Spatial Extent of Amyloid- β Levels and Associations with Alzheimer's Disease Biomarkers

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Article

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Abstract

Objective: To investigate the biological and clinical correlates of A β spatial extent deposition levels in cognitively unimpaired older adults.

Methods: We included cognitively unimpaired older adults from three cohorts, totalling 529 participants (PREVENT-AD, n=129; ADNI, n=400 and HABS, n=288) who underwent A β positron emission tomography (PET). We used Gaussian-mixture models to identify region-specific thresholds of A β positivity in seven brain regions prone to early A β accumulation. Individuals were classified as having “widespread” A β deposition if they were positive in all seven regions, “regional” A β deposition if they were positive in one to six regions, or A β negative if negative in all regions. We compared demographics, genetics, tau-PET binding, and cognitive performance and decline between the three groups.

Results: In all cohorts, most participants with regional A β -PET binding did not meet the cohort-specific criteria for A β -positivity (79% for PREVENT-AD, 57% for ADNI, and 100% for HABS). Regional A β groups had normal baseline cognition and relatively normal tau-PET binding, but a greater proportion of *APOE* ϵ 4 carriers, decreased CSF A β ₁₋₄₂ levels, and greater amount of longitudinal A β -PET binding accumulation (only available in ADNI and HABS) when compared with the Negative A β groups. Widespread A β groups had lower baseline cognitive performance (PREVENT-AD only), faster cognitive decline (all cohorts) and greater amount of longitudinal tau binding than the other groups (only available in ADNI and HABS).

Conclusions: Individuals with regional A β deposition might be the best candidate for preventive trials since they do not yet have widespread tau and cognitive decline. Widespread levels of A β seem to be needed for tau spreading.

Introduction

Amyloid-beta (A β) and tau are the main pathological hallmarks of Alzheimer’s disease (AD). The deposition of these pathological proteins is a continuous process that starts decades before the onset of AD symptoms^{1,2}. While tau deposition may initiate prior to A β accumulation³, it is widely held that A β pathology is required to make tau spread out of the temporal lobe and start the pathological cascade leading to AD dementia, making it an ideal target for clinical trials^{4,5,6,7}. Several clinical trials have now successfully reduced brain A β without slowing down AD clinical progression⁸⁻¹⁰. While the role of A β in the pathological cascade of AD has been questioned based on large-scale clinical trial failures¹¹, one could argue that A β needs to be targeted before the spread of tau pathology¹². The appropriate timing likely corresponds to a stage where there is a limited amount and spreading of A β pathology, hence making it challenging to identify^{13,14}.

Accumulation of A β starts in a few distinct brain regions almost simultaneously, which makes it possible to characterize early regional A β deposition *in vivo* using positron emission tomography (PET) imaging, before it rapidly evolves to widespread distribution¹⁵⁻¹⁷. In general, most studies have used global brain

load to classify individuals with intermediate or high levels of A β ^{15,18,19}. We took advantage of the spatial distribution of A β deposition to identify different groups of cognitively unimpaired individuals based on the extent of A β tracer uptake with the objective of identifying early A β deposition. In three cohorts of cognitively unimpaired older adults, including one with a family history of AD dementia, we sought to investigate the characteristics of the different groups based on various AD markers

Methods

Methods

a. Participants and Study Design

PREVENT-AD

One hundred twenty-nine participants were recruited from the Presymptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) cohort. The PREVENT-AD cohort is an ongoing longitudinal observational study launched in 2011 comprising a total sample size of 385 individuals²⁰. Only the subsample of PREVENT-AD participants who underwent A β and tau PET imaging were included in the current study. Enrollment criteria included: (1) having a parent or multiple siblings with a history of AD; (2) age >60 years or age between 55 and 59 years if the onset of symptomatic dementia of their youngest affected relative was within 15 years of their age; (3) no major neurological diseases; and (4) no evidence of cognitive impairment at enrollment²¹.

ADNI

Four hundred participants were included from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). The current study included individuals from the ADNI-2 extension who underwent A β PET.

HABS

Two hundred and eighty-eight participants were drawn from the Harvard Aging Brain Study (HABS), an ongoing longitudinal study focusing on preclinical AD, launched in 2010, funded by the National Institute on Aging²². Inclusion criteria included: (1) scores of 0 on the Clinical Dementia Rating, (2) 11 or less on the Geriatric Depression Scale, (3) 27 or more on the education-adjusted Mini-Mental State Examination, and (4) performed within education-adjusted norms on Logical Memory–delayed recall. Participants who had a score of 5 or more in Hachinski, history of stroke with residual deficits, and history of intercranial

hemorrhage were excluded from the study. Data were obtained from the HABS data release 2.0 in October 2020 via habs.mgh.harvard.edu.

Note that all participants from the three different cohorts were cognitively normal at the time of A β PET to be included in the study.

Standard protocol approvals, registrations, and patient consents. All PREVENT-AD participants were fully briefed and gave their explicit consent for participation using procedures and consent forms approved by the Institutional Review Board of the McGill University Faculty of Medicine. Data collection and sharing in ADNI were approved by the Institutional Review Board of each participating institution and written informed consent was obtained from all participants. Participants from the HABS cohort provided written informed consent prior to study procedures, which used protocols approved by the Partners Healthcare institutional review board.

b. Neuropsychological Evaluation

In the three cohorts, participants underwent cognitive testing annually. We analyzed both baseline (corresponding to the time of A β PET scan) and longitudinal cognitive performance.

In PREVENT-AD, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)²³ was used as the main neuropsychological test. The total score and the five RBANS composite domain scores (Immediate Memory, Attention, Visuospatial Construction, Language and Delayed Memory), derived from twelve tasks were the measures of interest. Longitudinal cognitive assessment was available for all subjects, with a median follow-up time of 7 [interquartile range (IQR): 2, 8] years.

