Diffusion Tensor Fractional Anisotropy and Compact Fiber Tracking of the Normal-Appearing Seven Segments of the Corpus Callosum in Healthy Adults and Relapsing-Remitting Multiple Sclerosis Patients

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INTRODUCTION

Conventional MRI, while very sensitive in visualizing MS plaques, is limited in its specificity because of the presence of multiple pathologies, such as axonal loss, demyelination and gliosis **[1]**. The availability of noninvasive and more specific methods for the quantification and localization of MS lesions may provide important insight and help identify surrogate markers of the disease occult activity **[1].** Recently, diffusion tensor imaging (DTI) has become increasingly useful in providing information about microscopic changes in normal-appearing white matter (NAWM) **[2].** The human corpus callosum (CC) has unique topology, location **[3]** and functionally specialized subdivisions **[5-9]** that may be affected differently by the disease, which may differ in response to pathology due to spatially dependent axonal packing, geometry and myelination **[4-7]**. In this report, we have focused on the NAWM of the seven segments of the CC as a disease marker **[3-8]**, using a recently described methodology and have applied it to 32 healthy adult controls and 26 relapsing and remitting (RRMS) patients **[8-9].** Our DTI results provide important clues to the interpretation of the callosal anisotropy heterogeneity and the possible Wallerian degeneration of connected pathways through the body of the CC.

HUMAN SUBJECTS and METHODS

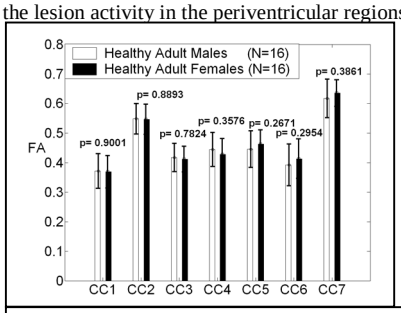
Twenty six clinically definite RRMS patients (22 females, 4 males; mean age ± SD = 37.9±11.7 years) and 32 age-matched healthy adult controls (16 females, 16 males; age = 38.1±12.1 years) were included in these studies. The median extended disability status score (EDSS) for the 26 RRMS patients was 1.25 (range 0.0, 6.0) and the median disease duration (DD) to imaging was 7.6 yrs (range 0.3, 17.6). All scans were performed on a GE 1.5 T NV MR scanner using a quadrature birdcage head RF coil. Axial brain images, covering the vertex and foramen magnum were acquired using graphically matched FLAIR, FSE, post-contrast T1 and DTI **[8,9].** Diffusion-encoded images were acquired with a dual-spin echo prepared and diffusion sensitized single shot echo planar sequence with spectral selective pulses for fat suppression. The tensor encoding scheme used is the multi-faceted icosahedral *Icosa21* with b=1400 s mm^{-2} and NEX=4 providing a total of 1+21 DW images per axial section **[9]**. The DTI acquisition time was under 11 minutes **[8,9].** The DT encoded data were distortion corrected, reformatted, decoded and diagonalized for further ROI and tracking analyses **[8,9].** A DTI based semi-automated 7 segment subdivision of the corpus callosum was implemented **[4-8]** (CC1-rostrum, CC2-genu, CC3-5 rostral-anterior-posterior midbody, CC6-isthmus and CC7-splenium)**.** The DTI regional measures were correlated with clinical variables such as EDSS and DD. DTI-based compact fiber tracking was conducted as described by Xu et al. **[10].**

RESULTS

Figure 1 summarizes the regional FA values from 16 age-matched healthy males and females. There were no significant differences between the age-matched males and females in any of the CC subregions; thus the male and female data were pooled to increase the power of the analysis with respect to RRMS. **Figure 2** shows the regional callosal FA on the combined age-matched healthy adults and the 26 RRMS patients. Based on the Bonferroni-adjusted two-tailed student t-test, the FA values of CC4, CC5, but not other structures that are investigated in these studies, differed statistically between normal subjects and MS patients. There were no correlations between EDSS, DD and FA of any of the CC segments **[8]. Figure 3** demonstrates—for the first time—the feasibility and utility of careful compact fiber tracking in MS. The figure provides representative adult DTI cases: a healthy control and two MS patients with NAWM of the genu and splenium but not the body of the CC.

