Widespread Amyloid Is Necessary to Detect Tau-PET Signal Beyond the Entorhinal Cortex and Cognitive Decline

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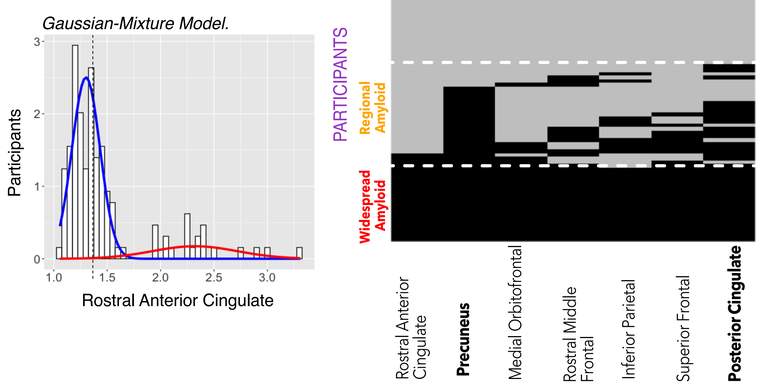
OBJECTIVES

Aβ accumulation starts almost two decades before the onset of the symptoms of Alzheimer's Disease (AD). Given increasing evidence suggesting that sub threshold Aβ accumulation in older adults is biologically relevant, we sought to investigate different markers of AD in relation with varying amount and spread of Aβ burden in asymptomatic individuals at risk of AD.

PARTICIPANTS

One hundred and twenty-nine cognitively unimpaired individuals with a family history of AD (PREVENT-AD cohort) underwent Aβ ([18F]NAV4694) and tau ([18F]AV1451) PET scans. We assessed the cognition with the RBANS (both cross-sectionally and longitudinally) and Subjective Cognitive Decline Score.

We used Gaussian-mixture models to create region-specific thresholds of Aβ positivity in seven regions identified previously to be sensitive to early Aβ accumulation (Villeneuve et al, Brain, 2015). Individuals who were Aβ-positive in all regions were classified as the Widespread Aβ group; those who were positive in one or more regions were included in the Regional Aβ group, while the others were considered Aβ-negative.

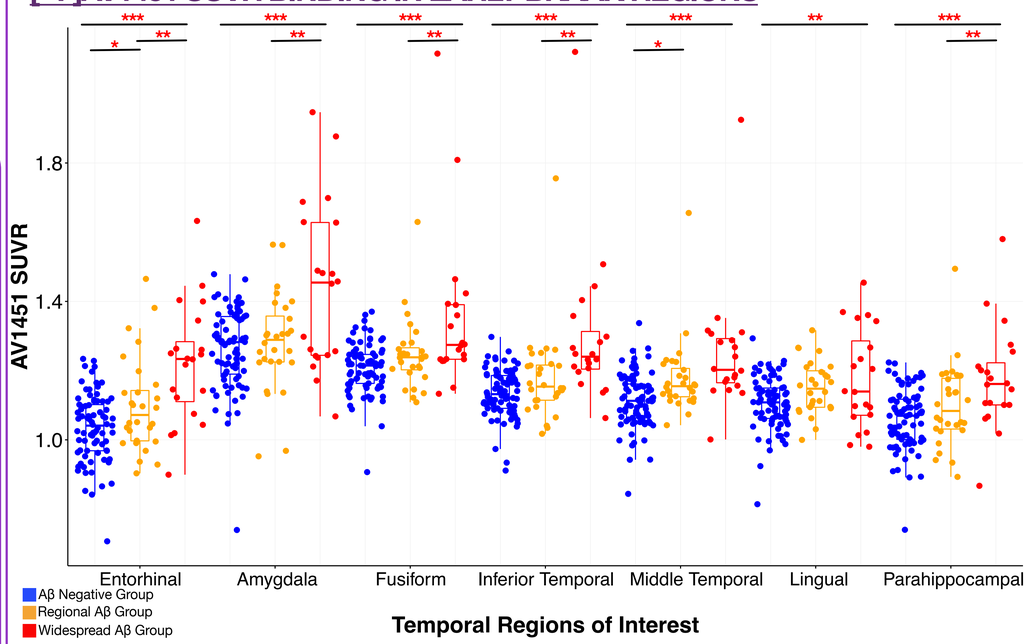


Sample Demographics.

	Aβ Negative Group (n = 81)	Regional Aβ Group (n = 28)	Widespread Aβ Group (n = 20)	P<0.05
Age (Mean(SD))	63 (± 4.6)	63 (±3.8)	66 (±5.6)	*b*
Education (Mean(SD))	15.6 (±3.56)	14.7 (±2.75)	13.75 (±2.4)	
Gender (Female %)	74% (60/21)	82% (23/5)	65% (13/7)	
APOE ε4	27.16% (22/59)	64.29% (18/10)	65% (13/7)	*a, b*
Subjective Cognitive Complaints (Mean(SD))	1.22(±0.23)	1.21(±0.18)	1.39(±0.30)	*b, c*

