Functional Correlation Of Brain Loci During Cognitive Tasks In Multiple Sclerosis

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ABSTRACT

Cognitive impairment (CI) is now considered a clinical marker in multiple sclerosis (MS). The most common CI and neuropsychological deficits in MS are in information processing, attention, memory, visual-spatial abilities, and executive function. Previous studies suggest that observed neuropathological changes in MS result from functional changes in connectivity or cortical reorganization to maintain a normal level of cognitive function and have an adaptive role in reducing the clinical effects of widespread tissue damage. Such alterations in connectivity could result in changes in neural activation as assayed by executive function tasks. We examined CI in relapsing-remitting MS patients with mild cognitive impairment and age-matched controls. We evaluated brain responses using functional magnetic resonance imaging (fMRI) during assays for executive function, namely the Flanker, Stroop and Wisconsin-card sorting tasks, presented in a randomized counterbalanced order. Preliminary analyses suggest no overt behavioral differences between patients and controls. As an initial step, a broad-spectrum analysis to assess functional connectivity between brain loci, determined significantly activated voxels throughout each session, and quantified the number and pattern of voxels that were correlated with each other at various spatially-distinct loci. Our preliminary analysis suggests that long-range correlations in MS patients may differ significantly from long-range correlations among matched controls when normalized according to a distance measure between the loci, a finding consistent with the demyelinating features of the disease. This pattern appears to be dependent on task demands. Ongoing analyses aim to determine if there are quantitative differences in the extent and distribution of correlated activated voxels that might scale with the degree of CI in MS patients. The combined fMRI-neuropsychological approach could yield important insights into the mechanisms of cognitive functioning and cortical reorganization in MS, and may provide a means to monitor treatment strategies to improve cognitive function in these patients.

INTRODUCTION

During the past decade functional MRI (fMRI) studies have shown that the human brain is capable of reacting to CNS injury (Rocca and Filippi, 2006). Several studies over these years have applied fMRI in the assessment of patients with multiple sclerosis (Forn et al., 2006; Pantano et al., 2006; Forn et al., 2007; Rocca and Filippi, 2007). Cognitive impairment (CI) is now considered one of the clinical markers of MS, and a leading cause of work-related disability in MS patients (Nocentini et al., 2006; Patti et al., 2009). It is estimated that about 50% of people with MS develop CI during the course of their MS (Patti et al., 2009). CI is only weakly correlated with the type of MS, disease duration, or physical disability (Bagert et al., 2002). However, there is a relatively strong correlation between CI and overall lesion burden and brain atrophy (Bagert et al., 2002; Nocentini et al., 2006).

A working hypothesis for these observations is that neuropathological changes that occur in multiple sclerosis result in altered functional connectivity patterns in affected neural areas. Such alterations in connectivity could result in changes in neural activation as assayed by executive function and decision-making tasks. These alterations may underlie overt behavioral dysfunction or indicate compensatory mechanisms engaged to maintain a normal level of cognitive function. They may provide a unique neural signature that could be indicative of disease severity or disease progression. We hypothesize that these behavioral changes should be reflected in altered functional brain connectivity in fMRI data from neuropsychological tests of executive function such as the Wisconsin card sorting task (WCS).

The data presented in this poster involve the use of a newly developed functional brain network analysis on fMRI data to obtain biometric measures in cognitively impaired MS patients performing the WCS task, and to investigate whether they show quantitative differences in these measures from age-matched controls. The computational procedure we have developed determines measures of connectivity in small, intermediate and large scale functional networks encompassing the entire brain, using a model-free data-driven approach. By performing voxel-to-voxel cross-correlation analysis and hierarchical cluster analysis we have been able to parcellate fMRI maps of the whole brain into functional networks of varying sizes (Figure 1), and determine changes in connectivity parameters such as the total number and sizes of functional networks, the connection strengths within and between networks, the spatial extent of networks and the brain area composition of networks.

