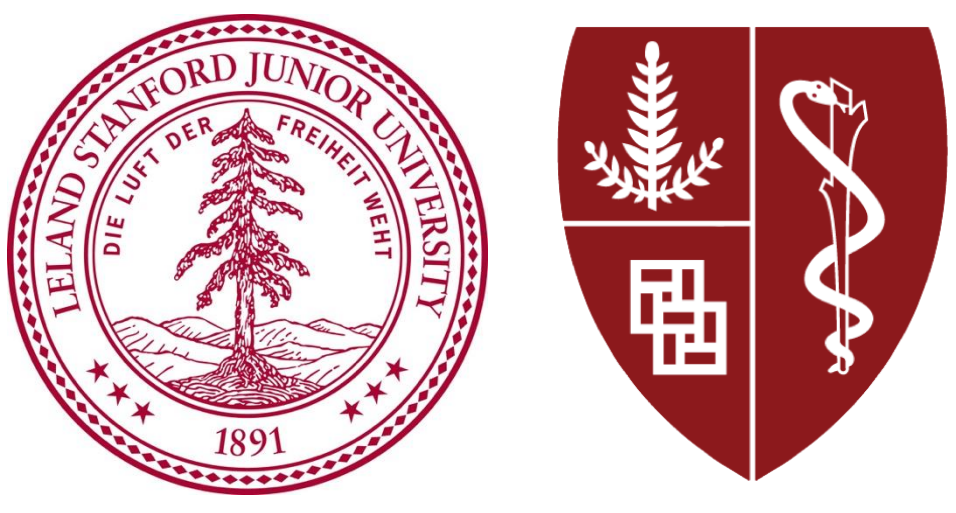




Studying Brain microstructural Changes in Aging Using Multi-Dimensional Diffusion Encoding MRI

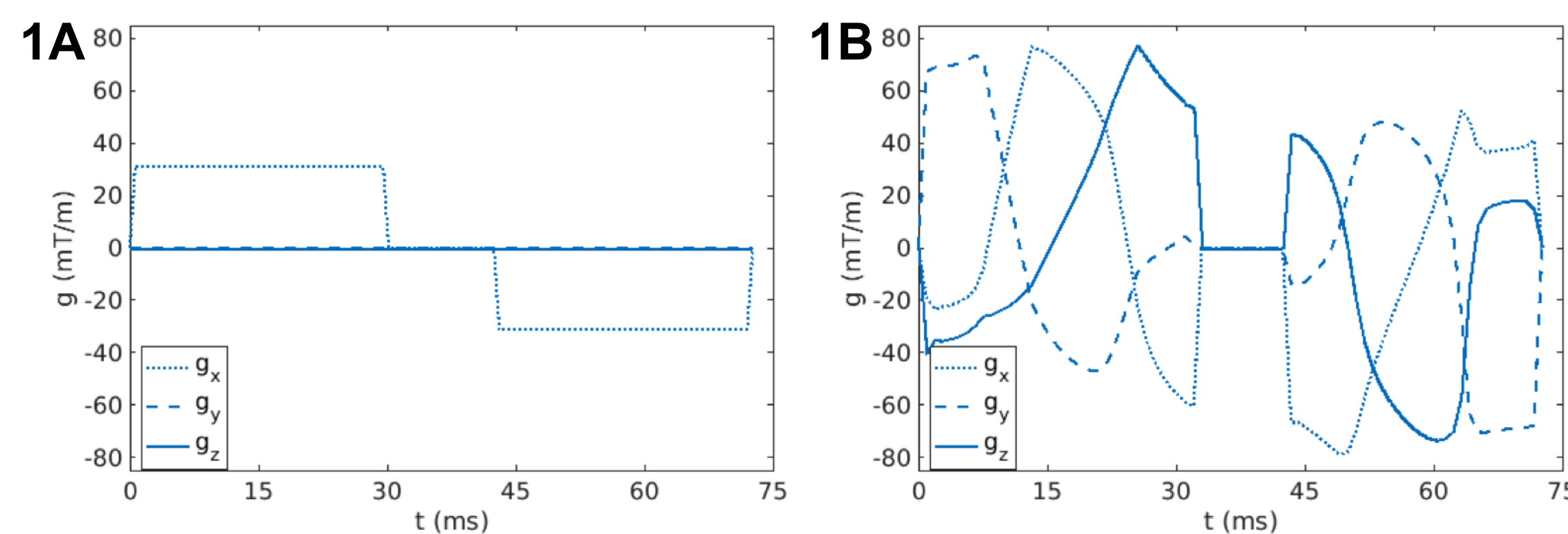


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Introduction:

