Age-related microstructural alterations increase the relationship between radial and axial diffusivities.

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Introduction: Fractional anisotropy (FA) and mean diffusivity (MD) are the most common measures of fiber coherence and integrity in diffusion-tensor imaging (DTI) studies on aging. FA and MD are composites of radial (RD) and axial diffusivities (AD), which in regions with coherent fiber orientation can serve as markers of myelin and axon integrity, respectively (Song et al., 2002, 2003, 2005). Adding to the knowledge on region-specific differences in the degree of preservation or decline of white matter (WM) tracts, we investigated region-specific correlations between RD and AD and their age dependence. Our prediction was that microstructural age-related alterations in mature WM (e.g. myelin loss) may result in an increased dependence between RD and AD values, which are mathematically orthogonal.

Methods: 143 neurologically healthy participants (80 younger: 45 men, M = 25.7 ± 3.2 years; 63 older: 34 men, M = 64.8 ± 2.9 years) underwent DTI examination (1.5 T Siemens Sonata, SE-EPI sequence: TR/TE = 8500/96 ms, 128 x 128 matrix, 2.5 mm^3 resolution, 52 slices, 12 non-collinear directions with b-value = 1000s/mm^2 and one b-value = 0 s/mm^2 acquisition, 4 NEX). Older participants were non-demented (≥28 points on the Mini Mental Status Exam), showed declining fluid abilities (Digit-Symbol Substitution $M_{younger}$ = 63.1 ± 10.9, M_{older} = 47.8 ± 12.7, $p < 0.001$), higher crystallized abilities (Spot-a-Word task $M_{younger}$ = 18.3 ± 5.3, M_{older} = 22.2 ± 5.8, $p < 0.001$), and moderate age-related WM hyperintensities on FLAIR images. We used FSL 4.1 Diffusion Toolbox to compute FA, MD, RD, and AD maps. We obtained the centre-of-tract parameter values using tract-based spatial statistics (Smith et al., 2006) with an FA skeleton threshold of 0.25. On the skeleton, we defined 10 regions of interest (ROIs): genu (GCC) and splenium (SCC) of the corpus callosum, anterior (AC) and posterior cingulum (PC), stria terminalis (ST), external capsule (EC), fornix (FX), anterior (ALIC) and posterior (PLIC) limbs of the internal capsule, and ventromedial prefrontal (VMPF) WM. Statistical analysis was performed using SPSS v.16. In the figures: *p<0.05, **p<0.01, ***p<0.001.

Results: RD was greater in older than in younger adults in all regions except PC, where RD was lower in older adults. Age-related differences in AD were both positive and negative (Fig. 1). In younger adults, except for RD GCC, correlations of age with RD or AD were not reliable (Table 1). By contrast, in older adults age correlated reliably with RD and AD for many ROIs (GCC, AC, EC, FX) (Table 1).
The RD-AD correlation differed across ROIs, regardless of age (Fig.2, blue bars). In all ROIs, RD correlated more strongly with AD in older than in younger adults (Fig. 2). This pattern was independent of the direction of mean age differences in both RD and AD.

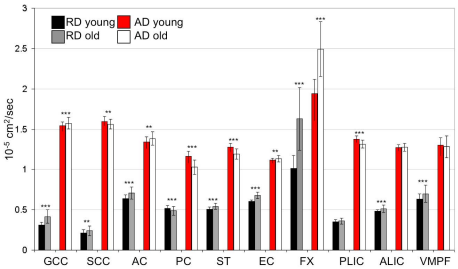

Fig. 1 AD and RD values in older and younger adults.

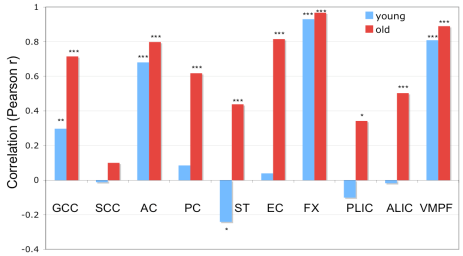

Fig. 2 AD- RD correlation differs by ROI and increases with age.

Table 1. Correlation of RD and AD with age, separately for the two age groups

ROI		YOUNG	OLD
GCC	RD	.26*	.41**
	AD	-.01	.42**
SCC	RD	.16	.23
	AD	-.08	-.04
AC	RD	.06	.33**
	AD	.09	.25*
PC	RD	-.07	.17
	AD	-.11	.10
ST	RD	.09	.24
	AD	.15	.06
EC	RD	.08	.31*
	AD	-.16	.26*
FX	RD	.11	.33**
	AD	.11	.34**
PLIC	RD	.10	.14
	AD	-.17	.13
ALIC	RD	-.08	.33**
	AD	-.09	.13
VMPF	RD	-.05	.07
	AD	-.16	-.15

Discussion: We sampled RD and AD values from the middle of tracts with parallel fiber orientation to allow inferences about WM microstructure in younger and older adults. In all ROIs, we observed significant age-related differences in RD and AD. Except for GCC, correlations of age with AD and RD were reliable in older adults only, predominantly in anterior WM regions. Interestingly, RD and AD of GCC were reliably correlated in younger adults as well, indicating that extensive loss of WM integrity observed in late adulthood may be due to early onset of microstructural changes. Differential region-specific patterns of RD and AD values as well as AD-RD correlations may reflect differences in fiber geometry (e.g. axon density, size). Increasing positive correlations between RD and AD with age may originate from an age-related microstructural mechanism common to most WM regions, such as changes in the extracellular volume and/or changes in free water content (Sen and Basser, 2002). In some regions, this may be caused by demyelination, whereas in the others it may be a result of axonal loss. Age-related histological alterations may translate into different patterns of diffusivity properties, depending on the local fiber geometry.