

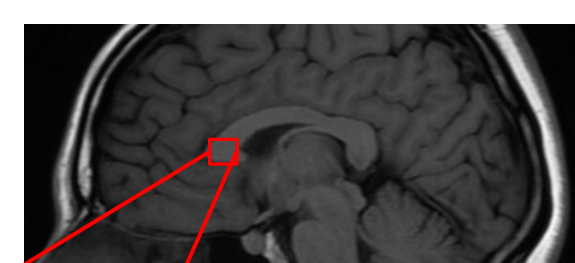
Mechanisms of Age & Vascular-related Microstructure Changes in the Corpus Callosum Using Biophysical Modeling of Diffusion MRI

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BACKGROUND

Figure 1: Visual Depiction of the Standard Model Biophysical Model



- Fractional anisotropy changes in the corpus callosum genu and body have been previously shown to be sensitive to cognitive impairment in cerebral small vessel disease (cSVD)¹, and sensitive to vascular risk factors, independent of beta-amyloid and tau deposition^{2,3}. However, DTI is inherently non-specific^{4,5,6}.
- Biophysical models improve specificity over DTI. The Standard Model has been shown to be superior to existing multi-compartment models (i.e. NODDI, WMTI) in ex-vivo simulation studies and in patients with multiple sclerosis^{7,8,9}.
- The objective of this study is to compare microstructure measures derived from DTI and DKI and those derived from “the Standard Model” to assess age and cSVD-related differences in corpus callosum microstructure.

METHODS

Participants

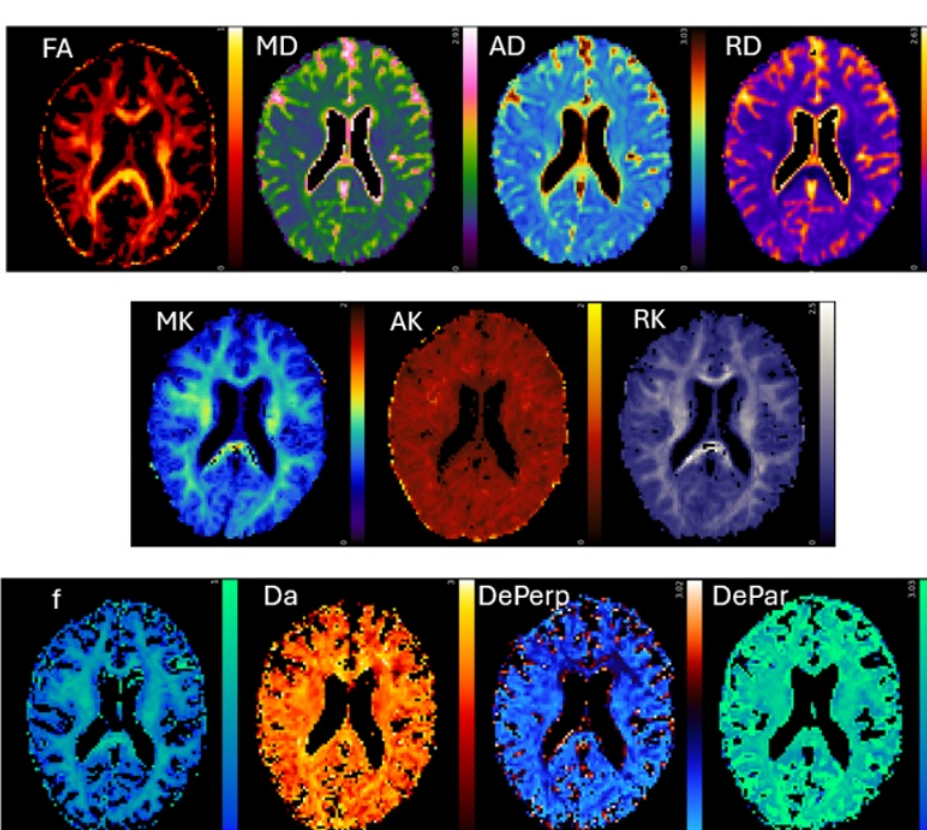
Cognitively normal participants (N=112, mean age 69.9 years, 27.6% male) from the Michigan Alzheimer Disease Center were included.

Imaging Methods

All participants were scanned at 3T with a 32-channel head coil. Diffusion MRI was a 2D spin echo, EPI sequence, 2mm isotropic resolution, 106 volumes (6 b=0, 10 b=500, 40 b=1000, 50 b=3000 s/mm²), TR 3400 ms, TE 79.6 ms. Pre-processing included noise removal, Gibbs correction, EPI distortion correction, eddy current correction^{10,11,12,13}. Multicompartment parameter estimation was performed using the Standard Model Imaging toolbox⁹; DTI and DKI fitting was also performed. WMH volumes were extracted from the 3D T2w FLAIR sequence using LST-AI¹⁴. Corpus callosum ROIs were extracted from the JHU atlas¹⁵.

