Increased Transverse Diffusivity of Water Observed in Transcallosal Motor Fiber Tracts in Multiple Sclerosis

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Introduction:

It has been shown that diffusion weighted MRI is sensitive to microscopic changes present in white matter in patients with multiple sclerosis (MS). In particular it has been shown that the isotropic diffusion of water in MS lesions is higher than in normal white matter(1) and that the anisotropy of water diffusion is lower in the diseased white matter of MS patients as compared to normal white matter(2). We hypothesize that the observed reduction in the anisotropy of diffusion in the white matter of MS patients is due to increased permeability of water transverse to the axonal direction due to the reduction or lack of myelin. We performed a comparison of the diffusivity of water transverse to the axonal direction in a cohort of MS patients to that of a cohort of control subjects.

In contrast to previous studies of the diffusion properties of white matter in MS, we adopted a method to compare the diffusion tensor in a subset of axons connecting bilateral motor regions of the brain. This was done using fMRI methods to identify cortical motor regions and DTI-based fiber tracking to select the axonal regions connecting the motor regions. The transverse diffusion was measured specifically along the tracts traversing the corpus callosum and connecting the bilateral motor regions. In this manner, our goal was to increase the sensitivity of the measurement by focusing on regions of the brain known to be principally affected in patients diagnosed with MS.

Methods:

Six patients with early stage MS (median EDSS=3+/-2) and six age and gender-matched control subjects were recruited to participate in this study. All subjects participated in a scan session using a Siemens Allegra 3T MRI scanner that included a high resolution T1-weighted anatomic scan, an fMRI activation study and a whole-brain isotropic diffusion tensor imaging study.

Scan Protocols: T1-weighted anatomic scan: 3D axial MPRAGE, 120 1.2mm thick slices, TE/TR/TI/flip= 1.7ms/900ms/1900ms/7°, 128x256 matrix, 256mmx256mm FOV, receive bandwidth=16KHz. FMRI Activation study: 160 volumes of 31-4mm thick axial slices were acquired using a prospective motion-controlled, gradient recalled echo, echoplanar acquisition with TE/TR/flip=29ms/2000ms/90° , matrix=64x64, 256mm x 256mm FOV, receive bandwidth=125KHz. During the execution of this scan, the subject executed a block-style fMRI motor paradigm consisting of interleaved blocks of 32 seconds rest, 32 seconds complex finger tapping. DTI acquisition: 50 2mm thick axial slices are acquired with six direction, b=1000 mm^{-2} s diffusion gradients, and one b=0 gradient image acquired for each slice. TE/TR=87ms/4200ms , 128x128 matrix, 256mm x 256mm FOV, 6/8 partial echo, receive bandwidth=125KHz.

Data Analysis: FMRI data were analyzed for activation by least-squares fitting the timeseries for each pixel to a boxcar reference function plus a slope (3). The resulting Student's t maps were used to produce seed regions in the white matter near the bilateral supplementary motor regions in each subject. DTI data were processed using a multi-step procedure consisting of eddy-current correction, motion-correction, followed by production of diffusion tensor eigenvalues (4). For each pixel, the eigenvalues are used to produce volume ratio index (VRI) , a measure of white matter anisotropy(5).

Fiber Tracking: The calculated diffusion tensor is used to track fibers in the white matter pathways using the method of Mori et al. (6). Threshold values used to terminate a given track were VRI<0.05, or deflection angle>80° . These parameters were observed to allow tracking to progress through some MS lesions. Seed regions were chosen as described above from the fMRI data. Tracks passing through the main part of the corpus callosum (excluding splenium and genu) were selected for further analysis. Mean VRI, mean principal eigenvalue (L1) and mean quadrature sum of non-principal eigenvalues (L2) were calculated for each callosal track in each subject.

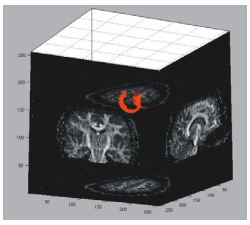
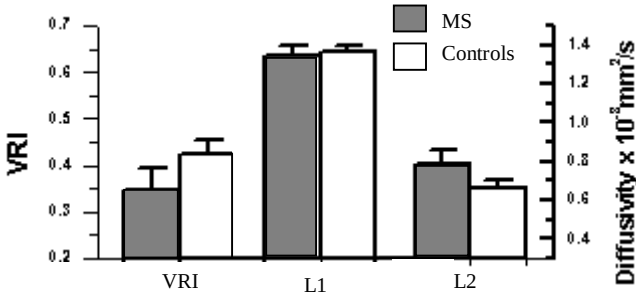


Figure 1



Results and Discussion

A typical set of transcallosal tracks from the fiber tracking is shown in Fig 1. Mean VRI, L1, and L2 are presented in Figure 2 (error bars represent the standard deviation across subjects). As can be seen from this figure, our hypothesis that the widely reported decrease in white matter anisotropy in multiple sclerosis is due to an increase in the diffusivity of water transverse to the axon is supported. Our observation that MS results in an increase in transverse diffusivity of water is consistent with a previous study of the diffusion properties of water using an animal model of MS(7). Our result is the first observation of this effect in a human population study. Additionally, an interesting observation is that the diffusivity along the direction of axonal transport is apparently unaffected by MS.

Conclusion

This study demonstrates that fiber tracts can be identified and isolated using DTI and fiber tracking algorithms. When combined with fMRI this can be performed and compared between individuals based on functionally defined anatomical areas. Using this methodology, we have shown for the first time that the diffusivity of water transverse to the direction of the fiber is reduced in the interhemispheric pathways connecting bilateral motor regions in MS patients when compared to a control population ($p<0.07$).

References

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