In ADNI, we used the available four composite scores reflective of memory, executive functions, language, and visuospatial functioning that have been previously described^{24,25}. Longitudinal cognitive assessment was available for 393 (98%) subjects, with a median follow-up time of 6 [IQR: 1, 14] years.

In HABS we used the preclinical Alzheimer's cognitive composite (PACC5) that is a composite score including memory, executive function and semantic processing²⁶ that was available through the HABS data release. All participants had a longitudinal cognitive assessment, with a median follow-up time of 6 [IQR: 1, 9] years.

c. APOE Genotyping

Genomic DNA was extracted from whole blood, and the apolipoprotein E (*APOE*) genotype was determined²⁷. The same procedure was done for all cohorts participants at their baseline visit. Participants were classified as *APOE* ϵ 4 carriers (*i.e.*, those who had at least one ϵ 4 allele) or noncarriers.

d. Cerebrospinal Fluid Biomarkers

In PREVENT-AD, a subsample of 77 participants underwent a lumbar puncture, with a maximum of up to 2 years before PET (mean difference to PET scan 10.42 ± 8.38 months). Cerebrospinal fluid samples (CSF) were collected in the morning after an overnight fast and stored in cryovial tubes at -80°C . CSF $\text{A}\beta_{1-42}$, p-tau₁₈₁ (phosphorylated at threonine 181) and total tau levels were assayed in duplicate with the INNOTEST ELISA (Fujirebio, Ghent, Belgium)^{20,28}.

In ADNI, 276 participants had CSF biomarkers available, based on a two-year interval between PET and CSF (mean time from PET scan 0.40 ± 0.75 months). CSF samples were frozen within 1 hour after collection and were shipped overnight frozen on dry ice to the Penn AD Biomarker Fluid Bank Laboratory. Aliquots of 500 μL were stored in polypropylene tubes at -80°C . CSF $\text{A}\beta_{1-42}$ and p-tau₁₈₁ were measured using Elecsys immunoassays²⁹.

e. PET Acquisition

PET imaging in PREVENT-AD was performed using [^{18}F]NAV4694 (NAV; Navidea Biopharmaceuticals, Dublin, OH) for $\text{A}\beta$ and Flortaucipir (FTP) (Eli Lilly&Co, Indianapolis, IN) for tau deposition. $\text{A}\beta$ scans were performed 40 to 70 minutes after injection ($\approx 6\text{mCi}$) and tau scans 80 to 100 minutes after tracer injection ($\approx 10\text{mCi}$). Most scans were operated on 2 consecutive days. Imaging was performed at the McConnell Brain Imaging Centre at the Montreal Neurological Institute (Montreal, Canada) between February 2017 and May 2019. T1-weighted structural MRI scans had been acquired prior to the PET scans (median delay 9.06 [interquartile range (IQR): 0.03,34] months) on a 3T Siemens Trio scanner (Siemens, Munich, Germany) (repetition time of 2300 milliseconds, echo time of 2.98 milliseconds, 176 slices, and 1-mm slice thickness²⁰).

Acquisition of the multicentric MRI and PET imaging data in ADNI has been reported previously and is described in detail at adni.loni.usc.edu/methods/. Briefly, $\text{A}\beta$ PET scans were acquired using Florbetapir ([^{18}F] AV45) during a 50-to-70-minute interval following a 370 MBq bolus injection ($\approx 10\text{mCi}$) and FTP scans were acquired during a 75-to-105-minute interval following a 370 MBq bolus injection ($\approx 10\text{mCi}$). T1-weighted structural MRI data were acquired on 3T scanning platforms using sagittal 3D magnetization-prepared rapid gradient-echo sequences. The T1 sequence was the same as for the PREVENT-AD cohort. A subsample of 176 participants (44%) underwent tau-PET scans. Tau-PET was added later on in the course of the study, around 2016, and thus most tau scans were acquired 5 years after the $\text{A}\beta$ -PET (median delay 5 [IQR: 0, 8] years in ADNI).

In HABS, PET data were acquired as described previously^{22,30}. $\text{A}\beta$ PET scans were acquired using PIB (^{11}C Pittsburgh Compound B) during a 60-minute dynamic acquisition starting directly after the injection and FTP scans were acquired from 80-100 minutes after a 9.0 to 11.0 mCi bolus injection. MRI scans were performed on a 3T Tim Trio (Siemens) with a 12-channel phased-array head coil. The imaging measures were typically collected every two years (mean delay between FTP and PIB scans 3.5 months). 195 participants (67%) in HABS underwent tau-PET scans.

f. PET Processing

In all cohorts, T1-weighted MRI were processed using FreeSurfer (version 5.3 or 6) and parcellated according to the Desikan-Killiany atlas³¹. PREVENT-AD PET images were processed with a standard, in-house pipeline (available on Github: <https://github.com/villeneuvevelab/vlpp>). Briefly, the 4D PET images were realigned, averaged, and registered to the corresponding T1-weighted MRI. Images were then masked to exclude CSF signal and smoothed with 6 mm³ Gaussian kernels. Standardized uptake value ratios (SUVRs) were computed by dividing the tracer uptake in each voxel by the uptake in the whole cerebellum gray matter for NAV scans³² and the inferior cerebellum gray matter for FTP scans³³.

PET images for ADNI went through standardized preprocessing steps in order to increase data uniformity across the multicentric data acquisition³⁴. Briefly, Florbetapir-PET frames were co-registered, averaged, reoriented into a standardized image and voxel size, and smoothed to produce a uniform resolution. FTP frames were co-registered and resliced to the structural MRI closest in time to the FTP-PET. The cerebellum gray matter was used as the reference region for Florbetapir scans and the inferior cerebellum gray matter was used for FTP scans. The A β (2019-12-04 version) and tau (2020-02-04) regional SUVR data were downloaded from the ADNI database.