Figure 2: Examples of Diffusion Parameter Maps

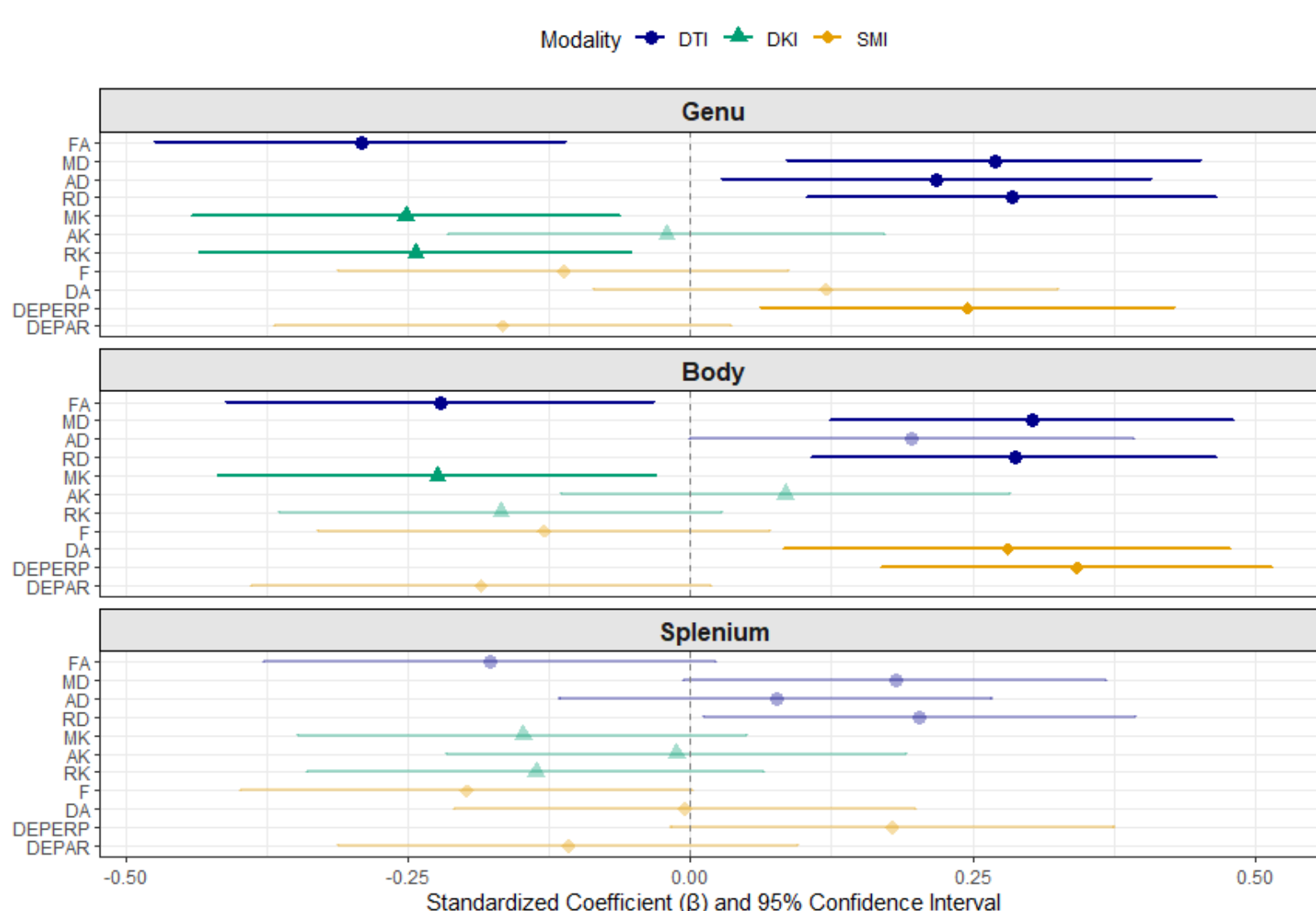
Examples of Diffusion Tensor Imaging (DTI), Diffusion Kurtosis Imaging (DKI) and Standard Model (SM) parameter maps generated from 3-shell diffusion MRI



DTI maps: Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD), Radial Diffusivity (RD); DKI maps: Mean Kurtosis (MK), Axial Kurtosis (AK), Radial Kurtosis (RK); SM maps: Axonal Water Fraction (f), Intra-axonal Diffusivity (Da), Extra-axonal Perpendicular Diffusivity (DePerp), and Extra-axonal Parallel Diffusivity (DePar)

