

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 (Aβ)**, **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

	Whole Cohort	Aβ+	Aβ-
Number	119	18	101
Mean Age ± SD y	67.5 ± 4.8	68.9 ± 5.9	67.1 ± 4.5
% Female (N)	73.9% (88)	61.1% (11)	76.2% (77)
% APOE4+ (N)*	40.3% (48)	66.7% (12)	35.6% (36)
Mean Education ± SD y*	15.1 ± 3.2	13.6 ± 2.2	15.4 ± 3.3
Mean MMSE ± SD	28.8 ± 1.2	28.5 ± 1.5	28.8 ± 1.1
Mean Global Aβ SUVR ± SD*	1.31 ± 0.32	1.98 ± 0.31	1.19 ± 0.09
Mean Entorhinal Tau SUVR ± SD*	1.08 ± 0.14	1.22 ± 0.18	1.05 ± 0.11
Mean Inferior Temporal Tau SUVR ± SD*	1.16 ± 0.14	1.29 ± 0.24	1.14 ± 0.1

* means differ between Aβ+ and Aβ- participants (Wilcoxon rank-sum test)

PET Imaging

- Siemens HRRT PET scanner
- Standardized uptake ratio values (SUVRs) were calculated from 35 FreeSurfer Desikan regions of interest (ROIs) using the cerebellum grey matter (Aβ-PET) and inferior cerebellum grey matter (flortaucipir) as the reference region.

Aβ-PET Positivity Threshold

- Literature-based global Aβ SUVR cut-off = 1.42 (Nai et al., 2017)
- Confirmed with Gaussian mixture modeling

Cerebrospinal Fluid P-tau

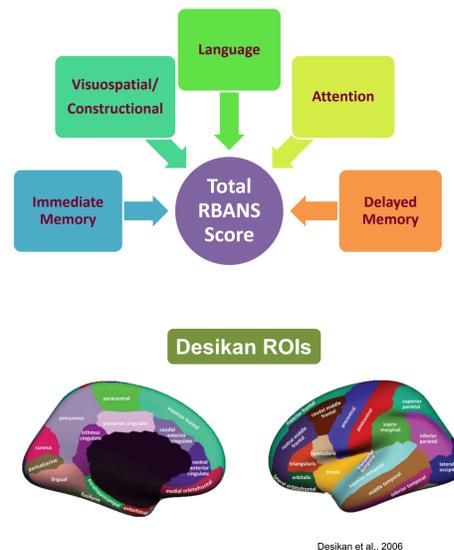
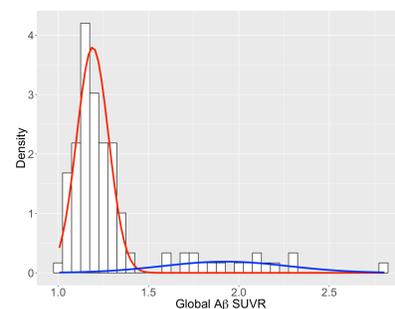
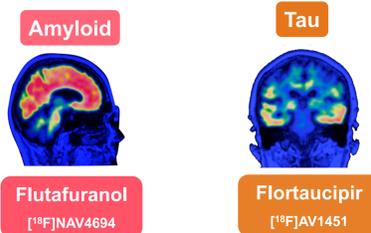
- Subsample of 59 subjects also underwent a lumbar puncture
- Innotest ELISA assay (Fujirebio, Ghent, Belgium) used to assess phosphorylated tau levels