In HABS, following the PET image acquisitions, a mean image was created (for PIB – the first 8-minute post-injection), and PET images were co-registered to the corresponding T1-weighted MRI with 6 DoF rigid body registration using `spm_coreg` from the SPM12 package. Bilateral cerebellum grey matter was used as the reference region for SUVR measurements.

Regions of interest regarding A β are described subsequently. For tau-PET, SUVR from six bilateral regions that represent early tau-PET deposition were investigated, i.e. entorhinal cortex, amygdala, fusiform, parahippocampal, inferior temporal, and middle temporal cortex³⁵. The hippocampus was not included given the off-target binding spillover from the choroid plexus^{36,37}.

g. Global Threshold of A β Positivity

Each cohort had an available global threshold described previously to categorize participants into A β positive and negative. All such thresholds were derived from the average SUVR of lateral and medial frontal, cingulate, parietal and lateral temporal regions. In PREVENT-AD, the NAV threshold for positivity was 1.37³⁵. In ADNI, the Florbetapir threshold was 1.1^{38,39}, and the PIB threshold in HABS was 1.19^{40,41}.

h. Regional Thresholds of A β Positivity

A β PET values were extracted across seven bilateral regions which were hypothesized to be sensitive to early A β accumulation: medial orbitofrontal, rostral anterior cingulate, posterior cingulate, precuneus, rostral middle temporal, superior frontal, inferior parietal³². Tracer uptake in those first five regions has also been found to be elevated in A β -negative individuals who subsequently had significant evidence of A β deposition¹⁴.

A Gaussian mixture modelling approach (GMM) was used to quantify region-specific A β thresholds in the 7 bilateral regions hypothesized to be sensitive to early A β accumulation. Typically, A β follows a bimodal distribution and thus we fitted two Gaussian distributions as commonly used to categorize A β positivity^{18,32,42}. The two distributions acquired from GMM assigned each participant a probability of belonging to either the lower or higher distributions. We set a cut-off at the 90th percentile of the lower distribution. Those who had higher SUVR values than the regional cut-off was classified as “positive” for that specific region. According to the region-specific positivity, individuals who were A β -positive in all 7 regions were classified as the “Widespread A β group”; those who were positive in at most 6 regions were included in the “Regional A β group”; those who were negative in all the regions were considered as the “Negative A β group”.

As expected, the SUVR regional distribution of the data in all cohorts differed because of tracer differences. In PREVENT-AD and HABS (NAV and PIB tracer respectively), GMM analyses provided a clear distinction between distributions using thresholds for each region corresponding to a 90% probability of belonging to the low A β distribution (Figure e-1). The distinction between regional positive and negative binding was less evident with Florbetapir (ADNI). As shown in Figure e-1, participants from ADNI followed a more continuous distribution without a distinctive cut-off between lower and higher distributions which might partly be due to the different properties of the tracers. This interfered with using the same cut-off criteria in ADNI. Based on previous publications^{41,43,44}, we therefore decided to use a 50% probability of belonging to the low-A β distribution as cut-off criteria instead of a 90% probability.

Statistical Analysis

We compared demographics, APOE4 status, baseline and longitudinal cognition, baseline and longitudinal tau-PET between the three A β groups in the three cohorts separately using analysis of covariance tests and chi-squared tests for normally distributed continuous variables and categorical variables, respectively. Tukey HSD post hoc test and Bonferroni correction were applied to examine differences between the three A β groups.

Linear mixed-effects models were used to investigate longitudinal A β and tau-PET accumulation (ADNI and HABS) and cognitive decline (all cohorts) between the three A β groups. Participants who had at least 2 assessments were included in the analysis. Models included random slope and intercept, where the time by subject interaction determined change in cognition or tau. The analyses were anchored at the participant’s baseline visit. For A β and tau accumulation, age and sex were included as covariates in the models, and for cognitive decline, education was further included as a covariate. Post-hoc tests are reported only when there was a significant main effect.

All statistical analyses were conducted using RStudio, version 1.2.5001⁴⁵. The cutoff and mixtools packages (github.com/choisy/cutoff) were used for GMM and lme4⁴⁶ for mixed-effects models. The criterion for statistical significance was $\alpha \leq 0.05$ after correction for multiple comparisons by Tukey’s test.

Results

a. Defining Amyloid Groups based on A β spatial extent

In each cohort, GMMs were fit to the 7 bilateral early A β regions (Figure 1). Region-specific thresholds for all cohorts are presented in detail in Table e-1. In PREVENT-AD, 81 participants (62%) were in the Negative A β group, 28 participants were in the Regional A β group (22%) and 20 exceeded the positivity thresholds in all regions and were placed in the Widespread A β group (16%). Applying the thresholds to the ADNI cohort resulted in 202 (50.5%) in the Negative A β group, 108 (27%) individuals in the Regional A β group and 90 (22.5%) individuals in the Widespread A β group. In the HABS cohort, 139 participants (48%) were in the Negative A β group, 76 (26%) participants in the Regional group and 73 (25%) participants in the Widespread group.

Using a more standard binary classifier of positive/negative based on a global A β , 26 PREVENT-AD participants (20%) would have been classified as A β positive (SUVR 1.37; Centiloid 26.7)³⁵, including all participants in the Widespread group and 6 out of the 28 participants from the Regional group. For ADNI, 137 (34%) participants would have been classified as positive (SUVR 1.1; Centiloid 18.5)^{38,47}, including all participants in the Widespread group and 47 out of 108 participants (43%) of the Regional group. In HABS, all the Widespread participants would have been positive on global A β (SUVR 1.19; Centiloid 23.9)^{40,41} but none of the Regional A β group.