- Diffusion MRI is a promising tool for detecting brain microstructural changes during neurodegeneration. Multi-dimensional diffusion encoding (MDE) is an emerging method for more specific brain microstructure mapping by jointly using diffusion encoding gradients with different shapes (**Fig. 1**)^{1,2}. As such, MDE offers a way to distinguish between anisotropies caused by the diffusion tensor shape (“microscopic anisotropy”) and orientation dispersions.
- This study aims to investigate brain microstructural changes between cognitively normal younger and older groups using MDE.**



Methods:

Sequence design: A customized MDE protocol was developed on a 3T GE scanner equipped with a UHP gradient coil ($G_{\max}=100$ mT/m and $SR_{\max}=200$ T/m/s), using an optimized MDE waveform design (**Fig. 1**) and an SNR-efficient signal readout³.

Data acquisition: Cognitively normal younger (3F/4M, 22~31 y/o) and older subjects (5F/6M, 62~71 y/o) were scanned using the developed MDE protocol. Detailed parameters are listed in **Table 1**. Each older subject was scanned twice (“older-1” and “older-2”) to assess the reproducibility of each diffusion measurement (as reported in our previous abstract³). Each younger subject was scanned once (“younger”).

Data processing & analysis:

- The preprocessing includes denoising⁴, Gibbs ringing artifacts⁵, distortion correction⁶, and motion correction⁷.
- The MD-DMRI toolbox⁸ was used to calculate quantitative diffusion metrics, including mean diffusivity (MD), fractional anisotropy (FA), microscopic FA (μ FA), anisotropic mean kurtosis (MK_A), isotropic MK (MK_I), and total MK (MK_T).
- Two regional WM bundles, the temporal part of cingulum bundle (CBT) and fornix (FX) were segmented by XTRACT⁹, and the global WM was segmented by Freesurfer¹⁰.
- The mean value of each metric was computed for each WM ROI. Subsequently, for each older subject, each ROI-averaged diffusion measure was averaged between the two scans (termed “older-average”), and the group differences of each diffusion metric between “older-average” and younger subjects were evaluated.
- The statistical significance of the inter-group difference was assessed using the Mann-Whitney U test ($p<0.05$), before (p_{uncorr}) and after (p_{corr}) the FDR correction.

Table 1. Detailed scan parameters.

Diffusion Encoding	STE: b=0.1 (6 avg), 0.7 (6 avg), 1.4 (15 avg), and 2.0 ms/ μm^2 (30 avg); LTE: b=0.1 (3 dir), 0.7 (3 dir), 1.4 (12 dir), and 2.0 ms/ μm^2 (24 dir)
Readout & Recon.	FOV=220×220 mm ² , 38 slices, resolution=1.8 mm isotropic, MB=2, $N_{\text{shot}}=2$, CAIPI w/ FOV/4 shift, PF=0.63 (w/ POCS recon.), TE=81 ms, TR=3.3 s, total scan time ~12 min.

Results:

