Diffusion Tensor Axial Diffusivities are Different In the Body of the Corpus Callosum of Age-Matched Male and Female Adults

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Introduction: The contributors to *in vivo* tissue diffusion anisotropy (DA) remain unresolved **[1-3]** even for the simplest white matter structure such as the corpus callosum (CC) which is known to have heterogeneous axonal density and myelination levels **[4]**. A few carefully conducted animal diffusion studies have used simple structures such as spinal cord **[1,5]**, optic nerve **[1,6-7]**, and CC **[1,8]** along with invasive histology to provide important clues as to the sources of DA **[1]**. Owing to its vital functional roles, disease-injury vulnerability and location, the human CC has been used by many researchers as a marker of brain tissue regional maturation and as an early sensitive index of pathology [**9-13**]. The human CC can also be used to provide a simple benchmark to understand the myelin and axonal contributors to in vivo DA **[1,10-12].** In addition, using optimized DTI at high SNR, the CC may be used to study some long-standing issues in neuroscience such as the noninvasive mapping of gender based-differences in axonal morphology. Many DTI reports on the CC have failed to detect DA differences between age-matched adult human males and females using rotationally-invariant indices such as FA, RA or VR **[10-13]**. More recent DTI studies have reported some conflicting results in regards to DA differences between males and females **[14-16].** For example, Shin et al. **[14]** reported that all segments of the male CC have higher anisotropy than that of females and could not explain their results by a myelination argument **[14]**. Westerhausen et al. **[15]** showed that left-handed males have the largest DA compared to right handed females and argued that myelination accounted for the measured differences between genders. Szeszko et al **[16]** showed that females have higher DA after correcting for age in the anterior brain areas. A postmortem study by Highley et al. **[9]** reported that CC axonal density in females is larger than that of age-matched males, which apparently contradicted an older study by Aboitiz et al. **[4]**. Other postmortem earlier studies highlighted both cortical and callosal structural differences between males and females **[17-19]**. Recent MRI studies report an increased cortical gyrification (or folding) in human females which were explained as a compensatory mechanism to account for the statistically smaller brain size **[19]**. Since some human neuropathologies (e.g. multiple sclerosis) target women at a hgher rate (70% females vs. 30% males), and conditions such as dyslexia and ADHD are more common in males than in females, we sought to use DTI to help identify the microstructural substrates that may lead to possible callosal differences between two age-matched male and female cohorts.

Methods: Subjects: 32 healthy adult controls (16 females and 16 age-matched males; age = 38.1±12.1 years; p = 0.998). **Conventional MRI and DTI Data Acquisition:** The DTI acquisition utilized a dual spin echo sequence that reduced eddy current related image distortion. A balanced *Icosa21b* tensor encoding protocol at high SNR was used **[10]**. **Data Processing and Analysis:** Residual diffusion weighted data image distortions were corrected using the AIR package as described elsewhere **[10]**. We also implemented and adapted a semiautomated Witelson 7-corpus callosum subdivision methodology to help in the CC-ROI sampling. The ROI placement and CC segmentation procedure are validated and detailed elsewhere **[10]**. **Statistical Analyses**: An analysis of variance was used to compare the two age-matched groups in the DTI metrics FA, D_{av}, and the longitudinal and transverse diffusivities ($\lambda_1=\lambda_l$, $\lambda_t = (\lambda_2+\lambda_3)/2$), respectively. An analysis of covariance incorporating age did not alter the results reported here.

Results: Figure 1 (**a, b**) shows a bar plot of both the FA and mean diffusivity (D_{av}) on the age-matched male and female groups in the seven segments of the CC (CC1-CC7). **Figure 1 (c, d)** shows the corresponding $\boldsymbol{\lambda_l}$ **&** $\boldsymbol{\lambda_t}$. Notice that **FA**, D_{av}, and $\boldsymbol{\lambda_t}$ showed no significant differences between males and females in any CC region. Surprisingly, the longitudinal eigenvalues show a trend of *increased longitudinal diffusivity* ($\boldsymbol{\lambda_l}$) in the CC3 and CC4 or the body of the CC in males relative to females.

Discussion: The human female brain has been documented to be less lateralized compared to an age-matched male brain **[18].** MRI volumetric studies on cortical gyrification presented early evidence of such a statistical difference **[18-19].** In this report, only λ_l were found to be different in a CC region that is populated by larger and more myelinated fibers (~2-4 μm) **[5,9,17].** Since myelination is better reflected by λ_t **[1,8]** which is not found here to be significantly different between the two genders, we argue that the differences detected here are due to (**I**) microfilament density or or/and (**II**) fiber alignment of the compact bundles in the voxel. Since more interhemispheric communication in the female brain assumes more fibers per unit area as shown in postmortem data **[9,17]**, then the axonal CC3-CC4 microfilament density may be larger in females than in males **[1,5,7]**. Anisotropy increases as fibers become less tortous and straighter with maturation **[6]**; this increased regularity in fiber alignment may contribute to the regional increase we identified in CC3-CC4. Since an early work by Sullivan et al. **[12]** did not show any alteration in the coherence index in the CC, the first hypothesis remains to be tested. Our studies, although conducted with optimized DTI **[10]**, are preliminary and need to be validated on a larger population.

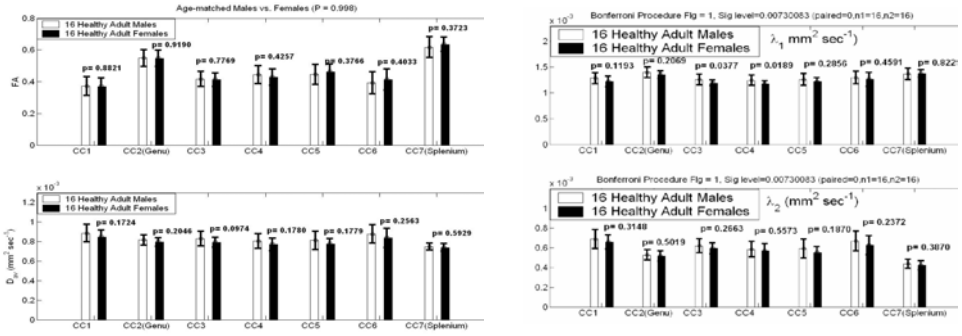

Figure 1. Bar plots showing the regional DTI metric comparisons between age-matched male and female corpora callosa. The metrics used are (a) FA, (b) $D_{av,}$ (c) λ_1, and (d) λ_t. Notice that only the longitudinal eigenvalues in CC3-CC4 indicate an increasing trend in males compared to adult age-matched females.

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