Longitudinal and cross-sectional analyses of white matter changes in the healthy aging population

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INTRODUCTION

- White matter (WM) declines in normal aging.[1,2,3]
- Non-specific WM changes are typically measured by fractional anisotropy (FA) and mean diffusivity (MD).
- Neurite Orientation Dispersion and Density Imaging (NODDI)[4] measures changes in neurite density (ICVF) and orientation dispersion (ODI) as more specific markers.
- Knowledge on aging effects are limited by cross-sectional studies or few longitudinal studies with small sample size.

Study aims

- **to characterise specific longitudinal white matter changes (i.e., neurite density and tract orientation dispersion) in a large population-based cohort of older adults in contrast to lifetime trajectory**
- **to identify if longitudinal changes corroborate findings on cross-sectional differences**

METHODS

1000BRAINS[5]	*N=399 (Whole sample)*	*N=322 (Older adults)*
Age range (years)	18-84	55-84
Mean age 1st visit *[+/-SD]*	61.8 *[+/-11.7]*	66.4 *[+/-6.5]*
Sex Ratio Female : Male	1 : 1.3	1 : 1.3

MR imaging (Tim-TRIO, Siemens)

- 2 EPI diffusion sequences: 60 directions (b = 1000 s/mm^2, 7 b0-images interleaved); 120 directions (b = 2700 s/mm^2, 13 b0-images interleaved), voxel resolution = 2.4 × 2.4 × 2.4 mm^3, resampled to 1.25 × 1.25 × 1.25 mm^3
- b0-images aligned to anatomical T1-weighted 3D-MPRAGE (176 slices, voxel resolution = 1 × 1 × 1 mm^3)

Advanced diffusion parameters (NODDI):

- Intra-cellular volume fraction (ICVF)
- Orientation dispersion index (ODI)

Standard diffusion parameters:

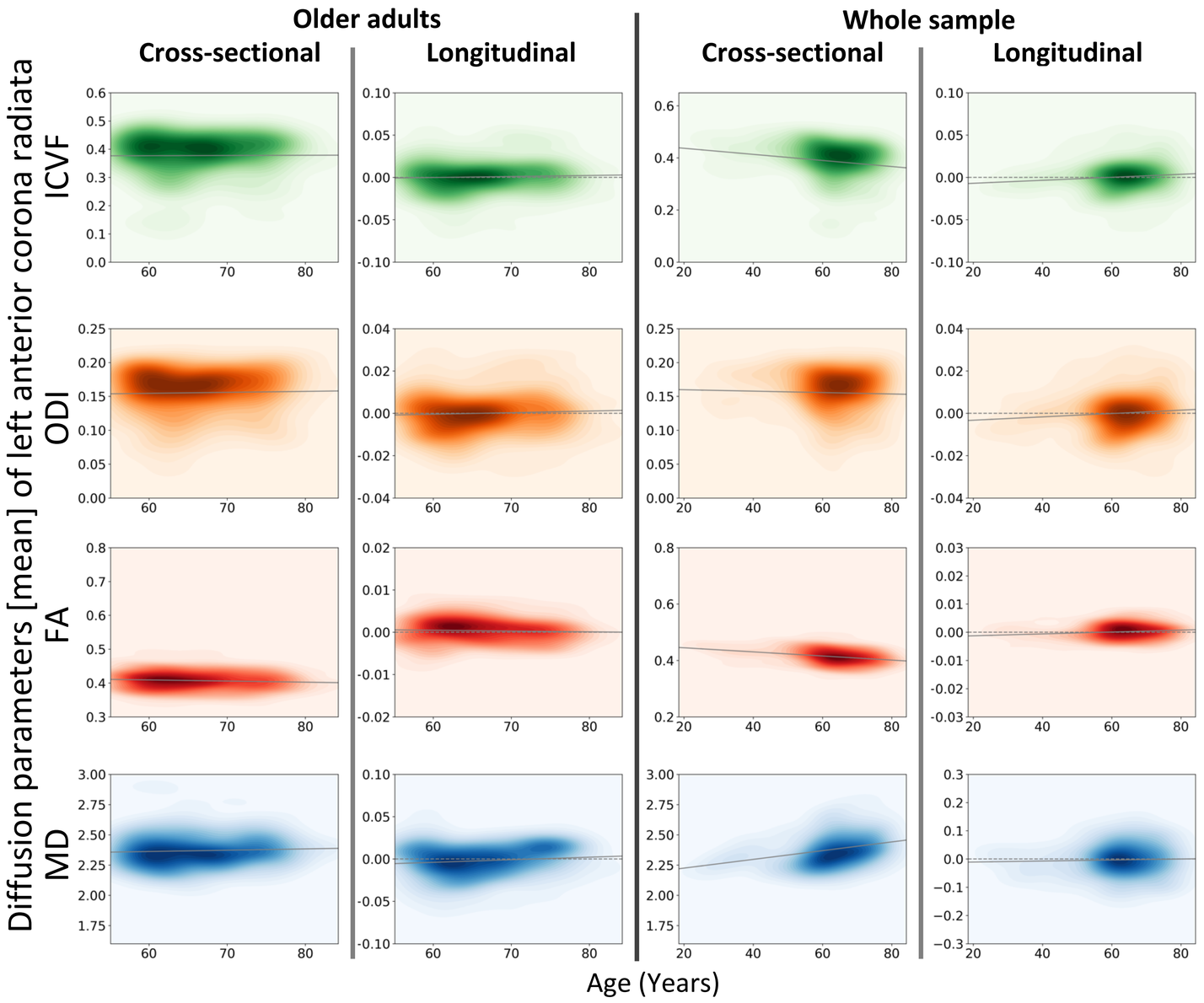
- Fractional anisotropy (FA)
- Mean diffusivity (MD)

