Statistical Brain Network Analysis in Female Relapsing Remitting Multiple Sclerosis Patients Using Diffusion Tensor Imaging

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Target Audience:
Multiple Sclerosis Researchers, Neurologists, Radiologists and Neuroscientists

Introduction:
Multiple Sclerosis (MS) is an autoimmune disease affecting myelin sheaths, causing axonal and neuronal injury [1]. Diffusion Weighted Imaging (DWI) and brain connectivity studies have been used to investigate different aspects of MS, and clinical correlations have been studied [2]. There have been structural connectivity studies showing alterations in brain connectivity parameters of MS patients [3, 4]. In the present study, we used a new metric, Network Based Statistics (NBS) [5], to investigate changes in WM structural networks of Relapsing Remitting Multiple Sclerosis (RRMS) patients using diffusion tensor imaging and graph theories.

Materials and Methods:
Data acquisition: 6 RRMS right-handed female patients (mean age = 32.5, SD = 1.37) diagnosed with 2010 McDonald Criteria [6] were included in our study. 7 age, sex, handedness matched healthy controls were also included (mean age = 30.7, SD = 2.49). There was no significant difference between ages of the two groups (p-value = 0.148). All participants were scanned using a 1.5T MRI scanner (Siemens Magnetom Avanto) with TR/TE = 9500/93msec, image matrix = 128×128, FOV = 256mm, number of slices = 68, voxel size = 2.0×2.0×2.1 mm^3.
Data Analysis: The DWI data were reconstructed using ExploreDTI [7]. The diffusion tensors were estimated based on weighted linear least squares that proposed in [8]. For EPI-distortion and head motion correction, DWI data were rigidly registered with MNI atlas. EPI-distortion correction was performed based on [9], also reorienting the B-matrix during motion correction was performed on [10]. Deterministic full brain tractography was performed using a stopping criteria of 0.2 FA and 30° curvature threshold. The whole-brain fiber tract reconstructions of the previous step were parcellated using the automated anatomical labeling (AAL) atlas. The inter-regional connectivity between the 90 ROIs demarcated on the AAL template was computed by applying the ROI masks to the reconstructed fiber tracts using the ExploreDTI. This determined the volume and number of tracts and average tracts length that originated in one ROI (i) and terminated in another ROI (j), for all 90 ROIs defined on the atlas, creating a 90 × 90 connectivity matrix (CM). An alternative measure like Linear Anisotropy (CL) of the tract could also be used. Then, for group analysis we used NBS. NBS is a method to control the family-wise error rate (in the weak sense) when mass-univariate testing is performed at every connection comprising the graph [5]. T-test statistics were applied with threshold of 3.5 and significant results (p-value < 0.05) were reported.

Results and Conclusion:
Tables I, II, III and IV show NBS analysis of CL, average tract length, tract volume and number of tracts, respectively. P-values for each analysis is: CL = 6e-04, Average Tract Length = 0.0156, Tract Volume = 1.0e-03 and number of tracts = 6e-04. **Fig. 1** shows the visual representation of the structural brain connectivity metrics.
We investigated structural connectivity parameters in female RRMS patients' diffusion tensor imaging data using NBS. We found that, compared to healthy controls, MS patients have significantly lower CL, number of tracts, average tract length and tract volume which is consistent with previous studies showing white matter structural abnormalities within MS patients [3, 4]. In particular, three regions and their connections manifested in different metrics of MS patients compared to healthy controls. These regions include Supplementary Motor Areas (Right and Left) and Right Precuneus. Supplementary Motor Area is associated with motor networks and is highly connected with different areas of frontal cortex and basal ganglia [11]. Precuneus is a part of the posterior parietal cortex associated with higher integrative brain functions, self-awareness, visuo-spatial imagery and episodic memory retrieval [12]. These findings may suggest a novel pathophysiological basis for some of the clinical conditions in MS like cognitive and memory dysfunctions and motor disabilities. Our data also suggest that a statistical-based brain network analysis can provide potential biomarkers for disease diagnosis.

References:
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Table I. Test Statistics of CL

Inter-regional pathway	Test stat
Supp_Motor_Area_R to Frontal_Sup_Medial_L	5.16
Cingulum_Mid_L to Cingulum_Mid_R	3.53
Postcentral_R to Parietal_Sup_L	5.47
Cingulum_Ant_L to Precuneus_L	3.96
Cingulum_Mid_R to Precuneus_L	3.67
Postcentral_R to Precuneus_L	4.47
Supp_Motor_Area_R to Precuneus_R	4.25
Cingulum_Ant_R to Precuneus_R	4.04
Cingulum_Mid_R to Precuneus_R	4.27
Frontal_Sup_Medial_L to Caudate_L	3.52
Precentral_R to Thalamus_R	3.65
Postcentral_R to Thalamus_R	5.86

Table II. Test Statistics of average tract length

Inter-region pathway	Test stat
Postcentral_R to Parietal_Sup_L	5.47
Postcentral_R to Precuneus_L	3.82
Supp_Motor_Area_R to Precuneus_R	3.66
Precuneus_L to Precuneus_R	3.59

Table III. Test Statistics of Volume of Tracts

Inter-regional pathway	Test stat
Supp_Motor_Area_L to Supp_Motor_Area_R	4.09
Supp_Motor_Area_R to Frontal_Sup_Medial_L	3.53
Supp_Motor_Area_L to Cingulum_Mid_R	3.54
Supp_Motor_Area_L to Precuneus_L	4.22
Supp_Motor_Area_R to Precuneus_R	4.94
Precuneus_L to Precuneus_R	4.71

Table IV. Test Statistics of Number of Tracts

Inter-regional pathway	Test stat
Supp_Motor_Area_L to Supp_Motor_Area_R	3.53
Supp_Motor_Area_L to Cingulum_Mid_R	4.38
Supp_Motor_Area_R to Precuneus_R	4.81
Precuneus_L to Precuneus_R	4.57

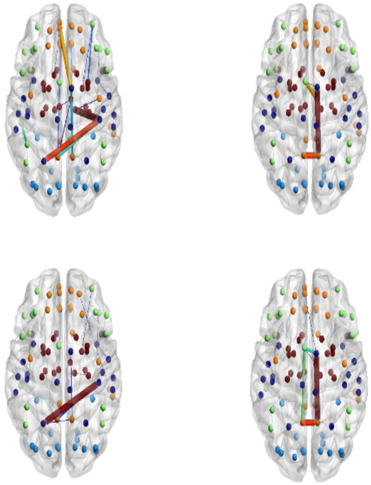

Figure 1 significant group differences in structural brain connectivity metrics: Top left, CL. Top right, Number of tracts. Bottom left, Average tract length. Bottom right, Volume of tracts