[^{18}F]AV1451 deposition pattern across the Alzheimer's disease spectrum - Characterization at the individual level

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BACKGROUND AND OBJECTIVES

The extent to which older adults along the Alzheimer's disease (AD) spectrum follow a similar tau-PET deposition pattern and have similar level of accummulation is not clear. We focused on inter-individual [^{18}F]AV1451-PET binding across the typical Braak stages and using a more fine-grained parcellation of 34 brain regions in ADNI participants, ranging from cognitively normal older adults (CN), participants with early mild cognitive impairment (EMCI), late MCI (LMCI) and AD dementia.
Our objective is to characterize deposition pattern across diagnostic groups, amyloid status, and to examine regional differences at the individual level by considering different regional thresholds.

PARTICIPANTS

Participants along the Alzheimer's disease spectrum (CN, EMCI, LMCI, AD) from ADNI who had a [^{18}F]AV1451 scan
Amyloid positivity was taken from the ADNI database, i.e. [^{18}F]AV45 global SUVR > 1.1

	Amyloid-negative (n=166)	**Amyloid-positive** (n=129)
Diagnosis	113 CN 33 EMCI 20 LMCI/AD	72 CN 30 EMCI 27 LMCI/AD
Age, mean ± sd (range)	70.32 ± 6.24 (56-87)	72.81 ± 6.54 (55-89)
Sex, F:M (%F)	85:81 (51%)	64:65 (50%)
APOE4[1] (%)	23 (20%)	55 (53%)
Education, mean ± sd (range)	16.77 ± 2.59 (8-20)	16.45 ± 2.55 (12-20)

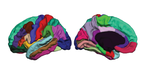
[1]APOE status available for 116 amyloid-negative and 104 amyloid-positive

A group of young adults (n=11, mean age=27.3 ± 2.6) from an independent study (PREVENT-AD group, McGill University, Montreal) who had a [^{18}F]AV1451 scan was included to compare tracer binding to older adults

REGIONS OF INTEREST

Standardized uptake value ratios (SUVR) were averaged in regions approximating the different **Braak stages (I, III, IV, V, VI;** see below**)**. The hippocampus (Braak II) was not included due to non-specific binding of the tracer.

SUVR in **34 regions from the FreeSurfer Desikan atlas** were also extracted, as a more fine-grained approach to examine binding across the AD spectrum and in young adults.



Braak I
1. Entorhinal

Braak III
2. Parahippocampal
3. Fusiform
4. Lingual gyrus
5. Amygdala

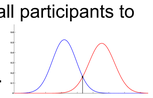
Braak IV
6. Inferior temporal
7. Middle temporal
8. Temporal pole
9. Caudal anterior cingulate
10. Rostral anterior cingulate
11. Isthmus
12. Posterior cingulate
13. Insula

Braak V
14. Middle frontal
15. Lateral orbitofrontal
16. Medial orbitofrontal
17. Pars opercularis
18. Pars orbitalis
19. Pars triangularis
20. Rostral middle frontal
21. Superior frontal
22. Inferior parietal
23. Superior parietal
24. Supramarginal
25. Lateral occipital
26. Transverse temporal
27. Superior temporal
28. Precuneus
29. Banks sup. temp. sulcus

Braak VI
30. Precentral
31. Postcentral
32. Paracentral
33. Cuneus
34. Pericalcarine

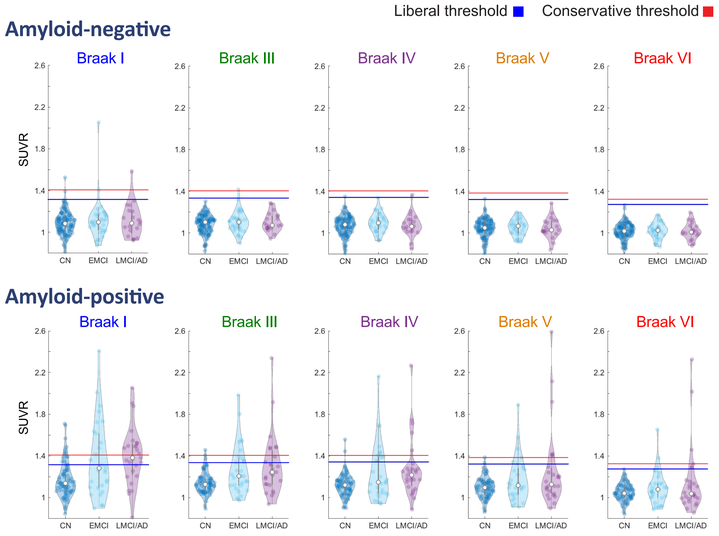
ANALYTICAL METHODS

We applied **Gaussian mixture models** with two components across all participants to derive a liberal threshold (50% probability to be in either distribution) and a conservative threshold (90% probability to be in the high distribution) for the Braak composite regions and the 34 brain regions.



We compared SUVR values and tau "elevation" based on the thresholds across diagnostic groups, amyloid status, and compared to young adults.