The results presented below were done on all participants. The analyses were repeated when only keeping individuals in the Regional group that would have been classified as A β -negative based on the cohort specific global A β thresholds ($n=22$ for the PREVENT-AD and $n=61$ for ADNI). The results were unchanged when removing A β positive participants from the Regional group (see Table e-2, Figure e-2 & Figure e-3).

b. Biological Markers of Interest

In all three cohorts, the Widespread group was older than the Negative group (PREVENT-AD $F(2, 126) = 3.95, p < 0.05$; ADNI $F(1, 292) = 5.94, p < 0.05$; HABS $F(1, 211) = 3.11, p < 0.05$). Participants in ADNI were also older in the Widespread A β group compared to the Regional A β group [$F(1, 198) = 5.94, p < 0.01$]. While there was no difference in education in both PREVENT-AD and ADNI, the Regional group had higher education compared to Widespread group in HABS [$F(1, 144) = 4.76, p < 0.01$]. Similarly, Widespread groups had greater proportion of females than males compared to compared to the Negative A β group in ADNI [$\chi^2(1, N = 292) = 4.39, p < 0.05$]. However, Regional group in HABS had higher percentage of females compared to Negative group females [$\chi^2(1, N = 211) = 16.54, p < 0.001$].

The Widespread and Regional A β groups had larger proportions of *APOE* $\epsilon 4$ carriers than the Negative A β groups in both the PREVENT-AD (Widespread vs. Negative $\chi^2(1, N = 101) = 8.54, p < 0.01$; Regional vs. Negative $\chi^2(1, N = 109) = 10.8, p < 0.01$) and ADNI (Widespread vs. Negative $\chi^2(1, N = 292) = 29.11, p <$

0.01; Regional vs. Negative χ^2 (1, N = 310) = 5.24, p < 0.05) cohorts (Table 1). In ADNI, the Widespread A β group also had a larger proportion of *APOE* ϵ 4 carriers compare to the Regional A β group [χ^2 (1, N = 198) = 6.98, p < 0.01]. In HABS, only Widespread A β group had larger proportions of *APOE* ϵ 4 carriers than both groups (Widespread vs. Negative χ^2 (1, N = 207) = 40.59, p < 0.001; Widespread vs. Regional χ^2 (1, N = 144) = 16.54, p < 0.001).

CSF biomarker measures were available for 77 PREVENT-AD participants and for 276 ADNI participants. In PREVENT-AD, when compared with the Negative group, both the Regional (F (2, 71) = 24.01, p < 0.001) and Widespread groups (F (2, 71) = 24.01, p < 0.001) had lower CSF A β_{1-42} levels. The Widespread group also had lower CSF A β_{1-42} levels than the Regional group (F (2, 71) = 24.01, p < 0.001). In ADNI, Regional A β (F (2, 275) = 71.76, p < 0.001) and Widespread groups (F (2, 275) = 71.76, p < 0.001) had lower A β_{1-42} levels when compared to the Negative A β group. The Widespread group also had lower CSF A β_{1-42} levels than the Regional group (F (2, 275) = 71.76, p < 0.001).

In PREVENT-AD, CSF p-tau was higher in the Widespread group compared to the Negative group [F (2,76) = 4.70, p < 0.05]. In ADNI, CSF p-tau levels were higher in the Widespread A β group compared to the Regional A β (F (2, 274) = 26.77, p < 0.001) and Negative A β groups (F (2, 274) = 26.77, p < 0.001).

c. Cross-sectional and Longitudinal Cognition

In PREVENT-AD, when compared with the Negative A β group, the Widespread A β group performed worse in Delayed Memory [F (2, 112) = 3.923, p < 0.05] at their baseline visit. There were no differences in baseline cognitive performance between the other groups (Table 3). In ADNI and HABS, there were no differences in baseline cognitive performance between any of the groups (Table 2).

We examined 129 participants with a cognitive assessment follow-up period of up to 8 years from the PREVENT-AD cohort (median follow-up time of 7 [interquartile range (IQR): 2, 8] years), 393 participants with a follow-up period of up to 14 years from the ADNI cohort (median follow-up time of 6 [interquartile range (IQR): 1, 14] years) and 280 participants with a follow-up period up to 9 years from the HABS cohort (median follow-up time of 6 [IQR: 1, 9] years).

In PREVENT-AD, the Widespread A β group experienced greater cognitive decline compared with the Negative A β group and to the Regional group on the Total (β [SE], -0.11 [0.03]; p < 0.001 for Negative; -0.08 [0.04]; p < 0.05 for Regional), Immediate Memory (β [SE], -0.13 [0.05]; p < 0.01; -0.11 [0.05]; p < 0.05 for Regional), and Delayed Memory (β [SE], -0.10 [0.04]; p < 0.05; -0.13 [0.05]; p < 0.01) RBANS index scores (Figure 3). Negative and Regional groups were not different. In ADNI, the Widespread A β group had faster cognitive decline compared with the Negative and the Regional A β groups on Memory (β [SE], -0.10 [0.006]; p < 0.001 for Negative; -0.07 [0.01]; p < 0.001 for Regional), and Executive Function (β [SE], -0.08 [0.008]; p < 0.001 for Negative; -0.06 [0.01]; p < 0.001 for Regional). Although the Regional A β group did not have worse cognitive performance at baseline than the Negative A β group, they experienced greater cognitive decline over the 14 year-follow up period compared to the Negative A β group in Memory (β [SE],

-0.03 [0.006]; $p < 0.001$) and Executive Function (β [SE], -0.03 [0.008]; $p < 0.001$). Similar to Prevent-AD, HABS Widespread A β group experienced greater cognitive decline compared with both the Negative A β group and the Regional A β group on the PACC5 score (β [SE], -0.13 [0.02]; $p < 0.001$ for Negative; -0.09 [0.02]; $p < 0.001$ for Regional) (Figure 3).

d. Longitudinal A β Trajectories

In ADNI, all groups showed A β accumulation rates significantly different from zero over up to 4 years, with a median follow-up time of 3 [interquartile range (IQR): 1, 4] years. The amount of A β accumulation, however, differed between the groups (e-Table 3). The Widespread A β group showed faster A β accumulation over time than the Negative A β group in all the 7 early regions of interest (e-Table 3). The Regional group also showed faster A β accumulation than the Negative A β group in all the 7 early regions of interest (e-Table 3). Interestingly, no difference was found between the Regional and Widespread A β group regarding A β accumulation over time in any of the 7 early regions of interest (e-Table 3).

