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 (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

PREVENT-AD Research Group

	Whole Cohort	Aβ+	Aβ-	Tau+	Tau-
Number	119	18	101	7	112
Age ± SD y	67.5 ± 4.8	68.9 ± 5.9	67.1 ± 4.5	69.6 ± 4.3	67.3 ± 4.8
% Female (N)	73.9% (88)	61.1% (11)	76.2% (77)	85.7% (6)	73.2% (82)
% APOE4+ (N) *	38.7% (46)	66.7% (12)	33.7% (34)	57.1% (4)	37.5% (42)
Education ± SD y *	15.1 ± 3.2	13.6 ± 2.2	15.4 ± 3.3	13.1 ± 2.5	15.2 ± 3.2
MMSE ± SD	28.8 ± 1.2	28.5 ± 1.5	28.8 ± 1.1	27.8 ± 1.5	28.9 ± 1.1
Global Aβ SUVR ± SD *^	1.31 ± 0.32	1.98 ± 0.31	1.19 ± 0.09	1.8 (0.4)	1.2 (0.2)
Entorhinal Tau SUVR ± SD ^	1.08 ± 0.14	1.22 ± 0.18	1.05 ± 0.11	1.43(0.11)	1.06 (0.1)

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

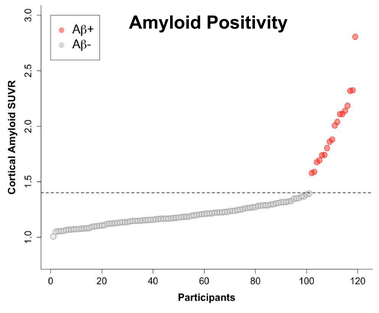
PET Imaging

- Siemens HRRT PET scanner
- Standardized uptake ratio values **(SUVRs)** were calculated from 35 Freesurfer Desikan regions using the cerebellum grey matter (tau-PET) and inferior cerebellum grey matter (Aβ-PET) as the reference region.

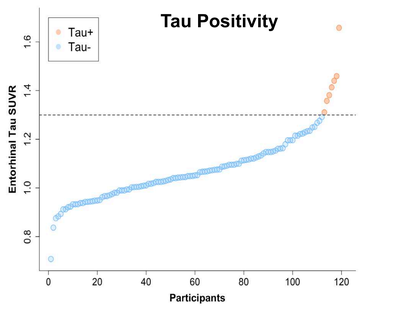
Amyloid [^{18}F]NAV4694 | **Tau** [^{18}F]AV-1451 | **Desikan Regions**

Desikan et al., 2006

Biomarker Positivity



*Global Aβ SUVR cut-off = **1.4***
(Mielke et al., 2012; Villeneuve et al., 2015)



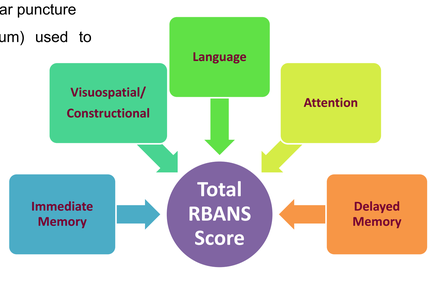
*Braak Stage I (Entorhinal) Tau SUVR cut-off = **1.3***
(Maass et al., 2017; Vermuri et al., 2017)

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)**



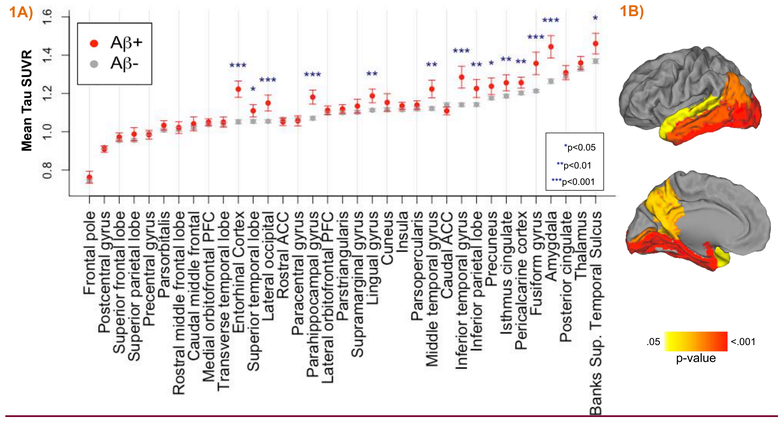
Statistics

- ROI-based analyses of AV-1451 binding
- Linear regressions adjusted for age and sex
- P-values corrected with use of 1000 permutations

Results

All participants (n=119)

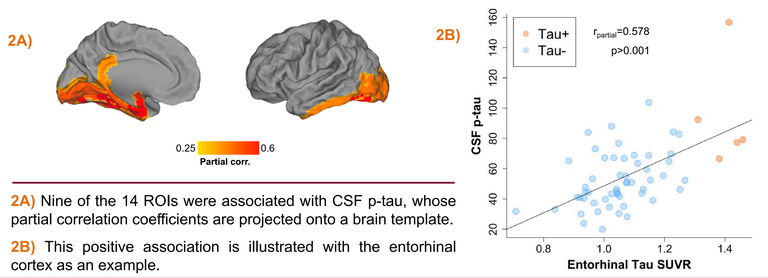
1) There is higher AV-1451 binding in AD-typical regions in Aβ-positive individuals.



1A) Mean AV-1451 SUVR across all FreeSurfer Desikan regions in Aβ-positive (red) and Aβ-negative (gray) groups.

