

WHITE MATTER FIBRE BUNDLE SIGNATURES OF TAU AND TDP-43 PROTEINOPATHIES IN FRONTOTEMPORAL LOBAR DEGENERATION

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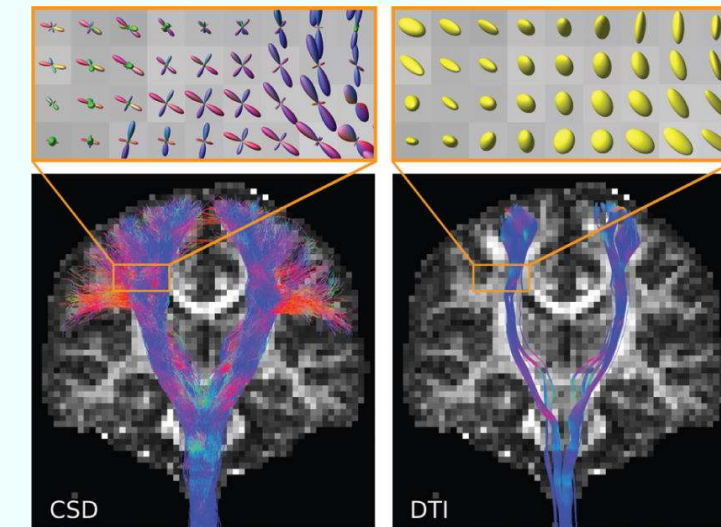
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Introduction

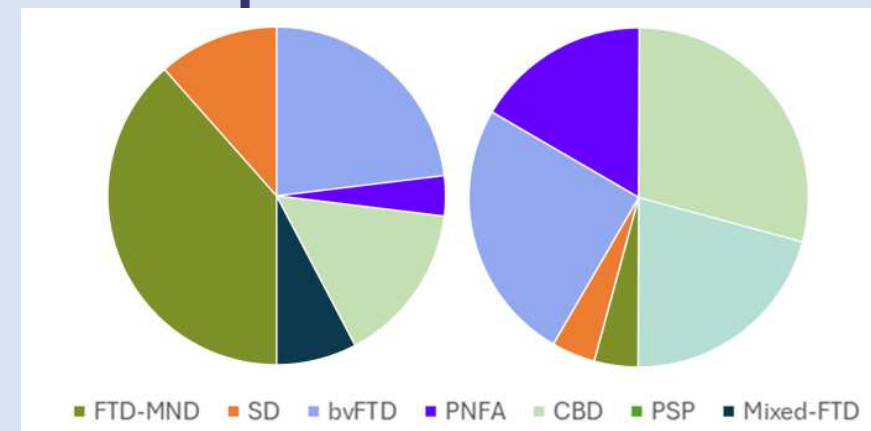
Background – Neurodegenerative diseases such as frontotemporal lobar degeneration (FTLD) are driven by the progressive spread and accumulation of distinct, often co-existing proteinopathies, including misfolded tau (FTLD-tau) and TAR DNA-binding protein 43 (FTLD-TDP). Although these pathologies arise from different molecular mechanisms, they converge on similar brain networks, producing overlapping patterns of atrophy and a broad spectrum of clinical presentations. In the absence of reliable molecular imaging markers, current MRI methods cannot reliably distinguish between these underlying pathologies *in vivo*.

Objective - This study aimed to apply advanced grey and white matter imaging techniques to identify pathology-specific network degeneration patterns in FTLD.



