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ARTICLE

Intermediate flortaucipir uptake is associated with Aβ-PET and CSF-tau in asymptomatic adults

Melissa McSweeney, MSc,* Alexa Pichet Binette, MSc,* Pierre-François Meyer, PhD, Julie Gonneaud, PhD, Christophe Bedetti, MSc, Hazal Ozlen, BSc, Anne Labonté, BSc, Pedro Rosa-Neto, MD, PhD, John Breitner, MD, MPH, Judes Poirier, PhD, and Sylvia Villeneuve, PhD, for the PREVENT-AD Research Group

Correspondence
Dr. Villeneuve
sylvia.villeneuve@mcgill.ca

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Abstract

Objective

To investigate relationships between flortaucipir (FTP) uptake, age, and established Alzheimer disease (AD) markers in asymptomatic adults at increased risk of AD.

Methods

One-hundred nineteen individuals with a family history of AD (Presymptomatic Evaluation of Experimental or Novel Treatments of Alzheimer's Disease [PREVENT-AD] cohort, mean age 67 ± 5 years) underwent tau-PET ([^{18}F]FTP), β-amyloid (Aβ)-PET ([^{18}F]NAV4694 [NAV]), and cognitive assessment. Seventy-four participants also had CSF phosphorylated tau and total tau data available. We investigated the association between age and FTP in this relatively young cohort of older adults. We also investigated regional FTP standardized uptake value ratio (SUVR) differences between Aβ-positive and Aβ-negative individuals and regional correlations between FTP and NAV retention. In cortical regions showing consistent associations across analyses, we assessed whether FTP was in addition related to CSF tau and cognitive performance. Lastly, we identified the lowest FTP value at which associations with Aβ-PET, CSF, and cognition were detectable.

Results

Increased age was associated only with amygdala and transverse temporal lobe FTP retention. Aβ-positive individuals had higher FTP SUVR values in several brain regions, further showing correlation with NAV load through the cortex. Increased FTP SUVRs in medial temporal regions were associated with increased CSF tau values and worse cognition. The SUVRs at which associations between entorhinal FTP SUVR and other AD markers were first detected differed by modality, with a detection point of 1.12 for CSF values, 1.2 for Aβ-PET, and 1.4 for cognition.

Conclusions

Relatively low FTP-PET SUVRs are associated with pathologic markers of AD in the preclinical phase of the disease. Adjustment in the tau threshold should be considered, depending on the purpose of the tau classification.

*These authors contributed equally to this work.

From the Departments of Psychiatry (M.M., A.P.B., P.-F.M., J.G., H.O., P.R.-N., J.B., J.P., S.V.) and Neurology & Neurosurgery (P.R.-N., S.V.), McGill University; Douglas Mental Health University Institute (M.M., A.P.B., J.G., P.-F.M., C.B., H.O., A.L., P.R.-N., J.B., J.P., S.V.); and McConnell Brain Imaging Center, Montreal Neurological Institute (S.V., P.R.-N.), Montreal, Quebec, Canada.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

PREVENT-AD Research Group coinvestigators are listed in Appendix 2 at the end of the article.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **FTP** = flortaucipir; **NAV** = [^{18}F]NAV4694; **p-tau** = phosphorylated tau; **PREVENT-AD** = Presymptomatic Evaluation of Experimental or Novel Treatments of Alzheimer's Disease; **RBANS** = Repeatable Battery for the Assessment of Neuropsychological Status; **ROI** = region of interest; **SUVR** = standardized uptake value ratio.

Alzheimer disease (AD) is characterized by the pathologic accumulation of β-amyloid (Aβ) and tau proteins starting decades before the onset of clinical impairment.[1–3] It is critical to understand the role of early pathology accumulation for preventive purposes. Tau-PET radiotracers such as [^{18}F]flortaucipir (FTP) have recently permitted investigation of the topologic distribution and progression of tau in vivo.[4–9] Little is known about the clinical validity of relatively low levels of tracer retention among cognitively normal individuals.[10]

To improve our understanding of early FTP-PET uptake and its implications in presymptomatic AD, we investigated associations between FTP retention and other validated AD biomarkers in a relatively young cohort of asymptomatic older adults with at least 1 first-degree relative diagnosed with sporadic AD. A family history of AD increases an individual's risk by 1.7- to 14.8-fold, depending on the number of first-degree relatives affected.[11] Given the slow progression of the disease and the fact that most individuals are diagnosed in their late 70s to early 80s,[12] older adults in their mid-60s are the optimal target population for studying early tau manifestations.

We first evaluated the association between Aβ-PET and FTP retention. We then assessed the relationships between regional FTP retention and CSF phosphorylated (p)-tau, total tau, and cognitive performance in brain regions where FTP retention was found to be associated with Aβ-PET. Finally, we evaluated whether our findings were driven by only a few individuals with high FTP SUVRs or if intermediate values are also biologically meaningful.

Methods

Participants

The present study included 119 cognitively normal late-middle-aged and older adults from the Presymptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) cohort.[13] PREVENT-AD is a longitudinal study of individuals who have a parent or at least 2 siblings diagnosed with AD-type dementia. Participants were required (1) to be at least 60 years of age or between 55 and 59 if their age was 15 or fewer years younger than their first-affected relative's age at dementia onset, (2) to have no history of major neurologic or psychiatric disorders, and (3) to test as cognitively normal on neuropsychological evaluation with clinical review.

Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Board at McGill University. All participants provided written informed consent before participation.

Data availability

All anonymized data and relevant documentation from this study can be made available to qualified investigators on request. Such an arrangement will be subject to a standard data-sharing agreement.

