Resting State Sensorimotor Functional Connectivity in Multiple Sclerosis Correlates with Transcallosal Motor Pathway Transverse Diffusivity

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Introduction

Synchronous spontaneous low frequency BOLD fluctuations (LFBF) are considered to reflect functional connectivity (1). Recently, they have seen increasing use in a variety of studies, in particular where activation-based studies may not be well-suited to the scientific question under investigation (2-4).

It has been shown previously that functional connectivity between the bilateral sensorimotor cortices (SMC) is reduced in multiple sclerosis patients(5). Recent studies have also shown that DTI measures in white matter are representative of disease burden in MS (6) and further, that pathway dependent measures are more sensitive at detecting this disease(7). We present a study comparing anatomic connectivity to functional connectivity as measured with LFBF in MS.

Methods

The following data were acquired in 11 MS patients and 10 healthy control subjects. All subjects were scanned using a 12 channel receive-only head array on a Siemens Trio 3T scanner (Siemens Medical Solutions, Erlangen). All subjects were fitted for a bite bar to restrict head motion during scanning.

Scan 1, Whole brain T1:T1-weighted inversion recovery turboflash (MPRAGE): One hundred twenty axial slices, thickness 1-1.2mm, Field-of-view (FOV) 256 mm x 256 mm, TI/TE/TR/flip angle (FA) 900ms/1.71ms/1900ms/8^0, matrix 256x128, receiver bandwidth (BW) 62kHz. **Scan 2**, Whole brain isotropic 71-direction diffusion weighted imaging (DWI): Forty eight-2mm thick axial slices acquired with 71 direction, b=1000 mm^{-2} s diffusion gradients, and eight b=0 gradient images acquired for each slice; TE/TR=102ms/7700 ms, 128x128 matrix, 256mm x 256mm FOV, 5/8 partial echo, receive bandwidth=1628Hz/pixel. Four volume averages were acquired per subject. For diffusion images, signals were averaged across each diffusion profile for each volume after motion correction. **Scan 3:** FMRI Activation study: One hundred sixty volumes of 31-4mm thick axial slices are acquired using a prospective motion-controlled, gradient recalled echo, echoplanar acquisition with TE/TR/flip=29ms/2800ms/80^o , matrix=128x128, 256mm x 256mm FOV, receive bandwidth=1954Hz/pixel. Subjects performed a unilateral complex finger tapping task in a block style . **Scan 4**, Whole brain LFBF fMRI study: One hundred thirty two repetitions of 31-4mm thick axial slices acquired with TE/TR=29ms/2800 ms, 128x128 matrix, 256mm x 256mm FOV, receive bandwidth=1954Hz/pixel. The subject is instructed to rest with eyes closed and refrain from any voluntary motion.

Image Post Processing

FMRI data:Retrospective motion correction, spatial filtering.

Functional connectivity data: slicewise mean signal regression, cardiac and respiratory signals are estimated using PESTICA(8) and removed using RETROICOR(9), motion correction, second order motion correction(10), spatially filtered, temporally filtered to remove all fluctuations above 0.08Hz(1, 5).

DTI data: motion correction, each of the 71 gradient directions were averaged across the four acquisitions. The eight b=0 images were similarly averaged, diffusion gradient information was updated in accordance with the motion correction transformation applied to the diffusion-weighted images(11).

Image Analysis

FMRI Data: The fMRI data are analyzed using a least-squares fit of a boxcar reference function, representing the 45 second off/45 second on activation paradigm, to the timeseries data of each voxel(12). The result is a whole brain Student's t map that was thresholded ($p<0.01$) to determine regions of significant involvement in the unimanual tapping task. For each subject, regions of interest were defined in right and left hemisphere SMC based on peak activation observed in the t-map.

Functional Connectivity data:The functional connectivity data are analyzed in a similar manner to that described previously in Lowe et al.(13). The left hemisphere SMC ROI determined from the fMRI data is used to produce a reference timeseries. The result is a whole-brain map of z-scores indicating significant correlation to the reference region. Functional connectivity, F_c, is calculated as the percent of voxels in the right hemisphere region of interest over a threshold corresponding to significance $p<0.05$.

Fiber Tracking: The fiber orientation distribution (FOD) is calculated for each voxel(14), a brain tissue mask is generated from scan 1, the FOD is used as the probability distribution to generate stepping directions using the three dimensional random walk probilistic tracking method adapted from Hagmann(15). Tracks that leave the brain tissue mask are terminated, Tracks are generated using the ROI in the left hemisphere SMC region selected from the fMRI data described above., one million tracks were propagated from the seed ROI. Tracks were terminated upon leaving the tissue mask. Tracks that pass through the right hemisphere SMC ROI selected from the fMRI data are kept as being transcallosal motor pathway tracks. .(see Fig. 1 for a map of track density for a typical subject).

DTI Data: Whole brain diffusion tensor maps of fractional anisotropy (FA), mean diffusivity (MD), longitudinal diffusivity (λ_1), and transverse diffusivity (λ_2) were calculated. Pathway based DTI measures are produced by using the formula

$$\left\langle D \right\rangle = \frac{\sum_T \sum_v D(v)}{\sum_T \sum_v}$$

where the D(v) is the particular tensor-based value of interest (e.g. FA) at voxel v. The inner summation is over all voxels on track T and the outer summation is over all tracksT he result is $\left\langle FA \right\rangle$, $\left\langle MD \right\rangle$, $\left\langle \lambda_1 \right\rangle$, and $\left\langle \lambda_2 \right\rangle$ for every subject.

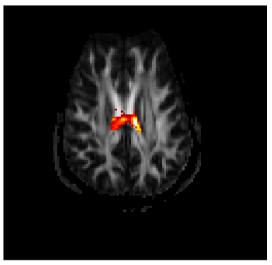

Figure 1: track density map through corpus callosum

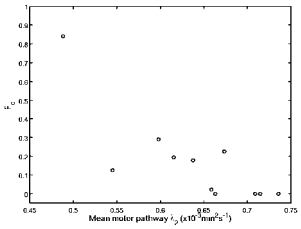

Figure 2: F_c versus transverse diffusivity

Results and Discussion

The correlation between $\left\langle FA \right\rangle$ and F_c for MS patients was r=0.68, p< 0.02. The correlation between $\left\langle \lambda_2 \right\rangle$ and F_c for MS patients was r=-0.87,p< 0.002**.** None of the control correlations were significant, nor were $\left\langle \lambda_1 \right\rangle$ or $\left\langle MD \right\rangle$ significantly correlated with F_c for MS patients. Figure 2 shows a plot of F_c as a function of $\left\langle \lambda_2 \right\rangle$ for MS patients.

Conclusion

We report an initial observation of significant correlation between DTI-based measures of anatomic connectivity and LFBF-based measures of functional connectivity in the resting state in a cohort of MS patients.

References

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