Methods

Participants

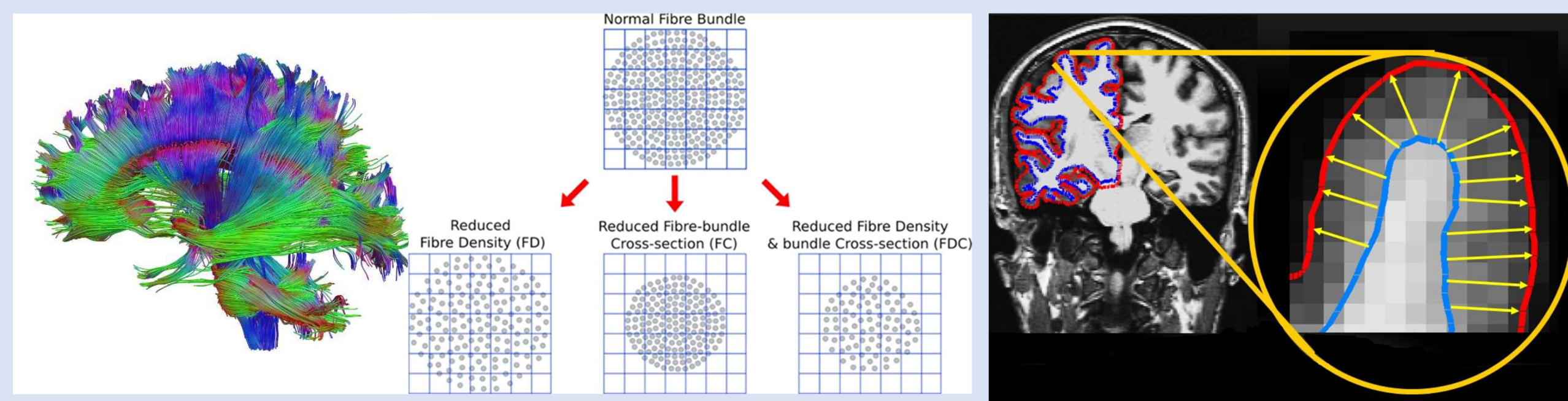


Variable	TDP-43 (n=26)	Tau (n=24)	Control (n=25)	p
Sex, M:F	14:12	13:11	13:12	.987
Age, years	64.77 (8.91)	65.40 (8.35)	65.52 (8.09)	.944
Education, years	12.27 (3.10)	12.51 (3.61)	12.42 (3.18)	.801
FRS Rasch score ^a	-.22 (1.49)	.69 (1.37)	-	.040
ACE-R total score ^b	67.79 (13.10)	74.6 (16.32)	-	.112
Disease duration at MRI, years	3.63 (2.58)	3.62 (2.54)	-	.995
Disease course from MRI, years	2.93 (2.12)	5.13 (2.28)	-	.001

Neuroimaging measures

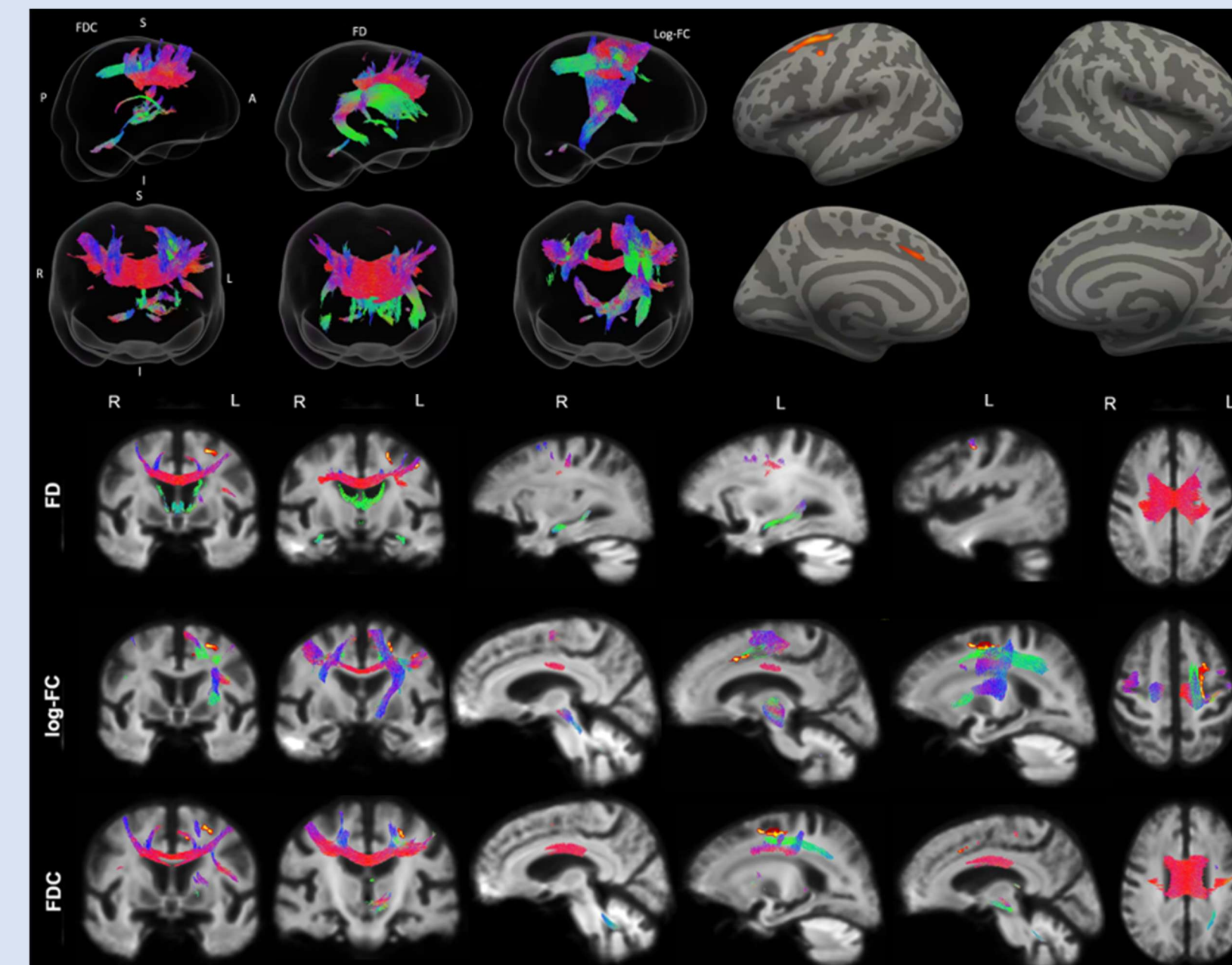
(a) Three measures of WM fibre integrity were computed: fibre density (FD), log-transformed fibre bundle cross-section (log-FC), and fibre density and cross-section (FDC).