Image acquisition

FTP ([^{18}F]AV1451, Eli Lilly & Co, Indianapolis, IN) and [^{18}F]NAV4694 (NAV; Navidea Biopharmaceuticals, Dublin, OH) were used to quantify the accumulation of tau and Aβ proteins in the brain. Most PET scans were carried out on 2 consecutive days, and all were acquired no more than 5 months apart (mean delay between PET scans 4.24 ± 16.7 days). Imaging was performed at the McConnell Brain Imaging Centre at the Montreal Neurologic Institute (Montreal, Quebec, Canada) between February 2017 and June 2018. Aβ scans were performed 40 to 70 minutes after injection (≈6 mCi) and tau scans 80 to 100 minutes after tracer injection (≈10 mCi). T1-weighted structural MRI scans had been acquired ≈1 year before the PET scans (mean delay 8.9 ± 4.8 months) on a 3T Siemens Trio scanner (Siemens, Munich, Germany) at the Brain Imaging Centre of the Douglas Mental Health University Institute (Montreal, Quebec, Canada) with the following parameters: repetition time of 2300 milliseconds, echo time of 2.98 milliseconds, 176 slices, and 1-mm slice thickness.

Image processing

T1-weighted MRIs were processed through FreeSurfer version 5.3[14] and parcellated according to the Desikan-Killiany atlas.[15] PET images were processed with a standard pipeline (github.com/villeneuvelab/vlpp). Briefly, the 4D PET images (5 minutes × 4 frames for FTP and 5 minutes × 6 frames for NAV) were realigned, averaged, and registered to the corresponding T1-weighted MRI. Registered PET images were then masked to exclude CSF signal and finally smoothed using a gaussian kernel of 6 mm^3. Standardized uptake value ratios (SUVRs) used cerebellum gray matter as the reference region for NAV scans[16,17] and the inferior cerebellum gray matter for FTP scans.[18] Our analyses included the average FTP SUVRs of 34 bilateral FreeSurfer brain regions of interest (ROIs). The hippocampus (i.e., Braak II), thalamus, and striatum were not included in the main analyses analyses due to nonspecific tracer retention.[19,20] Analyses were conducted with and without correction for partial volume effect,[18] and results were similar. Data without partial

volume correction are presented in the text. Results with partial volume-corrected data (including the hippocampus) are available on Dryad (tables e-1–e-3, doi.org/10.5061/dryad.4q4h8q1).

Amyloid-positivity threshold

To quantify a global Aβ SUVR for each participant, we calculated the average SUVR from the precuneus, posterior cingulate, parietal lobe, frontal lobe, and lateral temporal regions.[16,17] A global Aβ threshold was derived with a 2-component gaussian mixture model,[16] yielding an estimated threshold of 1.37 (data available from Dryad, figure e-1, doi.org/10.5061/dryad.4q4h8q1). The threshold corresponds to an observation having a 90% probability of belonging to the lower Aβ distribution and a 10% probability of belonging to the higher Aβ distribution. This conservative threshold was chosen to reduce the number of false positives, but we cannot exclude the possibility that some individuals classified as Aβ negative might in fact be Aβ accumulators or have meaningful subthreshold levels of Aβ. We used the cutoff R package (github.com/choisy/cutoff) to derive the estimated positivity threshold and the mixtools R package (cran.rstudio.com/web/packages/mixtools/mixtools.pdf) to confirm the probabilities of each observation. Twenty participants were classified as being Aβ+.

CSF analyses

A subsample of 74 individuals had undergone a lumbar puncture up to 4.5 years before their PET scans (mean delay 8.9 ± 9.8 months). Because of the range and variance of time differences between these 2 measurements, the time between lumbar puncture and PET was included as a covariate in all CSF-related analyses.

CSF p-tau (phosphorylated at threonine 181) and CSF total tau levels were determined with a previously described protocol.[21] In brief, lumbar punctures were performed the morning after an overnight fast, and CSF was stored in cryovial tubes at −80°C. CSF p-tau and total tau levels were assayed in duplicate with the INNOTEST ELISA (Fujirebio, Ghent, Belgium).

Neuropsychological testing

Each participant underwent a cognitive evaluation with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[22] within the year before the PET scans (mean delay 3.9 ± 3.2 months). The RBANS comprises 12 subtests assigning performance to 5 cognitive domains: Immediate Memory (list learning and story memory), Visuospatial/Constructional Skills (figure copy and line orientation), Language (picture naming and semantic fluency), Attention (digit span and coding), and Delayed Memory (list recall, list recognition, story recall, and figure recall). Age-scaled index scores were calculated for each cognitive domain. The 5 index scores and the Total Scaled Index Score were used in the present study to assess the relationship between FTP retention and cognitive performance.

Statistical analyses

We first compared demographic and clinical characteristics of the whole cohort (n = 119) with the subset of participants with CSF assays (n = 74) using 2-tailed Wilcoxon rank-sum tests and χ^2 tests for continuous and categorical measures, respectively. All regression models were implemented in R 3.4.1, RStudio version 1.1.383. Partial Pearson correlation coefficients were obtained with the ppcor R package (cran.r-project.org/web/packages/ppcor/index.html). The criterion for statistical significance was $\alpha \leq 0.05$ after correction for multiple comparisons. The p values from the linear models were calculated through a permutation procedure with 1,000 iterations and subsequently corrected for multiple comparisons with the Benjamini-Hochberg false discovery rate.[23] The permutation procedure has the advantage of limiting the influence of outliers or variance differences.[24]

Age-related increase in FTP retention

Given that tau accumulation, especially in the early Braak regions, is known to increase with age (i.e., independently from AD-related processes),[25] we first investigated the relationships between age and FTP SUVR in the 34 FreeSurfer brain regions (outcome variable).

Aβ and FTP associations

To determine whether Aβ+ individuals had higher FTP retention than Aβ− individuals, we analyzed the association between Aβ status (independent variable) and FTP SUVR in the 34 FreeSurfer brain regions (outcome variable) via independent linear models controlling for age and sex. To evaluate the effect size of FTP retention between Aβ+ and Aβ− participants, we calculated the Cohen *d*.

