Are Regional Fractional Anisotropy Values Better Surrogates than Conventional MR Measures in Multiple Sclerosis?

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Introduction

Identification of a surrogate marker in multiple sclerosis (MS) would be of great use in multi-center clinical trials. Unfortunately, conventional MRI measures such as lesion load show relatively poor correlation with clinical measures in multiple sclerosis (MS). There is considerable evidence based on both MRS and histology that axonal pathology occurs early on in the disease. Diffusion tensor MRI (DT-MRI)-based anisotropic indices such as fractional anisotropy (FA) reflect the fiber tract integrity and might exhibit better correlation with the clinical scores. Unfortunately, the published FA values in MS have been inconsistent and contradictory, perhaps reflecting the use of suboptimal encoding schemes, poor signal-to-noise ratios (SNR) and variable region of interest (ROI) placement. To increase the accuracy of the DT-MRI metric estimation we have measured regional fractional anisotropy (FA) values using optimized DT-MRI protocols at high SNR from functionally distinct regions within the corpus callosum (CC) and posterior limb of the internal capsule (plIC).

Methods

Subjects: Fifteen normal controls (4 Females, 11 Males; age 35.2±12.6 years) and 30 clinically definite MS subjects (22 relapsing-remitting and 8 primary progressive; 23 females, 7 males; age 40.4±13.9) were recruited for these studies. The mean extended disability status score (EDSS) was 2.1±2.0 (range 0.0, 6.5) and disease duration to scan time (DD) was: 8.7±8.2 yrs (range 0.1, 39.0).

MRI Protocol: 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 the *affirmative* protocol for lesion visualization and image segmentation **[1].** DT-MRI data from the same region as the *affirmative* 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 Icosa21 with b=1000 s mm^{-2} **[2].** The acquisition parameters were: slice thickness=3mm with no gap, total number of slices =42, FOV=24 cm x 24 cm, acquisition matrix of (*ky* = 80, ramp sampling), image matrix after homodyne construction is 256 X 256, NEX=4, TE=80 ms and TR~7 seconds.

Data Processing and Analysis: *Affirmative* images were segmented into gray matter, white matter, CSF, lesions, and black holes **[3].** The DTI data were processed as described in **[2].** A semi automated subregional division of the corpus callosum as described by Witelson **[4]** was implemented in which CC is divided into 7 segments: CC1-rostrum, CC2-genu, CC3-rostral midbody, CC4-anterior midbody, CC5-posterior midbody, CC6-isthmus and CC7-splenium**.** The DTI measures obtained from 3x3 regions were correlated with other MRI measures (lesion load (LL) and black hole volumes (LL2)) and EDSS by computing the Pearson's correlation coefficient.

Results

Figure 1 summarizes the regional FA values of normal subjects and patients. Based on the two tailed student t-test, the FA values of CC4, but not other structures that are investigated in these studies, differed statistically between normal subjects and MS patients. **Table 1** summarizes the Pearson correlation r and P values between EDSS, LL, and LL2 and the regional FA values. Statistically significant correlation was observed between EDSS and the FA of rpIC. The total lesion load correlated with the FA value of CC6 (isthmus) while the black hole volume correlated with the FA values of anterior and posterior midbody of the corpus callosum (CC4 & CC5).

Discussion and Conclusions

Using optimized full brain DT-MRI at high SNR, and careful ROI placement, this study implicates the anterior midbody of the CC in the MS population that we examined. This finding is consistent with some recent clinical reports on MS callosal involvement in coordination **[5].** This finding is also consistent with a histopathological report on axonal density loss observed in this structure **[6]**. The CC4 sub-region contains the highest proportion of heavily myelinated, large diameter axonal fibers found in the CC **[7].** The decrease in the FA may also be attributed to Wallerian degeneration of distally connected cortico-cortical pathways that traverse CC4 **[6].** The implications of this finding to MS clinical diagnosis, pathogenesis and therapeutic trials are being investigated and await further data collection and future research. Our results also indicate that the FA values of genu and splenium are not significantly different between normal subjects and patients are in contradiction to recent reports **[8, 9].** We attribute these discrepancies to different acquisition, SNR, processing, ROI selection methods, and possibly the patients studied.

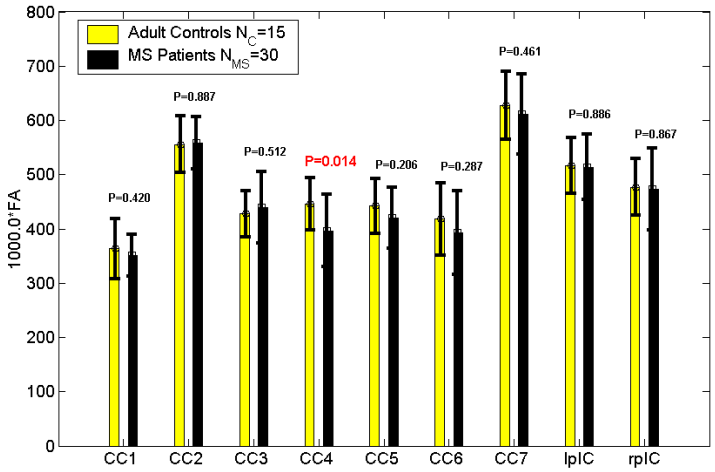

Figure1. A bar plot of the Normal and MS groups of the regional FA (mean ± SD) and the P values from the different subregions using the two tailed t-test for unpaired comparisons.

Table1. A summary of the Pearson correlation coefficient (r) and p values between regional FA values and clinical measures. LL: lesion load, LL2: black hole volume, DD: disease duration in years. (rpIC, lpIC): right and left posterior limb of the internal capsule. Statistically significant values (**p≤0.05**) are underlined.

	EDSS r (p)	LL r (p)	LL2 r (p)
CC1	-0.0455 (0.8113)	0.0387 (0.8392)	-0.0115 (0.9517)
CC2	-0.1456 (0.4426)	-0.3277 (0.0771)	-0.1351 (0.4766)
CC3	-0.2005 (0.2881)	-0.1697 (0.3698)	-0.1224 (0.5192)
CC4	-0.0286 (0.8805)	-0.3045 (0.1019)	**-0.3919 (0.0322)**
CC5	-0.0506 (0.7908)	-0.3506 (0.0575)	**-0.3813 (0.0376)**
CC6	-0.3115 (0.0938)	**-0.5040 (0.0045)**	-0.2014 (0.2858)
CC7	-0.1839 (0.3308)	-0.3351 (0.0702)	-0.2943 (0.1145)
rpIC	**-0.4572 (0.0111)**	0.0477 (0.8022)	-0.2307 (0.2201)
lpIC	-0.0322 (0.8657)	0.0443 (0.8162)	0.1567 (0.4082)

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