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Ex vivo MRI and histopathology detect novel iron-rich cortical inflammation in frontotemporal lobar degeneration with tau versus TDP-43 pathology

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State of the art: Current *in vivo* MRI-derived measures currently cannot differentiate FTLD-Tau and FTLD-TDP. T2*-weighted (T2*w) *ex vivo* MRI is sensitive to non-heme iron in healthy intracortical lamination and myelin, and to pathological iron deposits in amyloid-beta plaques and activated microglia in Alzheimer's disease neuropathologic change (ADNC). However, an integrated, ex vivo MRI and histopathology approach is understudied in FTLD.

- **Methodology**: We apply joint, whole-hemisphere *ex vivo* MRI at 7T and histopathology to the study autopsy-confirmed FTLD-Tau (n=4) and FTLD-TDP (n=3), relative to ADNC disease-control brains with antemortem clinical symptoms of frontotemporal dementia (n=2), and an age-matched healthy control. We compared T2*w MRI cortical laminar patterns of signal intensity to histopathologic measures of iron and neurodegeneration in matched tissue samples.

- **Results**: In FTLD-TDP we found distinct upper layer hypointense bands and diffuse speckling on T2*w MRI which corresponded to both iron-rich astrocytic processes surrounding small blood vessels and dystrophic microglia, respectively. In contrast, these patterns were not observed in FTLD-Tau and instead we found large irregular hypointense signal in deep cortical layers on T2*w MRI that correlated with iron-rich hypertrophic microglia. These unique histopathological and radiographic features were distinct from healthy control and ADNC brains.

- **Conclusion**: We detected distinct laminar patterns of novel iron-laden glial pathology in both FTLD-Tau and FTLD-TDP brains in this pilot cohort. These data suggest that iron-sensitive T2*w MRI, adapted to *in vivo* application at sufficient resolution, may eventually offer an opportunity to improve antemortem diagnosis of FTLD proteinopathies using tissue-validated methods.

Conflicts of interest

N/A