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Review on Graph Theoretical Framework of Brain Networks

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Abstract
Network research gives strong access to the entire human brain organisation. It was applied to characterise the brain communication patterns in combination with graph theory. Multiple sclerosis (MS) offers new insights into pathological processes within grey and white matter. It analyses brain networks derived from structural or functional imaging. In addition to focal lesions and diffuse tissue damage, network connectivity patterns may be significant in close monitoring and disease prediction. This study explains the graphical theory principles, highlights new issues related to acute and chronic tissue reorganisation, and discusses network analysis in MS patients. We also describe functional and structural communication trends observed in MS from disconnection and disturbance to modification and compensation. Also, based on current literature, we link network change and its connection to clinical incapacity. Finally, we explore the network science perspective in MS for future research and postulate its position in the clinical environment.
Keywords:Multiple sclerosis, Network analysis, Graph theory, Network reorganisation, Functional connectivity, Structural connectivity.

Introduction:

Multiple sclerosis diseases (MS) are a chronic and heterogeneous central nervous system autoimmune disease that results in gradual clinical disability [6]. Inflammation and demyelization characterise the underlying pathology. The disorder is characterised by more remixing, repair, functional and systemic reorganisation processes. This method was important when diagnosing and tracking magnetic resonance imaging (MRI) for acute and chronic white matter (WM) lesions [2]. Therefore, conventional MRI techniques do not portray brain reorganisation and indicate the long-term clinical course [1]. Standard MRI protocols (i.e., lesion load weighted on T2) correlate only faintly with clinical incapacity emerging. In addition to T2-visible lesions, MS also has a widespread effect of normal-appearing WM (NAWM) and grey matter (GM). This common pathology causes changes in connectance between interacting regions of the brain and emerging functional dysfunction (e.g., motor and cognitive deficits, fatigue, psychiatric comorbidities such as depression or anxiety). For clinical and disability development, further adaptive processes of plasticity and metaplasticity may be necessary. For the prediction of disease course and the monitoring of the effectiveness of potential preventive or therapeutic action, the holistic characterisation of focal lesions, WM and GM properties is important.

Focal demyelination spreads through the whole brain, primarily through WM. At the same time, GM lesions become increasingly recognised as essential features of the disease and play a major part in the long-term functional result. The connection between brain areas is entirely conceivable as a result of WM and GM lesions. Despite sites of predilection, inflammatory

lesions vary unpredictably in their position, form and scale. Moreover, no research methods were currently used to estimate the injury load to account for topographical, neuroanatomical features other than lesion counts or volume measurements. Also, adequate longitudinal analytical lesion mapping strategies are essential.

A potential way of depicting the topology of the brain of MS patient is through network-based approaches. This allows for the overall patterns of connectivity to be visualised. The brain's global organisation characterises quantitatively and offers a structure to elucidate the connection between brain and function [4].

Graph theory has been a critical approach to modelling brain networks as interconnected and complex in recent years. Current applications have demonstrated outstanding usefulness in characterising physiological and pathological cerebral processes and offering a complete neurological model. The theoretical graph analysis of brain networks in patients with MS has presented new avenues for the non-invasive characterisation of structural and functional alterations associated with the disease that robustly represent the disease's course and its clinical conditions [3]. As most brain systems analysis with graph theory on CIS and RRMS have been performed in this study, we concentrate on these types of MS and analyse only selected results in progressive types of MS. In this review, we discussed MS in the most common analysis and analysis. We will introduce the graphic theoretical metrics in this study, examine the latest MS functional and structural research, and explore the future's clinical implications and directions. Mahapatra and Samanta [10-21] presented many applications of the fuzzy graph.

