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Neuroimaging

Tau pathology in cognitively normal older adults

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Abstract

Introduction: Tau pathology, a hallmark of Alzheimer's disease, is observed in the brains of virtually all individuals over 70 years.

Methods: Using ^{18}F-AV-1451 (^{18}F-flortaucipir) positron emission tomography, we evaluated tau pathology in 54 cognitively normal participants (mean age: 77.5 years, SD: 8.9) from the Baltimore Longitudinal Study of Aging. We assessed associations between positron emission tomography signal and age, sex, race, and amyloid positivity. We investigated relationships between regional signal and retrospective rates of change in regional volumes and cognitive function adjusting for age, sex, and amyloid status.

Results: Greater age, male sex, black race, and amyloid positivity were associated with higher ^{18}F-AV-1451 retention in distinct brain regions. Retention in the entorhinal cortex was associated with lower entorhinal volume ($\beta = -1.124$, SE = 0.485, $P = .025$) and a steeper decline in memory performance ($\beta = -0.086$, SE = 0.039, $P = .029$).

Discussion: Assessment of medial temporal tau pathology will provide insights into early structural brain changes associated with later cognitive impairment and Alzheimer's disease.

Keywords: Tau; AV-1451; T807; Flortaucipir; FTP; PET; Cognition; Volume; Longitudinal; Cognitively normal

1. Introduction

Pathological tau is a hallmark of several neurodegenerative diseases, most notably Alzheimer's disease (AD). Tau promotes assembly and stability of microtubules in the nervous system [1], but its hyperphosphorylation leads to the formation of neurofibrillary tangles, which are observed at autopsy in brains of almost all individuals older than 70 years [2]. Neurofibrillary tangles in the medial temporal lobe in the absence of amyloid deposition and clinical symptomatology have been referred to as primary age-related tauopathy [3], although it is not clear if primary age-related tauopathy is distinct from the continuum of AD [4].

Tau pathology is hypothesized to be one of the earliest pathophysiological changes [5] in preclinical AD, spreading from the entorhinal cortex and hippocampus to the neocortex at later disease stages [6]. Positron emission tomography (PET) tau radiotracers have enabled the *in vivo* characterization of pathological tau. Cross-sectional studies

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including cognitively normal (CN) participants in addition to those with mild cognitive impairment and AD indicate that lower cognitive performance is associated with higher tau tracer retention in the temporal lobe [7,8] and the neocortex [9]. Lower hippocampal volume has also been associated with greater tau radiotracer retention in the hippocampus [8,10]. Longitudinal studies including individuals ranging from CN to demented have further found that higher baseline tau tracer retention is associated with greater rates of brain volume loss [11,12] and global cognitive decline [13–15].

Although pathological tau burden has been shown to be related to cognition and brain volume in individuals across the AD spectrum, the influence of tau in CN individuals who may or may not go on to develop clinical impairment remains unclear. There is a growing body of literature on the characterization of tau pathology using PET in this population. Several studies have observed associations between tau PET and brain volume in CN individuals. Lower gray matter volume intensity has been associated with greater tau PET retention in the medial temporal lobe [16], and studies utilizing retrospective longitudinal MRI data have further demonstrated that cortical thinning is related to tau PET particularly in medial and lateral temporal areas [17,18]. However, the relationship between tau PET and cognitive performance is less clear. Results in CN individuals indicate that medial temporal lobe tau PET is associated with lower cross-sectional episodic memory and steeper retrospective decline in episodic memory adjusting for age, sex, and amyloid burden [18,19]. Other studies have not found associations between regional tau PET and cognition [20], or have shown that tau PET interacts with amyloid to predict greater episodic memory decline only in amyloid+ individuals [21].

The lack of consensus in studies of CN individuals indicates a further need to analyze tau PET in this population and examine its association with brain volume loss and cognitive decline. The main goal of the present study was to determine whether age- and amyloid-related differences in tau deposition can be detected among CN older adults, and if so, to investigate whether tau deposition is associated with regional brain volume and cognitive performance changes among CN. We first investigated factors associated with tau tracer retention in a sample of 54 CN older adults from the Baltimore Longitudinal Study of Aging (BLSA). We then examined regional tracer retention in regions where early tau accumulation is known to occur (i.e., the entorhinal cortex, hippocampus, and inferior temporal gyrus) in relation to retrospective longitudinal brain volume (over the course of about 7 years) and cognitive changes (over the course of about 13 years). We hypothesized that age and amyloid positivity would be associated with tau tracer retention given the relevance of these two factors for pathology spread, and that tau tracer retention would explain retrospective brain volume and cognitive decline in areas known to be affected early in AD. Understanding these relationships in a CN sample will allow us to better evaluate tau as a potential target for study and interventions to address brain aging and disease.

