

Fronto-parietal Cingulum White Matter Changes in Down syndrome: Cross-sectional and Longitudinal Diffusion MR Tractography

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Background

Diffusion MRI studies have identified cingulum white matter (WM) degeneration in Down syndrome (DS) as a key feature of Alzheimer’s disease (AD) progression^{1,2}.

Using advanced spherical deconvolution tractography (MegaTrack)³, we examined regional and longitudinal cingulum WM changes in adults with DS compared with typically developing controls.

Methodology

Population

Demographics	DS aged ≤35	DS aged >35	DS entire cohort (baseline)	Longitudinal (baseline)	TD Controls
Participants, n	27	29	56	24	36
Age, m (SD)	26.6 (5.9)	45.7 (6.2)	36.5 (11.3)	43.5 (10.1)	40.1 (11.6)
Sex					
Male, n (%)	10 (37.0%)	13 (44.8%)	23 (41.1%)	11 (45.8%)	20 (55.6%)
Female, n(%)	17 (63.0%)	16 (55.2%)	33 (58.9%)	13 (54.2%)	16 (44.4%)
Level of Intellectual Disability					
Mild	15	11	26	11	NA
Moderate	10	14	24	12	NA
Severe	2	4	6	1	NA
Clinical dementia status, n	0	0	0	0	0

Imaging & Tractography

GE 3T MR750 scanner, 32-channel Nova coil using multi-shell single-shot spin-echo DW-EPI: 12, 48, 60 directions (b=500, 1000, 2000 s/mm² with 12 non-DW volumes and 6 reversed phase-polarity non-DW volumes (TE/TR= 65/4000ms, multi-band factor=2, in-plan acceleration ARC=2).

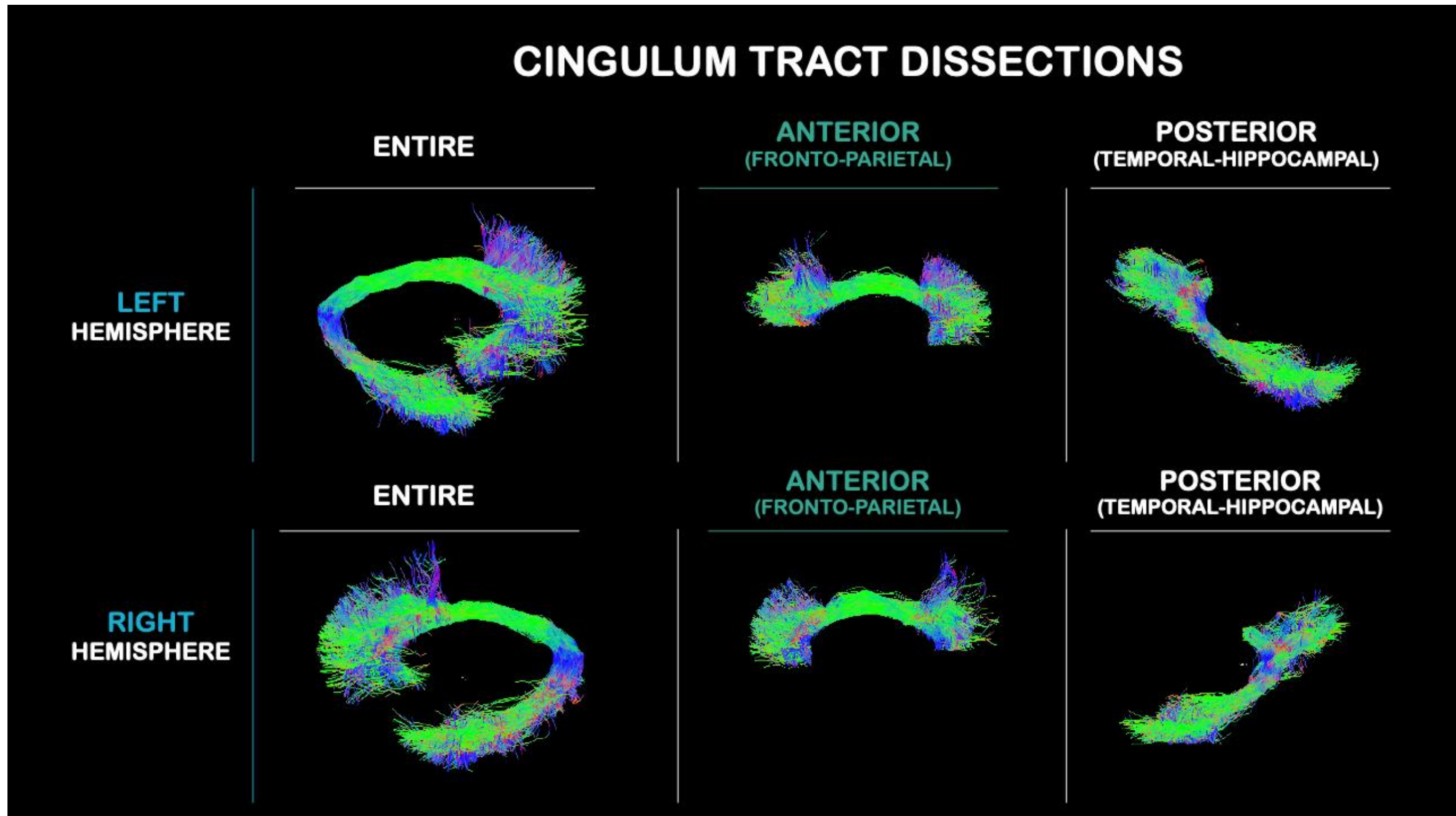
Whole-tractograms registered to a population template for manual MegaTrack dissection in TrackVis.