DISCUSSION and CONCLUSIONS

Using optimized full brain DTI at high SNR, high angular resolution and careful ROI placement, our preliminary results on the spatial variation in the anisotropy of the callosal segments is consistent with histological data on age-matched controls [**3,5,7].** This study implicates the midbody of the CC (CC4, CC5) in the RRMS population that we examined is consistent with other MRI and clinical reports on MS callosal involvement **[8].** This finding is also in harmony with a histopathological report on axonal density loss observed in this structure **[4]**. The body of the CC contains the highest proportion of heavily myelinated, large diameter axonal fibers found in the CC which also contains a larger concentration of myelin progenitor cells (Oligodendrocites) **[5-7].** The decrease in FA may also be attributed to Wallerian degeneration of distally connected cortico-cortical pathways that traverse the CC4-CC5 (**Fig 3**) **[2,4].** The decrease in FA in the NAWM CC4 and CC5 may also reflect the lesion activity in the periventricular regions proximal to the CC **[2,4,8,11].** A detailed account of this study and its implications are in press **[8].**



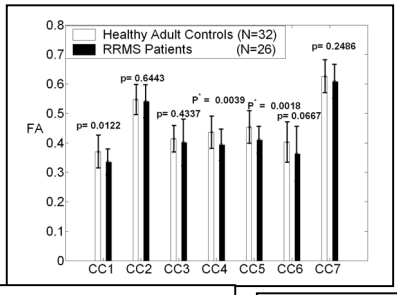
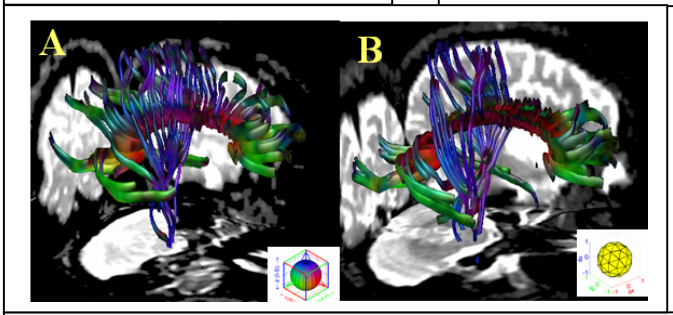
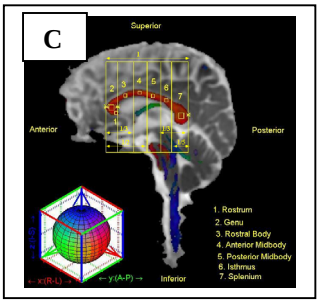


Figure1 A bar plot showing the comparison of FA group means and SD (μ ± σ) of the 7 subdivisions of the CC (**Fig 3.C**) between the age-matched healthy males and females (p=0.998).

Figure 2 A bar-plot of the (μ ± σ) fractional anisotropy values of the 7 segments of the CC (**Fig 3.C**) in the 26 RRMS and the 32 age-matched healthy adult control groups. The p values are computed using the two-tailed t-test for unequal samples. Significance was considered for p ≤0.007. Notice that: FA(MS) < FA(Controls): FA(splenium) > FA(genu) > FA(body of CC) and CC4-CC5 are significantly different between the two groups.





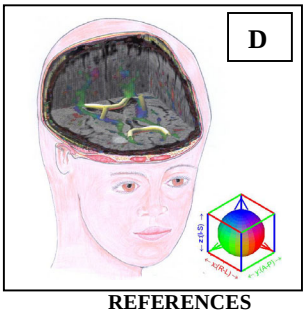


Figure 3. An Illustration of the feasibility of optimized entire brain DTI compact fiber tracking on both healthy controls **(A)** and RRMS patients (**B, D**). **A.** a 33-year adult female and a 38-year RRMS female (DD=11 years, EDSS=2.0). The figure shows commisural fibers (red: CC), long association fibers (green) and projection fibers (blue: tracks coursing through the posterior limb of the internal capsule, corticospinal and corona radiata). The directional color table and encoding scheme are also shown on the unit sphere. The 3D view is set so that most of the callosal and projection fibers are shown. The gray scale background maps (axial, sagittal and coronal) is obtained from the b=0 interpolated and DTI coregistered volumes. The seed placement and density were guided by the CC subdivisions as shown in **C**. **Fig 3.D** is an artistic fusion of DTI tracking and FLAIR coregistered volumes. Notice the lesion in the right frontal lobe and the feasibility of tracking at this stage of the disease. These cases are being studied and followed up longitudinally.

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