1B) P-values of the 14 brain regions in which AV-1451 SUVRs are higher in Aβ+ individuals when compared to Aβ- individuals regions projected onto a brain template.

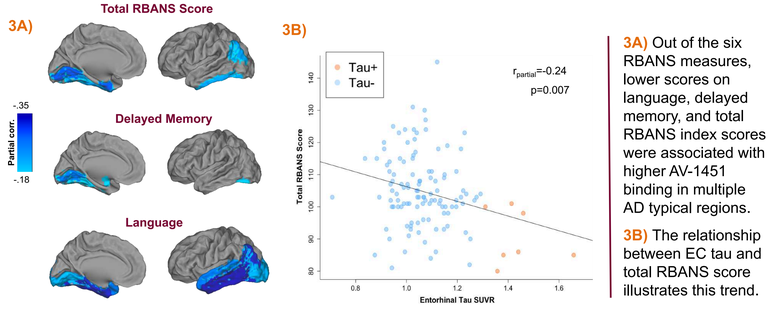
2) Higher AV-1451 binding in AD-typical regions is associated with higher CSF p-tau levels.



2A) Nine of the 14 ROIs were associated with CSF p-tau, whose partial correlation coefficients are projected onto a brain template.

2B) This positive association is illustrated with the entorhinal cortex as an example.

3) Higher AV-1451 binding in AD-typical regions is associated with worse cognitive performance.

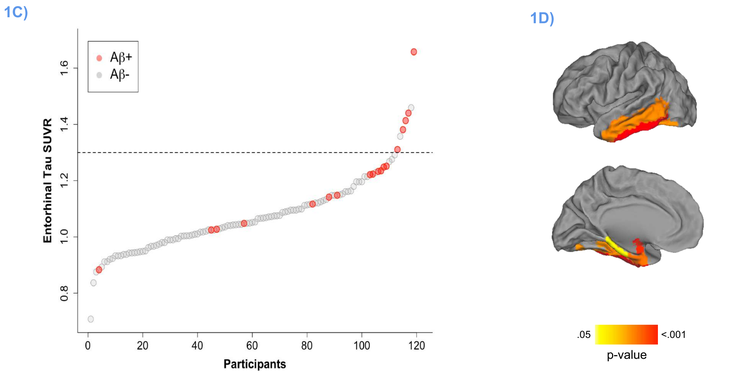


3A) Out of the six RBANS measures, lower scores on language, delayed memory, and total RBANS index scores were associated with higher AV-1451 binding in multiple AD typical regions.

3B) The relationship between EC tau and total RBANS score illustrates this trend.

Tau-"negative" participants (n=112)

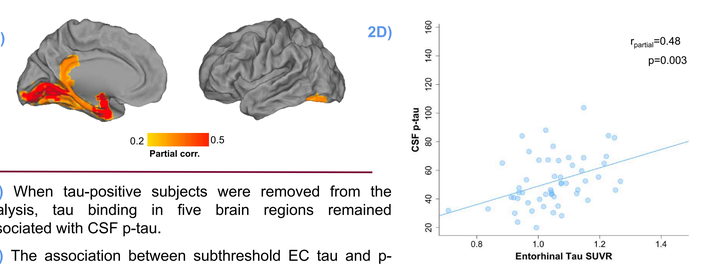
Subthreshold AV-1451 binding is associated with Aβ-positivity.



1C) Participants ordered from low to high entorhinal cortex (EC) AV-1451 tau binding. Individuals who are amyloid positive (red) are largely clustered near the tau-positivity threshold (dashed line), suggesting that subthreshold levels of tau might still be clinically meaningful.

1D) P-values of the six brain regions in which AV-1451 SUVR is still higher in Aβ+ individuals when compared to Aβ- individuals when the participants above the tau threshold were removed and the analysis was rerun projected onto a brain template.

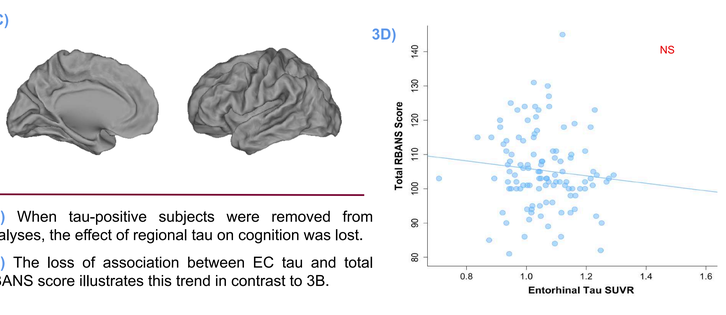
Subthreshold AV-1451 binding is associated with higher CSF p-tau.



2C) When tau-positive subjects were removed from the analysis, tau binding in five brain regions remained associated with CSF p-tau.

2D) The association between subthreshold EC tau and p-tau.

Subthreshold AV-1451 binding is not associated with cognitive performance.



3C) When tau-positive subjects were removed from analyses, the effect of regional tau on cognition was lost.

3D) The loss of association between EC tau and total RBANS score illustrates this trend in contrast to 3B.

Conclusions

These findings indicate that, even in cognitively normal adults with relatively low AV-1451 SUVRs, AV-1451 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 cognition. Except for the association with cognition, these findings were still present when removing the seven individuals with the highest levels of tau (classified as tau positive individuals), supporting the idea that very **early elevation in tau-PET signal is clinically meaningful.**

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