In HABS, 222 participants with a follow-up period up to 4 years were included in the analysis (median follow-up time of 2 [IQR: 1,4] years). The Widespread group accumulated greater A β compare to Negative group in 6 of the 7 regions of interests (e-Table 3). The Regional group had greater A β accumulation compare to Negative group in the Rostral Anterior Cingulate (β [SE], 0.03 [0.01]; $p < 0.05$), Precuneus (β [SE], 0.03 [0.01]; $p < 0.05$), Medial orbitofrontal (β [SE], 0.03 [0.02]; $p < 0.05$) and in Rostral Middle Frontal (β [SE], 0.04 [0.01]; $p < 0.05$). Widespread group accumulated greater A β only in Rostral Anterior Cingulate (β [SE], 0.05 [0.02]; $p < 0.01$) and Precuneus (β [SE], 0.04 [0.02]; $p < 0.05$) compare to Regional A β group.

e. Cross-sectional and Longitudinal Tau Trajectories

In PREVENT-AD, the Widespread A β group had elevated Tau-PET signal when compared with Negative and Regional A β groups across the five regions investigated (Entorhinal, Amygdala, Fusiform, Inferior Temporal, and Parahippocampal) (Table 2). The Regional A β group had elevated tau-PET binding only in the Entorhinal cortex ($F(2, 128) = 19.21$, $p < 0.05$) and Middle Temporal gyrus ($F(2, 128) = 14.06$, $p < 0.05$) compared with the Negative A β group. In both ADNI and HABS, the Widespread A β group had elevated Tau-PET signal compared with Negative and Regional A β groups across all regions investigated (Table 2) (Figure 2).

The longitudinal analysis showed that in ADNI (median follow-up time of 2 [interquartile range (IQR): 1, 4] years), there is a main effect of A β groups on tau accumulation in Amygdala [$X^2(1) = 10.52$, $p < 0.05$], Fusiform [$X^2(1) = 12.59$, $p < 0.05$], Inferior Temporal [$X^2(1) = 12.80$, $p < 0.05$] and Middle Temporal [$X^2(1) = 16.10$, $p < 0.01$]. The Widespread group accumulated greater tau compare to Negative group in Fusiform (β [SE], 0.02 [0.007]; $p < 0.01$), Inferior Temporal (β [SE], 0.02 [0.008]; $p < 0.01$) and Middle Temporal (β [SE], 0.02 [0.008]; $p < 0.001$). The Widespread group accumulated greater tau compare to Regional group only in Middle Temporal (β [SE], -0.02 [0.008]; $p < 0.05$). In the HABS cohort (median follow-up time of 2 [interquartile range (IQR): 1, 3] years), there is a main effect of A β groups on tau accumulation in the 7 early tau regions of interest (Figure 5). However, only in Amygdala, Fusiform,

Inferior Temporal and Parahippocampal, the Widespread group accumulated greater tau compared to both the Negative A β group and the Regional A β group (Figure 5). In addition, in the Middle temporal, the Widespread group accumulated greater tau only compared to Negative group (β [SE], 0.01 [0.004]; $p < 0.05$). The Regional group did not show any difference from Negative A β regarding tau accumulation over time both in ADNI and HABS.

Discussion

Most Alzheimer's drugs are targeting single disease pathways. Removing A β when tau has already disease progression even if administered in preclinical individuals. One way to identify individuals with A β that do not yet have tau or cognitive decline could be to assess A β spatial extent severity. The hypothesis would be that individuals that have A β -PET binding restricted to few brain regions might not yet have tau and related cognitive decline and therefore be optimal candidates for anti-A β therapies.

We investigated the biological and clinical relevance of A β spatial extent severity on AD biomarkers in three independent cohorts of cognitively normal older adults. We focused on seven regions hypothesized to be early A β accumulating regions^{14,32} and classified participants into Widespread (7 regions with significant A β -PET binding), Regional (1-6 regions with A β -PET binding) and Negative groups. Our results suggest that when A β is spread out throughout the cortex, which in most cases equals being A β positive on classical whole brain measures, tau is also already spread and cognitive decline is prevalent. Individuals with regional binding however do not yet have significant tau or cognitive impairment and are probably ideal candidates for anti-A β clinical trials.

We found that individuals with Regional A β -PET binding have a higher proportion of *APOE* $\epsilon 4$ carriers when compared to individuals with no A β -PET binding in two cohorts out of three. This proportion of *APOE* $\epsilon 4$ carriers reached 64% in the PREVENT-AD cohort, a cohort of cognitively normal individuals with a first-degree family history of AD dementia and therefore with a higher risk to develop the disease themselves. In PREVENT-AD and ADNI, we found a grading effect of (quasi-continuous) A β_{1-42} levels such that participants in the Widespread and Regional groups had decreased CSF A β_{1-42} levels when compared to the Negative group, and the Widespread group had decreased CSF A β_{1-42} levels compared to the Regional group (this information was not available in the HABS cohorts). Furthermore, in ADNI and HABS, the Regional group had greater amount of A β -PET accumulation when compared to the Negative group (information that was not available in the PREVENT-AD cohort). Of interest, however, the Regional groups showed no or very little tau-PET binding and no baseline cognitive impairment. While these findings suggest that the regional A β PET-binding signal is biologically relevant, they also suggest that widespread A β is necessary to detect tau-PET signals outside of the entorhinal cortex and significant cognitive impairment.