(b) Cortical thickness was calculated as the closest distance between the grey/CSF and grey/white boundaries at each vertex on the surface of the brain.

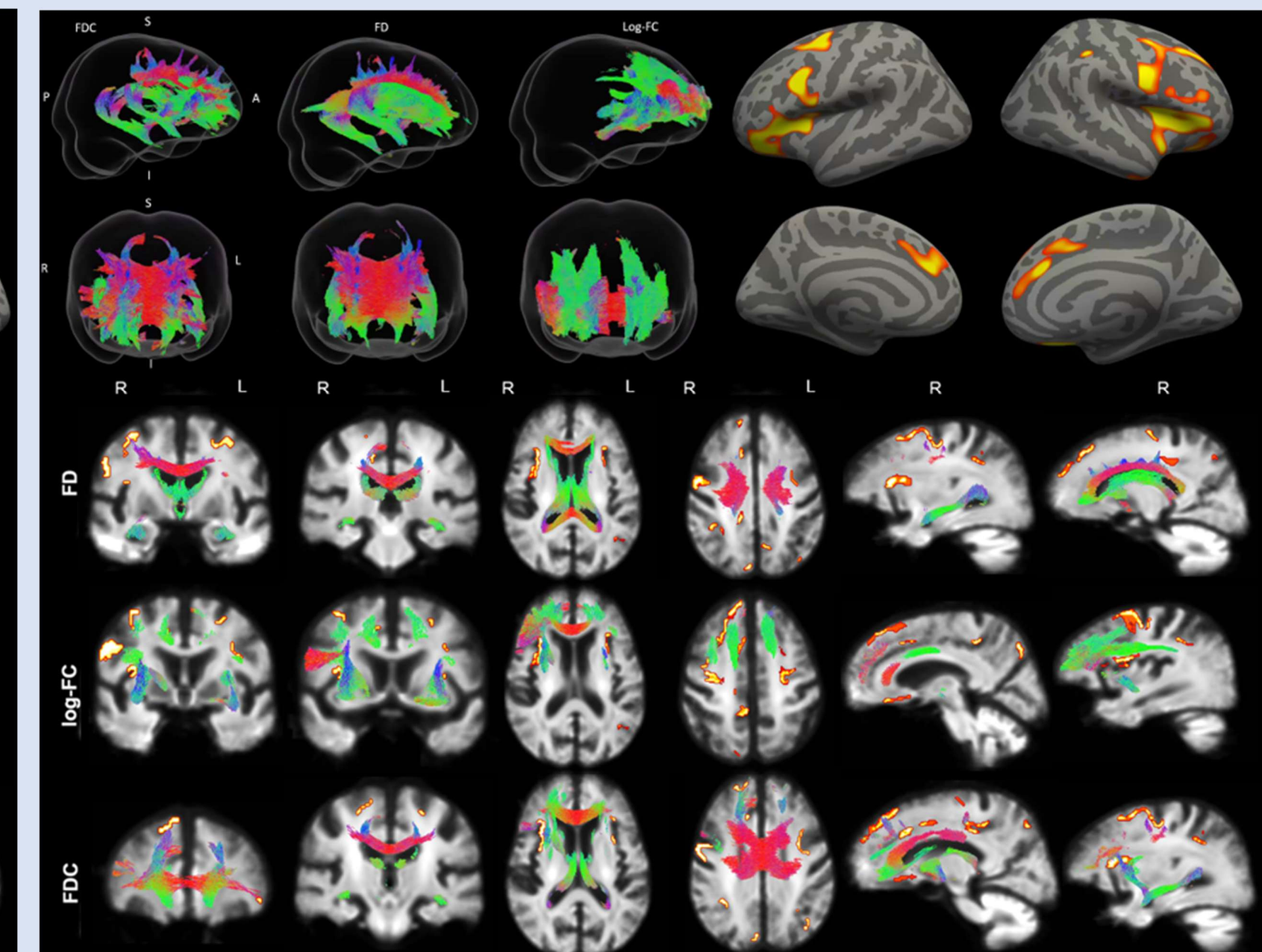


Analysis - Whole brain GLMs were employed to compare each neuroimaging measure between groups.