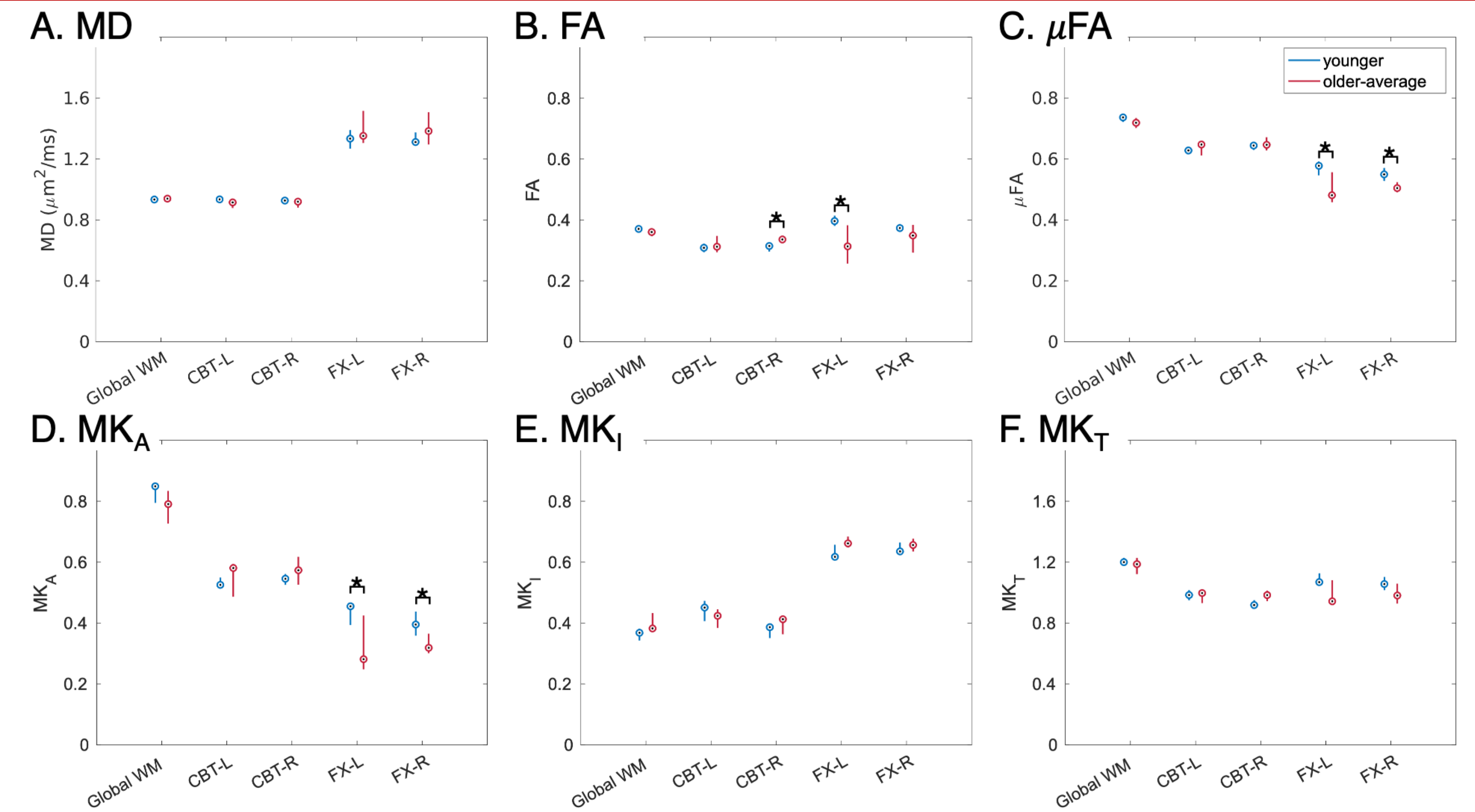


Fig. 2: Boxplots of diffusion metrics (**A: MD, B: FA, C: μ FA, D: MK_A , E: MK_I , and F: MK_T**) between the younger (color: blue) and older (color: red) groups across WM ROIs. In each box, the central circles denote the median values, while the down and up whiskers denote the 25th and 75th percentiles, respectively. No inter-group differences are statistically significant after the FDR correction, probably due to the small sample size. The inter-group differences with statistical significance before the FDR correction ($p_{\text{uncorr}}<0.05$) are marked with asterisks.

Table 2: Statistical analysis of diffusion metric differences between the younger and older groups across WM ROIs. Columns 1 and 2 display names of diffusion metric and WM ROIs. Columns 3 and 4 are the median values along with the 25th (Q1) and 75th (Q3) percentiles of each group. Column 5 presents the inter-group percentage differences of the median values. Column 6 reports p -values for pairwise group comparisons, before (p_{uncorr}) and after (p_{corr}) the FDR correction. P -values <0.05 and corresponding percentage differences are highlighted in bold, including FA in the right CBT and left FX, μ FA in the left and right FX, and MK_A in the left and right FX.