Continuous variables are often dichotomized in the clinic to provide a straightforward diagnosis or identify patients that would benefit from treatment⁴⁸. They are also used in research to simplify the interpretation of results and provide empirical evidence for clinical practice. The most common approach

to analyzing A β -PET is to classify individuals into two groups, A β -negative and A β -positive. This approach is not always optimal to detect individuals with early A β levels, mainly if A β has accumulated regionally but is not yet globally widespread^{32,47}. There is a growing body of literature documenting the earliest topographical distribution of A β -PET binding in individuals with and without cognitive impairment^{15,18,49}. We took advantage of this literature to identify seven regions with early detectable A β -PET binding, and instead of classifying our participants on a “global” A β index, we dichotomized A β positivity/negativity within each of these regions and counted the number of regions with positive A β -PET binding. While PREVENT-AD, most of the participants with regional binding (79%) would have been classified as negative using a “global” A β index, all the Regional A β group participants in HABS would have been classified as negative. This number was slightly lower in ADNI (57%), which can probably be explained by the fact that their global threshold is slightly lower than what was used in the PREVENT-AD (centiloid 26.7 vs 18.5) and HABS (centiloid 23.9 vs 18.5).

Anti-A β therapeutic trials have failed to improve or slow down cognitive symptoms^{8,50,51}. The association of cognition and neuronal loss is stronger with the tau-PET signal compared to A β ⁵². The failure of these trials could be partly due to the inclusion of individuals who already have elevated tau-PET signals. Our results showed that cognitively normal individuals with widespread A β , which would most have been considered A β -positive using a classical global threshold, have detectable tau-PET signals in several temporal brain regions. Interestingly, elevated tau PET-binding was absent (ADNI and HABS) or restricted to the entorhinal and the middle temporal cortices (PREVENT-AD) in individuals showing regional A β -PET. Binding in the entorhinal cortex is common with advanced age⁵³. Furthermore, the Widespread A β groups in ADNI and HABS accumulated greater amount of tau compared to the Negative and Regional group over longitudinal follow-ups. The CSF data corroborate these findings in ADNI and PREVENT-AD cohorts, with CSF p-tau being higher in the Widespread group compared to the two other groups, with an absence of significant differences between the Regional and the Negative groups. Previous studies have shown that when A β pathology reaches “widespread” spatial distribution, tau-PET uptake increases faster compared to the individuals with lower A β ⁵⁴, and the rate of tau-PET change is associated with cognitive decline⁵⁵. In line with these results, baseline cognitive impairment was only found in the Widespread groups, and cognitive decline was also mainly restricted to the Widespread groups. The ADNI regional group also showed a cognitive decline when compared to the Negative group after a decade of follow-up, by which time most Regional individuals probably developed Widespread A β binding¹⁴.

Furthermore, our findings highlight the biological relevance of the Regional A β group. Our result showed that the Regional A β groups had intermediate CSF A β_{1-42} levels between the Widespread (lower A β_{1-42}) and Negative (higher A β_{1-42}) A β groups, showing signs of incipient cerebral accumulation of A β ⁵⁶. Even though A β increases with older age, Regional A β group participants were in the same age range as the Negative A β group, which was younger than the Widespread A β group in all cohorts. Furthermore, the Regional A β groups in ADNI and HABS accumulated greater amount of A β compared to the Negative group. Another crucial difference between groups was marked by *APOE* ϵ 4 carrier status; compared to the Negative A β group, both Regional and Widespread A β groups had higher percentages of *APOE* ϵ 4 carriers

in two cohorts, which places them at increased risk for developing the disease⁵⁷. There is an increasing interest in the biological relevance of regional A β and the assessment of regional patterns^{15,16}. Recent studies have shown decreased CSF A β_{1-42} levels in participants with regional A β ^{18,58}, as well as higher proportions of *APOE* ϵ 4 carriers, compared to A β negative participants⁵⁹. Even in individuals categorized as A β negative, subthreshold A β predicted a slight memory decline⁶⁰ and the development of tau pathology over five years⁶¹. *APOE* ϵ 4 carriership has also been associated with increased A β load compared to non-carriers across all clinical diagnostic groups⁶². Taken together, our findings highlight the biological relevance of the Regional A β group, for which tau and cognitive impairments are still minimal. Therefore, most individuals with regional A β binding are at the earliest stage of the AD continuum and only a few years away from when cognitive decline is about to start.

There are several limitations to take into account. An important factor that may have impacted the current study results is the A β groups' disproportion due to the small sample size of the Widespread and Regional groups in PREVENT-AD. More than 63% of the cohort were in the Negative A β group, which led to the Regional and Widespread groups consisting of less than 30 individuals each. To address this limitation and to validate the results, the ADNI cohort with 400 participants and the HABS cohort with 288 participants were included in the study. ADNI, however, used the Florbetapir tracer, for which it might be more difficult to establish clear dichotomized values given the high variability related to white matter signal⁶³. In addition, previous studies also reported that this tracer had shown a low correlation between tracer-specific regional rankings compared to four other tracers^{41,58}. Despite the differences in the study designs, it is nevertheless important to mention that most of the results across cohorts were comparable.

In conclusion, assessing the spatial A β burden could be a powerful way to identify the best candidates for preventive clinical trials. Assessing the presence of A β -PET binding in early accumulating regions can help identify individuals with biologically relevant signals that would have been classified as being negative using more established whole-brain thresholds for A β positivity. While these individuals accumulate A β over time, they do not yet have significant tau or cognitive decline. In individuals with widespread A β (most of whom would have been included in current clinical trials), tau pathology might be too advanced to stop the cognitive decline or disease progression after the removal of the A β plaques from the brain. Our results suggest that anti-A β trials should be performed in individuals with regional binding at the latest since even individuals classified as being Negative showed A β -PET binding accumulation over time

Declarations

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Author Contributions

Hazal Ozlen: study concept and design, analysis, and interpretation of data, drafting and revision of the manuscript.