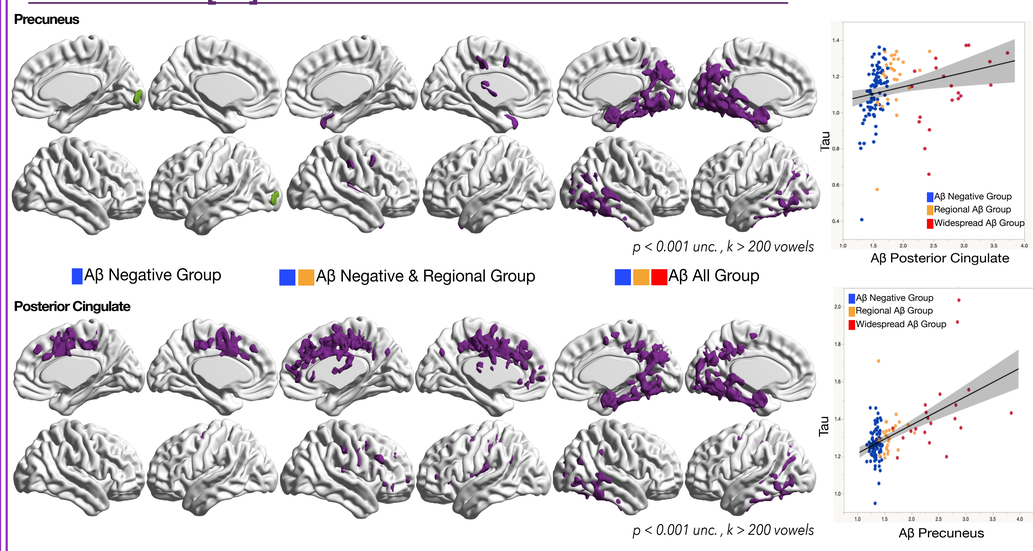
APOE: Apolipoprotein ε4; BL: Baseline; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; ECoG: Score on Everyday Cognition questionnaire assessing subjective cognitive complaint. a = p<0.05 between Aβ Negative and Regional Aβ Groups; b = sig. p<0.05 between Aβ Negative and Widespread Aβ Groups; c = sig. p<0.05 between Regional Aβ and Widespread Aβ Groups.

[18F]AV1451 SUVR BINDING IN EARLY BRAAK REGIONS



The Regional Aβ group had elevated tau-PET binding in the entorhinal cortex and middle temporal gyrus when compared with the Aβ-negative group. The Widespread Aβ group had elevated tau PET signal compared with the two other groups across all seven regions investigated.
(* p<0.05; ** p<0.01; ***p<0.001)

PATTERN OF [18F]AV1451 BINDING ACROSS INDIVIDUALS



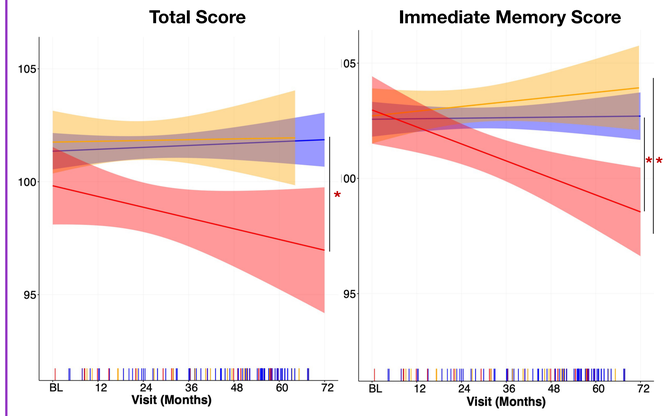
These figures represent the vowel-wise correlations between Tau-PET signal binding and local Aβ-PET for our 3 groups. Regardless of the Aβ region chosen, associations for the Aβ negative and Regional Aβ groups occur in *non tau* regions suggesting unspecific binding. When the Widespread Aβ group is included, vowel-wise analyses show a consistent pattern across the 7 regions of interest.

COGNITION

Linear mixed-effects models compared cognitive trajectories over up to seven years of assessments. The three groups did not differ in the cognitive assessment at their baseline visit.

Baseline Cognition.

	Aβ Negative Group (n = 81)	Regional Aβ Group (n = 28)	Widespread Aβ Group (n = 20)	P<0.05
Immediate Memory Score	102.7 (± 11.3)	104.5 (± 11)	104.5 (± 10.3)	
Delayed Memory Score	103.9 (± 8.5)	100.9 (± 8.9)	97.2 (± 10.7)	*b*
Total Index Score	102.8 (± 9.6)	102.4 (± 9.7)	101.3 (± 9.2)	
Attention Score	106.7 (± 1.7)	105.6 (± 2.9)	109.6 (± 3.4)	
Language Score	103.5 (± 9.4)	104.6 (±10)	103.6 (± 8.6)	
Visuospatial Score	95.5 (± 13.3)	94.7 (± 12.2)	92.45 (± 13.7)	



Cognitive test scores of "Total Score" and "Immediate Memory Score" on the RBANS over time in the three different groups, other RBANS domains were not significant between the three groups.

PET scans have been done in different visits for each participants. The lines on x-axis represent the PET scan visit for each participant. Statistics were obtained from linear mixed-effect models corrected for sex, education and apolipoprotein ε4 status. (* p<0.05)

CONCLUSIONS

Elevated tau-PET signal outside of the entorhinal cortex and measurable cognitive decline are detected when Aβ deposition is widespread across the cortex. It is hard to detect any change in the Regional Aβ group because the Prevent-AD cohort is quite young and longitudinal follow-up is required in order to investigate whether they will progress to the Widespread Aβ group and show cognitive decline over time.

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