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In vivo tau is associated with change in memory and processing speed, but not reasoning, in cognitively unimpaired older adults

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ABSTRACT

The relationship between tau deposition and cognitive decline in cognitively healthy older adults is still unclear. The tau PET tracer ^{18}F-MK-6240 has shown favorable imaging characteristics to identify early tau deposition in aging. We evaluated the relationship between in vivo tau levels (^{18}F-MK-6240) and retrospective cognitive change over 5 years in episodic memory, processing speed, and reasoning. For tau quantification, a set of regions of interest (ROIs) was selected a priori based on previous literature: (1) total-ROI comprising selected areas, (2) medial temporal lobe-ROI, and (3) lateral temporal lobe-ROI and cingulate/parietal lobe-ROI. Higher tau burden in most ROIs was associated with a steeper decline in memory and speed. There were no associations between tau and reasoning change. The novelty of this finding is that tau burden may affect not only episodic memory, a well-established finding but also processing speed. Our finding reinforces the notion that early tau deposition in areas related to Alzheimer's disease is associated with cognitive decline in cognitively unimpaired individuals, even in a sample with low amyloid-β pathology.

1. Introduction

In vivo neuroimaging biomarkers of tau and amyloid-β pathology have become essential tools in research into normal cognitive aging and preclinical Alzheimer's disease (AD), as deposition of both proteins begins several years before clinical symptoms emerge (Jack et al., 2013; Marks et al., 2017; Price and Morris, 1999; Rowe et al., 2013; Vogel et al., 2021). Despite the well-accepted involvement of amyloid-β and tau pathology in AD, questions remain regarding the role of these proteins in age-related cognitive decline. For instance, previous studies found normal aging to be associated with the deposition of tau pathology in the form of neurofibrillary tangles in the medial temporal lobe (MTL) and neocortex even in the absence of or in the context of low amyloid-β pathology (Braak et al., 2011; Hanseeuw et al., 2019; Vogel et al., 2020). Recently, this condition has been termed primary age-related tauopathy (Crary et al., 2014; Jellinger et al., 2015), and there is still debate as to whether this is part of the AD spectrum or is just part of "normal" aging (Duyckaerts et al., 2015).

In recent years, positron emission tomography (PET) studies in cognitively unimpaired older adults showed in vivo deposition of amyloid-β and tau (Chen et al., 2021a; Hanseeuw et al., 2019; Maass et al., 2018; Ossenkoppele et al., 2022; Pontecorvo et al., 2019; Sperling et al., 2019; Ziontz et al., 2019) and indicated that elevated tau PET tracer retention is frequently seen first in the MTL (particularly entorhinal cortex), followed by the inferolateral temporal and medial parietal lobes (Scholl et al., 2019). In addition, previous work reported that tau pathology in transentorhinal regions precedes amyloid-β deposition (Braak and Braak, 1991) and that the spread of tau outside of the MTL, such as inferior temporal gyrus (Lee et al., 2022), has been reported to be associated with the presence of amyloid-β (Lee et al., 2022; Scholl et al., 2019). Despite the implication of both proteins in the AD biomarker cascade, tau PET studies indicate a close relationship between patterns of early tau deposition and cognitive impairment (Brier et al., 2016; Johnson et al., 2016; Marks et al., 2017; Ossenkoppele et al., 2016,

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2022; van Rossum et al., 2012) in contrast to weaker associations seen between cognition and amyloid-β.

Tau accumulation has been associated with longitudinal cognitive decline, typically in episodic memory (Chen et al., 2021b; Jack et al., 2020; Kwan et al., 2023; Maass et al., 2018; Marks et al., 2017). Due to the initial tau accumulation in the MTL, memory has been the domain typically investigated; however, some longitudinal studies have reported tau accumulation to be associated with a decline in global cognition (Aschenbrenner et al., 2018; Biel et al., 2021; Pontecorvo et al., 2019) and composite scores including not only memory but also tasks of executive function, speed, and language (Hanseeuw et al., 2019; Ossenkoppele et al., 2022). Therefore, the impact of early tau accumulation on cognitive trajectories beyond memory in cognitively unimpaired older adults still needs to be further characterized and understood, particularly with second-generation tau tracers.

While many in vivo biomarker studies indicate that tau may accumulate in the absence of objective cognitive impairment (Chen et al., 2021a; Hanseeuw et al., 2019; Maass et al., 2018; Pontecorvo et al., 2019; Sperling et al., 2019; Ziontz et al., 2019), it is important to explore whether any of the cognitive changes that we consider reflective of normative age-related cognitive decline could be in part driven by the preclinical or "normal" accumulation of tau pathology. Most of the variance in age-related cognitive decline can be accounted for by considering 3 domains: memory, processing speed, and fluid reasoning. Early AD is typically characterized by memory impairment, but healthy aging is linked with more subtle difficulties in memory, processing speed, and reasoning (Salthouse, 2005, 2009, 2019; Salthouse et al., 2008, 2015; Simon et al., 2022). Thus, it is important to investigate whether tau burden in AD-related regions can also account for cognitive change in the context of healthy aging. This may help disentangle tau-cognition associations present in both AD and healthy aging.