Modelling brain connectivity using graph theory:

In graph theory, the brain is modelled on the nodes identified by separate anatomic regions and boundaries, which reflect the presence or strength of the interactions of two regions. A neuroanatomic scheme that expresses functional knowledge usually follows brain parcellation in nodes. The node description strategy is evolving and is an active research area, as choosing the parcellation scheme changes the resulting network structure. In addition, the nodes are considered in the geometrical representation but, for the reconstruction of the network, the anatomical distance between the two regions is not guided. This study is beyond the reach of the presentation of the general software tools available to rebuild the brain networks [5]. We invite the reader to consider recent feedback on these subjects for further information. Only related aspects are addressed for MS imaging.

A functional or structural image may be used to represent possible links between anatomical regions—measurement of functional connectivity from time-dependent statistical ties between signals (e.g., from fMRI) [7]. Brain activity can be divided into task-driven or resting status (no task), each with distinct activation profiles and different sets of regions involved. There are various methods for constructing functional brain networks that can be achieved in both the time and frequency domain. Analytical approaches such as independent analysis of materials, seed-based analyses and granger causality analyses have been commonly used, whereas theoretical graphs have become more relevant over the last few years.

The intensity of anatomical connections between pairs of regions representing fibre packaging features can be described as structural connectivity as rebuilt from the diffusion imagery. Deterministic or probabilistic tractography analyses from MRI diffusion are typically performed to estimate WM fascicles and their projections so that structural linkages inferred are fed into connectivity arrays. A second choice is using structural covariance parameters (i.e., volume or cortical thickness measures) to calculate interregional correlations for structural graph reconstruction.

Regardless of whether structural or functional imaging is applied, the result is a connectivity matrix with a set of elements representing the connections' implicit strength. This matrix can be threshold and additionally binaries to reduce spurious or false-positive associations.

The topology of the network is based on the relationships between nodes and edges (Figure-1). To calculate the global or local network organisation, different measures can be computed. Global metrics (e.g., route and efficiency) indicate the network's overall information integration capacity [8]. Moreover, segregation measures such as clusters and modularities are of special interest in local

information processing since they characterise an individual node's relationships with its immediate neighbours. Small-world action can also be used to determine the trade-offs that enable successful communication between local and global connectivity. Table 1 provides an overview of the network parameters selected, with definition and results. Through these network actions, essential aspects of the brain's normal and abnormal organisation and the underlying brain disease can be disclosed.

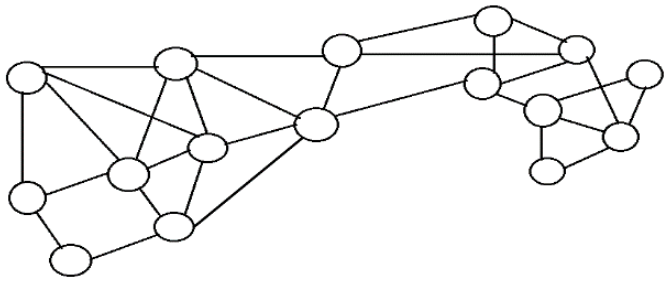

Figure1: Brain networks are described as a graph comprising a collection of nodes (representing anatomical brain regions) and edges (representing structural connections).

Measures	Description & interpretation	Sources
Eigenvector centrality	Nodes are weighted considering not only by their number but also connections quality. Higher eigenvector centrality brain regions are linked to regions that are central in the network themselves.	Schoonheim et al. (2014)
Nodal efficiency	The shortest minimum path length between a single node and all other nodes. An increases a region's ability to spread knowledge with the other nodes.	Liu et al. (2017)
Modularity	A module is a group of densely linked nodes that are slightly linked to the rest of the network. Greater modularity means a better subdivision into different node groups. An increase in modularity shows an optimised theory of the brain network organisation in response to changing conditions.	Muthuraman et al. (2016) Kocevar et al. (2016)

Table1: Theoretical graph parameters and their description as well as related findings

Network analysis and pitfalls in MS:

Different connectivity designs with unique MS phenotypes have increasingly been linked with graph theory. The disease course can be linked to a dominant trend of lower global connectivity due to acute neuroinflammation or increased lesion load. Furthermore, possible adaptation patterns with increased local and modular connectivity wereidentified, reflecting compensatory mechanisms and network rearrangement. This dynamic relationship between

the long-term division with a less efficient transfer of information and a local reorganisation may be important to the long-term outcome. However, the exact impact of these mechanisms on the interplay of focal demyelination with diffuse tissue damage for the whole function of the network is still uncertain.