To further explore the association between Aβ and potential tau burden, we ran Pearson correlation tests between regional FTP SUVRs and regional NAV SUVRs across the 34 brain regions. We ran complete linkage hierarchical clustering to identify the regions where the associations between FTP and NAV showed similar retention patterns across regions. The regions showing consistent associations with Aβ burden in both of these analyses (higher FTP retention in Aβ+ vs Aβ− and correlating with regional NAV SUVRs) were retained as ROIs (FTP-ROIs) for subsequent analyses because they likely represent early AD-related tau pathology.

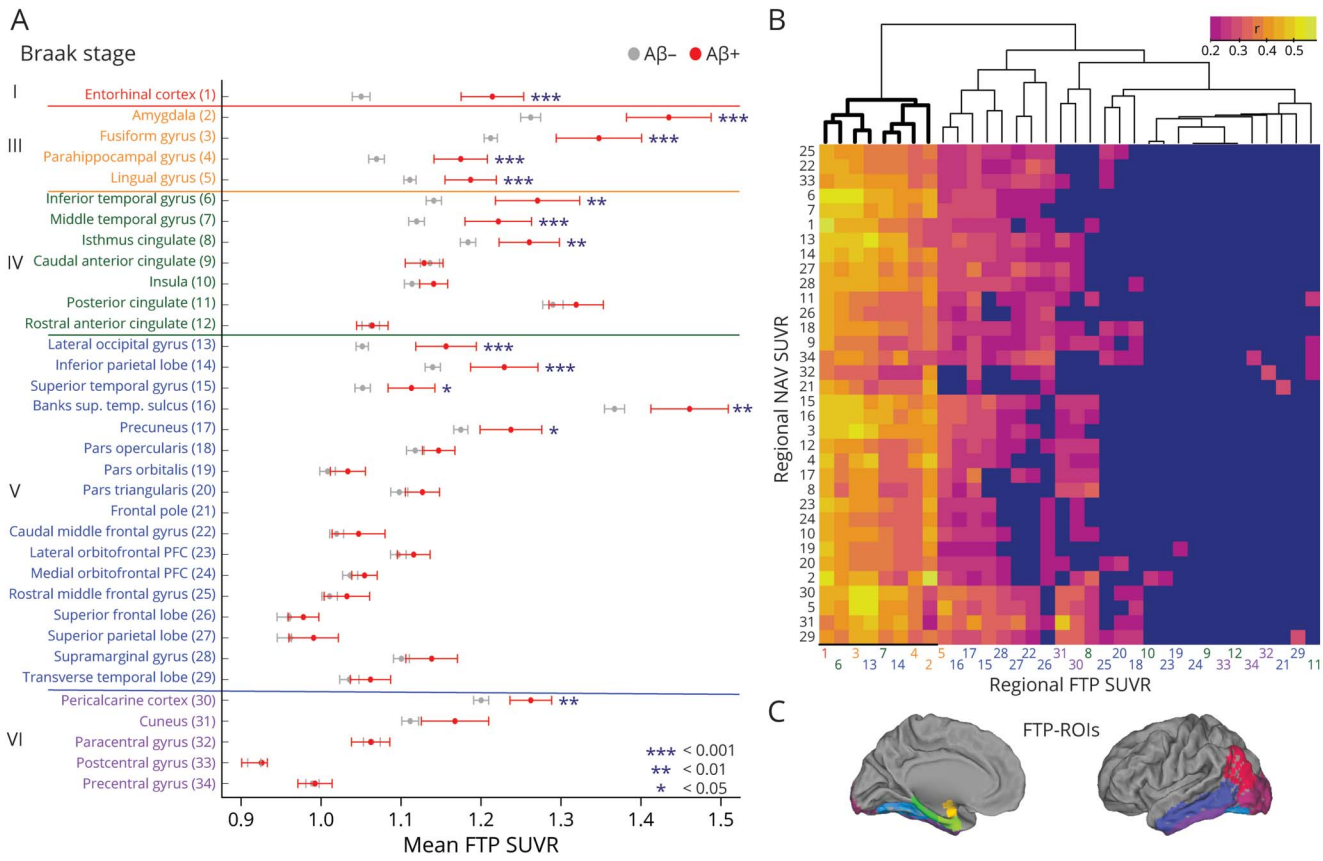
CSF tau and FTP associations

Next, we assessed whether FTP SUVRs in the FTP-ROIs were related to CSF p-tau and CSF total tau (independent variables) using linear regressions controlling for age, sex, and years between lumbar puncture and PET scan acquisition. Box-Cox transformation was applied to CSF p-tau and total tau data to fulfill normality assumptions.

Cognition and FTP associations

Similarly, we assessed whether FTP SUVR (independent variable) was related to age-scaled RBANS index scores (outcome variable) in the FTP-ROIs using independent linear regressions controlling for sex and education. Box-Cox transformation was applied to each of the cognitive domains to fulfill normality assumptions.

Figure 1 Higher FTP uptake in several medial and lateral posterior cortical regions is associated with NAV retention



(A) Mean flortaucipir (FTP) standardized uptake value ratios (SUVRs) across the FreeSurfer Desikan regions, organized and color-coded by Braak stages, in global β-amyloid (Aβ)–positive (red) and global Aβ-negative (gray) groups and their respective standard error bars. Asterisks indicate the regions in which FTP retention is higher in the Aβ+ group than the Aβ− group (after false discovery rate [FDR] correction). (B) Heat plot of the regional Pearson correlation coefficients between regional FTP retention and regional [^{18}F]NAV4694 (NAV) retention. Cells in dark blue represent regions with correlation test *p* values that did not survive FDR correction. We applied complete linkage hierarchical clustering to correlation coefficients surviving FDR correction to identify regions with similar FTP-NAV uptake correlation patterns. Regions are labeled with numbers corresponding to the numbers in panel A, and the FTP regions are color-coded by Braak stage corresponding to panel A. The dendrogram branches of the most consistent FTP-Aβ associations clustered together and are emphasized in bold. (C) Projected onto a brain template are the 8 FTP regions of interest (ROIs) that showed a reliable pattern between the group analyses presented in panel A and the cluster analysis presented in panel B. These 8 regions showed increased FTP uptake in the analyses comparing Aβ+ to Aβ−; they are also the brain regions showing the highest and most consistent regional associations between NAV and FTP and are the focus of the subsequent analyses. PFC = prefrontal cortex.

