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Trajectories of brain changes predicting distinct pathology subtypes in frontotemporal dementia

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State of the art: Frontotemporal dementia (FTD) is a clinically and pathologically heterogenous disease. Critically, accurate ascertainment of the pathology underlying FTD is only possible post-mortem. Here we investigated in-vivo trajectories of white and grey matter changes associated with the most common FTLD pathology subtypes, Tau and TDP-43.
Methodology: A clinically heterogeneous cohort of FTD and motor-degenerative cases with *post-mortem* pathological confirmation (Tau =24; TDP-43=26) and longitudinal MRI available were age-, sex- and education-matched with healthy controls (n = 25). Novel fixel-based and FastSurfer analyses were performed to investigate trajectories of brain changes between pathology subgroups and controls. Interactions between pathology and clinical diagnosis were further examined.
Results: Analyses revealed Tau-specific white matter changes in motor, brainstem, and cerebellar regions. In TDP-43, white matter loss was observed in right lateralised frontal and temporal lobes. Tau showed greater grey matter loss in frontal regions, whereas TDP-43 was associated with greater involvement of posterior regions. In FTD>motor syndromes, Tau was associated left temporal changes while TDP-43 showed greater white matter frontal loss. In Motor>FTD syndromes, Tau showed greater white matter loss in the motor cortex and cerebellum, while TDP-43 showed greater loss in midbrain and basal ganglia regions.
Conclusion: Our findings reveal the staging of progressive brain changes and emergent clinical syndromes underpinned by Tau and TDP-43 pathologies in FTD-spectrum disorders. The prediction of pathology underlying FTD syndromes in *in-vivo* can enable accurate diagnosis, monitoring of disease and inform the development of clinical trials of disease-modifying treatments.

Conflicts of interest

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