Functional connectivity analysis using whole brain and regional network metrics in MS patients*

Chirumamilla VC, Fleischer V, Droby A, Anjum T, Muthuraman M, Zipp F, Groppa S

Abstract—**In the present study we investigated brain network connectivity differences between patients with relapsing-remitting multiple sclerosis (RRMS) and healthy controls (HC) as derived from functional resonance magnetic imaging (fMRI) using graph theory. Resting state fMRI data of 18 RRMS patients (12 female, mean age ± SD: 42 ± 12.06 years) and 25 HC (8 female, 29.2 ± 5.38 years) were analyzed. In order to obtain information of differences in entire brain network, we focused on both, local and global network connectivity parameters. And the regional connectivity differences were assessed using regional network parameters. RRMS patients presented a significant increase of modularity in comparison to HC, pointing towards a network structure with densely interconnected nodes within one module, while the number of connections with other modules outside decreases. This higher decomposable network favours cost-efficient local information processing and promotes long-range disconnection. In addition, at the regional anatomical level, the network parameters clustering coefficient and local efficiency were increased in the insula, the superior parietal gyrus and the temporal pole.**

Our study indicates that modularity as derived from fMRI can be seen as a characteristic connectivity feature that is increased in MS patients compared to HC. Furthermore, specific anatomical regions linked to perception, motor function and cognition were mainly involved in the enhanced local information processing.

INTRODUCTION

In remitting relapsing multiple sclerosis (MS), functional brain reorganization may be an essential mechanism to counteract continuous damage resulting from demyelination and neuronal loss [1-4]. The brain networks need to respond to the focal and diffuse damage through functional and structural reorganisation and changes in connectivity patterns. These connectivity patterns can be derived from functional magnetic resonance imaging (fMRI) and quantified through graph theoretical approaches. This provides important information about synchronous neuronal activities in the entire cerebral networks and might be highly relevant for describing adaptive mechanisms of brain functioning despite continuous damage. In the present study we investigated network connectivity profiles between MS patients and healthy controls to demask functional reorganization patterns and compensation fingerprints.

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Chirumamilla VC, Fleischer V, Drogby A, Muthuraman M, Zipp F and Groppa S are with Department of Neurology, Johannes Gutenberg University Mainz, 55131 Germany. Venkata.Chaitanya@unimedizin-mainz.de, Vinzenz.Fleischer@unimedizin-mainz.de, amgaddrogby@yahoo.com, m.muthura@uni-mainz.de, frauke.zipp@unimedizin-mainz.de, segroppa@uni-mainz.de.
Anjum T is with Computational and Systems Neuroscience (INM-6) & Theoretical Neuroscience (IAS-6), Forschungszentrum Jülich. t.anjum@fz-juelich.de

METHODS

A. Data acquisition and preprocessing

The resting state rs-fMRI data of 18 RRMS patients and 25 healthy subjects were inlcuded in this study. The rs-fMRI data were collected using echo planar imaging (EPI) sequence (repetition time (TR): 3000 ms, echo time (TE): 30 ms, flip angle: 90°, matrix size: 64*64, slice thickness: 2 mm, and number of slices: 45). None of the healthy subjects presented a history of neurologic or psychiatric disorders. The study was approved by the local ethical committee of University Medical Center, Mainz. The fMRI data was preprocessed using the Statistical Parametric Mapping software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Mainly the preprocessing steps included: (1) realignment (2) spatial normalization to Montreal neurological institute (MNI) space and (3) smoothing with a Gaussian kernel of full width at half maximum (FWHM) 8mm. Realignment was performed to remove head movement artifacts, and it can be done using rigid body transformations. In group comparison studies normalization is needed to eliminate inter subject variability in brain sizes, and also to map all the individual subject brains into a standard MNI space, which allows comparison and validation of different studies.