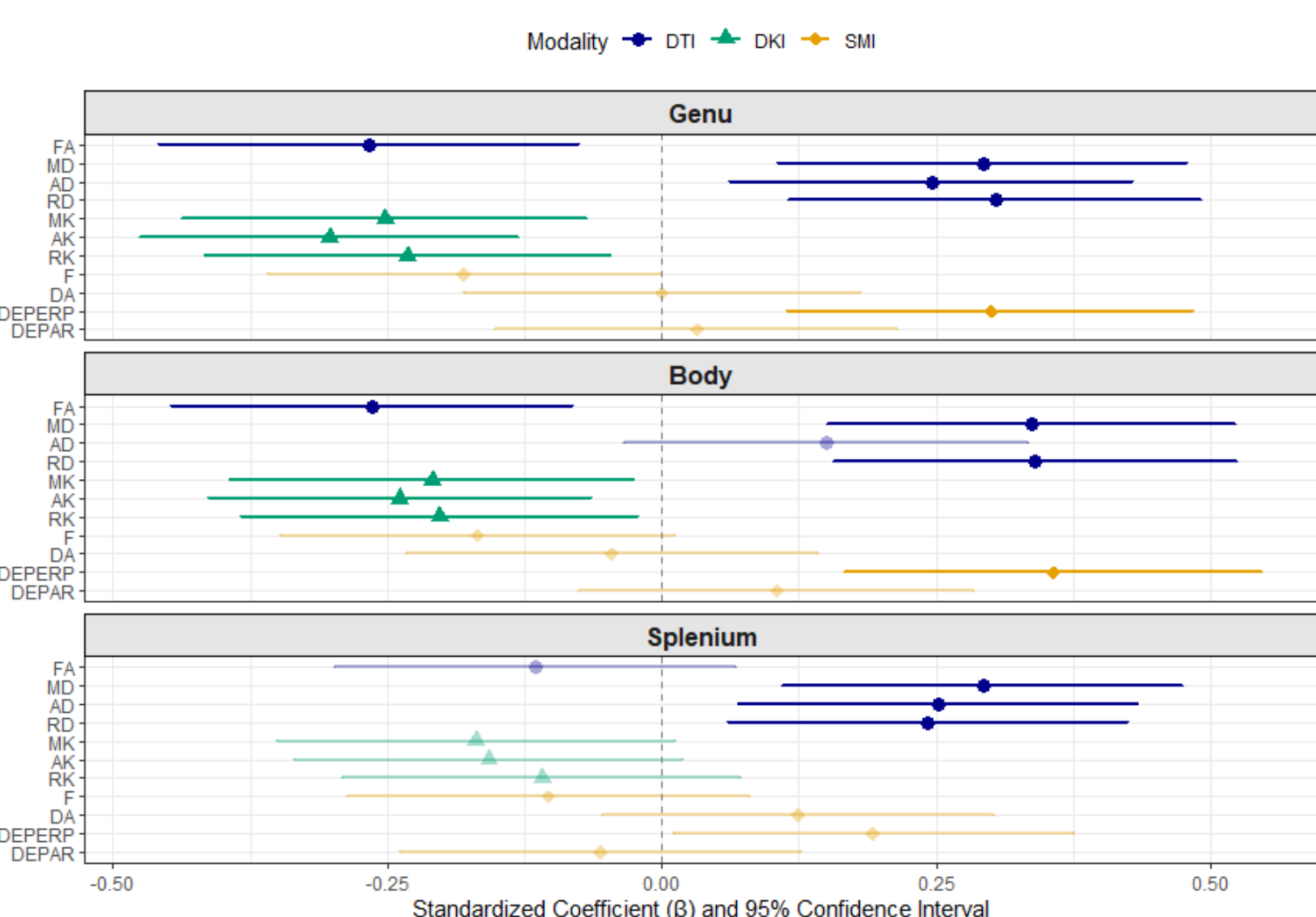
RESULTS

Figure 3: Forest Plot of Aging Effects on Microstructure Measures by Corpus Callosum sub-Region



- Sex, Education, WMH volume included as covariates; all p-values FDR-corrected by region
- Age-related microstructural changes were seen predominantly in the genu and body, not the splenium.
- Extra-axonal perpendicular diffusivity (demyelination) in the body had the highest standardized β coefficient.
- DKI measures overall not as sensitive to age compared to DTI measures.