Table 1 Demographics summary

	Whole cohort (n = 119)	CSF subsample (n = 74)	Statistic	*p* Value
Mean age, y	67.5 ± 4.8	67.2 ± 4.8	4,639.5	0.53
Female, % (n)	73.9 (88)	69 (51)	2.57	0.14
***APOE* ε4+, % (n)**	40.3 (48)	41 (30)	0.03	1.00
Mean ± SD spEYO	−5.95 ± 7.7	−6.15 ± 7.4	3,847	0.62
Mean ± SD global Aβ SUVR	1.31 ± 0.32	1.3 ± 0.26	4,186	0.57
Mean ± SD EC tau SUVR	1.08 ± 0.14	1.08 ± 0.14	4,327.5	0.84
Mean ± SD education, y	15.1 ± 3.2	14.8 ± 2.9	4,656	0.50

Abbreviations: Aβ = β-amyloid; EC = entorhinal cortex; spEYO = years to estimated symptom onset (sporadic AD) (participant's age − age of relative at symptom onset); SUVR = standardized uptake value ratio.
Demographic and clinical characteristics of the cohort comparing the whole cohort and the subsample of 74 individuals with CSF data. Wilcoxon rank-sum tests were performed on continuous measures (statistic = Wilcoxon W), and χ^2 (statistic = χ^2) was performed on categorical measures. There are no significant differences between the whole cohort and the CSF subsample.

Table 2 Table of statistics for FTP uptake in Aβ+ vs Aβ− individuals

	ROI	*p* Value	Cohen *d*	*t* Score
Braak I	Entorhinal cortex	<0.001[a]	1.121	5.311
Braak III	Amygdala	<0.001[a]	0.916	4.524
	Fusiform gyrus	<0.001[a]	0.757	4.617
	Parahippocampal gyrus	<0.001[a]	0.834	4.101
	Lingual gyrus	<0.001[a]	0.663	3.885
Braak IV	Inferior temporal gyrus	0.001[a]	0.722	4.113
	Middle temporal gyrus	<0.001[a]	0.688	3.587
	Isthmus cingulate	0.004[a]	0.559	2.891
	Caudal anterior cingulate	0.973	−0.064	−0.039
	Insula	0.264	0.313	1.158
	Rostral anterior cingulate	0.883	0.020	0.135
	Posterior cingulate	0.341	0.208	0.936
Braak V	Lateral occipital gyrus	<0.001[a]	0.798	4.662
	Inferior parietal lobe	<0.001[a]	0.601	3.386
	Superior temporal gyrus	0.011[a]	0.533	2.649
	Banks of the superior temporal sulcus	0.004[a]	0.531	2.830
	Precuneus	0.017[a]	0.457	2.560
	Frontal pole	0.271	0.246	1.116
	Caudal middle frontal gyrus	0.261	0.227	1.153
	Lateral orbitofrontal PFC	0.432	0.205	0.817
	Medial orbitofrontal PFC	0.438	0.215	0.813
	Rostral middle frontal gyrus	0.306	0.191	1.070
	Superior frontal lobe	0.243	0.301	1.205
	Superior parietal lobe	0.098	0.316	1.747
	Supramarginal gyrus	0.122	0.305	1.671
	Transverse temporal lobe	0.137	0.227	1.499
	Pars opercularis	0.223	0.290	1.222
	Pars orbitalis	0.344	0.260	0.960
	Pars triangularis	0.243	0.288	1.197
Braak VI	Pericalcarine cortex	0.008[a]	0.586	3.071
	Cuneus	0.03	0.368	2.355
	Paracentral gyrus	0.958	−0.013	−0.045
	Postcentral gyrus	0.766	0.003	0.303
	Precentral gyrus	0.757	0.035	0.273

Abbreviations: Aβ = β-amyloid; FTP = flortaucipir; PFC = prefrontal cortex; ROI = region of interest.
Corresponds to figure 1. Desikan FreeSurfer regions are organized by their respective Braak stage. The *p* values of regions with significantly elevated tau in Aβ+ vs Aβ− individuals that survive false discovery rate (FDR) correction are indicated. The reported *t* scores are the raw scores from the nonpermuted regressions, and the reported *p* values are from permutations before FDR correction.
[a] Significant *p* values and corresponding regions that survived FDR correction.

FTP SUVR detection points

As a last step, we ranked participants according to their FTP SUVRs and reran our linear regressions by progressively (i.e., iteratively) removing the individuals with the highest FTP SUVR until the association between FTP SUVRs and the AD markers was lost, here referred to as FTP SUVR detection points. These analyses were performed to evaluate whether associations between AD biomarkers and FTP retention were driven by high FTP SUVRs (or tau positive according to published thresholds[26]) or whether they reflect associations with more intermediate FTP values. We were particularly interested to know whether detection points differ across the AD markers. Thus, we applied the abovementioned procedure for the linear regression between FTP SUVR and Aβ-PET, CSF, and cognition. The Aβ detection point analysis included NAV SUVR as a continuous variable. For these specific analyses, we focused on FTP SUVR in the entorhinal cortex because it is among the earliest regions showing tau accumulation in AD.[27,28] To visualize how these detection points were associated with FTP retention in later Braak stages, we also calculated the average SUVR of the regions in Braak stages III to VI.

Results

Demographics

Participants' demographic and clinical characteristics are detailed in table 1. Among the 119 participants, the mean age was 67.5 years. The subset of the participants with both PET and CSF data were similar on all relevant measures compared to the rest of the cohort (table 1).