2. Methods

2.1. Participants

The study sample included CN BLSA participants with a ^{18}F-AV-1451 (^{18}F-flortaucipir) tau PET, a ^{11}C-Pittsburgh compound B (^{11}C-PiB) amyloid PET within 2.2 years of tau PET, and a structural MRI. As of January 18, 2018, tau PET scans were acquired on 63 participants. Four had a non-CN status, two did not have an MRI at the time of analysis, one was subsequently discovered to have had an unreported myocardial infarction before enrollment (therefore meeting the exclusion criteria for PET study enrollment), and one was determined to be an outlier because of highly lateralized cortical signal. The final sample, after excluding these cases, consisted of 54 individuals (Table 1). For 47 of these participants, MRI and PET scans were $\leq$ 6 months apart. They were 0.6, 2.1, 2.1, 4.1, 4.6, 5.8, and 7.3 years apart for the remaining 7 participants.

CN status was based on either (1) a Clinical Dementia Rating score [22] of zero and $\leq$ 3 errors on the Blessed Information-Memory-Concentration Test [23], and therefore the participant did not meet criteria for consensus conference; or (2) the participant met criteria for consensus conference and was determined to be CN based on thorough review of clinical and neuropsychological data.

Research protocols were approved by local institutional review boards, and all participants gave written informed consent at each visit. At enrollment into the PET neuroimaging substudy of the BLSA, all participants were free of CNS disease (dementia, stroke, bipolar illness, epilepsy), severe cardiac disease, severe pulmonary disease, and metastatic cancer. One participant had a myocardial infarction and another was diagnosed with congestive heart failure after PET substudy enrollment but before tau PET scan.

2.2. Structural imaging

Magnetization-prepared rapid gradient echo images were acquired on a 3 T Philips Achieva scanner (repetition time = 6.8 ms, echo time = 3.2 ms, flip angle = 8°, image matrix = 256 × 256, 170 slices, voxel size = 1 × 1 × 1.2 mm). Anatomical labels and global and regional brain volumes were obtained using Multi-atlas region Segmentation using Ensembles of registration algorithms and parameters [24]. We performed intracranial volume (ICV) correction using the approach used by Jack et al. [25], computing residual volumes for each region, which is the difference, in cm^3, from the regional volume that would be expected at a given ICV.

Table 1
Participant demographics

Characteristic	Amyloid−	Amyloid+
a. Voxelwise analysis sample (n = 54)	(n = 41)	(n = 13)
Age at ^{18}F-AV-1451 PET scan (yrs), mean (SD)	77.2 (8.9)	78.2 (9.3)
Male, n (%)	16 (39)	8 (62)
Black, n (%)	8 (20)	4 (31)
Yrs of education, mean (SD)	17.9 (2.1)	16.6 (2.2)
APOE ε4+, n (%)	11 (27)	7 (54)
b. Cognition sample (n = 53)	(n = 40)	(n = 13)
Age at ^{18}F-AV-1451 PET scan (yrs), mean (SD)	77.6 (8.7)	78.2 (9.3)
Male, n (%)	16 (40)	8 (62)
Black, n (%)	8 (20)	4 (31)
Yrs of education, mean (SD)	17.8 (2.1)	16.6 (2.2)
APOE ε4+, n (%)	10 (25)	7 (54)
Number of cognitive assessments, mean (SD)	8 (5.2)	6.5 (5.5)
Duration of cognitive follow-up (yrs), mean (SD)	13.9 (8)	11.5 (8.7)
c. Brain volume sample (n = 50)	(n = 38)	(n = 12)
Age at ^{18}F-AV-1451 PET scan (yrs), mean (SD)	77.3 (8.9)	77.8 (9.5)
Male, n (%)	15 (39)	7 (58)
Black, n (%)	8 (21)	3 (25)
Yrs of education, mean (SD)	17.9 (2.1)	16.7 (2.3)
APOE ε4+, n (%)	10 (26)	6 (50)
Number of MRI scans, mean (SD)	5.3 (4.9)	4.3 (4.6)
Duration of MRI follow-up (yrs), mean (SD)	7.4 (6.8)	6.2 (6.5)

Abbreviation: PET, positron emission tomography.

