Preferably large fiber damage in the corpus callosum of progressive MS compared with relapsing MS and controls

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TARGET AUDIENCE: Imaging scientists and clinicians interested in the corpus callosum, NAWM, and multiple sclerosis.

BACKGROUND: Corpus callosum (CC) is one of the most frequently affected white matter structures in patients with multiple sclerosis (MS) 1, and the degree of injury may be different among different regions of the structure 2. However, findings on the segmental preference of tissue damage in the CC are inconsistent in relapsing-remitting (RR) MS and extremely sparse in secondary progressive (SP) MS 3. This may be partially attributed to the technical challenge in CC parcellation, which relies heavily on the time-consuming tractography in diffusion tensor imaging (DTI). In this study, we developed a simple method to segment the CC using sagittal DTI images, based on the functional connections of the CC4. We aimed to evaluate the microstructure of each CC segment, and determine how tissue injury differs across CC regions and between RRMS, SPMS, and control subjects.

METHODS: We recruited 19 patients [mean (range) age = 47.8 (29-75) years] and 19 age-, gender, and education-matched controls. Ten patients with mild RRMS (disability score=2; ranged 0-3) and 9 with advanced SPMS (disability score=6.2; all ≥ 6). All participants were scanned at a 3T scanner including DTI and conventional MRI. Besides routine axial images, we conducted sagittal whole brain DTI using TR/TE = 10000/78 ms; and b=1000 sec/mm², 23 directions. Identical FOV (24 cm²), matrix size (256x256), and slice thickness (3 mm) were used for all MRI sequences. Diffusion-weighted images were co-registered with the b0 MRI with eddy current corrections using FSL (FMRIB, Oxford), wherein fractional anisotropy (FA), and mean (MD), axial (AD), and radial diffusivity (RD) were calculated. In the midsagittal FA image of the CC, we built a 6-segment template (Fig. 1) modified from the Witelson Scheme4 and matched it on the para-middle sagittal images, totaling 3 per subject. For each subject, DTI measures were averaged across the 3 images per segment. The DTI of the entire CC were also assessed for normalization. Any visible lesions abutting or in the CC were avoided from the analyses. Mixed effects modeling was used for statistical analysis; p≤0.05 was set as significance.

RESULTS: We observed significant differences in DTI matrices between CC segments in control subjects, where part 1 had the lowest FA, but highest MD, RD, and AD, opposite to those in segment 4. The difference between CC segments was maintained in both MS groups. When compared between cohorts, we found that FA was significantly lower and RD, AD, and MD higher in each segment of the CC in SPMS than in controls. The SPMS group also had lower FA in all but segment 4, greater MD, RD, and AD in segments 3 and 6, and greater RD in segments 1 and 5, than the RRMS group. Compared to controls, the RRMS patients had only lower FA in segment 5 and higher MD, RD, and AD in 2 and 5, besides higher AD and MD in 4 (Fig. 2).

DISCUSSIONS: We found differential tissue organization and damage between CC segments. Tissue damage is significantly greater in advanced SPMS than in RRMS and controls, which is most severe in the body and splenium of the CC as shown by RD and FA then AD, suggesting greater myelin plus axonal damage5. There was only minimal increased injury in our mild RRMS patients compared to controls, mostly notable in the anterior body and isthmus of the CC. Postmortem studies6 suggest that the genu is comprised of large number of small-caliber fibers, while the middle and posterior segments of highly packed large-caliber fibers. Our results suggest the vulnerability of large caliber axons in the CC.

CONCLUSIONS: We demonstrate a preferable damage to large-caliber axons in MS patients, especially those with advanced SPMS, which may relate to the severe deficit in motor, sensory, and visual functions in these subjects.