The algorithms used to estimate cortical thickness for reconstructing the structural network are focused mainly on T1 weighted sequences, usually assuming that brain pathology is not present. Morphometric measurements such as cortical thicknesses, therefore, correspond to MS lesion load. The existence of focal lesions, requiring paradigms for quantifying lesion load and topography, can prejudice the cortical recomposition. The ability to apply previously mapped injuries (cortical and juxtacortical) to the surrounding topology has been added with tools such as Free Surfer. In this correction phase, surface reconstruction and additional cortical density measurements have been shown. Assessment and evaluation of focal lesions on restoration networks are of considerable importance as new lesions could significantly affect structural and functional brain networks in specific regions. The importance of longitudinal network studies to open up new avenues for understanding MS pathophysiology is rising because of the varieties of network alterations in various SD populations, disease courses and disease durations.

Functional Network Connectivity in MS:

An fMRI study has been given important insights into the cerebral reorganising process via acute and chronic inflammatory activity. Changes in functional connectivity describe functional deficiencies and represent disease patterns. In most of the studies, brain networks were analysed during the rest period. This task-free approach has the benefits of being autonomous of task-based MRI from the levels of impairment and performance of patients [9]. As well as theoretical chart analyses, other approaches have also previously been used to identify such networks, often in contrast with healthy controls, such as independent component analysis or large-scale Granger causality. In comparison with healthy controls, increased functional activation of the basal ganglia and thalamo was thus observed as part of the motor network and relaying centres for cortico-subcortical interactions. The authors found increased connectivity after an acute recurrence in primary and secondary driving areas while the connectivity decreased after engine function rebounds. Accordingly, enhanced connectivity adjacent to and contrary to lesions has been documented, indicating that functionally connected brain areas compensate for focal damage in the structure.

Notable was the possibility of notification of functional connectivity increase and functional connectivity decreases, which may occur due to reorganisation or adaptation to acute or chronic inflammation, as a possible compensatory mechanism for MS patients. However, these mechanisms cannot differ from the degree of connectivity on their own and thus are not insightful for continuing pathological processes. The apparently conflicting results come primarily from the complex existence of the interactions that are largely overlooked. For example, the connectivity levels determined by the fMRI signal do not take account of the fact that increases in functional connectivity are caused by activations of neuronal populations inhibited and excited.

At present, few studies have applied graph theory to MS fMRI results, mostly investigating the rest of the brain [7]. Schoonheim et al. (2014) used central mapping of the proprietor to select clusters of interest and observed a rise in the centrality of the back cingulate gyrus and a reduction in the centrality of sensorimotor and ventral range. Since the Thalamus, an area with increased central importance demonstrated greater connectivity to areas with decreased centrality, thalamic connections were redefined as a response to continuing inflammatory activity. Moreover, a recent study has found that the centrality of the network anomalies in

MS patients with a period of relapse-free of at least two months was linked to the degree of cognitive impairment. In comparing cognitively disabled sufferers both with cognitively preserved MS patients and healthy subjects, the authors observed significantly decreased centrality in the mid-story regions and improved the default mode network (DMN) and frontal regions. In the occipital, sensor, hippocampal and caudate regions, in patients with cognitive disabilities, additional decrease in centrality was observed compared to the healthy population, while centrality of the brain and thalamus was increased. The thalamus is one of the earliest microstructural degeneration regions of MS between GM structures and is important for its functioning connectivity. Accordingly, one study recently revealed an increase in thalamic-cortical intersections based on seeds. Still, the network parameters resulting from a graphic analysis were not different between the groups in a heterogeneous sample of MS patients relative to healthy subjects. Liu et al. (2017) also studied alterations to the Resting-State network, which indicated the decreased performance of RRMS patients at the local and global levels. Nodal effectiveness in both CIS and RRMS patients has been decreased in the Superior Time Gyrus, left rolandic and left insula. In addition, with an interrelation of 77 per cent between the two groups of patients for each group and the median connectivity intensity relative to disease length, the division of RRMS and CIS patients from healthy controls could not be distinguished from those in each group. RRMS, but not CIS patients, showed a substantial reduction in local efficiency and clustering compared to management in a dual structural and functional network approach, although there were no variations in each community on the global level. The fact that the CIS Community lacks major improvements in the network reflects slight functional changes at the start of the disease stage.