2.3. PET imaging

Amyloid PET imaging is described in Supplementary Material B. Tau PET scans were obtained over 30 min on a Siemens high resolution research tomograph scanner starting 75 mins after an intravenous bolus injection of approximately 370 MBq (10 mCi) of ^{18}F-AV-1451. Dynamic images were reconstructed using ordered subset expectation-maximization to yield 6 time frames of 5 mins each with approximately 2.5 mm full-width at half-maximum (FWHM) at the center of the field of view (image matrix = 256 × 256, 207 slices, voxel size = 1.22 × 1.22 × 1.22 mm). We aligned the time frames between 80 and 100 minutes to the first frame in this interval. The 20-min average PET image was registered onto the inhomogeneity-corrected magnetization-prepared rapid gradient echo using rigid registration. Anatomical labels defined in MRI space were transformed into PET space. The 20-min average PET image was partial volume corrected using the region-based voxelwise method [26]. For the geometric transfer matrix step of region-based voxelwise, we used 26 bilateral Multi-atlas region Segmentation using Ensembles of registration algorithms and parameters regions (see Supplementary Material D). We computed standardized uptake value ratio (SUVR) images by dividing the partial volume corrected PET intensities by the mean within the inferior cerebellar gray matter, which was defined using the approach described by Baker et al. [27] based on the SUIT atlas [28]. We computed the average SUVR in three regions of interest (ROIs) corresponding to early stages of tau pathology: the entorhinal cortex, hippocampus, and inferior temporal gyrus (ITG). SUVR images were mapped into MNI space using the warp computed from deformable registration of the corresponding MRIs to a study-specific MRI template, and smoothed with a Gaussian filter (6 mm FWHM) before statistical analysis.

2.4. Neuropsychological testing

Cognitive domain scores were obtained for memory (California Verbal Learning Test [29] immediate and long-delay free recall), attention (Trail Making Test [30] Part A and Digit Span [31] Forward), executive function (Trail Making Test Part B and Digit Span Backward), fluency (Category [32] and Letter Fluency [33]), visuospatial processing (Card Rotations Test [34], Clock Drawing Test [35]), and processing speed (Digit Symbol Substitution Test) [31]. To obtain domain scores, each test score was first converted to a z-score using the baseline mean and standard deviation, and these z-scores were averaged within each cognitive domain. Before computing the z-scores for Trail Making Test Parts A and B, the individual cognitive test scores (time to completion, in seconds) were log-transformed and negated so that higher z-scores indicated shorter time to completion.

2.5. Statistical analysis

2.5.1. Factors associated with tau accumulation

We used multiple linear regression to assess the associations between demographics, amyloid positivity, and voxelwise ^{18}F-AV-1451 SUVR. Independent variables included age, sex, race, amyloid status, and age × amyloid status. Education was not included as a predictor because of its low variance in our sample. Each independent variable was mean-centered to facilitate interpretation of model results. Voxelwise linear regression was conducted using SPM12. Statistical significance was based on two-tailed t tests with $P < .001$ (uncorrected for multiple comparisons) and restricted to clusters of ≥ 400 voxels.

2.5.2. Longitudinal regional brain volume change and colocalized tau accumulation

Using separate linear mixed effects models for each of the three PET ROIs (entorhinal cortex, hippocampus, and ITG), we assessed the associations between regional ^{18}F-AV-1451 SUVR and retrospective change in the volume of the same region (3 models total). The dependent variable was ICV-adjusted regional volumes prior to and concurrent with the tau PET scans. Age at and time from tau PET scan, sex, amyloid status (+ vs. –), amyloid status × time, regional ^{18}F-AV-1451 SUVR, and SUVR × time were included as

