Phonological Fluency and functional connectivity in multiple sclerosis

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Introduction

Cognitive impairment is common among those diagnosed with multiple sclerosis (MS), with estimates of affected individuals ranging from 40-60% [1]. Several structural and functional MRI measures show correlation with cognitive impairment on a variety of tasks, presumably as a consequence of compromised white matter integrity [2-4]. More recent research has found evidence of cortical reorganization in multiple sclerosis, in the form of both compensatory activation and altered functional connectivity [5-8].

One of the more sensitive measures of cognitive impairment in MS is the Controlled Word Association Test, a word generation task measuring phonological fluency [9]. In healthy controls, fMRI of phonological word generation tasks typically shows activation in areas including bilateral Broca's area (BA 44/45), superior temporal gyrus (BA 22), left middle temporal gyrus (BA 21), and left inferior parietal lobule (BA 40) [10, 11]. A neural network analysis of PET data from healthy controls during word generation showed negative connectivity between left lateral frontal cortex and left superior, middle, and inferior temporal gyri, left lingual gyrus, left inferior parietal lobule, left fusiform gyrus, and left insula [12]. Even at rest language networks can be identified, and resting state connectivity data has shown correlations consistent with known language and reading circuitry, including connections from Broca's areas to superior and middle temporal gyri [13, 14].

Though we could find no studies of brain activation during word generation in MS in the literature, there is evidence to suggest that functional connectivity is compromised in other motor and cognitive tasks [7, 8, 15]. The nature of MS as a demyelinating disease leads us to expect that patients will show decreases in functional connectivity in a known language circuit during a resting state. It is also expected that performance on the Controlled Word Association Test will correlate with altered connectivity in the MS group. Though one study [7] found no correlation between altered connectivity and scores on the PASAT, there is evidence to suggest that connectivity may vary according to task performance [14]. In a sample of healthy controls, a correlation was found between IQ and functional connectivity in regions responsible for language processing [16].

We hypothesize that MS patients will have reduced resting state functional connectivity as measured with low frequency BOLD fluctuation (LFBF), between the anterior and posterior language regions (i.e. Brodmann’s areas 44/45 and 22) when compared with healthy controls. We further hypothesize that connectivity will correlate directly with performance of a language task.

Methods

The following two scans were performed on 22 subjects. Scan1: anatomic whole-brain T1-weighted inversion recovery turboflash (MPRAGE), 120 axial slices, thickness 1.2mm, Field-of-view (FOV) 256mm x 256mm, matrix=256 x 128. Resting state whole-brain EPI scans: 132 volumes of 31-4mm thick axial slices TE/TR/flip=29ms/2800ms/80 , matrix=128 x128, 256mm x 256mm FOV, BW=250KHz. Corrections include slice average covariate removal and physiologic noise correction using PESTICA [17] and RETROICOR [18], motion correction, a regression of the second order motion parameters of each voxel [19], and spatial filtering with a 2D hamming filter [20]. Finally, all timeseries were detrended and digitally filtered to remove fluctuations above 0.08Hz [21].

Sixteen right handed subjects with multiple sclerosis (mean age 44.87, (8.34); 5 males) and 6 right handed controls (mean age 45.3, (8.39); 2 males) were administered the Controlled Word Association Test. Subjects were given three 60 second trials using the target letters F, A, and S and were asked to generate as many words as possible which begin with the target letter. The total number of responses for each trial was added, corrected for age and sex, and assigned a percentile. Subjects were split into low (n = 6) and high (n = 10) performing groups at the 50th percentile. All controls included in the analysis performed at the 50th percentile or greater.

ROIs were drawn in each subject using scan 1. ROI’s were drawn in left hemisphere (LH) Broca’s area (Brodmann areas (BA) 44 and 45) and the LH posterior language region (BA 22) using Talairach locations determined from previously published data [10-12, 14]. A reference timeseries was produced by averaging across each pixel included in the Broca's ROI. The cross correlation (cc) was calculated between the reference timeseries and all voxels in the BA 22 ROI. Voxels with cc above a given threshold were counted and the percentage of voxels above threshold in the BA 22 ROI was calculated (Fc). The correlation between this percentage and performance on the Controlled Word Association Test was calculated separately for MS patients and control subjects. A between-group analysis (two sample t-test) was used to determine if the Fc showed significant differences between patients and controls.

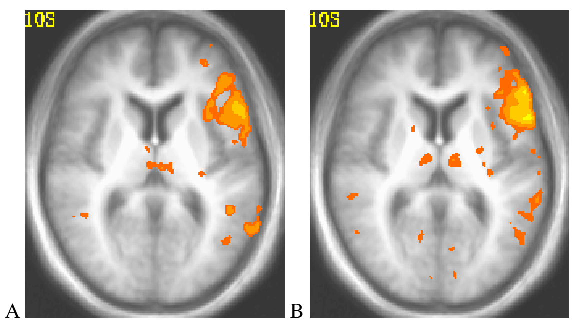

Fig 1. Axial averages from control (A) and MS (B) groups.

Results

Figure 1 shows connectivity maps for controls and patients. No significant between-group differences were found in Fc. However, the MS group performance on the Controlled Word Association Test showed significant correlation to Fc (.488, $p < .05$).

Discussion and Conclusion

Though between-group connectivity measures did not show significant differences, the resting state correlation between left Broca's area and left posterior BA 22 is correlated with performance on a test of phonological fluency in MS. The observation of a significant correlation between performance of a language task and resting state connectivity is consistent with our hypothesis. The fact that 1) there was no significant difference observed between connectivity in controls and patients and 2) no correlation was observed between control task performance and connectivity may indicate that the MS patients represent a spectrum of anatomic connectivity impairment. The significant correlation of functional connectivity between the posterior and anterior language regions and language function indicates that functional connectivity may be a sensitive marker of pathway specific white matter disease in MS.

References

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