.g., increased functional connectivity at rest in cognitively impaired patients (Hawellek et al., 2011). Hence, future studies need to set network connectivity alterations in relation to the broad MS phenotype considering clinical characteristics like relapse rate, cognitive performance, disease course, disease duration, etc. Ultimately, it needs to be addressed whether network changes also have an impact on the clinical outcome over years, again supporting the need for longitudinal network studies.

Beyond that, data need to be processed with an integrative approach, for example by combining structural and functional connectivity analyses. So far, functional and structural connectivity is most commonly assessed independently of each other. However, several procedures have been proposed to investigate the human brain network by jointly modelling functional and structural connectivity. For example, information about structural connectivity can be used as a prior for functional connectivity in a Bayesian framework (Xue et al., 2015). A further method, called track-weighted functional connectivity, was recently proposed which merges both connectivity data into a four-dimensional image, providing a new approach to investigate dynamic connectivity (for details see Calamante, 2017).

In order to delineate lesions and cortical pathology more precisely, higher resolution 7 Tesla MRI is already increasingly used (Tallantyre et al., 2010; Obusez et al., 2016; Kolber et al., 2017), which enables studying the exact impact on structural and functional network efficiency.

Studies on mouse models, used to determine underlying processes of de- and remyelination during relapse and remission phases of MS (Praet et al., 2014; Hubner et al., 2017), can also serve as *in vivo* models for translational network analyses in functional data. Graph theoretical analyses of the mouse and rat brain have already shown to be informative about functional processing (Mechling et al., 2014; Phomvisith et al., 2016), and can be used to study how pathophysiological processes in the animal model contribute to the observed results of network analyses in MS patients.

Connectivity measurements as derived from electrophysiological tools such as EEG or MEG with graph theoretical network analysis have been conducted as well (Hardmeier et al., 2012; Schoonheim et al., 2013; Tewarie et al., 2014a; Van Schependom et al., 2014). These methods provide advantages in terms of the temporal resolution for the quantification of information transfer in specific frequency bands, which is mostly inaccessible for fMRI.

In addition, it is important to note that network reconstruction based on graph theory may also be applied to effective connectivity data that depict the causal interactions between elements of a neural system (Friston, 2011). Thus, future effective connectivity studies in MS patients should also investigate the local and global organization of effective brain networks.

Thorough functional assessments of patients are required to ensure a valid depiction of behavioral and clinical outcomes of the disease activity. To investigate network-derived characteristics that foster disease progression in MS, connectivity parameters should also be set in association with other known surrogate markers from the blood, cerebrospinal fluid and genetic variants.

It is crucial to initiate multicenter-based research with merged patient cohorts, which allows the acquisition and analysis of large data sets (Keshavan et al., 2016). However, an emerging difficulty originating from multisite studies is the variability due to technical and methodological issues such as differences in scanning equipment and pre- and post-processing procedures. Interestingly, in a recent study on this topic graph theory was the only

method that consistently discriminated patients (with frontotemporal dementia) from healthy controls and other neurological samples across several centers (Sedeno et al., 2017). Such studies in MS patients are needed to address the reliability and reproducibility of network metrics in a multicenter setting.

The major goal of identifying predictors for the classification of MS types, as well as the disease course based on graph theoretical analyses, will be best achieved by a strong collaboration of several MS research centers sharing data sets that were obtained as homogeneously as possible. Once we understand the network's behavior during neurodegenerative and neuroinflammatory processes in more detail using graph theory, network measures will add reliable and quantifiable value in monitoring patients' disease progression and will have an impact on treatment decisions.

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