B. Correlation maps extraction and connectivity analysis

The functional correlation maps for each individual were extracted from preprocessed resting state fMRI data using connectivity 'Conn' toolbox [5]. The correlation maps considered as an input to GAT toolbox [6] were of size 116*116*43 (116: number of brain regions based on Automated Anatomical Labeling (AAL) atlas, healthy subjects correlation maps were (1:25), and MS patients correlation maps were (26:43)). A 116*116 correlation matrix estimated for each individual was thresholded at various densities within the range [0.1, 0.5] with an interval of 0.02. Within the selected density range both groups exhibited small world network characteristics [6]. At each density, differences between two groups were quantified using permutation test in terms of local connectivity parameters (clustering coefficient and local efficiency), and

global network parameters (modularity and global efficiency). In permutation test 1000 iterations were performed. In each iteration the network metrics are assigned to one of the groups to create two randomized groups. The difference between these two randomized groups is used to calculate the permutation distribution function, by using which we can calculate the significance of the difference between original groups at each density. In addition, we analyzed two network parameters clustering coefficient and local efficiency for the between group differences at regional anatomical level. This comparison was done using functional data analysis (FDA) technique [7, 8]. The advantage of using FDA technique is that the between group comparison is less dependent on the thresholding process. The network parameters that we used for showing between group differences are explained in this section [9].

Clustering coefficient (CC):
Clustering coefficient of a node indicates how densely the neighbors of a specific node are connected with each other. The clustering coefficient of a node is calculated by using equation (1).

$$C_e = \frac{2r_e}{g_e(g_e - 1)} \quad (1)$$

r_e : number of triangles around a node e and g_e : degree of a node e .

Local efficiency (LE):
Local efficiency is estimated at every node including disconnected nodes in a network. The local efficiency of specific node shows how the neighbors of this node communicate in the absence of this node [10]. Local efficiency of a network can be calculated using equation (2).

$$E_{local} = \frac{1}{z}\sum_{e \in Z} E_{local}(e) \quad (2)$$

Z : set of all nodes in the network and z : total number of nodes in network.

Modularity:
Modularity defines how a network can be subdivided into various modules, densely interconnected nodes which sparsely connect to nodes outside. Modularity of a network can be calculated by following equation (3).

$$M = \sum_{s \in R}\left[a_{ss} - \left(\sum_{f \in R} a_{st} \right)^2 \right] \quad (3)$$

R : number of modules and a_{st} : proportion of links that connect nodes in module s with nodes in module t .

Global efficiency (GE):
This metric shows the average inverse shortest path length and is calculated using the equation (4)

$$E_{global} = \frac{1}{z}\sum_{e \in Z} E_e \quad (4)$$

E_e : efficiency of a node e .

RESULTS

A. Whole brain network differences

The network parameter modularity showed significant differences between MS and healthy controls. Across 21 density intervals, these two groups significantly differed at 17 densities ($p \leq 0.05$) as shown in figure 1. The average mean difference across all densities was also significant ($p \leq 0.02$). No significant between group differences were observed in terms of the other network parameters CC, LE, and GE. All the p values shown here are uncorrected.

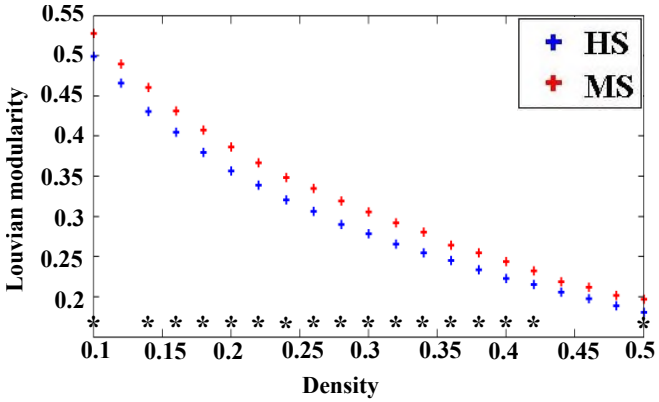

Figure 1. The plot shows the difference in modularity between healthy controls and MS patients. * represents the densities at which between group difference is statistically significant ($p \leq 0.05$).

B. Regional network differences

The FDA analysis for the regional network measures CC and LE was done over the density range [0.1 0.5]. The regions with significant between group differences are shown in Table 1. In the right hemisphere both CC and LE were reduced in the anterior cingulate and paracingulate gyri and in the left hemisphere in middle temporal gyrus in MS patients. In right hemisphere both CC and LE were increased commonly in rolandic operculum, medial superior frontal gyrus, insula, superior parietal gyrus, temporal pole superior temporal gyrus and in the left hemisphere in superior parietal gyrus in MS patients. All the regions given in Table.1 were mapped onto 'Brainmesh_ch2with cerebellum' template using brainnet viewer (Figure 2).