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

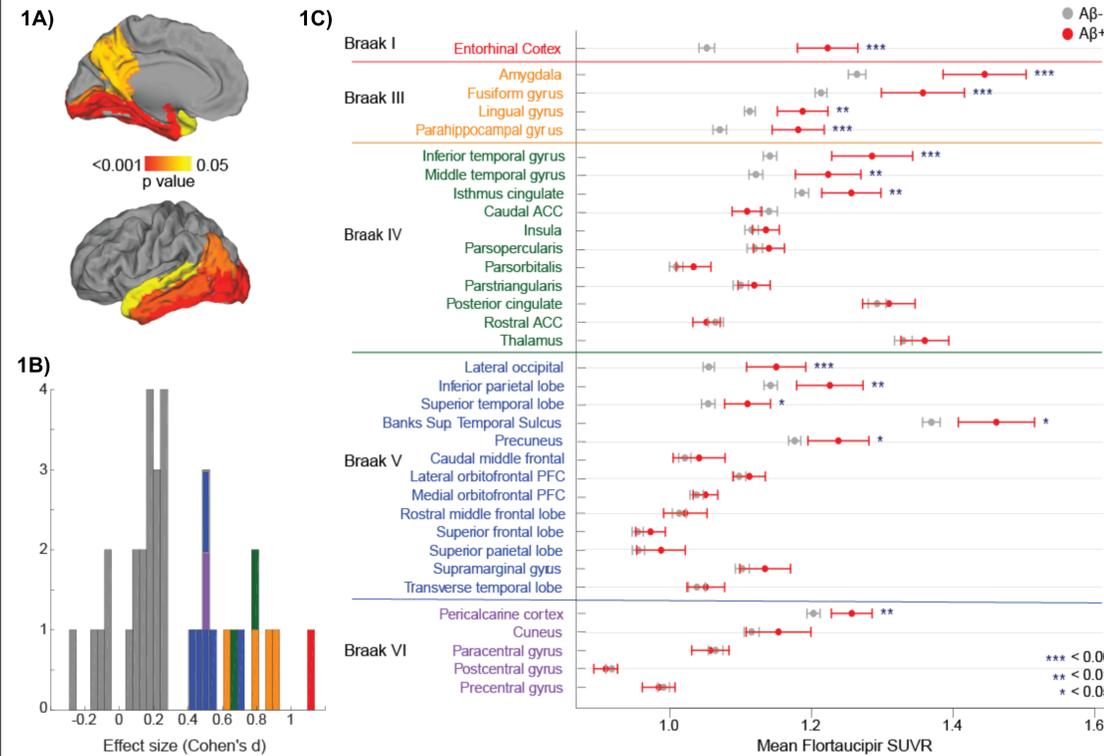
Statistics

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



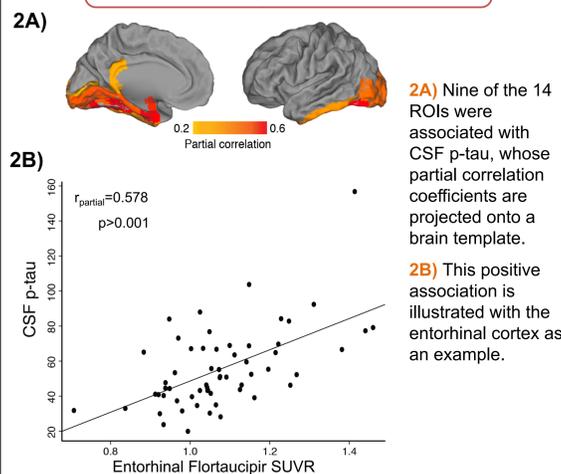
Results

1: There is higher flortaucipir binding in AD-typical regions in Aβ-positive individuals.

