Regional Variability of Aging and Gender Difference in Human Corpus Callosum: a Diffusion Tensor MRI study at 4 Tesla

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Introduction: The corpus callosum (CC) is the largest compact fiber bundle that connects cortical and subcortical regions, accommodating interhemispheric transfers of auditory, sensory, and motor information. The compact CC fibers run through mid-sagittal plane with high directional coherence. Postmortem studies showed that the CC fiber distribution is heterogeneous [1] and different CC portions project fibers to different cortical regions. Morphological studies of age and gender related changes based on segmented CC portions in normal adults yielded conflicting results [2,3]. Recently, diffusion tensor imaging (DTI) has become increasingly useful to study fiber integrity in terms of fractional anisotropy (FA) and mean diffusivity (MD). Moreover, Diffusion Tensor Tractography (DTT) provides information about main fiber pathways. Although some of the studies found age-related FA variations in the anterior and posterior regions of the CC [4,5], DTI changes in the central body of CC and their relation through anterior to posterior CC have not thoroughly been investigated. Furthermore, DTI studies of gender differences in the context of healthy aging have yielded controversial results [6,7]. In this study, we investigated effects of age and gender on the CC, using DTT approach for region of interesting (ROI) determination, and a 4 Tesla magnet to achieve high SNR and spatial resolution. Specifically, our goals were: 1) to evaluate the underlying structural heterogeneity of the CC, 2) to explore whether different CC portions are differentially affected by age and sex.

Methods: Fifty-three healthy subjects (28 male, 25 female; Age 18-71 yrs) were involved in the study. DTI was performed on a 4.0 Tesla scanner using single-shot EPI sequence (TR/TE=6000/77ms, voxel size: 2x2x3mm^3, 40 contiguous slices, b=0, 800s/mm^2, and 6 directions, 4 averages). FA, MD, and color-coded maps were generated using Volume One and Diffusion Tensor Visualizer (dTV) software (http://www.ut-radiology.umin.jp/people/masutani/dTV.htm), and interpolated to 2x2x2mm^3 resolution for fiber tracking. For callosal fiber tracking, one seed ROI was placed manually on the mid-sagittal slice with an FA threshold set at 0.3 to avoid partial volume artifacts from adjacent CSF and gray matter. The tracked fibers were displayed as fiber maps for further ROI determination. The DTI maps (FA, MD and fiber maps) were reorientated to the conventional position, with the bottom of genu and splenium along the same level on sagittal view. The reorientated DTI maps were then transferred to MRIcro (http://www.sph.sc.edu/ comd/rorden/mricro.html) for ROI analysis: Three contiguous mid-sagittal slices from fiber maps were extracted (Figure1a) as ROIs, ROIs were divided into 5 equidistant portions (CC1-CC5) [8], starting from the anterior (CC1) to posterior (CC5) edges (figure1b). Mean and standard deviation of FA and MD values for each ROI were measured by overlaying fiber maps (ROIs) on FA and MD maps, separately for each subject.

Figure1. (a). Axial view: ROIs were selected from 3 adjacent slices. **(b).** Mid-sagittal view of the CC with indication of the five ROI portions. Green area indicates the fiber map, which was overlaying on the FA map. **(c).** An illustration of fiber tracts from 5-divided CC segments projecting to different cortical regions.

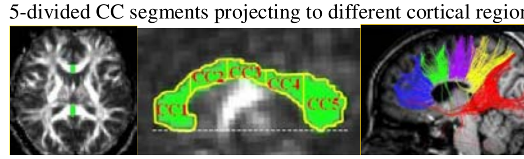
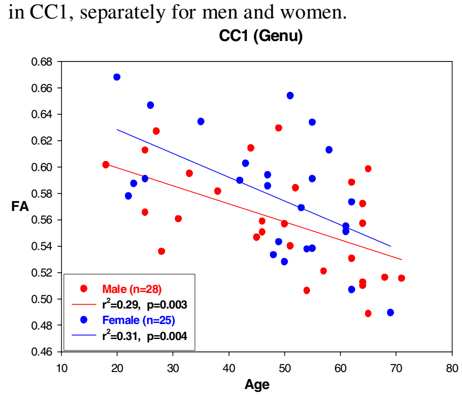


Table 1. Age and gender effects on FA and MD in CC1-CC5

	Regions	Age		Sex	
		coefficient	*p*	coefficient	*p*
FA	CC1	-0.0016	**<0.001**	-0.019	***0.099***
	CC2	-0.0012	**0.003**	0.0061	0.76
	CC3	-0.0006	0.17	0.0023	0.19
	CC4	-0.0012	**0.04**	-0.0193	0.11
	CC5	-0.0002	0.4	0.0116	0.5
MD	CC1	3.55	**<0.001**	-5.3	0.79
	CC2	3.81	**0.003**	-24.8	0.15
	CC3	3.99	**<0.001**	-62.8	**0.01**
	CC4	3.56	**0.009**	48.7	0.11
	CC5	1.1	0.11	-27.7	0.75

Results: 1) <u>Heterogeneity of CC</u>: Figure1c illustrates fiber connections between each selected CC portions and cortical regions. CC1 (approximately encompasses the genu) connects to the orbital and medial frontal cortex, CC2 to dorsal frontal cortex, CC3 to sensori-motor cortex, CC4 to parietal cortex, and CC5 (approximately encompassing the splenium) to temporal and occipital cortex. FA varied substantially ($p< 0.001$) between portions from CC1 to CC5, except that CC3 and CC4 had similar FA values ($p > 0.05$). FA was the highest in CC5 (mean± standard deviation: 0.64±0.03), followed by CC1 (0.57±0.04), CC4 (0.51±0.06), CC3 (0.49±0.05), and CC2 (0.44±0.04). 2) <u>Age and Gender differences:</u> FA and MD values in each portion of the CC were modeled as function of age, gender, and age by gender interaction and the explanatory power of each variable was tested by maximum likelihood. Table1 summarizes the statistical results, separately for each CC portion. With increasing age, FA significantly decreased in CC1, CC2, and CC4, while remaining stable in CC3 and CC5. Overall, there was a trend ($p = 0.1$) of higher FA values in women than in men, predominantly in CC1, but without an age by gender interaction. The age-related FA reduction in CC1 is depicted in Figure 2, separately for men and women. As expected, MD significantly increased with age – contrarily to FA - in CC1, CC2, CC3, CC4, but not in CC5. Moreover, women had surprisingly higher MD values than men in CC3 ($p = 0.01$).

Figure2. Linear regression of Age and FA relations in CC1, separately for men and women.



Discussion and Conclusions: The finding of age-related FA reductions in anterior CC, presumably reflecting reduced fiber density or thinning of myelin sheets, replicates previous reports of age-related FA changes [9]. Furthermore, the strong relationship of FA reduction with age in frontal CC regions agrees with anatomical brain MRI studies of age-related loss of white matter volume [10]. In contrast to FA, age-related alterations of MD extended from frontal regions to the CC body. The reason for the regional dissociation between FA and MD in the CC body is currently unclear. Taken together, the white matter alterations seem to be restricted to frontal regions, while both FA and MD values in posterior regions in CC remained stable across the life span. In addition to age, we found a trend of higher FA values in women than in men, which was more prominent in the frontal region. This finding agrees with postmortem studies [11] showing higher fiber density in anterior aspects of the CC in women than in men. In summary, the results indicate that healthy aging is associated with diminished fiber integrity in anterior aspects of the CC, which may help to better understand the topology of age-associated brain alterations.

References:

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