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White matter tau pathology mediates inter-regional tau associations in clinically heterogeneous Alzheimer's disease

Jeffrey Phillips, Min Chen, Daniel Ohm, Sanaz Arezoumandan, Edward Lee, David Wolk, Murray Grossman, Corey McMillan, John Trojanowski, David Irwin

State of the Art: MRI and PET imaging studies have reported that structural connectivity predicts Alzheimer's disease (AD) tau progression in amnestic AD. While these studies provide antemortem support for axonal transport of tau, there is limited data from non-amnestic AD, and gold-standard postmortem studies are crucial to model microscopic tau progression in humans. We used digital histopathology data to test the hypothesis that white matter (WM) tau pathology would statistically mediate associations between grey matter (GM) tau in anatomically-connected regions, supporting the axonal transport model.

Methodology: Digital histopathologic measurements (% area occupied, %AO) of phosphorylated-tau pathology (AT8) were obtained in GM and subjacent WM of angular gyrus (ANG), middle frontal cortex (MFC), and superior/middle temporal cortex (SMTC) in 40 amnestic and 40 non-amnestic AD patients. To model axonal spread, mediation analysis within each group assessed whether tau %AO partially explained the association between tau values in region pairs.

Results: In amnestic AD, mediation was significant between ANG and SMTC (16.5% mediated, p=0.034); in non-amnestic AD, mediation was significant between SMTC and MFC (24%, p=0.026) and marginal between ANG and MFC (28.8%, p=0.082).

Conclusion: The mediating effect of WM tau on inter-regional GM tau associations provides postmortem support for axonally-mediated tau spread across clinical presentations of AD. Tract-wise differences in significance for amnestic vs. non-amnestic patients may reflect syndrome-specific anatomy. Future work will integrate antemortem imaging with postmortem pathology to build predictive models of tau spread in amnestic and non-amnestic AD, providing prognostic markers for tau-directed treatment trials.

Conflicts of interest

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