DISCUSSION AND CONCLUSION

In this study, we analyzed functional network connectivity patterns between patients with MS and healthy controls. Our results demonstrate a significant increase of modularity in MS patients in comparison to healthy controls. A higher

modular architecture in patients with MS indicates an increase in local connectivity and reduced strength of long

Parameter	MS < HS	MS > HS
CC	Anterior cingulate and paracingulate gyri (R) Hippocampus (L) Calcarine fissure (L) Calcarine fissure (R) Middle temporal gyrus (L) Temporal pole middle temporal gyrus (L) Temporal pole middle temporal gyrus (R)	Precentral gyrus (R) Rolandic operculum (R) Medial superior frontal gyrus (R) Insula (R) Superior parietal gyrus (L) Superior parietal gyrus (R) Temporal pole superior temporal gyrus (R)
LE	Supplementary motor area (L) Anterior cingulate and paracingulate gyri (R) Lenticular nucleus pallidum (L) Lenticular nucleus pallidum (R) Middle temporal gyrus (L) Middle temporal gyrus (R) Temporal pole middle temporal gyrus (R)	Rolandic operculum (R) Medial superior frontal gyrus (R) Insula (R) Superior parietal gyrus (L) Superior parietal gyrus (R) Temporal pole superior temporal gyrus (R)

Table1. The table shows the list of all regions that have shown significant between group differences in terms of regional network measures CC and LE . Here R = right and L = left.

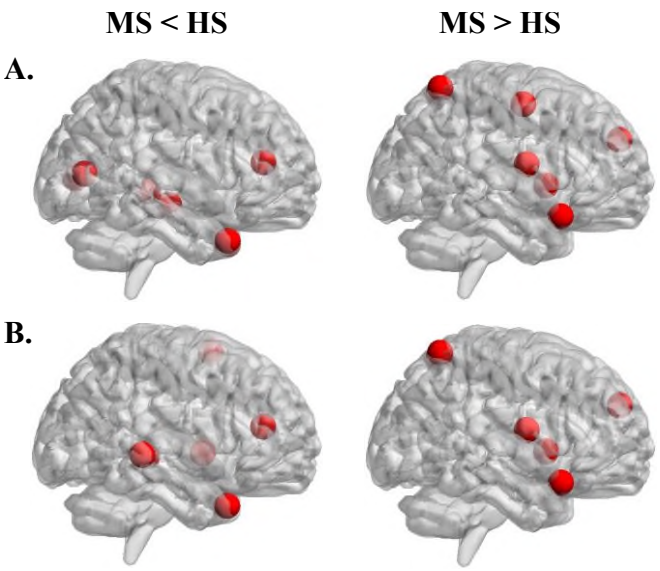

Figure 2. The regions that have shown significant between group differences in terms of clustering coefficient (A) and local efficiency (B).

range connections. Our results supplement the previous findings on modularity changes in MS patients [4] and our own data on modularity increase as derived from structural network reconstruction in patients with clinically isolated syndrome and MS in comparison to healthy controls [11]. In addition we are able to show that the region insula is effected in MS patients [12]. Moreover, the regional network analysis showed the presence of significant alterations at the regional anatomical level. Two anatomical lobes were mainly involved. Increased local information processing as shown by higher CC was seen in the frontal and temporal lobe. In the close proximity of these anatomical areas we found a simultaneously decrease of local connectivity (Figure 2). In summary, our findings show concomitant processes of adaptive and maladaptive network changes suggesting mechanisms of functional compensation in the presence of chronic damage that might be an important fingerprint of the network response in MS patients. To translate these findings into clinical settings, further studies are needed in larger patient cohorts and considering age as a covariate in the statistical analysis. In conclusion, we postulate modularity as derived from fMRI as a possible network connectivity marker of local integration and global segregation in patients with MS in comparison to healthy controls. Concomitant processes of damage and functional adaptation as reflected by beneficial connectivity changes co-occurring with detrimental connectivity changes in the close proximity are hallmarks of the brains in MS patients.

Acknowledgment

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