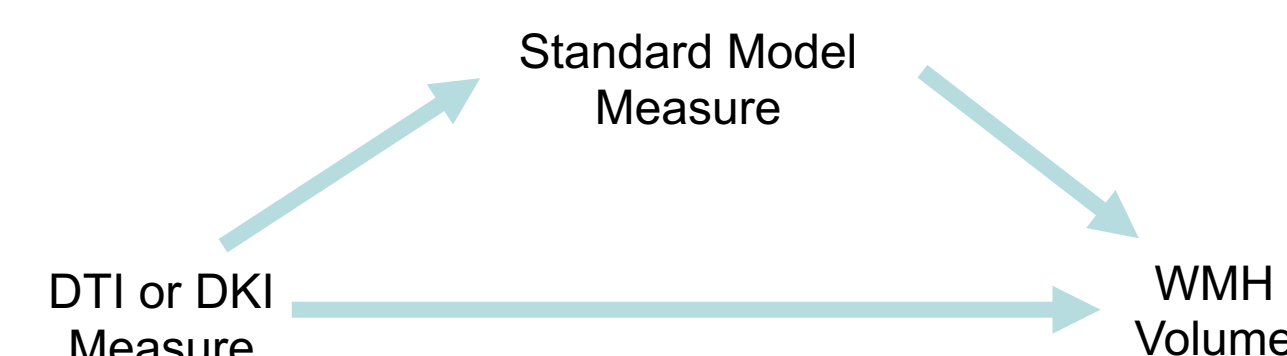
Figure 4: Forest Plot of Microstructure Effects on cSVD burden (WMH volume) by Corpus Callosum sub-Region



- Sex, Education, age included as covariates; all p-values FDR-corrected by region
- Extra-axonal perpendicular diffusivity in the body had the highest standardized β coefficient, marginally improved over DTI measures MD and RD.
- DTI measures were the only significant measures in the splenium.

Mediation Analyses

Can Standard Model diffusion measures help explain underlying mechanisms in DTI and DKI-related microstructure changes and cSVD burden?



CC Region	DTI/DKI Metric	SM Mediator	Indirect Effect (ACME)	Direct Effect (ADE)	Total Effect	% Mediated
GENU	FA	DePerp	Est: -7.28 [-15.27, -0.38]	Est: -7.20 [-19.46, 6.54]	Est: -14.49 [-25.52, -3.40]	50.2%
	MK	DePerp	Est: -2.34 [-5.50, -0.42]	Est: -4.97 [-10.31, 0.03]	Est: -7.32 [-12.96, -2.52]	32.0%
	RK	DePerp	Est: -0.99 [-2.44, -0.15]	Est: -2.26 [-4.78, 0.29]	Est: -3.25 [-5.89, -0.81]	30.4%
BODY	FA	DePerp	Est: -9.22 [-18.03, -1.65]	Est: -7.24 [-21.81, 6.94]	Est: -16.47 [-28.88, -4.06]	56.0%
	MD	Da	Est: -8.16 [-14.53, -3.78]	Est: 25.20 [15.60, 34.19]	Est: 17.04 [7.86, 25.05]	-47.9%
	RD	Da	Est: -3.78 [-7.98, -0.88]	Est: 18.38 [9.56, 26.21]	Est: 14.60 [6.41, 21.71]	-25.8%
	MK	DePerp	Est: -3.89 [-9.24, -0.69]	Est: -4.61 [-11.98, 3.21]	Est: -8.51 [-15.94, -1.39]	45.7%
	AK	DePerp	Est: -7.58 [-16.91, -1.50]	Est: -16.28 [-31.80, 1.61]	Est: -23.86 [-39.87, -6.56]	31.7%
	RK	DePerp	Est: -1.29 [-3.17, -0.15]	Est: -2.01 [-4.91, 1.13]	Est: -3.31 [-6.25, -0.32]	39.1%

- Demyelination may be the dominant mechanism underlying diminished anisotropy (as quantified by DTI) in the corpus callosum in cSVD.
- Da (Intra-axonal integrity) showed inconsistent mediation for DTI-derived MD and RD effect on WMH volume → demonstrates non-specificity and limited interpretability.
- Demyelination may be an important mechanism underlying tissue heterogeneity quantified by kurtosis in cSVD.

CONCLUSIONS

- Age-related microstructural changes occur predominantly in the genu and body, not the splenium of the corpus callosum.
- Corpus callosum microstructure (predominantly in the genu and body) correlates with degree of cSVD, using WMH volume as a correlate.
- Extra-axonal perpendicular diffusivity (measure of demyelination) in the body of the corpus callosum was the most sensitive to age- and cSVD-related microstructure changes in the corpus callosum, marginally improved over DTI.
- Mediation analyses highlight that demyelination may be a dominant mechanism of cSVD-related microstructure changes reflected in reduced fractional anisotropy (DTI).
- Mediation analyses highlight the non-specificity of DTI measures, particularly MD and RD.

REFERENCES

CONTACT INFO



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