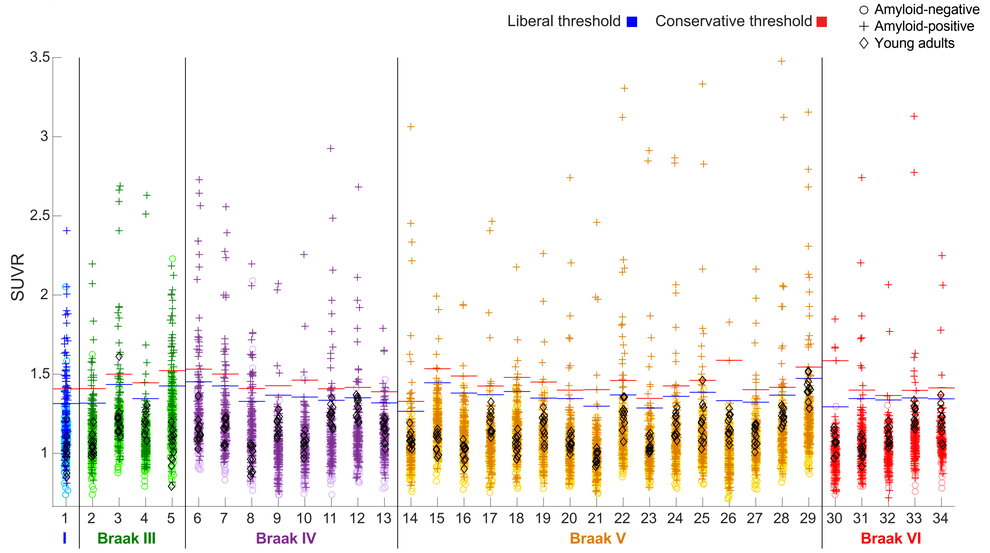
[^{18}F]AV1451 SUVR ACROSS BRAAK STAGES



Using composite regions approximating the different Braak stages, only 4% of amyloid-negative individuals, regardless of their clinical diagnosis, had elevated SUVR in Braak I or in further stages.

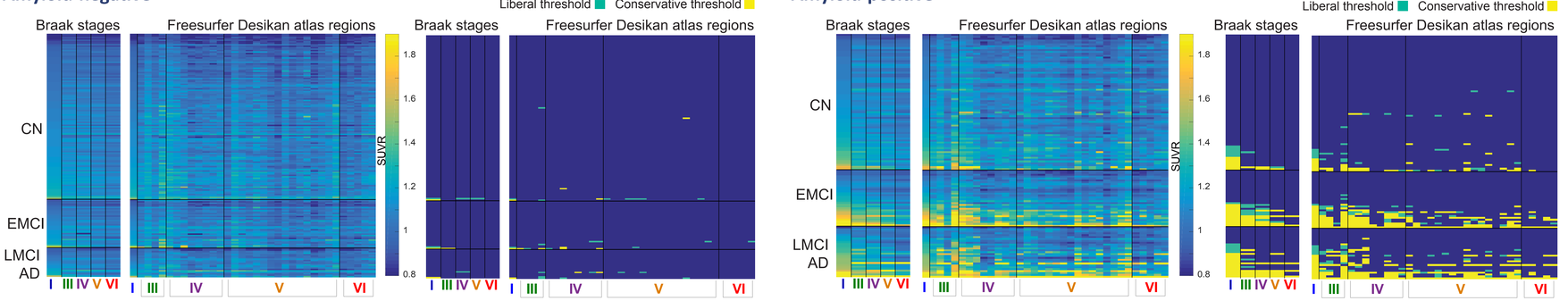
In the amyloid-positive group, 17% CN, 43% EMCI and 67% LCMI/AD had elevated SUVR in Braak I. Across all participants, few had elevated tau further than Braak stage IV, with either a liberal or conservative threshold.

[^{18}F]AV1451 SUVR ACROSS FINE-GRAINED BRAIN REGIONS



Using a parcellation of 34 brain regions, very few amyloid-negative individuals showed elevated tau signal in any region (using either liberal or more conservative thresholds), while amyloid-positive individuals tended to have elevated tau across all regions.
Of note, the binding pattern of [^{18}F]AV1451 seemed to differ between young adults and ADNI participants. In regions corresponding to early Braak stages (I-III), young adults generally presented low SUVR, while in many regions part of Braak IV to VI, they presented SUVR close to or higher than most older adults. Given this, young adults were not used further to derive alternative thresholds

PATTERN OF [^{18}F]AV1451 BINDING ACROSS INDIVIDUALS



We looked at the individual level, to assess whether there was a sterotypical pattern of elevated tau deposition across Braak stages and across the 34 brain regions (based on liberal and conservative thresholds; shown in figures above). SUVR matrices are shown on the left and thresholded matrices based on the thresholds are shown on the right.
In the amyloid-negative group (left), only 5 participants showed focal binding in one or more brain regions despite having low SUVR in the entorhinal cortex/Braak I. In amyloid-positive participants (right) with elevated tau in Braak I, 25% CN and only 50% LMCI/AD had elevated SUVRs in one or multiple further stages, compared to 92% EMCI. Looking across the 34 brain regions, [^{18}F]AV1451 spreading became evident in LMCI/AD and 8% of CN showed focal cortical binding in the absence of elevated entorhinal SUVR.
Regions presenting the most often elevated SUVR were the entorhinal cortex, the parahippocampal gyrus, the amygdala, the inferior and middle temporal gyri, and the temporal pole.

CONCLUSIONS

There was significant overlap in SUVR ranges across all individuals for the majority of regions, which yielded only small differences between using a liberal or conservative threshold to define elevated tau.
Almost no amyloid-negative individuals had elevated tau, regardless of clinical diagnosis. Amyloid-positive participants followed the expected pattern of tau spreading using composite Braak regions, but only 50% of LMCI/AD showed abnormal binding outside of the entorhinal cortex even with liberal thresholds of elevated tau. Looking across the 34 brain regions, there was widespread tau in LMCI/AD, but also in some CN individuals who did not follow the expected spatial progression of tau. This unexpected focal binding might indicate non-AD neurodegenerative processes or false positives.

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