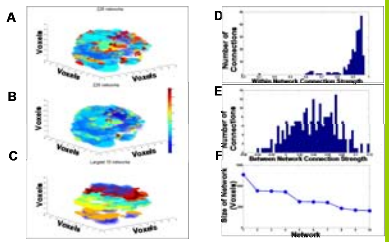

Figure 1

Global Brain Functional Networks

A. All 226 functional networks in the entire brain derived from a resting state ~8 min fMRI scan are depicted as a color-coded image. The color-coding simply demarcates the distinctions between networks i.e. each color represents one type of network. B. The same data as above, except the color-coding and color scale represents the strength of the functional connectivity (correlation coefficient) between pairs of voxels. C. The largest 10 networks are depicted. Color-coding is the same as in A. D. Histogram showing the distribution of connection strengths (correlation coefficients) between pairs of voxels within each network. E. Distribution of connection strengths (correlation coefficients) between pairs of voxels across pairs of networks. F. Sizes (number of voxels per network) of the largest 10 networks plotted in decreasing order.

METHODS

Males and females aged 24 through 58 were used in this study. They had normal vision or were vision corrected to be able to see the computer display clearly with or without eyeglasses. Control subjected were age-matched and cognitively normal. Multiple sclerosis patients had mild to moderate cognitive dysfunction. During the fMRI scan, subjects performed a WCS task on the computer by looking at the display through a mirror positioned above their head. They selected their choice by overlaying a selector box on the right choice using a device similar to a computer mouse. The computerized version of the WCS task (Figure 2) involved a set of 60 response cards. On each card there was up to four identical patterns (stars, crosses, triangles and circles) all of the same color (red, yellow, green, or blue). The participant was asked to put each card under one of four stimulus cards and to figure out the sorting rule based on feedback (correct, incorrect). Responses were scored in terms of errors and latencies of response. The scanning experiments lasted 20 – 30 in duration. The subjects were monetarily compensated for their participation in this study.

Subjects were scanned at the Human Neuroimaging Laboratory on Siemens 3T Trio machines. Functional imaging data was acquired via echo-planar imaging with the following timing parameters: TR = 2000 ms, TE=25ms. The 37 slice protocol (4 mm thickness, hyperangulated to 30 degrees) resulted in voxel dimensions of 3.4 mm x 3.4 mm x 4.0 mm. A Siemens T1-weighted MPRage sequence was used to acquire structural scans. Data were preprocessed with SPM2 by performing slice timing correction, realignment, spatial normalization to standard space and smoothed.

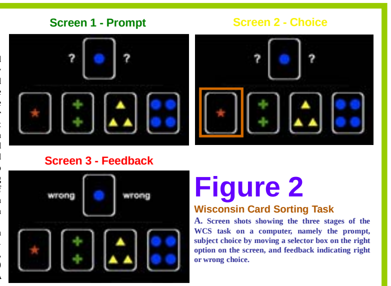

Figure 2

Wisconsin Card Sorting Task

A. Screen shots showing the three stages of the WCS task on a computer, namely the prompt, subject choice by moving a selector box on the right option on the screen, and feedback indicating right or wrong choice.

Functional Network Analysis

The steps in the computational procedure for functional network analysis are as follows:

- Get scaled time series data for each thresholded brain voxel for a session of ~10 minutes duration
- Low-pass filter at 0.1 Hz
- Obtain correlation coefficients (r) between filtered data from all pairs of a manageable number (500 – 2500) of voxels
- Express r as a distance measure, i.e. (1-r)
- Set the partitioning threshold for hierarchical cluster analysis to a distance measure equal to 0.95.
- Perform hierarchical cluster analysis on the distance measures using the nearest neighbor clustering method:

$$d(r, s) = min(dist(x_{ri} - x_{sj})), i \in (1, ..., n_r), j \in (1, ..., n_s)$$