Association between age and FTP retention

After FDR correction older age was associated only with increased amygdala ($r = 0.33$, $p = 0.002$) and transverse temporal lobe ($r = -0.30$, $p = 0.001$) FTP retention.

Association between NAV and FTP retention

Higher FTP retention in Aβ+ individuals was observed in 14 cortical regions (figure 1A and table 2). A Cohen *d* value >0.8 suggested a large effect of Aβ status on FTP retention

in medial temporal regions, viz., entorhinal cortex, amygdala, and parahippocampal gyrus, thus encompassing Braak stage I/III regions (table 2). The hippocampus, which constitutes Braak stage II, was excluded from these analyses due to the aforementioned nonspecific binding. Aβ status showed an apparent medium effect ($0.5 \leq$ Cohen $d \leq 0.8$) on FTP retention in the fusiform gyrus, lingual gyrus, inferior temporal gyrus, middle temporal gyrus, isthmus cingulate, lateral occipital gyrus, inferior parietal lobe, superior temporal gyrus, banks of the superior temporal sulcus, and pericalcarine cortex (Braak stage III to VI regions, table 2). A small effect of Aβ status was observed in the precuneus. The correlation matrix in figure 1B illustrates that 8 of these 14 brain regions further showed robust associations with NAV retention throughout the cortex and were clustered together. The remaining regions, while still showing some associations with NAV retention in many regions, were part of different clusters with weaker correlations. Given that AD-related tau propagation is hypothesized to be Aβ dependent, the subsequent analyses are restricted to FTP retention in the top cluster, which includes 8 ROIs: the entorhinal cortex, amygdala, the parahippocampal and fusiform gyri, the inferior and middle temporal gyri, lateral occipital gyrus, and inferior parietal lobe (FTP-ROIs, figure 1C).

Table 3 Table of correlations for FTP and CSF p-tau levels

	ROI	*p* Value	Partial correlation	*t* Score
Braak I	Entorhinal cortex	<0.001[a]	0.524	5.110
Braak III	Amygdala	0.006[a]	0.352	3.124
	Fusiform gyrus	<0.001[a]	0.414	3.779
	Parahippocampal gyrus	0.007[a]	0.322	2.828
Braak IV	Inferior temporal gyrus	0.016[a]	0.311	2.714
	Middle temporal gyrus	0.167	0.168	1.416
Braak V	Lateral occipital gyrus	0.016[a]	0.280	2.418
	Inferior parietal lobe	0.881	0.019	0.160

Abbreviations: FTP = flortaucipir; ROI = region of interest.
Summary of linear regressions evaluating associations between regional FTP uptake and CSF p-tau. Corresponds to figure 2, A and C. Only the 8 FTP-ROIs were included in the current analyses. Linear regressions and partial correlation coefficients were controlled for age, sex, and years between lumbar puncture and FTP scan.
[a] Significant *p* values surviving false discovery rate correction.

Association between CSF tau values and FTP retention

CSF p-tau was associated with higher FTP retention in 6 of the 8 FTP-ROIs (table 3). CSF p-tau was associated with FTP retention in the entorhinal cortex, fusiform gyrus, parahippocampal gyrus, inferior temporal gyrus, and lateral occipital gyrus (figure 2A and table 3). Again, the strongest association was observed in the entorhinal cortex (figure 2C). The regional associations between FTP retention and CSF total tau were identical, which could be due to the strong correlation between CSF p-tau and total tau levels in this cohort (Spearman rho = 0.95).

Association between cognitive performance and FTP retention

The delayed memory index showed the strongest associations with FTP retention. Lower delayed memory scores were associated with higher FTP retention predominantly in the Braak I/III regions (figure 2, B and D and table 4). Higher FTP SUVRs in subsets of the FTP-ROIs were also associated with language, visuospatial/constructional, and total RBANS index scores (data available from Dryad, figure e-2 and table e-4, doi.org/10.5061/dryad.4q4h8q1), but there were no associations with immediate memory or attention index scores. The entorhinal cortex was the only region associated with all 4 of the cognitive index scores that showed association with FTP retention.