Alexa Pichet-Binette: study concept and design, analysis and interpretation of data, revision of the manuscript.

Theresa Köbe: data analysis, revision of the manuscript.

Pierre Francois Meyer: data analysis, revision of the manuscript.

John Breitner: data acquisition, protocol concept and design.

Judes Poirier: data acquisition, protocol concept and design, revision of the manuscript.

Sylvia Villeneuve: data acquisition, study concept and design, interpretation of data, revision of the manuscript.

Ethics declarations

Competing Interests

The authors declare no competing interests.

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Tables

Table 1. Biological and Clinical Characteristics of A β groups.

	PREVENT-AD A β Groups				ADNI A β Groups				HABS A β Groups			
	Negative (n = 81)	Regional (n = 28)	Widespread (n = 20)	<i>p</i> < 0.05	Negative (n = 202)	Regional (n = 108)	Widespread (n = 90)	<i>p</i> < 0.05	Negative (n = 139)	Regional (n = 76)	Widespread (n = 73)	<i>p</i> < 0.05
Age	63 (0.51)	63 (0.87)	66 (1.03)	<i>b</i>	73 (0.41)	73 (0.57)	76 (0.62)	<i>b,c</i>	73 (0.52)	74 (0.70)	75 (0.72)	<i>b</i>
Education	16 (0.36)	15 (0.61)	14 (0.72)		17 (0.19)	17 (0.26)	16 (0.28)		16 (0.26)	15 (0.35)	16 (0.35)	<i>c</i>
Sex, female (%)	60 (74%)	23 (82%)	13 (65%)		94 (47%)	61 (57%)	55 (61%)	<i>b</i>	75 (54%)	55 (72%)	41 (56%)	<i>a</i>
<i>APOE</i> ϵ 4 carriership (%)	22 (27%)	18 (64%)	13 (65%)	<i>a, b</i>	38 (19%)	34 (31%)	45 (50%)	<i>a,b,c</i>	20 (14%)	18 (24%)	41 (56%)	<i>b,c</i>
CSF A β ₁₋₄₂ *	1265 (37.78)	1043 (60.09)	718 (71.53)	<i>a,b,c</i>	1448 (30.13)	1158 (40.07)	802 (45.69)	<i>a,b,c</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	
CSF pTau*	46 (3.14)	55 (4.89)	67 (6.15)	<i>b</i>	19 (0.72)	22 (0.96)	29 (1.10)	<i>b,c</i>	<i>n/a</i>	<i>n/a</i>	<i>n/a</i>	

The values are reported as Mean (SD) except for Sex, *APOE* ϵ 4, and Subjective Cognitive Decline which are reported as the Number of participants (% of the group). BOLD text represents the groups between which there were significant differences: a = *p* < 0.05 between Negative A β and Regional A β groups; b = *p* < 0.05 between Negative A β and Widespread A β groups; c = *p* < 0.05 between Regional A β and Widespread A β groups. *In PREVENT-AD, CSF samples were available for 46 Negative, 19 Regional, and 12 Widespread; in ADNI, CSF samples were available for 138 Negative, 78 Regional and 60 Widespread. *APOE* ϵ 4: Apolipoprotein ϵ 4; A β : beta-amyloid; CSF: Cerebrospinal fluid.

Table 2. Tau-PET Uptake in Early Tau Regions

A. PREVENT-AD	Negative A β (n = 81)	Regional A β (n = 28)	Widespread A β (n = 20)	P<0.05
Entorhinal	1.04 (0.01)	1.10 (0.02)	1.22 (0.03)	<i>a,b,c</i>
Amygdala	1.26 (0.02)	1.28 (0.03)	1.44 (0.03)	<i>b,c</i>
Fusiform	1.20 (0.01)	1.25 (0.02)	1.35 (0.03)	<i>b,c</i>
Inferior Temporal	1.13 (0.01)	1.18 (0.02)	1.30 (0.03)	<i>b,c</i>
Middle Temporal	1.11 (0.01)	1.18 (0.02)	1.25 (0.02)	<i>a,b</i>
Parahippocampal	1.06 (0.01)	1.10 (0.02)	1.18 (0.02)	<i>b,c</i>
B. ADNI	Negative A β (n = 91)	Regional A β (n = 54)	Widespread A β (n = 31)	
Entorhinal	1.10 (0.01)	1.13 (0.02)	1.24 (0.03)	<i>b,c</i>
Amygdala	1.19 (0.02)	1.20 (0.02)	1.32 (0.03)	<i>b,c</i>
Fusiform	1.16 (0.01)	1.17 (0.02)	1.29 (0.02)	<i>b,c</i>
Inferior Temporal	1.18 (0.02)	1.20 (0.02)	1.33 (0.03)	<i>b,c</i>
Middle Temporal	1.13 (0.01)	1.17 (0.02)	1.27 (0.02)	<i>b,c</i>
Parahippocampal	1.07 (0.01)	1.09 (0.02)	1.18 (0.02)	<i>b,c</i>
C. HABS	Negative A β (n = 99)	Regional A β (n = 48)	Widespread A β (n = 48)	
Entorhinal	1.09 (0.01)	1.12 (0.02)	1.22 (0.02)	<i>b,c</i>
Amygdala	1.26 (0.01)	1.29 (0.02)	1.39 (0.02)	<i>b,c</i>
Fusiform	1.19 (0.01)	1.20 (0.01)	1.27 (0.01)	<i>b,c</i>
Inferior Temporal	1.18 (0.01)	1.18 (0.01)	1.28 (0.01)	<i>b,c</i>
Middle Temporal	1.12 (0.01)	1.13 (0.01)	1.19 (0.01)	<i>b,c</i>
Parahippocampal	1.11 (0.01)	1.12 (0.01)	1.20 (0.01)	<i>b,c</i>

Using ANCOVA and multiple comparisons corrected for age and sex, we test whether Tau-PET uptake in early tau regions significantly differed between the A β groups in the (A) PREVENT-AD cohort, (B) ADNI cohort and (C) HABS cohort. For post-hoc analysis, Bonferroni correction was applied when comparing the pair of group means. BOLD text represents the significant between-group differences. a = p<0.05 between Negative A β and Regional A β Groups; b = p<0.05 between Negative A β and Widespread A β Groups; c = p<0.05 between Regional A β and Widespread A β Groups.