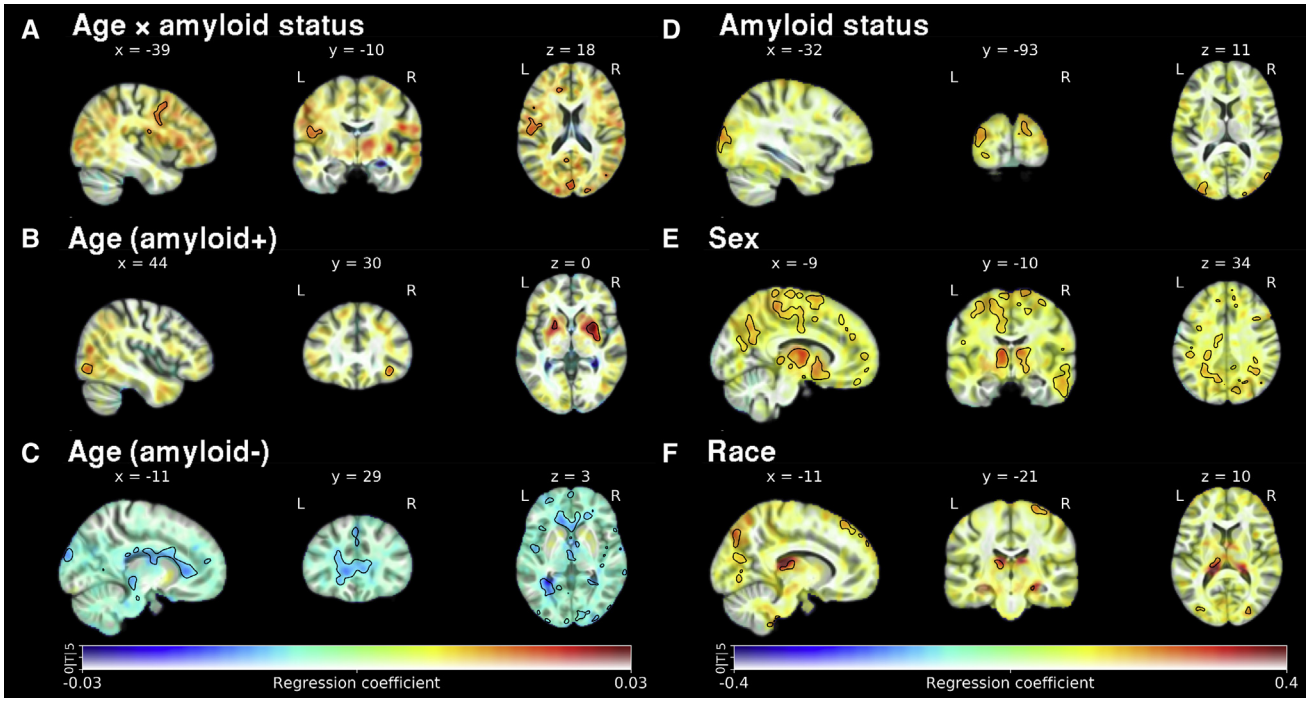

Fig. 1. Predictors of ^{18}F-AV-1451 tau tracer retention among cognitively normal older adults. In these dual-coded representations of voxelwise linear regression results, color indicates the estimated regression coefficient (indicated along the horizontal axis of the color bar) and transparency corresponds to the absolute t value (with 0 as completely transparent and ≥5 as completely opaque, as indicated along the vertical axis of the color bar). Voxels that reach significance (uncorrected $P < .001$, cluster size ≥400 voxels) are circumscribed by black contour to help with the interpretation of transparency. (A) Age by amyloid status interaction. (B) Main effect of age in amyloid+ individuals. (C) Main effect of age in amyloid− individuals. (D) Main effect of amyloid positivity. (E) Main effect of male sex. (F) Main effect of black race. Color bars on the left and right correspond to panels A–C and D–F, respectively.

independent variables. To facilitate interpretation, regional ^{18}F-AV-1451 SUVRs were mean-centered. Random effects were included for intercept and time. This analysis was restricted to individuals who had a volumetric measurement before and within 3 years of tau PET (n = 50, total number of longitudinal MRI assessments = 253). Longitudinal MRI time points per participant relative to the time of tau PET scan are shown in Figure A.1. Statistical significance was based on two-tailed t tests with $P < .05$ (uncorrected for multiple comparisons).

