Reduced fractional anisotropy in ageing: Is it driven by changes in tissue microstructure or by partial volume effects?

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Purpose: The partial volume effect (PVE), arising due to large voxel-sizes, is a known limitation in diffusion tensor imaging (DTI)[1]. For example, recent reports on tractography describe a positive correlation between fractional anisotropy (FA) and structure size[2, 3], demonstrating the need to differentiate between 'true' microstructural change and PVE, especially in ageing with progressive atrophy of white matter tracts. A small PVE on FA in the body of the corpus callosum has been reported[4] (R^2 0.14 – 0.31), but few elderly (>65) were included. Here we investigate to what extent the FA is reduced as a function of age[5] and how much of this reduction can be explained by atrophy separate from true microstructural changes in a cross-sectional design. To that end we correlated FA with age, ventricular volume as a proxy for atrophy, the number of voxels in segments of the corpus callosum (CC) and the volume of the corpus callosum estimated using Freesurfer. In addition, the cingulum (CG) that is not adjacent to CSF but to grey matter, and the periventricular segment of the cortiocospinal tract (CST), were studied as comparisons.

Methods: 150 healthy subjects, aged 65 – 85 years (mean 71 years, 66 males, 84 females), were scanned using a 3T Siemens Magnetom TRIO with a protocol including; DTI (SE-EPI-sequence, 2 mm isotropic voxels, b-value of 1000 s/mm^2 in 64 encoding directions) and an MPRAGE-sequence (1 mm isotropic voxel size). The diffusion images were co-registered using ELASTX and the DTI calculation was performed with in-house developed software. All analys were performed in subject space. The CC was divided into 4 parts defined with deterministic tractography (FA>0.2, angle<45°); cut-off-gates were placed 6 mm laterally of the AND-gate placed sagitally in the centre of each segment (Fig 1). The central part of the CG and the CST were investigated with a similar approach. AND-gates were placed in the CST at the level of the lowest part of the CC with cut-off-gates 6 mm superiorly and inferiorly (Fig 1C). In the CG, AND-gates were placed at the level of the central CC body with cut-off-gates 6 mm anteriorly and posteriorly (Fig 1B). The volume of each segment of a tract, here denoted 'tract volume', was defined as the number of voxels x voxel volume as described in[1]. The ventricular volume was divided with total intracranial volume (normalized) to account for head-size differences. The lateral ventricles and the CC were segmented with Freesurfer; the parameter here denoted 'CC volume' [mm^3] is the volume of a midsagittal cross-section, 5 mm wide, as rendered by Freesurfer. Subdivisions of the ventricles and the CC were added to calculate their total volume. Statistical evaluation was performed using Pearson's correlation, partial correlation and multiple linear regression. Bonferroni-adjustment was used to correct for multiple comparisons: the adjusted significance level was set to 0.0125 (0.05/4), as we compare 4 factors. Subjects with enlarged ventricles (>77 cm^3, 4 subjects) and small callosal volumes (<2000 mm^3, 2 subjects) were excluded. A total of 144 subjects were included.

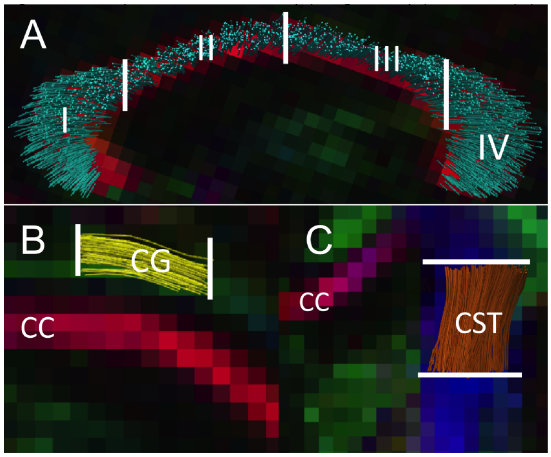

Figure 1. Gate placement in the CC (A)*, right CG (B) and CST (C). *I: Genu, II: Anterior, III: Isthmus and IV: Splenium

Table 1. Pearson correlation to FA values in each area.