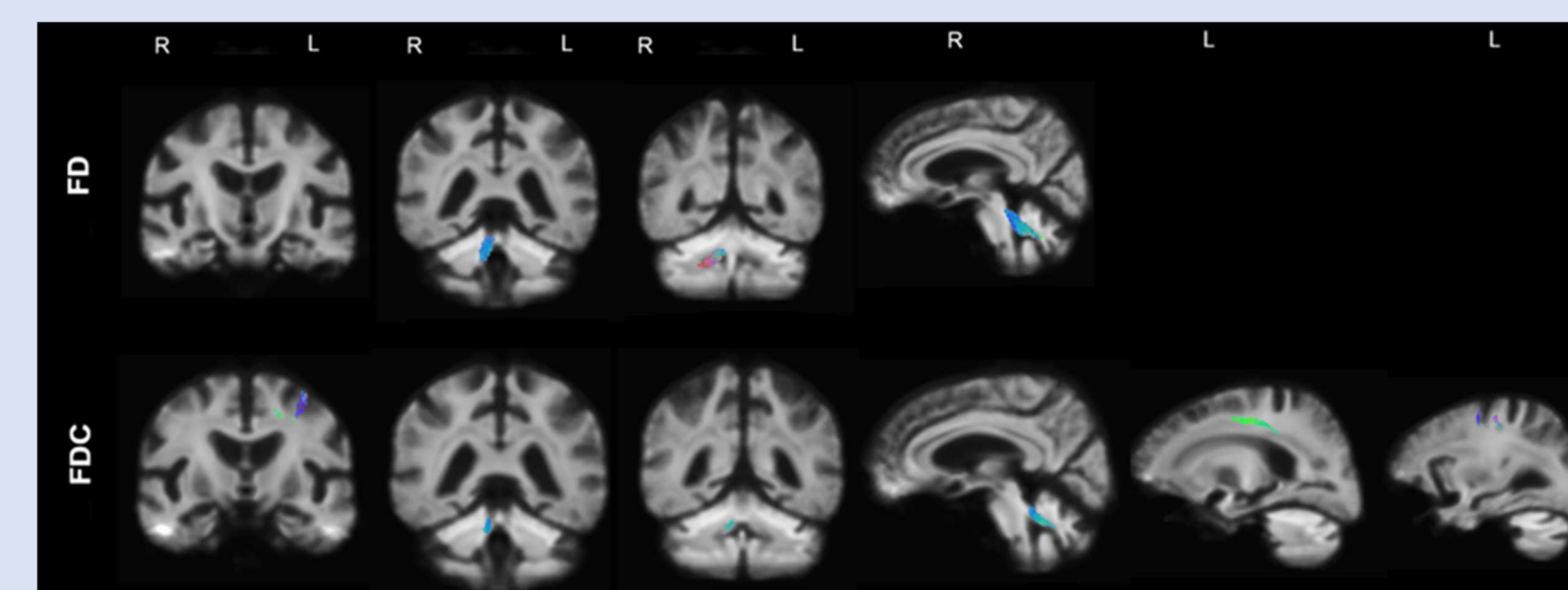
Results



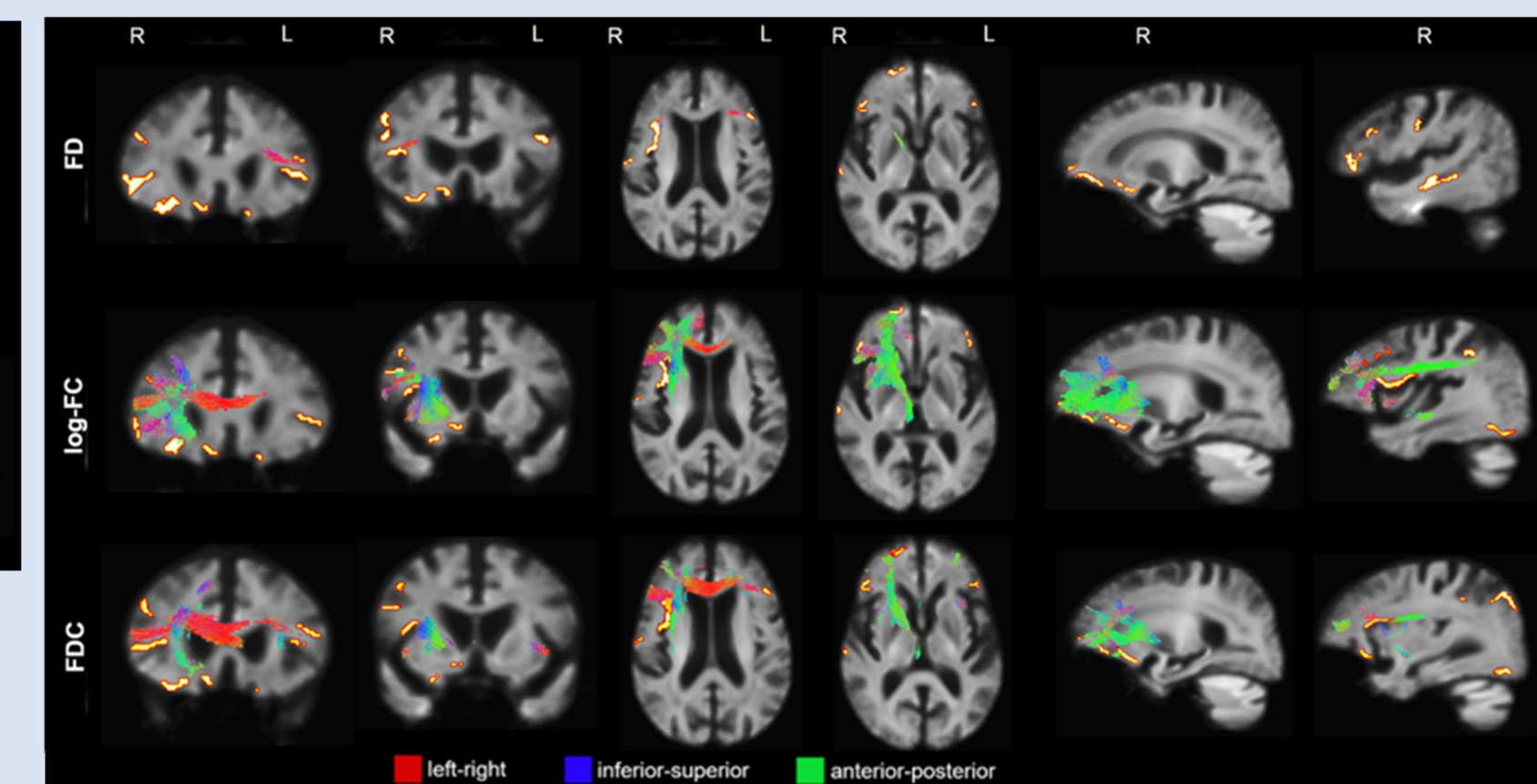
White matter and cortical atrophy in Tau patients compared to Controls



White matter and cortical atrophy in TDP-43 patients compared to Controls



White matter and cortical atrophy in patients (Tau < TDP-43)



White matter and cortical atrophy in patients (TDP-43 < Tau)

Streamline segments were cropped from a template tractogram to include only streamline points that correspond to fixels with a significant decrease in white matter metrics. Yellow clusters show regions with significant reductions in cortical thickness. Significance was set at FWE-corrected, p-value < 0.05 for both analyses.

Conclusions

This study distinguishes tau and TDP-43 related network degeneration in FTLD, highlighting key differences in affected brain systems. FTLD-tau was associated with microstructural motor-pathway loss and predominantly motor syndromes, whereas FTLD-TDP showed right-lateralized frontotemporal-parietal atrophy with mixed language, motor, and behavioural presentations. These imaging biomarkers enhance mechanistic understanding of FTLD to support improved diagnosis and patient stratification for the development of biologically informed trials of disease-modify interventions.

We would like to thank the participants and their families who have given up their own time to support our research. We would also like to acknowledge the contributions made by the research assistants at FRONTIER.

References:

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- Raffelt, D.A. et al. (2017). Investigating white matter fibre density and morphology using fixel-based analysis. *Neuroimage* 1;144(PtA):58-73