The combination of all the published findings with a clear network setup is insufficient because the results are heterogeneous because of several factors of influence that vary. For instance, a loss of information is caused by establishing the connectivity matrix that ignores all negative correlations. Furthermore, the patient's characteristics vary greatly between illness, disability, age, gender, course of disease and other populations, demographic and disease-specific variables. In addition, most studies have been conducted with cross-sectional data obtained, which do not permit information on MS brain network dynamics. In the course of Alzheimer's disease, Jack et al. (2010) related possible imaging biological and clinical markers to show their modifications. It has been adapted to MS and relates continuous systemic harm to network performance improvements causing cognitive impairment. From the present viewpoint, in addition to clinical disability and tissue damage, we suggest a change in this model by incorporating mechanisms for compensating networks over time. Our model is based on evidence that increased or sustained modular and local interconnection can represent an important characteristic of network reorganisation, which is supposed to mediate robustness and performance instead of functional decay. Once this adaptation to the network cannot be maintained because of continuous tissue injury, the network fails and the clinical damage happens.

Structural Network Connectivity in MS:

Graph theory structural network analysis could provide new instruments representing ongoing pathological processes in various anatomical locations. GM and WM properties' modelling is essential to the exact characterisation of tissue phenomena such as demyelination, remyelination, and neurodegeneration. Correlations of cortical thicknesses or GM intensities as obtained from voxel morphometry in different areas of the brain at the community levels are used to classify GM networks. Regions with similar microstructural characteristics are more likely to show structural connections. However, this is an indirect degree of interregional interactions that cannot be directed at individual subjects' level to

calculate connectivity. A variety of analytical disadvantages have been suggested, and structural connectivity quantifications at the single topic level were proposed. Another issue is the structural covariance of semiquantitative behaviour. A more reliable evaluation of tissues' properties may be carried out using direct quantitation measurements, but the characteristics of bio change still have to be discussed. These techniques have still not been incorporated into network analysis or clinical practice due to long scanning times and the need to determine the exact relation between measured values and histological properties.

The application of diffusion imaging has made an impressive move towards developing biologically relevant network reconstruction methods. WM structural connectivity can be reconstructed with either detergent or probabilistic tractography from diffusion tensor imaging (DTI). WM Network Reconstruction has a major benefit is the ability to analyse connectivity properties at a single stage.

Longitudinal approaches:

Longitudinal network methods include the ability to properly examine whether network changes are mechanisms that partially or completely offset tissue damage so as to ensure that there is no clinical decline. Because adjustment mechanisms likely arise in the first year following the onset of the disease, although no other quantifiable variations occur, the network behaviour of MS patients who have been followed over months and years is important to obtain information. Thus, it can be calculated if graph-theoretical measurement changes are consistent over time compared to safety controls or other MS subtypes. The robust reproducibility over time and low network property variability derived from DTI or functional MRI is important for longitudinal analyses.

An improvement in synchronisation at rest in particular brain networks suggests early reorganisation in a CIS analysis of functional communication without cognitive impairments. This functional reorganisation was seen in the absence of observable atrophy, but in patients with specific RRMS and increased brain damage, it was not (or no longer) detectable and indicated that cortical reorganisation was an early and potentially finite phenomenon of MS. This may mean that various processes, such as atrophy and network changes, do not completely share the same time pattern. Longitudinal multimodal methods are thus strongly justified, assessing adaptive or degenerative dimensions of the disorder.