Area	Age	Normalized ventricle volume	Tract Volume	CC Volume [mm^3]
Genu	-0.197	-0.211*	0.259*	0.260*
Anterior	-0.215*	-0.242*	0.479†	0.477†
Isthmus	-0.039	-0.150	0.455†	0.414†
Splenium	-0.007	-0.121	-0.027	-0.208*
CST R	-0.142	0.328†	0.142	-0.188
CST L	-0.120	0.376†	0.161	-0.081
CG R	-0.237†	-0.088	0.161	0.090
CG L	-0.267*	-0.021	0.138	0.071

$p < 0.0125$ is indicated by an asterisk *, $p < 0.001$ by a dagger (†).

Table 2. Mean FA in the Anterior CC.

Normalized ventricle volume	Young(<71)		Old (>71)	
	Mean	SEM	Mean	SEM
Small (<0.02)	0.689	0.004	0.691	0.008
Medium (0.02 – 0.03)	0.686	0.006	0.686	0.005
Large (>0.03)	0.684	0.006	0.655	0.005

Presented as Mean±SEM. Corrected for tract volume.

Results: We found significant correlations between FA and measures of structure size, tract and callosal volume, throughout the whole CC with the strongest correlation in CSF exposed areas (Table 1). Age correlated significantly with FA only in the anterior CC, however after correction for tract volume this was no longer significant (Fig 2, p 0.027). Similar results were obtained when correcting for ventricular volume. Ventricular volume correlated with FA only in the anterior parts of the CC, but a strong correlation was found in the CST (Table 1). The correlation between FA and age was non-significant in all areas except the CG when controlling for tract volume (not shown). The correlation between FA and age in the CST was not affected by ventricular volume. When subjects were grouped according to ventricle volume and mean age (71 years), an interaction between age and ventricular volume was demonstrated in the older individuals with large ventricles (>0.03, normalized ventricular volume) in the anterior CC, which drove the change in FA (Table 2). CC volume differed between young and old subjects with large ventricles ($p = 0.012$), however voxel count in the genu and anterior was similar ($p = 0.029$, $p = 0.016$).

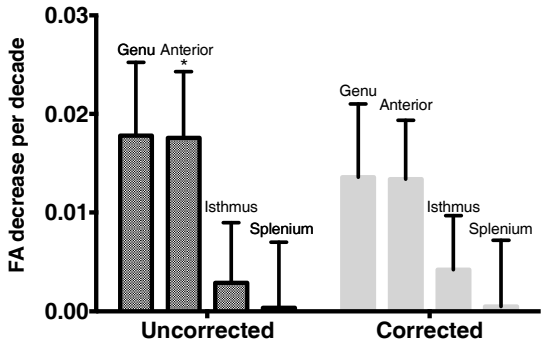

Figure 2. Mean FA-change per decade in the CC, uncorrected and corrected for tract volume. $p < 0.0125$ indicated by an asterisk (*). Presented as B coefficient with SEM.

Discussion: We have found a significant correlation between FA and measures of structure size as proxy for cerebral atrophy, but to a greater extent then previously reported[2,3]. In addition, we found a correlation for FA with age in the anterior part of the CC, which decreased significantly when corrected for tract volume (Table 1, Fig 2). These findings indicate that atrophy and its associated increase in PVE are more relevant in explaining the inter-individual variation in FA than ageing. This is also evident from the comparison between young and old subjects, as elderly subjects without ventricular enlargement did not show evidence of FA reduction (Table 2) or reduced callosal volume. Thus increasing atrophy during aging would represent a significant confounder in studies aiming at estimating microstructural change, as callosal volume is significantly correlated with FA (Table 1). The correlation between ventricular volume and FA in the CST might be due to straightening of the fibres, which has been predicted to affect FA[6].

Conclusion: We show that the effect of ageing on FA in the corpus callosum is reduced when correcting for tract volume, indicating a significant impact of PVE. Reduced CC volume in combination with ventricular enlargement and age drives this reduction in the anterior CC; a longitudinal design might demonstrate true microstructural change in this subgroup.

References: **1**. Alexander AL, et al. Magn Reson Med. 2001;45:770–80 **2**. Vos SB, et al. Neuroimage. 2011;55:1566–76 **3**. Szczepankiewicz F, et al. Neuroimage. 2013;76:145–54 **4**. Lebel C, et al. Neuroimage. 2012;60:340–52 **5**. Ota M, et al. Neuroimage. 2006;31:1445–52 **6**. Nilsson M, et al. NMR Biomed. 2012;25:795–805