2.5.3. Longitudinal cognition and tau accumulation

Using separate linear mixed effects models for each of the six cognitive domains and each of the three ROIs, we assessed associations between regional ^{18}F-AV-1451 SUVR and retrospective change in cognition (18 models total). Age at and time from tau PET scan, sex, years of education, amyloid status, amyloid status × time interaction, regional ^{18}F-AV-1451 SUVR, and regional SUVR × time interaction were included as independent variables. This analysis was restricted to individuals who had a cognitive assessment before and within 3 years of tau PET (n = 53). Longitudinal cognitive visits per participant relative to the time of tau PET scan are shown in Figure A.1. There were 401 total observations for memory, 351 for attention and executive function, 363 for fluency, 293 for visuospatial processing, and 249 for processing speed, with differences in sample sizes primarily reflecting historical differences in age at which specific tests were administered. Amyloid status and regional ^{18}F-AV-1451 SUVRs were centered around the sample mean as before. Random effects were included for intercept and time. Statistical significance was based on two-tailed t tests with $P < .05$ (uncorrected for multiple comparisons).

3. Results

3.1. Factors associated with tau accumulation

The association between age and ^{18}F-AV-1451 SUVR was stronger among amyloid+ than amyloid− individuals in the right middle temporal gyrus, left middle frontal gyrus, and bilaterally in the cuneus, cingulate, superior frontal, and postcentral gyri (Supplementary Table F.1). In the amyloid+ group, greater age was associated with higher ^{18}F-AV-1451 SUVR in bilateral putamen, right inferior frontal, and right middle occipital gyri (Supplementary Table F.2). Amyloid+ individuals had greater ^{18}F-AV-1451 SUVR compared with amyloid− individuals in the right middle frontal gyrus, right superior and middle temporal gyri, left superior occipital gyrus, bilateral middle temporal gyri, middle occipital gyri, and cuneus (Supplementary Table F.3). Men compared with women had higher ^{18}F-AV-1451 SUVR in bilateral frontal, parietal, and lateral temporal cortices as well as in bilateral

Table 2
Linear mixed effects models of the relationship between entorhinal ^{18}F-AV-1451 SUVR and intracranial volume adjusted entorhinal cortex volume

	Dependent variable
Characteristic	Entorhinal volume (cm^3)
Intercept	−0.301* (0.063)
	P = .000004
Age at PET scan	−0.030* (0.007)
	P = .0002
Sex (ref = female)	0.338† (0.129)
	P = .013
Amyloid group (ref = amyloid−)	0.231 (0.152)
	P = .136
Entorhinal SUVR	−1.124† (0.485)
	P = .025
Time from PET	−0.055* (0.007)
	P < .000001
Amyloid group × time	−0.001 (0.017)
	P = .960
Entorhinal SUVR × time	−0.047 (0.046)
	P = .308

NOTE. Estimated fixed effects are reported along with their standard errors in parentheses.

Abbreviations: SUVR, standardized uptake value ratio; PET, positron emission tomography.

*P < .001.

†P < .05.

limbic areas (Supplementary Table F.4). Black race was associated with higher ^{18}F-AV-1451 SUVR in bilateral occipital and temporal lobes as well as superior frontal areas (Supplementary Table F.5). These effects are visualized for select brain slices in Fig. 1. Unthresholded statistical maps are available at https://neurovault.org/collections/4780/ [36].

3.2. Regional brain volume and tau accumulation

Cross-sectionally, higher entorhinal cortex ^{18}F-AV-1451 SUVR was associated with smaller volume in this region (β = −1.124, SE = 0.485, P = .025) (Table 2). We did not find any associations between tau and volume in the hippocampus or ITG.

3.3. Cognition and tau accumulation

Cross-sectionally, greater ^{18}F-AV-1451 SUVR in the hippocampus was associated with lower memory (β = −0.833, SE = 0.405, P = .046), and greater ^{18}F-AV-1451 SUVR in the ITG was associated with lower attention scores (β = −2.451, SE = 1.046, P = .024) (Table 3).