Manual MegaTrack dissections were performed for bilateral anterior, posterior, and entire cingulum segments.

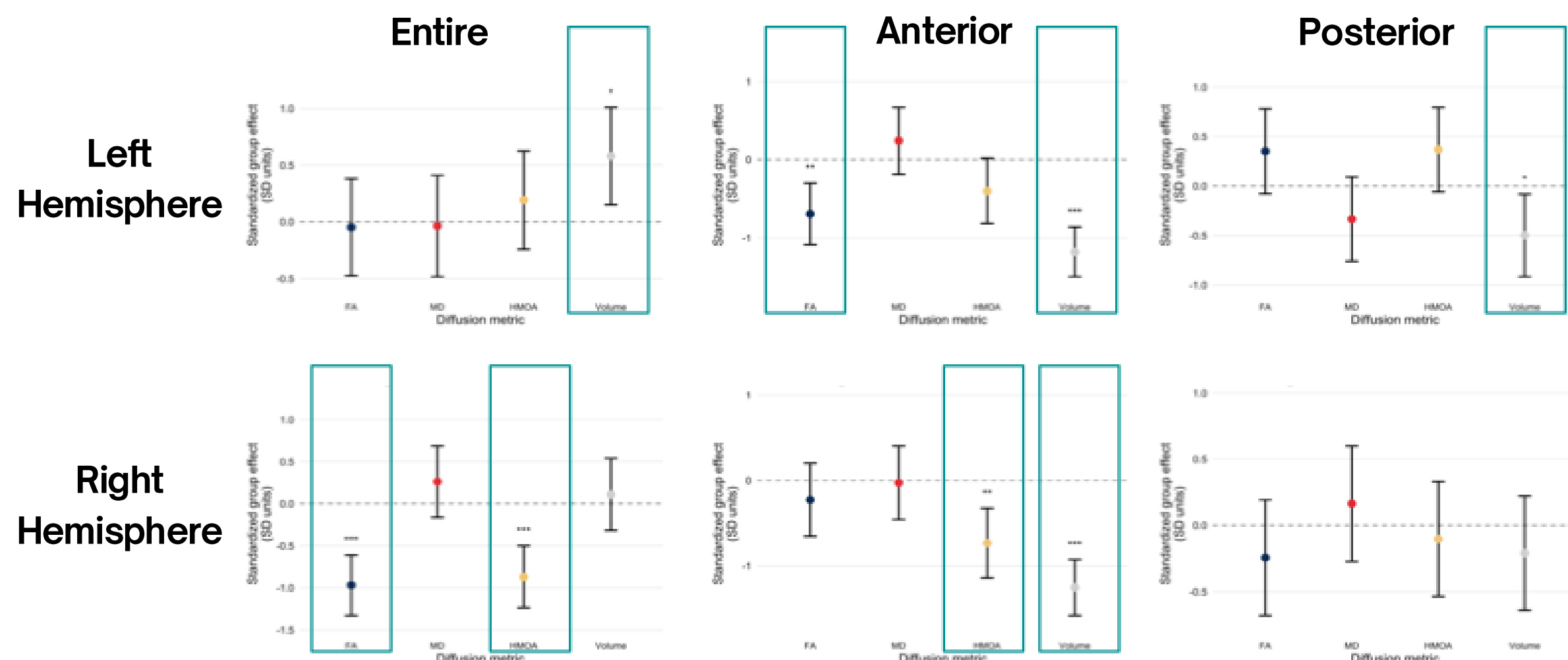
Preprocessing

NBL pre-processing pipeline including denoising, Gibbs ringing, distortion correction (top-up), motion and eddy correction, and outlier rejection and replacement.

