Altered White Matter Connectivity in Early Relapsing-Remitting Multiple Sclerosis Patients With High Lesion Load

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BACKGROUND: A previous network analysis of cerebral white matter in relapsing remitting multiple sclerosis (RRMS) patients has shown reduced global and local network efficiency that correlated with clinical variables such as expanded disability status scale (EDSS), disease duration and lesion load (1). Another study found altered gray and white matter neuroconnectivity in early RRMS patients that is relevant to disease related tissue injury (2). In early RRMS patients, measures of clinical disability such as EDSS are not sensitive enough as a predictor of later disability. Changes in the white matter network connectivity could be a potential biomarker of disease progression.

OBJECTIVE: We hypothesize that early RRMS patients with low disability and high lesion load (LL), while compared with controls, will have more profoundly reduced network efficiency than patients with similar levels of disability and low LL.

METHODS: Nineteen women with RRMS (median EDSS=1.5; 40±8 years) and eighteen age-matched healthy women (39±7 years) underwent brain MRI. Whole-brain FLAIR (voxel size=1x1x2 mm^3) was used for detecting MS plaques and calculating LL, subsequently normalized to the ICBM152 T_1 template using SPM8 nonlinear transformation to account for head size variation. MS Patients were grouped into low (n=9) or high lesion load (n=10) groups, based on LL cutoff of 2000 mm^3. We acquired fifty 2.5 mm axial slices of DTI with TR=7100 ms, TE=95 ms, 4 averages, b=1000 s/mm^2, 12 directions, voxel dimension = 2x2x2.5 $mm^3$and AQ time ~ 6 min at 1.5T (Siemens Sonata). Each structural brain network was constructed using whole brain tractography and 78 cortical regions were extracted using Anatomical Automatic Labeling (AAL) template (3). A region-to-region connecting weight function utilized volume normalized fiber number (minimum 3 fibres) and FA (only voxels > 0.25) between any two regions. We applied graph theoretical analysis to obtain network parameters in each subject. We used linear regression (age effect removed) to compare network parameters between all 3 groups. Spearman's correlation test was used to investigate network versus clinical parameters in the patient groups.

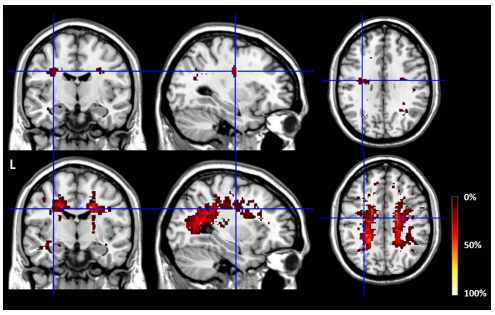

Figure 1: A lesion distribution map of RRMS patients in the low lesion load (top) and the high lesion load (bottom) group.

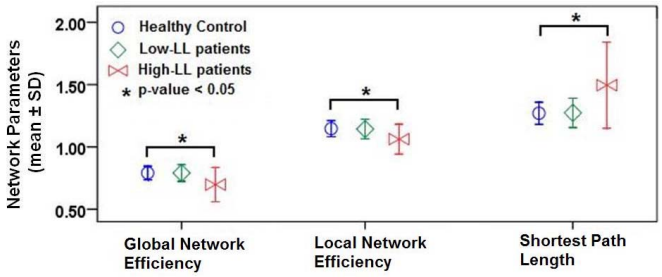

Figure 2: Mean plots of global and local network efficiency and shortest path length in controls and both MS patient groups.

RESULTS: Mean age and median EDSS were similar between low (40±6 years, EDSS: 1.5) and high (40±9 years, EDSS: 1.5) LL groups. Normalized lesion volume ranged between 58-1976 mm^3 in the low and 3680-37174 mm^3 in the high load group (Figure 1). In agreement with our hypothesis, when compared to controls, the high-LL group showed decreased global and local network efficiency, with increased shortest path length (Figure 2). There were no differences between the low-LL group and controls. Our results also revealed a significant correlation between lesion load and global network efficiency (ρ= -0.721, p= 0.019), local network efficiency (ρ= -0.636, p= 0.048) and shortest path length (ρ= 0.721, p=0.019) in the high-LL group, but not in the low-LL group. No correlation was found between EDSS and any network parameters in either early RRMS patient group.

DISCUSSION: In early RRMS patients with high lesion load, a more profound disruption of the global network and local efficiency were observed with increased shortest path length between brain regions. These findings might be attributed to the reduced communication efficiency between local (adjacent) nodes, i.e. short-range connections due to the presence of larger lesions in high lesion load patients. Our study shows a significant disruption in the white matter networks at the very early stages of the disease when patients have very low clinical disability. Our results build on previous studies of network connectivity in RRMS patients that had a wider range of disability (1). Measures from the network analysis provide a unique insight into the alterations of cerebral white matter connectivity, which is sensitive even in early RRMS patients with low disability, and could be explored as a biomarker for disease progression.

REFERENCE: 1. Shu et al. Multiple Sclerosis 2011. 2. Li et al. Human Brain Mapping 2012. 3. Gong et al. Cerebral Cortex 2009