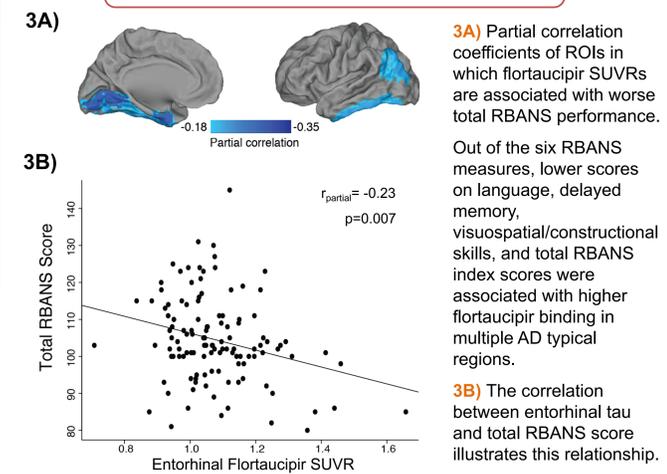


1A) P-values of the 14 brain regions in which flortaucipir SUVRs are higher in Aβ+ individuals when compared to Aβ- individuals projected onto a brain template.
1B) Effect sizes of flortaucipir binding in Aβ+ vs. Aβ- individuals in each ROI. The effect sizes of the 14 significant ROIs are color-coded by Braak stage.
1C) Mean flortaucipir SUVRs across all FreeSurfer Desikan regions, organized by Braak stages, in Aβ+ (red) and Aβ- (gray) groups. Asterisks indicate the 14 regions in which the flortaucipir SUVR is different between the Aβ+ and Aβ- groups.

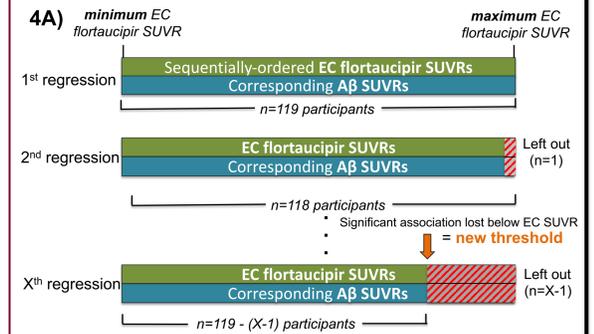
2: Higher flortaucipir binding is associated with higher CSF p-tau.



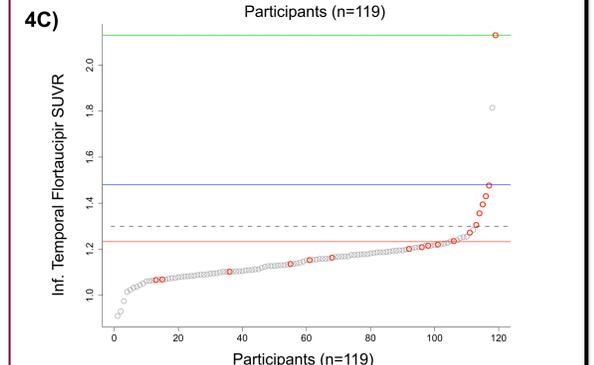
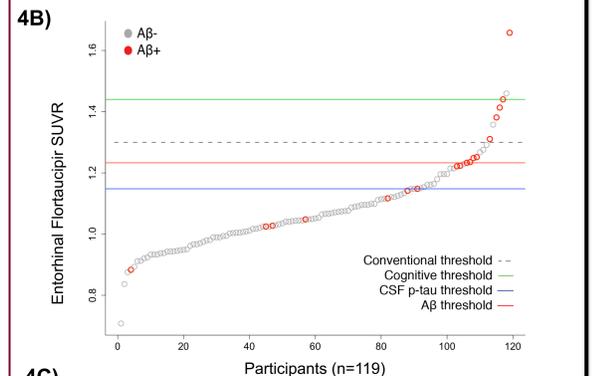
3: Higher flortaucipir binding is associated with worse cognitive performance.



4: Examining "turning points" of associations between flortaucipir binding and Aβ, CSF p-tau, and cognition



4A) To further evaluate whether low levels of flortaucipir binding are related to continuous Aβ, CSF p-tau, and total cognitive performance, we iteratively ran linear regressions (with a permutation procedure) and removed the subject with the highest entorhinal (EC) or inferior temporal (IT) flortaucipir SUVR for each iteration. We recorded the lowest SUVR at which the association between flortaucipir and the variable of interest was maintained (p<0.05) to get a better idea of the turning point, or threshold, at which the association is lost.



4B-C) Both in the entorhinal cortex (4A) and inferior temporal gyrus (4B), the relationship between flortaucipir and cognition is mostly driven by one or a few subjects with the highest SUVRs. Relationships with Aβ and p-tau are still maintained at SUVR values lower than proposed literature-based cutoffs in the entorhinal cortex. This is also true for Aβ-PET and inferior temporal SUVRs.

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 Aβ-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**.