Table 3. Baseline Cognition

A. PREVENT-AD	Negative A β (n = 81)	Regional A β (n = 28)	Widespread A β (n = 20)	P<0.05
Immediate Memory Score	103.15 (1.26)	104.82 (2.14)	104.05 (2.54)	
Delayed Memory Score	104.28 (1.02)	100.71 (1.73)	97.20 (2.05)	<i>b</i>
Total Index Score	102.98 (1.06)	102.61 (1.81)	101.30 (2.15)	
B. ADNI	Negative A β (n = 202)	Regional A β (n = 108)	Widespread A β (n = 90)	
Memory Score	1.08 (0.04)	1.11 (0.05)	0.95 (0.06)	
Executive Function Score	0.95 (0.06)	0.84 (0.08)	0.62 (0.08)	
C. HABS	Negative A β (n = 137)	Regional A β (n = 73)	Widespread A β (n = 70)	
PACC5	0.04 (0.06)	-0.09 (0.08)	0.01 (0.08)	

gCognitive test scores were compared at the baseline visit corrected for age and sex; test scores are reported as Mean (SD). **(A)** As part of the PREVENT-AD battery, all participants undergo annual cognitive testing using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). **(B)** In ADNI, participants received detailed cognitive assessments from which composite scores are derived. All the composite scores have a mean of 0, and a standard deviation of 1. **(C)** HABS participants undergo annual cognitive testing with PACC5 to derive a cognitive composite score including memory, executive function and semantic processing. BOLD text represents the significant between-group differences: a = $p < 0.05$ between Negative A β and Regional A β groups; b = $p < 0.05$ between Negative A β and Widespread A β groups; c = $p < 0.05$ between Regional A β and Widespread A β groups.

Figures

Figure 1

Defining the A β Groups. Individuals were separated into three groups based on their A β status in seven cortical regions: rostral anterior cingulate, precuneus, medial orbitofrontal, rostral middle frontal, inferior parietal, superior frontal, and posterior cingulate. According to the region-specific positivity, individuals who were A β -positive in all 7 regions were classified as the “Widespread A β group”; those who were positive in at most 6 regions were included in the “Regional A β group”, while those negative in all the regions were considered as the “Negative A β group”.

Figure 2

Tau-PET Uptake Across the 3 A β groups. Six regions were chosen to represent areas of early tau-PET accumulation³⁵. Tau-PET scans were available for 129 PREVENT-AD participants and 176 ADNI participants. (A) In PREVENT-AD, the Widespread A β group had elevated Tau-PET signal when compared with Negative and Regional A β groups across six regions. The Regional A β group had elevated tau-PET binding only in the Entorhinal cortex and Middle Temporal gyrus when compared with the Negative A β group. (B; C) In both ADNI and HABS, the Widespread A β group had elevated Tau-PET signal compared with Negative and Regional A β groups across all regions. One PREVENT-AD Regional participant and one PREVENT-AD Widespread participant were considered influential cases based on their Cook's distance. Removing these participants did not influence the results. Analyses were corrected for age and sex. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. SUVR: standardized uptake value ratio.

Figure 3

Change in Cognition Over Time Between the three A β Groups. Linear mixed-effect models were used to assess the main effect of A β groups on longitudinal cognition, corrected for age, sex and education. The analyses were anchored at the participants' baseline visit date. Cognitive test scores (A) for PREVENT-AD; (B) for ADNI; and (C) for HABS were represented over time in the three different groups. The Widespread A β group showed a greater decline in their cognition scores when compared with the two other groups in all cohorts. In both ADNI and HABS, the Regional group showed a greater cognitive decline compared to the Negative group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

A. ADNI

B. HABS

Figure 4

Change in Aβ Uptake Over Time Between the three Aβ Groups in ADNI and HABS. Linear mixed-effect models investigating the effect of the groups on Aβ accumulation rate over time in ADNI and HABS cohorts corrected for age and sex. Plotted is the association between Aβ groups based on (A) Precuneus SUVR score and (B) Medial orbitofrontal SUVR score over the years from their first scan. While both the Regional and Widespread Aβ groups accumulated Aβ at a faster rate compared to the Negative Aβ group

in both cohorts; while only in HABS, the Widespread group accumulated A β at a faster rate compared to the Regional A β group in Precuneus. * p<0.05; ** p<0.01; ***p<0.001; etc. SUVR: standardized uptake value ratio.

Figure 5

Change in TAU Uptake Over Time Between the three A β Groups in ADNI and HABS. Linear mixed-effect models investigating the effect of the groups on tau accumulation rate over time in ADNI and HABS cohorts corrected for age and sex. Plotted is the association between A β groups based on Fusiform, Inferior Temporal and Middle Temporal SUVR scores over the years from their first scan. In both cohorts, the Widespread group accumulated a greater amount of tau compare to the Negative group. However, only in Fusiform and Inferior Temporal (in HABS) and Middle Temporal (in ADNI) regions, compared to the Regional A β group, Widespread group accumulated a greater amount of tau. * p<0.05; ** p<0.01; ***p<0.001; etc. SUVR: standardized uptake value ratio.

Supplementary Files

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