Steeper decline in memory was associated with greater ^{18}F-AV-1451 SUVR in the entorhinal cortex (β = −0.086, SE = 0.039, P = .029) (Fig. 2), hippocampus (β = −0.041, SE = 0.017, P = .018), and ITG (β = −0.132, SE = 0.066, P = .048) (Table 3). The strength of this association was greater for the California Verbal Learning Test long-delay free recall component than for the immediate recall component for all three regions (Supplementary Table G.4). In addition, steeper decline in fluency was associated with ^{18}F-AV-1451 SUVR in the hippocampus (β = −0.028, SE = 0.008, P < .001).

The full set of results for each ROI and each cognitive domain are reported in Supplementary Tables G.1, G.2, and G.3.

4. Discussion

Our study investigated tau tracer retention among cognitively normal individuals. We evaluated the cross-sectional associations of ^{18}F-AV-1451 SUVR with age, sex, race, and amyloid status, and further assessed the associations between ^{18}F-AV-1451 SUVR and rates of volumetric and cognitive change. We found that higher ^{18}F-AV-1451 retention in the entorhinal cortex was associated with lower volume in this region. We also found that greater ^{18}F-AV-1451 retention in the entorhinal cortex, hippocampus, and inferior temporal gyrus were each associated with steeper decline in verbal memory.

Our finding of higher ^{18}F-AV-1451 SUVR in temporal, temporoparietal, and frontal cortical areas among amyloid+ compared with amyloid− individuals is in agreement with previous studies of cognitively normal older adults [19,37]. In the amyloid− group, ^{18}F-AV-1451 SUVR was lower at greater ages in periventricular white matter and CSF, which might be due to age-related differences in radiotracer clearance among amyloid− individuals. Conversely, ^{18}F-AV-1451 SUVR was higher at older ages among amyloid+ individuals in the putamen, right inferior frontal, and right middle occipital gyri. The association between tracer retention and age modulated by amyloid status did not reach significance in the putamen, but amyloid+ individuals exhibited stronger associations in several cortical regions. These findings suggest that the association in the putamen may be driven by nonspecific binding whereas cortical associations may more likely be due to tau pathology. Similarly, the observed interaction between amyloid status and age might be reflective of cortical areas of faster tau accumulation among amyloid+ individuals. This interpretation is supported by the finding of a previous longitudinal tau PET study showing that amyloid+ individuals had steeper tau tracer retention increases in basal and midtemporal, retrosplenial, posterior cingulate, and entorhinal cortex [38]. Another study of longitudinal tau accumulation showed increases in ^{18}F-AV-1451 retention over 1–3 years in temporal and medial parietal areas in healthy older adults [39]. These findings were further expanded on by a recent study reporting that individuals with baseline ^{18}F-AV-1451 SUVRs in the second

Table 3
Linear mixed effects models of the relationship between entorhinal and hippocampal ^{18}F-AV-1451 SUVR and cognition

	Dependent variable: Cognitive testing performance (*z*-score)				
Characteristic	Memory	Memory	Fluency	Memory	Attention
Intercept	0.126 (0.125) $P = .312$	0.126 (0.121) $P = .300$	0.059 (0.121) $P = .627$	0.122 (0.124) $P = .327$	0.118 (0.092) $P = .202$
Age at PET scan	−0.029* (0.012) $P = .021$	−0.028* (0.012) $P = .023$	−0.026* (0.013) $P = .046$	−0.029* (0.012) $P = .021$	−0.024* (0.010) $P = .022$
Sex (ref = female)	−0.082 (0.217) $P = .708$	−0.113 (0.213) $P = .597$	0.008 (0.226) $P = .972$	−0.096 (0.225) $P = .670$	−0.042 (0.189) $P = .825$
Education (years)	−0.066 (0.051) $P = .205$	−0.051 (0.052) $P = .333$	−0.048 (0.056) $P = .392$	−0.062 (0.051) $P = .237$	0.023 (0.043) $P = .598$
Amyloid group (ref = amyloid–)	0.131 (0.308) $P = .673$	0.071 (0.293) $P = .810$	−0.202 (0.293) $P = .494$	0.284 (0.338) $P = .406$	0.316 (0.251) $P = .215$
Entorhinal SUVR	−0.769 (0.942) $P = .419$				
Hippocampal SUVR		−0.833* (0.405) $P = .046$	−0.766 (0.405) $P = .065$		
ITG SUVR				−1.647 (1.410) $P = .249$	−2.451* (1.046) $P = .024$
Time from PET	−0.023† (0.006) $P = .0001$	−0.024† (0.006) $P = .0001$	−0.013† (0.004) $P = .001$	−0.024† (0.006) $P = .00005$	−0.020† (0.006) $P = .001$
Amyloid group × time	0.007 (0.014) $P = .646$	0.002 (0.015) $P = .917$	0.017* (0.009) $P = .050$	0.017 (0.016) $P = .300$	−0.015 (0.016) $P = .344$
Entorhinal SUVR × time	−0.086* (0.039) $P = .029$				
Hippocampal SUVR × time		−0.041* (0.017) $P = .018$	−0.028† (0.008) $P = .001$		
ITG SUVR × time				−0.132* (0.066) $P = .048$	−0.010 (0.062) $P = .879$