Registration with DTI-TK[6] pipeline → Tract-based spatial statistics → Major projection & association fibers (JHU ICBM-DTI-81 White Matter Labels[7]) → Spearman rho rank correlation* age & diffusion parameters

* controlling for sex, handedness, head motion

RESULTS

Exemplary cross-sectional & longitudinal age effects of diffusion parameters



Example of cross-sectional and longitudinal tract mean diffusion values plotted against age in older adults and in younger to older adults (whole sample). Longitudinal values were computed as annual difference (tract mean value at visit 1 minus tract mean value at visit 2, then divided by the visit interval in years). Darker areas of the kernel density plots show greater degree of data point overlap. Continuous grey line denotes the linear regression line. Broken grey line denotes zero at the y-axis of longitudinal plots.

Complete overview of age-related changes & differences of tract-specific diffusion parameters

● = significant ($p < 0.05$) corrected for multiple comparisons using Benjamini and Hochberg false discovery rate (FDR)

● = significant ($p < 0.05$) uncorrected

	Older Adults								Whole Sample (Younger and Older Adults)							
	Cross-sectional				Longitudinal				Cross-sectional				Longitudinal			
Tract	FA	MD	ICVF	ODI	FA	MD	ICVF	ODI	FA	MD	ICVF	ODI	FA	MD	ICVF	ODI
ACR_L						●			●	●	●				●	●
ACR_R									●	●	●		●		●	●
AIC_L	●	●			●	●			●	●	●	●	●		●	
AIC_R		●							●	●	●	●	●		●	●
CCG_L									●	●	●					
CCG_R		●							●	●	●				●	
CH_L															●	●
CH_R													●			
PCR_L		●				●			●	●	●			●	●	●
PCR_R		●							●	●	●				●	●
PIC_L		●			●				●	●	●				●	●
PIC_R	●	●							●	●	●				●	●
PTR_L									●	●	●		●	●	●	
PTR_R	●								●	●	●		●	●	●	
SCR_L						●			●	●	●	●			●	●
SCR_R									●	●	●	●			●	●
SLF_L		●				●			●	●	●				●	●
SLF_R	●	●							●	●	●		●		●	●
SS_L									●	●			●		●	
SS_R									●	●			●	●	●	
UNC_L										●					●	●
UNC_R		●								●	●	●			●	

Key: ACR_L, left anterior corona radiata; ACR_R, right anterior corona radiata; AIC_L, left anterior limb of the internal capsule AIC_R, right anterior limb of the internal capsule; CCG_L, left cingulum at the cingulate gyrus area; CCG_R, right cingulum at the cingulate gyrus area; CH_L, left cingulum at the hippocampus area; CH_R, right cingulum at the hippocampus area; PCR_L, left posterior corona radiata; PCR_R, right posterior corona radiata; PIC_L, left posterior limb of the internal capsule; PIC_R, right posterior limb of the internal capsule; PTR_L, left posterior thalamic radiation; PTR_R, right posterior thalamic radiation; SCR_L, left superior corona radiata; SCR_R ,right superior corona radiata; SLF_L, left superior longitudinal fasciculus, SLF_R, right superior longitudinal fasciculus; SS_L, left sagittal stratum; SS_R, right sagittal stratum, UNC_L, left uncinate fasciculus; UNC_R, right uncinate fasciculus.

DISCUSSION

- Aging effects in longitudinal observation across the whole age range do not reflect cross-sectional differences in WM.
- Longitudinally, neurite density (ICVF) is a more sensitive parameter for detecting aging effects than orientation dispersion in most projection and association fibers in contrast to previous cross-sectional observations[8,9].
- WM microstructural decline in older adults might be driven by factors other than age.

Conclusions

- ❖ **WM aging effects in cross-sectional observations tend to be overestimated.**
- ❖ **Diffusion parameters seem to have differential sensitivity for aging in longitudinal settings.**
- ❖ **Age effects in lifespan aging trajectories may dissipate in older age.**

References

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This project was partially funded by the 1000BRAINS-Study of the Institute of Neuroscience and Medicine, Research Centre Jülich, Germany. We thank the Heinz Nixdorf Foundation (Germany) for the generous support of the Heinz Nixdorf Study. We thank the investigative group and the study staff of the Heinz Nixdorf Recall Study and 1000BRAINS. This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 945539 (HBP SGA3; SC) as well as from the Initiative and Networking Fund of the Helmholtz Association (SC).