- Calculate the number of clusters in pairs of manageable sets (500 – 2500) of sequential voxels of the entire brain.
- Average the time courses of all voxels in each cluster, and perform hierarchical cluster analysis on the averages with a new estimate of partitioning threshold, in accordance with the above procedure.
- The second level of clustering allows one to reduce the number of clusters of functionally correlated voxels, and to group the old clusters under the new reduced number of clusters.
- Reject all non-contiguous voxels and clusters containing < 3 contiguous voxels
- Calculate the connectivity strengths (correlation coefficients) within and between clusters, which are essentially functional networks of brain areas showing correlated activity.
- Plot a 3D representation of the functional brain networks using a color coding scheme reflecting the functional correlation within and between networks (see Figure 1A, B and C).
- Plot the intra-network and inter-network connectivity strengths and the mean distance between correlated voxels within a network, as a measure of its spatial extent (see Figure 1D, E and F).
- Using the automated anatomical labeling scheme, plot the percentage of voxels in each anatomical area that form the nodes of each functional network, as a 2D grid (see Figure 3).

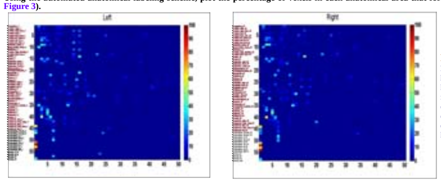

Figure 3

Brain Area Composition of Networks

Pseudocolor-coded images of neuroanatomical composition of 50 largest functional networks in the left (Left) and right (Right) hemispheres during resting state fMRI scanning. Brain areas are represented on the y-axis and the networks in the order of decreasing size are represented on the x-axis. The color-coding depicts the percentage of voxels of any given brain area that is part of each network. Parts of the cerebellar vermis are depicted in both left and right panels.

RESULTS

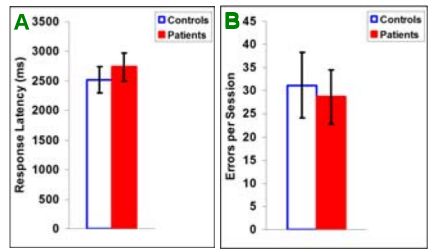

Figure 4

No Difference in Response Latencies and Error Rates Between MS Patients and Controls

A. A plot of the mean latency to respond in the WCS task showing no statistically significant difference between MS patients (n = 14) and controls (n = 18). The error bars in this and all other figures represent standard errors of the mean.

B. A plot of the errors in each WCS scanning session also shows no statistically significant difference between MS patients (n = 14) and controls (n = 18).

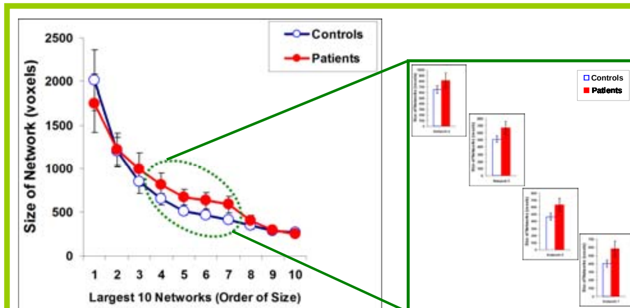

Figure 5

Changes in the Size of Networks in Multiple Sclerosis

A plot of the sizes of the ten largest networks, expressed in terms of number of voxels per network. Three of the ten networks are significantly larger in MS patients compared to controls. Data in this figure and all subsequent figures are taken from 10 minute scanning sessions of subjects performing the computerized version of the Wisconsin Card Sorting task. The inset on the right shows data from four networks as bar plots, representing an increase in size in MS patients compared to controls, three of which are found to be statistically significant (networks 5, 6 and 7, p = 0.044, 0.045 and 0.025, respectively; n = 21 and 11, for controls and patients, respectively) using Student's unpaired t test.

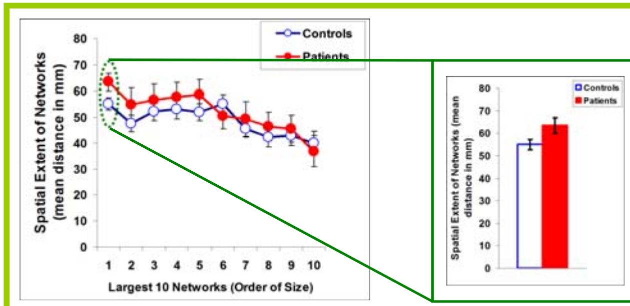

Figure 6

Changes in the Spatial Extent of Networks in Multiple Sclerosis

A plot of the spatial extents of the ten largest networks, expressed in terms of mean distance between all pairs of voxels within each network. The MS patients (n = 12) show a trend towards an increase in the mean distance in six of the ten networks compared to controls (n = 21), with the difference in the largest network being statistically significant (p = 0.022) using Student's unpaired t test.