Metric	ROI	Median (Q1, Q3)		Percentage difference of Median (%)	p_{uncorr} (p_{corr})
		younger	older-average		
MD	Global WM	0.93 (0.92, 0.94)	0.94 (0.92, 0.96)	0.61	0.54 (0.64)
	CBT-L	0.93 (0.92, 0.94)	0.91 (0.88, 0.94)	-1.66	0.29 (0.48)
	CBT-R	0.93 (0.89, 0.94)	0.92 (0.88, 0.93)	-0.93	0.54 (0.64)
	FX-L	1.33 (1.27, 1.39)	1.35 (1.30, 1.52)	1.35	0.48 (0.64)
	FX-R	1.31 (1.29, 1.37)	1.38 (1.30, 1.51)	5.47	0.29 (0.48)
FA	Global WM	0.37 (0.37, 0.38)	0.36 (0.35, 0.37)	-2.74	0.07 (0.30)
	CBT-L	0.31 (0.29, 0.32)	0.31 (0.29, 0.35)	-0.41	1.00 (1.00)
	CBT-R	0.32 (0.30, 0.32)	0.34 (0.33, 0.35)	8.72	<0.01 (0.11)
	FX-L	0.40 (0.38, 0.41)	0.31 (0.26, 0.38)	-20.84	0.01 (0.11)
	FX-R	0.37 (0.37, 0.39)	0.35 (0.29, 0.38)	-6.55	0.13 (0.38)
μ FA	Global WM	0.74 (0.72, 0.74)	0.72 (0.70, 0.73)	-2.4	0.21 (0.48)
	CBT-L	0.63 (0.62, 0.64)	0.65 (0.61, 0.66)	3.36	0.60 (0.64)
	CBT-R	0.65 (0.63, 0.66)	0.65 (0.63, 0.67)	0.23	0.60 (0.64)
	FX-L	0.58 (0.55, 0.59)	0.48 (0.46, 0.56)	-16.73	0.02 (0.12)
	FX-R	0.55 (0.53, 0.57)	0.50 (0.49, 0.52)	-8.24	0.01 (0.11)
MK_A	Global WM	0.85 (0.79, 0.86)	0.79 (0.73, 0.83)	-6.89	0.29 (0.48)
	CBT-L	0.53 (0.52, 0.55)	0.59 (0.49, 0.60)	11.22	0.54 (0.64)
	CBT-R	0.54 (0.53, 0.57)	0.58 (0.52, 0.62)	7.91	0.29 (0.48)
	FX-L	0.46 (0.39, 0.46)	0.28 (0.26, 0.42)	-38.01	0.03 (0.17)
	FX-R	0.40 (0.36, 0.44)	0.32 (0.30, 0.36)	-19.61	0.03 (0.17)
MK_I	Global WM	0.37 (0.34, 0.38)	0.38 (0.37, 0.43)	3.88	0.25 (0.48)
	CBT-L	0.45 (0.40, 0.47)	0.42 (0.38, 0.45)	-6.74	0.37 (0.59)
	CBT-R	0.38 (0.35, 0.40)	0.40 (0.36, 0.43)	4.35	0.60 (0.64)
	FX-L	0.62 (0.61, 0.66)	0.66 (0.65, 0.68)	7.14	0.18 (0.45)
	FX-R	0.64 (0.63, 0.66)	0.66 (0.64, 0.68)	3.3	0.60 (0.64)
MK_T	Global WM	1.20 (1.18, 1.23)	1.19 (1.12, 1.23)	-1.09	0.60 (0.64)
	CBT-L	0.99 (0.95, 1.02)	1.00 (0.93, 1.03)	1.28	0.86 (0.89)
	CBT-R	0.93 (0.89, 0.95)	0.98 (0.94, 1.01)	5.57	0.18 (0.45)
	FX-L	1.07 (1.04, 1.13)	0.94 (0.93, 1.08)	-11.7	0.13 (0.38)
	FX-R	1.06 (1.02, 1.10)	0.98 (0.93, 1.06)	-7.16	0.13 (0.38)

Discussion & Conclusion:

- We evidence the potential of MD-DMRI for detecting WM microstructural changes during neurodegeneration, particularly with FA in the right CBT and left FX, μ FA in the left and right FX, and MK_A in the left and right FX.

References: 1. Topgaard D. JMR 2017; 2. Westin CF. NIMG 2016; 3. Dai E. AAIC 2025; 4. Veraart J. NIMG 2016; 5. Kellner E. MRM 2016; 6. Andersson JLR. NIMG 2003; 7. Nilsson M. PLoS One 2015; 8. Nilsson M. ISMRM 2018. 9. Warrington S. NIMG 2020. 10. Fischl B. NIMG 2012. **Funding:** NIH K99AG080076 and R01NS095985.