Results



Cross-sectional: DS vs. Controls (adjusted for sex)

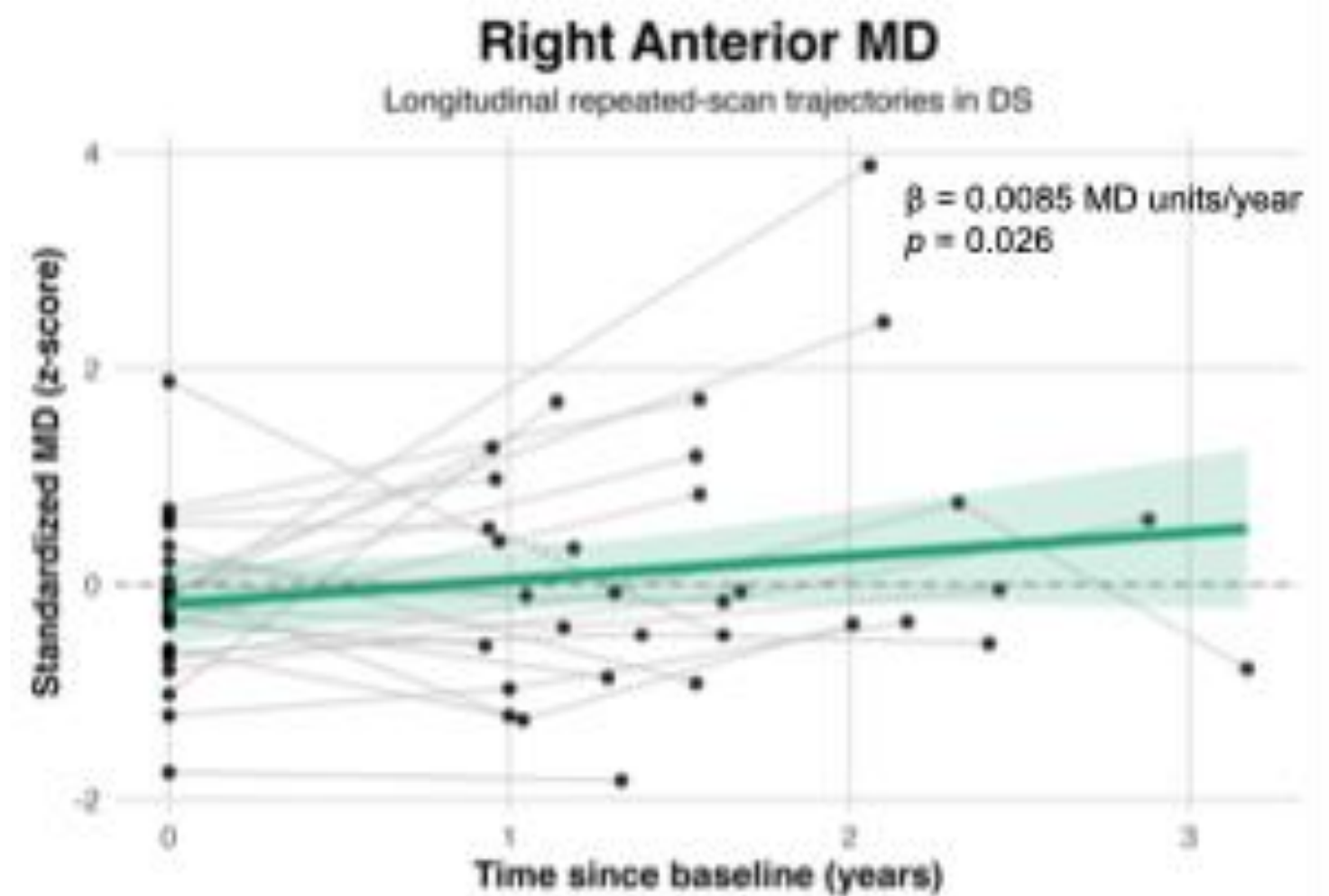


Forest plots of standardized cross-sectional group effects (DS vs. TD controls) across entire, anterior, and posterior cingulum subdivisions for diffusion metrics (FA, MD, HMOA, volume). Points represent standardised effect estimates (β), with error bars indicated 95% confidence intervals. Negative values indicate lower metric values in DS relative to controls. Effects were standardised by each metric’s SD for visualization. Significance from unstandardised models: $p<0.05^*$, $p<0.01^{**}$, $p<0.001^{***}$.

Conclusion

Selective anterior cingulum vulnerability suggests anatomically specific neurodegenerative trajectories that may precede clinical symptom onset.

Longitudinal



No longitudinal effects survived FDR correction

Key Findings

- Bilateral anterior cingulum differences between DS and Control cohort.
- Comparatively, changes in the posterior cingulum were limited.
- Cross-sectional effects were strongest for volume, FA & HMOA suggesting a change in microstructural organization and/or fibre density.
- Right anterior MD showed a longitudinal increase over repeated scans, suggesting possible early microstructural vulnerability.

References

1. Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: Anatomy, function, and dysfunction. *Neurosci Biobehav Rev.* 2018;92:104-127.
2. Saini F, Dell’Acqua F, Strydom A. Structural Connectivity in Down Syndrome and Alzheimer’s Disease. *Front Neurosci.* 2022;16:908413.
3. Dell’Acqua F, Beyh A, Stones R, et al. MegaTrack: a framework for the anatomically accurate and time-efficient virtual dissection and analysis of large-scale tractography datasets. *bioRxiv.* 2025:2025.2005.2027.656234.