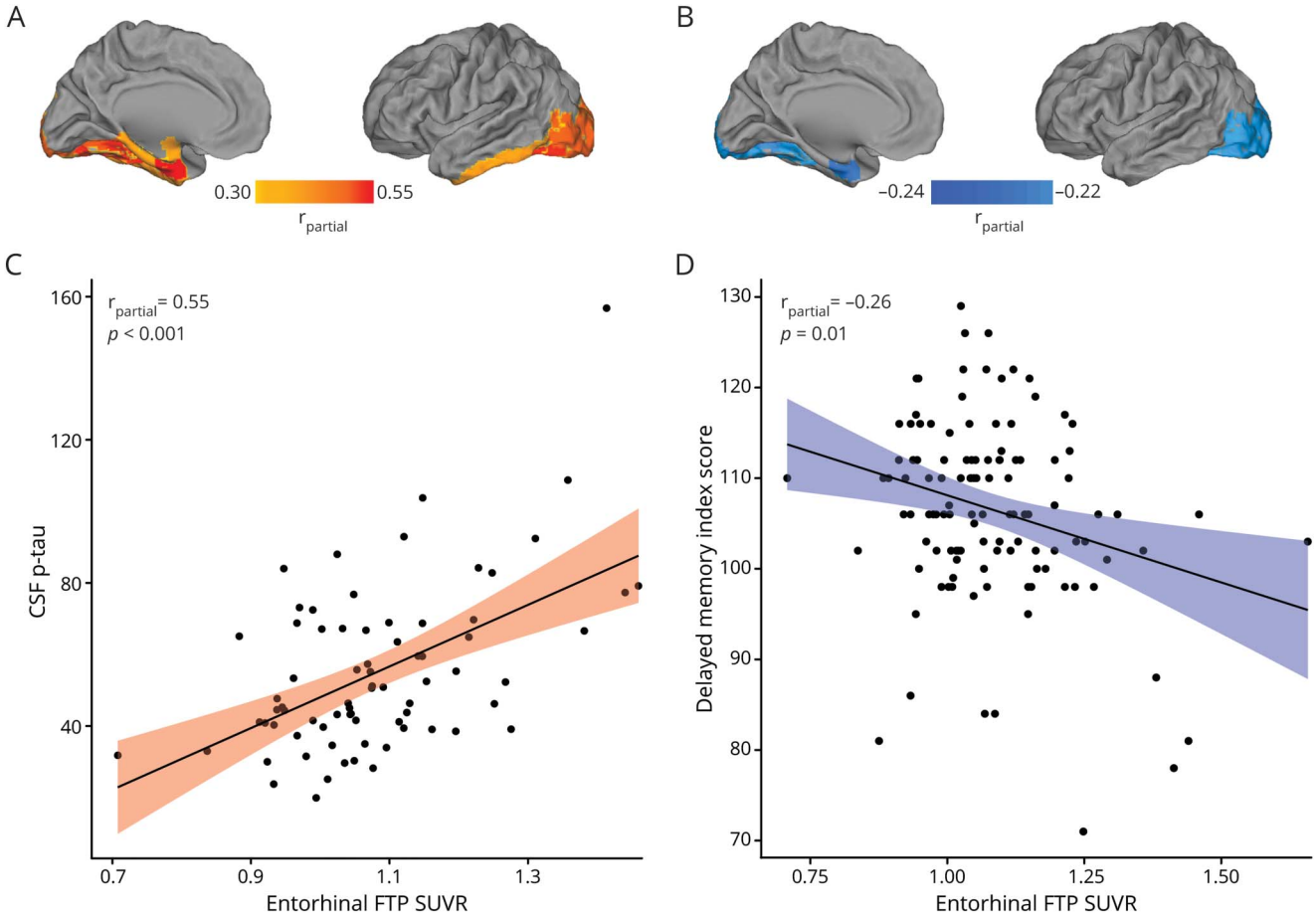
Detection points for FTP SUVR associations vary across modalities

To investigate to what extent the associations found between FTP retention and Aβ burden, CSF tau, and cognition were influenced by high FTP SUVRs, we assessed the entorhinal FTP SUVRs at which these associations were lost. The highest entorhinal FTP SUVR detection point was for cognition, with the delayed memory index score association being lost at an SUVR of 1.41 (figure 3A). Detection points for the other cognitive domain scores were in the same range (1.36, 1.66, and 1.38 for visuospatial/constructional, language, and total RBANS scores, respectively). The FTP SUVR detection point for associations with global NAV SUVR was at 1.23, and the detection point for associations with both CSF p-tau and CSF total tau was as low as 1.12. The 4 individuals exceeding the delayed memory detection point (entorhinal FTP SUVR ≥1.41) also had the highest mean SUVRs in later Braak stages (figure 3B).

Discussion

Cross-sectional studies have estimated that changes in CSF tau can be detected ≈15 years before disease onset in autosomal dominant AD.[29] In the last decade, different classes of tau-PET tracers have been developed, the most widely used one being FTP. The goal of this study was to assess early associations of FTP retention with other well-established pathologic and clinical AD biomarkers in a cohort of relatively young (mean age 67.5 years), cognitively healthy older adults at increased risk for AD dementia. Considering that about half of patients with sporadic AD dementia are diagnosed between 75 and 84 years of age,[12] older adults in their 60s are an ideal population in which to study early tau accumulation.

Figure 2 Higher FTP uptake in several brain regions is associated with greater levels of CSF p-tau and worse delayed memory



(A) Partial correlation coefficients of the regions associated with CSF phosphorylated (p-) tau (Box-Cox transformed) projected onto a brain template. Only the 8 regions of interest (ROIs) presented in figure 1C were included in the current analysis. Partial Pearson correlations were performed on a regional basis and adjusted for age, sex, and years between lumbar puncture and flortaucipir (FTP) scan. (B) Partial correlation coefficients of the regions associated with lower age-scaled delayed memory performance (Box-Cox transformed) on the Repeatable Battery for the Assessment of Neuropsychological Status projected onto a brain template. Only the 8 ROIs presented in figure 1C were included in the current analyses. Partial Pearson correlations were performed on a regional basis and adjusted for sex and education. (C) Higher entorhinal FTP standardized uptake value ratio (SUVR) is associated with higher CSF p-tau. Entorhinal FTP uptake had the strongest association with CSF p-tau among the 8 ROIs in this analysis. The 95% confidence interval (CI) is indicated in red, and the nontransformed CSF p-tau values are presented. Number of participants with CSF data = 74. (D) Higher entorhinal FTP SUVR is associated with a lower delayed memory index score. Entorhinal FTP uptake had the strongest association with delayed memory among the 8 ROIs in this analysis. The 95% CI is indicated in blue, and the nontransformed delayed memory scores are presented. Number of participants with neuropsychological data = 119.

With the objective of identifying individuals with evidence of tau pathology using PET imaging, several studies have aimed to define a threshold for tau positivity. Even though FTP positivity thresholds are not fully comparable between cohorts due to methodologic differences (e.g., data collection, ROIs, images preprocessing, analyses), most reported medial temporal thresholds fall between 1.25 and 1.4.[10,26,30,31] On the basis of these published thresholds, the PREVENT-AD cohort shows relatively low FTP retention, with only 9% of the participants showing entorhinal SUVRs >1.25 (median entorhinal SUVR 1.05, range 0.71–1.67), leaving the vast majority of the participants with what could be qualified as subthreshold values. We show that these apparently small elevations in FTP retention are already related to an ongoing pathologic process, as reflected by the robust associations with Aβ-PET, CSF p-tau, and total tau. More importantly, our detection points for Aβ and CSF tau (both p-tau and total tau) were as low as 1.23 and 1.12, respectively. As more and more acknowledged in the field of Aβ-PET,[32,33] subthreshold or intermediate FTP values should not be discarded in the context of research or clinical trials because, in some individuals, they might reflect early pathologic processes, a finding that will need to be validated by autopsy studies.

