Early increase in tau-PET signal is associated with changes in amyloid, CSF p-tau, and cognition in cognitively normal adults

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Background and Objectives
The role of early cortical tau accumulation in the pre-symptomatic stages of Alzheimer’s disease (AD) remains unclear. In a cohort of cognitively normal, late-middle-aged individuals at increased risk of developing AD, we used Positron Emission Topography (PET) imaging to investigate the relationships between cortical tau and cortical beta-amyloid (Ab), cerebrospinal fluid phosphorylated tau (p-tau), and cognitive performance.

Methods
Participants
- One hundred and nineteen (119) cognitively normal older adults with a familial history of AD

PET Imaging
- Siemens HRRT PET scanner
- Standardized uptake ratio values (SUVRs) were calculated from 35 FTL4/FTL6 DESikan regions of interest (ROIs) using the cerebellum grey matter (Ab-PET) and inferior cerebellum grey matter (flortaucipir) as the reference region.

Ab-PET Positivity Threshold
- Literature-based global Ab SUVR cut-off = 1.42 (Nel et al., 2017)
- Confirmed with Gaussian mixture modeling

Cerebrospinal Fluid p-tau
- Subsample of 59 subjects also underwent a lumbar puncture
- Innest ELISA assay (Janssen, Gent, Belgium) used to assess phosphorylated tau levels

Cognitive Assessment
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
- Index scores of cognitive domains and total RBANS score were included in this experiment

PET SUVRs and RBANS scores were negatively correlated (r=-0.41) in an additive fashion.

Statistics
- ROI-based analyses of flortaucipir binding
- Linear regressions adjusted for age and sex
- P-values corrected with use of 1000 permutations

Results
1A. Flortaucipir binding in AD-typical regions in Ab-positive individuals.
2A. Higher flortaucipir binding is associated with higher CSF p-tau.
3A. Higher flortaucipir binding is associated with worse cognitive performance.
4A. Examining “turning points” of associations between flortaucipir binding and Ab, CSF p-tau, and cognition

Conclusions
These findings indicate that, even in cognitively normal adults with relatively low flortaucipir SUVRs, flortaucipir binding in AD signature regions is significantly increased among Ab-positive individuals. Higher tau binding is also associated with higher CSF p-tau and lower cognitive performance. Except for the association with cognition, these findings were still present when removing individuals with the highest entorhinal and inferior temporal flortaucipir binding, supporting the idea that relatively low tau-PET signal is clinically meaningful.