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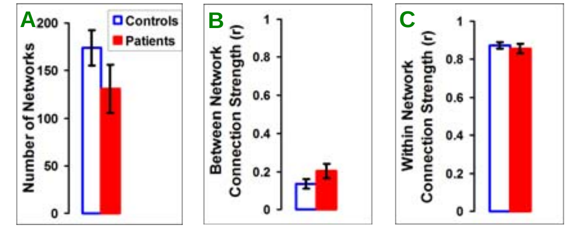

Figure 7

Number and Connection Strengths of Networks in Multiple Sclerosis

A. A bar plot of the total number of functionally correlated networks shows a decrease in MS patients (n = 12) compared to controls (n = 21). However, this decrease is not statistically significant. B. A bar plot of the mean strength of the connections (expressed as the correlation coefficient) between pairs of voxels belonging to two different networks shows a slight but not statistically significant enhancement in patients compared to controls. C. A bar plot of the mean strength of the connections between pairs of voxels belonging to the same network shows no statistically significant difference between patients and controls.

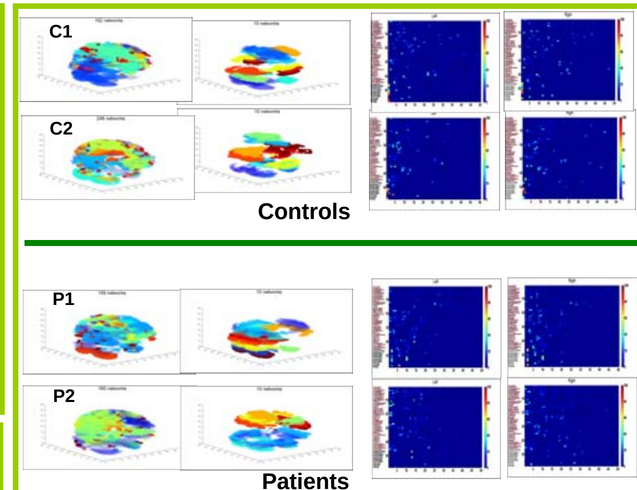

Figure 8

Variability in the Brain Area Composition of Networks

Color-coded 3D images of functional brain networks in two representative controls (C1 and C2) and two representative patients (P1 and P2). The color-coding demarcates the distinctions between networks i.e. each color represents one type of network. The left 3D images show all networks in each subject. The right 3D images show the largest ten networks. The values on the axes represent voxels. The 2D grids on the right half of the figure depict neuroanatomical composition of 50 largest functional networks in the left (Left) and right (Right) hemispheres during WCS task fMRI scans. Brain areas are represented on the y-axis and the networks in the order of decreasing size are represented on the x-axis. The color-coding depicts the percentage of voxels of any given brain area that is part of each network. Parts of the cerebellar vermis are depicted in both left and right panels. These data show that brain area composition of functional networks in highly variable both in controls and patients.

CONCLUSIONS AND DISCUSSION

Global functional brain network analysis in patients with relapsing remitting type of multiple sclerosis with no overt deficit in the performance of Wisconsin card sorting task shows significant increase in the size of medium to large sized networks compared to age-matched controls. There is also a concomitant increase in the spatial extent of the largest networks, as measured by the mean distance between pairs of functionally correlated voxel time series.

These findings are consistent with previous observations of alterations in the functional connectivity of specific networks such as the primary sensorimotor (Rocca et al., 2009; Lowe et al., 2008), working memory (Au Duong et al., 2005), and cerebellar (Saini et al., 2004) networks. While it is possible that the present results reflect changes due to primary white matter lesions, the lack of deficit in the performance of the cognitive task indicates that they are at least in part due to compensatory neuroplastic changes.