Autoradiographic and immunohistochemical studies have suggested that FTP binds with high avidity to tau paired helical filaments and neurofibrillary tangles in AD brains while showing minimal binding to Aβ or deposits of straight tau filaments in non-AD tauopathies.[34,35] FTP tracer retention patterns have been found to mirror Braak tau staging in older

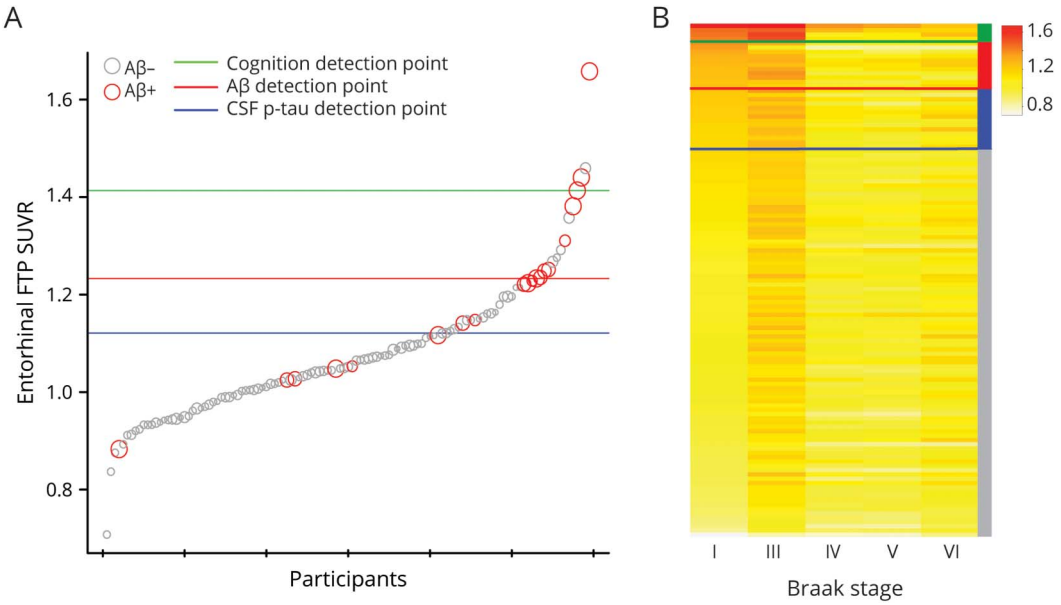
Table 4 Table of correlations for FTP and delayed memory performance

	ROI	*p* Value	Partial correlation	*t* Score
Braak I	Entorhinal cortex	0.009[a]	−0.245	−2.714
Braak III	Amygdala	0.037	−0.195	−2.135
	Fusiform gyrus	0.013[a]	−0.224	−2.468
	Parahippocampal gyrus	0.09	−0.156	−1.699
Braak IV	Inferior temporal gyrus	0.137	−0.139	−1.508
	Middle temporal gyrus	0.272	−0.106	−1.145
Braak V	Lateral occipital gyrus	0.012[a]	−0.222	−2.447
	Inferior parietal lobe	0.122	−0.142	−1.541

Abbreviations: FTP = flortaucipir; ROI = region of interest.
Summary of linear regressions evaluating associations between regional FTP uptake and the age-scaled Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index score. Corresponds to figure 2, B and D. Only the 8 FTP-ROIs were included in the current analyses. Linear regressions and partial correlation coefficients were controlled for sex and years of education.
[a] Significant *p* values and corresponding regions that survived false discovery rate correction.

individuals across the AD spectrum[7–9,36] and are correlated with clinical and neuroanatomic variability in distinct AD variants.[37] We found increased FTP uptake in Braak stages I/III in addition to a subset of Braak stages IV to VI in Aβ+ individuals compared with Aβ− individuals. In general, the strengths of these associations followed the known progression and distribution of aggregated tau in the brain.[27] These associations were present when age was controlled for, suggesting that our findings are more likely to reflect an AD-related process than (only) age-related tauopathy. The association between FTP retention and age was in fact relatively sparse and restricted to amygdala and transverse temporal

Figure 3 Relatively low entorhinal FTP SUVR values are associated with CSF p-tau and Aβ-PET uptake, while worse cognition is driven by individuals with higher entorhinal FTP uptake



(A) Individual participants are ranked in order of entorhinal flortaucipir (FTP) uptake. Global β-amyloid (Aβ)–positive individuals are indicated in red, and Aβ−negative individuals are indicated in gray. Size of the data points is reflective of each individual's Aβ-PET standardized uptake value ratio (SUVR), with larger sizes indicating higher SUVRs. Horizontal lines indicate at which entorhinal FTP SUVR values the associations between CSF phosphorylated (p-) tau (blue), continuous Aβ-PET (red), and delayed memory (green) are first detected. These detection points were obtained by iteratively running linear regressions (with 1,000 iterations of permutations) and removing the participant with the highest entorhinal FTP SUVR for each iteration. (B) Individual participants are ranked in order of entorhinal FTP (Braak I) uptake in descending order. For each participant, we calculated the mean SUVRs of the regions in Braak stages III to VI to visualize global tau distribution in individuals who fell above the delayed memory, Aβ, or CSF p-tau detection points. Delayed memory detection point was reached only in individuals who had high FTP uptake (>1.4) in Braak stages equal to or higher than stage III.

lobe uptake. This finding is in line with previous results also reporting a strong association between increased age and elevated FTP binding in the amygdala.[7,9]