NOTE. Each column represents a separate model. Each model includes tau measured in a single ROI. Estimated fixed effects are reported along with their standard errors in parentheses.

Abbreviations: SUVR, standardized uptake value ratio; ITG, inferior temporal gyrus; PET, positron emission tomography.

*$P < .05$.

†$P < .001$.

quartile exhibited tau tracer retention increases in inferior and lateral temporal cortex and in posterior cingulate over 18 months [15].

Men in our sample had higher ^{18}F-AV-1451 SUVR than women, mainly in frontal and parietal white matter and thalamus. Previous studies utilizing tau PET imaging have not shown widespread or consistent sex differences in tracer retention [37,40], and given that women exhibit a greater degree of AD pathology than men in *ex vivo* measures of tau [41], it seems likely that the sex differences we observed are largely driven by nonspecific binding. In addition, we found higher ^{18}F-AV-1451 SUVR among black individuals in confined regions of the cortex. Black individuals exhibit lower levels of CSF-tau than white individuals [42], but greater incidence of postmortem neurofibrillary tangle in Braak V/VI in black individuals has also been observed [43]. Race-related differences in ^{18}F-AV-1451 retention in the choroid plexus have been previously reported [44], but the proximity of most statistically significant clusters to the edge of the brain in our sample suggests that these findings may be in part due to spill-over from nonspecific binding of the tracer to meningeal neuromelanin. Potential sex and race differences in tau deposition will require further study in large and diverse samples.

Adjusting for age, sex, and amyloid status, we found that higher entorhinal ^{18}F-AV-1451 SUVR was associated with lower brain volume in the entorhinal cortex. These results are in line with previous findings suggesting that tau accumulation may help explain differences in regional brain volumes while individuals are still cognitively normal [16–18], although these studies report more extensive associations.

Adjusting for age, sex, education, and amyloid status, we observed that greater ^{18}F-AV-1451 retention in the entorhinal cortex, hippocampus, and inferior temporal gyrus was associated with steeper decline in verbal memory performance. This finding reinforces the notion that pathological tau in areas of early accumulation may influence changes in cognitive domains known to be affected in AD even in cognitively normal individuals. In a previous analysis using the BLSA amyloid PET data, we had reported an association between amyloid status and steeper memory decline [45]. Interestingly, this association was not statistically significant in our current analyses including regional ^{18}F-AV-1451 SUVR as an independent variable. This suggests