Two research, which examined the age-related changes in brain networks, showed a drop in the model structure with a higher age in safety checks in the sense of a reorganisation into a more localised network. This highlights the importance of longitudinal approaches and emphasises the need for safe control group support in brain network research involving MS patients. The decline in modularity with increasing age in the normal brain, on the other hand, supports the idea that the increased modular brain structure found in patients with MS is not associated with early degeneration and tissue damage but rather with an early adaptive reaction.

The first clues of adaptive mechanisms in network analyses in Alzheimer's disease were seen as reflected by the increased modularity limited to the initial phase of the disease. Later on these adaptive mechanisms would be reduced if the integrity of the network can no longer be preserved and result in functional disability.

Clinical utility:

The study and validation of possible clinical applications of brain network analytics is an important problem. Despite its important value for diagnostics and for therapeutic monitoring, the low to moderate association between the MRI loads and clinical disabilities ("clinical-radiological paradox") of the patients remains a pending problem in future research,

despite the important value of traditional MRI (e.g., focal lesions, lesion load or atrophy of the brain) [9].

Instead of lesion load, it can be introduced to monitor long-term diseases burden through the management of the systemic network properties (i.e., local and global efficiency). While the powerful small-world properties of MS patients remain, major disruptions in the global and local topology networks may be seen as disruptive points in disease progression and clinical decrease. However, only aberrant cortical GM properties cannot clarify the clinical deterioration. In addition to changes in GM networks, it has been shown that the topological organisation of DTI-based WM networks is linked to the clinical condition – decline in global efficiency significantly associated with EDSS, disease period and TWMLL rates. In areas of lower nodal efficiency – precentral gyrus, post-cingulate gyrus, precautionary, rolandic operculum – important correlations with the clinical variables (EDSS, period of disease and TWMLL) were observed, which suggest that the clinical phenotype in MS is crucial in this region. Their effects are significant.

From a conceptual standpoint, at disease beginning, a functional reorganisation of the networks may offset focal structural damage to the brain. Significant systemic damage at some stage in illness reduces adaptive restructuring, leading to the breakdown and cognitive deterioration of the network [3]. Further explications maybe that cerebral networking is linked with the exhaustion of network compensation in divergent WM and GM connectivity models or the absence of functional reorganisation phenomena and sub-continent networks, which may lead to diffuse tissue damage and focusing lesions. MRI connectivity fingerprints may represent significant cognitive reserve proxy indicators and deficiencies for clinicians and their patients by mapping malfunctioning networks appropriate for cognitive competence and allow for cognitive recovery monitoring.

In order to face up to the forthcoming challenges, brain network organisation research in MS addressing network therapy approaches will be vital. The development of alternative methods for MS care is based on an awareness of important network improvements for MS and long-term disability. For example, future studies might use the network fingerprints to assess the efficacy of disease- or symptom-modifying therapies and to track disease progression through therapeutic interventional trials in MS. Otherwise, innovative clinical methods may be built to reverse the flow of knowledge from excessive hubs. Graphical theoretical network techniques will help us sensibly monitor network changes in healthcare, but network-cutting treatment methods are still a long way from practical use.

Conclusions:

Despite significant progress in recent years, graph-theoretical network research in MS remains in its infancy. Many issues need to be resolved before a large clinical assessment is carried out. Second, the topological classification of brain networks modelled on graph theory is based upon the covariance of functional and structural measurements between brain regions in a set of mathematical definitions. Therefore, one of the key challenges is to understand exactly the processes of physiology and pathophysiology underlying signals obtained by imagery methods. Also, the theoretical graph measures must be determined to represent neuronal processes, i.e., interregional communication.

Graph theory offers modes of invariant brain network information to enable quantification and correlation of different data kinds. Signals from the molecules to the whole brain and body and different temporal resolutions from milliseconds to months and years are also equivalent at the different spatial stages. Predictions can be produced by combining information obtained from different network parameters by applying data mining to graph-theoretical analyses.

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