To further explore the regional pattern of associations between NAV and FTP tracer retention, we computed a correlation matrix and used hierarchical clustering to identify brain regions in which FTP uptake was associated with NAV uptake. Assuming that Aβ leads to the cortical spreading of tau,[38] only brain regions expressing such associations should capture AD-related tau. Increased FTP tracer uptake in 8 brain regions that showed elevated FTP tracer retention in Aβ+ individuals was also associated with increased NAV retention throughout the cortex. These 8 regions (entorhinal cortex, amygdala, parahippocampal and fusiform gyri, inferior and middle temporal gyri, lateral occipital gyrus, and inferior parietal lobe) are known to exhibit postmortem tau neurofibrillary tangle distribution in sporadic AD in Braak stages I through V.[27,28]

We found that higher CSF p-tau was associated with increased FTP retention in medial temporal, lateral temporal, and occipital regions. Elevated CSF p-tau has high sensitivity and specificity for AD dementia; it distinguishes AD from other tauopathies and is elevated in patients compared to normal controls.[39] In our experiment, a subset of structures affected by tau in Braak stages I and III had the strongest associations with CSF p-tau levels. The associations with total tau were extremely similar, which can be explained by the almost perfect correlation between both tau CSF markers reported here and by others.[40,41]

Previous work assessing the relationships between FTP retention and CSF p-tau in cognitively normal older adults has found varying strengths of associations,[42–44] including several groups reporting an absence of associations between FTP retention and CSF p-tau among cognitively normal controls.[42,44] Such discrepancies may be attributable in part to the younger age of the cohort and differences in risk factors between cohorts. Overall, the PREVENT-AD cohort is composed of individuals with a family history of sporadic AD; thus, individuals in this sample are more likely to be on a path toward AD than a sample randomly selected from the general population. Participants are also ≈10 years younger than most other cohorts investigating tau-PET in preclinical late-onset AD,[42,45,46] including the well-known Alzheimer's Disease Neuroimaging Initiative study (adni.loni.usc.edu; mean age of cognitively normal participants with FTP data 75.42 ± 7.53 years).

Finally, higher FTP SUVRs were associated with lower delayed memory, language, visuospatial/constructional, and total RBANS scores. These associations were all driven by only a few cases with the highest FTP SUVRs in the entorhinal cortex. These cases also had among the highest SUVRs in advanced Braak stages. This finding aligns with previous work showing that global cognitive decline is associated with the spread of tau in isocortical regions beyond the limbic network and medial temporal lobe.[7] More specifically, it suggests that small increases in entorhinal FTP retention reflect an ongoing pathologic process that is still in an early phase, while higher levels of tau and propagation to later Braak stages are needed to affect cognitive functioning. The fact that the detection points for cognitive associations were higher than the detection points for CSF tau and Aβ associations raises the question of whether FTP thresholds to define positivity should vary depending on the purpose of the study. For example, while higher thresholds might be optimal to detect individuals close to or already entering the clinical phase of the disease, lower thresholds might be favored in clinical trials to target the best candidates for anti-tau therapies.

FTP retention in Braak stages I and III and the lateral occipital gyrus was consistently associated with the established AD biomarkers we studied, as well as cognitive performance. The predominant place of the Braak V lateral occipital gyrus in our analyses, although previously reported by others,[10] warrants further investigation. A key finding in this study is that the associations of FTP retention with Aβ-PET and CSF p-tau emerge when individuals have relatively low entorhinal FTP SUVRs. These findings may point toward an intermediate stage of FTP retention in which early tau elevation, going as low as 1.23 if we assume that Aβ is needed for tau propagation in AD, indicates early AD-related pathologic changes. These intermediate cases would not yet express the clinical manifestation of the disease, but they would nevertheless be a critical target population for anti-tau clinical trials.

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Disclosure

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Appendix 1 Authors

Name	Location	Role	Contribution
Melissa McSweeney, MSc	McGill University, Montreal, Quebec, Canada	Author	Study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, drafting and revising the manuscript for intellectual content
Alexa Pichet Binette, MSc	McGill University, Montreal, Quebec, Canada	Author	Study concept and design, data acquisition, analysis and interpretation of data, statistical analysis, revising the manuscript for intellectual content
Pierre-François Meyer, PhD	McGill University, Montreal, Quebec, Canada	Author	Statistical analysis, revising the manuscript for intellectual content
Julie Gonneaud, PhD	McGill University, Montreal, Quebec, Canada	Author	Acquisition of data, revising the manuscript for intellectual content
Christophe Bedetti, MSc	McGill University, Montreal, Quebec, Canada	Author	Analysis of PET scan data
Hazal Ozlen, BSc	McGill University, Montreal, Quebec, Canada	Author	Data acquisition
Anne Labonté, BSc	McGill University, Montreal, Quebec, Canada	Author	Laboratory analysis of CSF data
Pedro Rosa-Neto, MD, PhD	McGill University, Montreal, Quebec, Canada	Author	Acquisition of data, revising the manuscript for intellectual content
John Breitner, MD, MPH	McGill University, Montreal, Quebec, Canada	Author	Acquisition of data, protocol concept and design, revising the manuscript for intellectual content
Judes Poirier, PhD	McGill University, Montreal, Quebec, Canada	Author	Acquisition of data, protocol concept and design, revising the manuscript for intellectual content
Sylvia Villeneuve, PhD	McGill University, Montreal, Quebec, Canada	Author	Acquisition of data, study concept and design, interpretation of data, revision of manuscript for intellectual content

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Mallar Chakravarty, PhD	McGill University, Montreal, Quebec, Canada	Investigator	Imaging processing and evaluation (MRI/PET)
Louis Collins, PhD	McGill University, Montreal, Quebec, Canada	MRI expert	Leader of brain volumetric data
Serge Gauthier, MD, PhD	McGill University, Montreal, Quebec, Canada	Executive member	Study cohort design
Natasha Rajah, PhD	McGill University, Montreal, Quebec, Canada	MRI expert	Imaging consulting

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Intermediate flortaucipir uptake is associated with Aβ-PET and CSF-tau in asymptomatic adults

Melissa McSweeney, Alexa Pichet Binette, Pierre-François Meyer, et al.

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