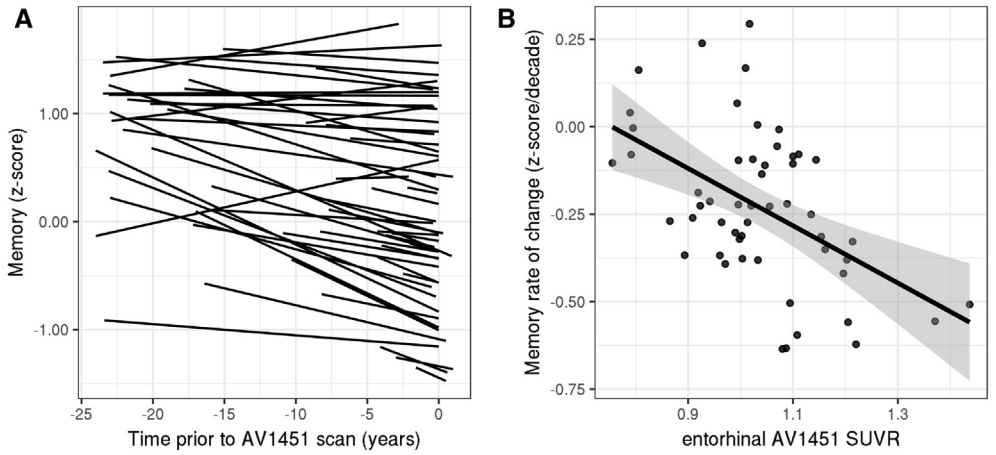

Fig. 2. Entorhinal ^{18}F-AV-1451 tau tracer retention is associated with steeper retrospective longitudinal decline in the composite memory score. (A) Individual-level memory change predicted by linear mixed effects model. (B) Rate of decline (z-score/decade) in memory performance as a function of ^{18}F-AV-1451 tau tracer retention in the entorhinal cortex. Fitted values for rate of change are plotted for each individual in the sample.

that tau rather than amyloid deposition may be more strongly associated with cognition, consistent with previous findings [7]. ITG tau PET retention was also associated with lower cross-sectional attention, and retention in the hippocampus was associated with steeper declines in fluency. Some studies have reported a relationship between tau burden and performance in cognitive domains other than memory [13,46], although these findings may have been driven by the inclusion of clinically impaired individuals, as this relationship is not consistently seen in CN individuals [21].

This study has several limitations. Although the ^{18}F-AV-1451 tracer has been demonstrated to have good specificity for tau tangles, it is also known to exhibit nonspecific binding in the basal ganglia, choroid plexus, and to MAO-A, neuromelanin, and pigmented or mineralized vascular structures [47]. We did not perform multiple comparison correction given that a consensus method for correcting for dependent tests in longitudinal data sets is not available. We assessed the relationships between tau tracer retention and cognitive and volume declines retrospectively rather than prospectively because of the relatively recent implementation of tau PET in the BLSA. For this same reason, our sample size was limited, particularly for amyloid+ individuals. Future studies in a larger sample will be necessary to more fully investigate associations between amyloid, ^{18}F-AV-1451 retention, and time.

Our study also has several strengths. The considerable amount of longitudinal cognitive testing and structural MRI data from the BLSA allowed us to assess the association between tau tracer retention and retrospective longitudinal decline in these measures over longer periods compared with other studies, and thereby yielding greater confidence in our estimates of rates of change. The spatial resolution of our tau PET scans, at approximately 2.5 mm FWHM at the center of the field of view, compares favorably with that of other studies of tau PET imaging among CN individuals. Better spatial resolution translates to less pronounced the partial volume effects, which is an advantage for image quantification, especially in medial temporal regions that are susceptible to spill-over from the choroid plexus.

Overall, our results point to a relationship between tau pathology and early changes in cognition in older individuals, even for those without a high degree of pathology or cognitive impairment. These findings also suggest the importance of ^{18}F-AV-1451 PET for characterizing tau pathology in cognitively intact individuals and as a potential tool for predicting cognitive change early in AD progression. Future studies should investigate prospective cognitive and volumetric changes in relation to both timing and spread of tau deposition and their utility in predicting the trajectory of AD pathologies and symptoms. Effects of tau deposition on changes in other measures of brain integrity, such as brain networks underlying cognitive function, may provide additional insights into the relationship between pathology and cognitive decline in cognitively normal individuals.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2019.07.007.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed and Human Amyloid Imaging conference abstracts for tau PET studies in cognitively normal samples. Our review indicated a lack of consensus in the literature assessing the relationships of tau PET with cognition in such samples.
2. Interpretation: We identified regions of likely tau pathology accumulation based on the relationship of tau PET signal with amyloid and age, and found evidence of tau-associated memory decline and lower regional volume among cognitively normal individuals without a high degree of pathology. These findings suggest that assessing tau pathology, particularly in medial temporal areas, can provide insight into early brain changes and cognitive decline.
3. Future directions: Future studies should use prospective data to confirm the observed retrospective cognitive and volumetric associations with tau pathology in cognitively normals. Regional tau pathology should also be studied in relation to other features of cognitive aging such as changes in brain network connectivity.

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