Extensive and Intensive Measures of Corpus Callosum Health in Multiple Sclerosis

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Introduction: Corpus callosum (CC) atrophy is a consistent and early finding in subjects with Multiple Sclerosis (MS)[1]. CC cross-sectional area is an extensive property and atrophy is thought to reflect irreversible demyelination and axonal loss. Quantitative relaxographic techniques also allow investigation of tissue intensive properties, which provide an efficient assessment of subtle abnormalities of normal appearing brain tissue. Intensive measures could provide an early index of tissue regions at risk for neurodegeneration. In this report, we investigate extensive and intensive callosal properties and explore the longitudinal relaxation rate constant (R_1) as a measure and potential use as a biomarker for neurodegeneration in MS.

Methods: *Data Acquisition:* 45 subjects (21 healthy controls, age: 43.6±13.7 years, 11F/10M, 24 subjects with MS (RRMS and SPMS, mean disease duration of 18 years), 53.4±7.8 years, 19F/5M) consented and participated in an IRB approved protocol at Siemens TIM Trio 3T MRI system[2]. A 3D MPRAGE image set (TE/TR/TI/FA: 3.41/2300/1200 ms/12º) was acquired with 192x256x128 matrix with 1mm isotropic resolution. Quantitative R_1 measurements were accomplished using global adiabatic inversion pulse followed by a 2D gradient echo EPI (128x128 matrix, TE/TR/FA: 16/10000 ms/90 º) sequence with 64 axial slices with 64 inversion times (34 ms ≤ TI ≤ 6000 ms) with isotropic 2 mm resolution.

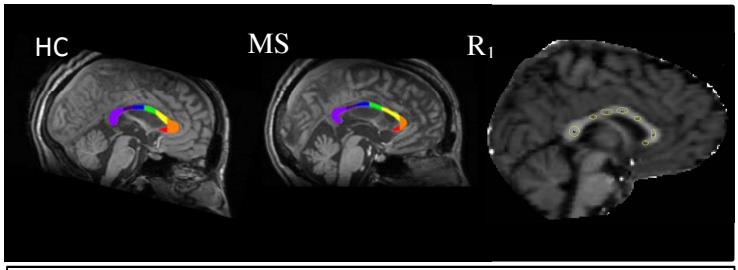

Figure 1. Automated CC parcellation according to Witelson's scheme is shown in a healthy and MS subject. Callosal loss is visually apparent in MS subject as compared to HC. The right panel depicts ROI locations in R_1 map for one of the subjects.

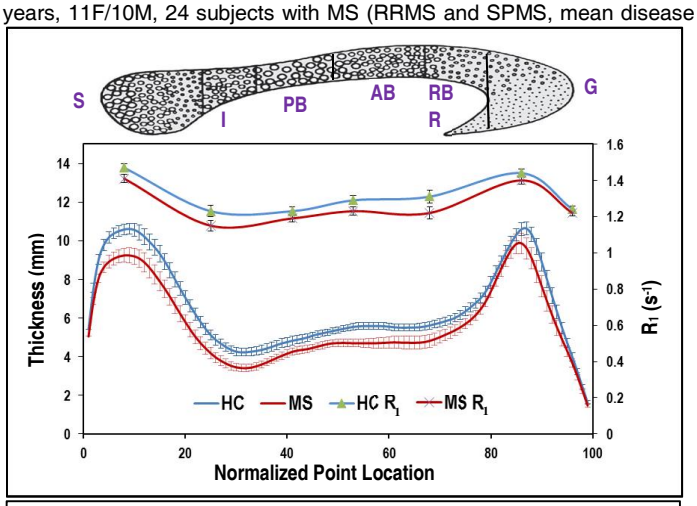

Figure 2. Bottom: Thickness of corpus callosum (posterior to anterior direction) in healthy controls (HC, blue) and subjects with multiple sclerosis (MS, red). Middle: Mean R_1 values at 7 locations (estimated) are plotted (error bars show standard error). Top figure shows the relative size and density of neuronal fibers in CC cross-sectional region (Adapted from Fig 1, Ref. 6). Labels for different colossal regions are shown based on Witelson's scheme (see text).

Data Processing: MPRAGE images were aligned to AC-PC line and mid-sagittal plane using acpcdetect[3] (ART package) and corrected for image inhomogeneity using SPM package's new_segment routine[4]. Parcellation of CC per Witelson's model[5] into seven regions (see **Figure 1**): rostrum (R), genu (G), rostral body (RB), anterior mid-body (AB), posterior mid-body (PB), isthmus (I) and splenium (S), and thickness measurements at 100 points along CC length were carried out by a model based parcellation program - yuki (v2.3) (http://www.nitrc.org/projects/art). Voxel wise determination of the water R_1 was performed using a single exponential fit to an inversion recovery function. The calculated R_1 maps (Fig. 1, right) were aligned and sampled to MPRAGE data matrix. Regions of interest were defined in the seven CC regions on two mid-sagittal slices of R_1 map, avoiding any lesions, to measure regional dependence (Fig. 1). *Statistical Analysis:* CC thickness and R_1 values were compared by paired t-test.

Results: MS subjects show a marked decrease (13.6%, p<0.01) in CC cross-sectional region thickness in most regions. An exception was the rostrum, where we found no difference in thickness between the groups. There was no difference in CC length between two groups (**Figure 2**). R_1 values are larger in CC compared to the normal central semiovale white matter (WM) in HC subjects[2] (R_1=1.23 s^{-1}) and vary spatially, reflecting CC tissue heterogeneity (Fig. 2). MS subjects show a decreased R_1 values compared to controls that is consistent with the changes in other WM regions[2] (R_1=1.21 s^{-1}). CC Rostrum and PB regions show no significant difference in thickness or R_1 values, indicating relative preservation of this region. The regions of atrophy are associated with neuronal fiber connections to supplementary motor, motor, temporal, parietal and occipital cortices.

Table 1. Mean R_1 values in Selected Regions (values±S.D., * = p<0.05)

R_1, s^{-1}	R	G	RB	AB	PB	I	S
HC	1.24±0.08	1.45±0.06	1.31±0.08	1.29±0.08	1.23±0.10	1.23±0.10	1.47±0.05
MS	1.22±0.08	1.40±0.10	1.22±0.17*	1.23±0.11*	1.19±0.11	1.15±0.14*	1.41±0.10*

Discussion and Conclusions: Intensive property changes may be subtle and reflect cell/tissue inflammations effects that are reversible[7]. A long term adverse effects may lead to cell death and consequent tissue loss that is irreversible. In this report, we show a direct correlation between decrease in callosal thickness and decrease in R_1 value, an intensive property, in MS subjects. These changes may reflect decrease in macromolecular fraction[8,9] or/and changes in blood-brain barrier. It is our hypothesis that decrease in R_1 may occur in the early stages of MS and is a potential biomarker of neurodegeneration.

Acknowledgement: The authors thank Dr. Babak Ardekani for providing a serial mode version of yuki 2.3 software.

Grant Support: NIH: R01-EB007258; RO1-NS040801; UL1-RR024140-S1; S10 OD018224 01

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