More recently, a new generation of tau PET ligands has been introduced with more specific binding in comparison to the previous generation. The tracer ^{18}F-MK-6240 (Hostetler et al., 2016) is a PET ligand for imaging neurofibrillary tangles in vivo that has shown favorable imaging characteristics and spatial distributions consistent with the neuropathological staging of neurofibrillary tangles in AD in preliminary studies (Betthauser et al., 2019, 2020; Lohith et al., 2019; Pascoal et al., 2018). Studies evaluating ^{18}F-MK-6240 in humans have indicated high affinity to neurofibrillary tangles in AD, minimal off-target binding in the brain, and the presence of extra-axial signals in some cases. In addition, the tracer ^{18}F-MK-6240 was shown to predict cognitive decline in cognitively unimpaired older adults (Betthauser et al., 2020; Kwan et al., 2023).

In the present study, we aimed to evaluate the association of late-life tau deposition with retrospective cognitive change. We hypothesized that early tau deposition would be associated with a decline in cognitive domains other than memory in cognitively unimpaired older adults, even in a sample mostly characterized as amyloid-β negative.

2. Material and methods

2.1. Study design

The present study reports on data from our ongoing longitudinal studies: the cognitive reserve (CR) and Reference Ability Neural Network (RANN) studies (Habeck et al., 2016; Stern, 2012; Stern et al., 2014). The Cognitive Reserve (CR) study was designed to elucidate the neural underpinnings of cognitive and brain reserve (Stern et al., 2018), and the RANN study was designed to identify networks of brain activity uniquely associated with performance across the adult lifespan (i.e., 20–80 years old) in 4 different reference abilities: fluid reasoning, episodic memory, processing speed, and vocabulary (Habeck et al., 2016; Stern et al., 2014). Both studies share similar recruitment and data collection procedures. The studies were approved by the Institutional Review Board of the College of Physicians and Surgeons of Columbia University.

2.2. Selection of participants

Participants were recruited primarily through randomized market mailing. An initial telephone screening determined whether participants met basic inclusion criteria, which included being right-handed, English speaking, at least a fourth-grade reading level, no psychiatric or neurological disorders, and normal or corrected-to-normal vision and hearing. Potentially eligible participants were further screened in person with structured medical and detailed neuropsychological evaluations to ensure that they had no neurological or psychiatric conditions, cognitive impairment, or clinical diagnosis of Mild Cognitive Impairment (MCI) and contraindication for Magnetic Resonance Imaging (MRI) scanning. For inclusion, a score greater than or equal to 130 was required on the Mattis Dementia Rating scale (Mattis, 1988) and preserved functionality in the Blessed Activities of Daily Living scale (Blessed et al., 1968). Participants were then followed over a 5-year period, after which they repeated the medical and neuropsychological evaluations and MRI exams. In addition, participants above 55 years were invited to undergo amyloid and tau PET imaging. Specifically, amyloid PET was included at baseline and 5-year follow-up visits, and tau PET was included only at follow-up. For the purpose of the current study, we only use PET imaging data collected at follow-up, as these were common to both amyloid and tau data. The overall schema of data collection is presented in Fig. 1.

Regarding tau data collection, we specifically oversampled individuals with higher levels of amyloid-β to prioritize the inclusion of participants who may represent a more vulnerable group for tau deposition. The total sample that underwent a tau PET scan consisted of 59 participants. For the current analyses, we excluded participants with clinical diagnoses of MCI or dementia (Braak stage greater than II) ($N = 2$), and with missing data on one of the cognitive assessments (baseline or follow-up) ($N = 16$). Therefore, for the current analysis, we included cognitively unimpaired participants with available longitudinal cognitive data (baseline and follow-up) and follow-up PET imaging; our final sample included 41 individuals.

2.3. Cognitive measures and latent change score model

At baseline and follow-up, participants underwent a comprehensive neuropsychological assessment and performed additional cognitive tasks during the MRI protocol (Gazes et al., 2023; Habeck et al., 2016; Salthouse et al., 2015; Stern et al., 2014). As per a previous study from our group (Salthouse et al., 2015), neuropsychological and cognitive measures were selected based on a factor analysis reflecting 4 domains: fluid reasoning, processing speed, episodic memory, and vocabulary. For the present longitudinal analysis, we excluded data from the vocabulary domain since its performance tends to increase or remain stable over time (Gazes et al., 2023; Habeck et al., 2016; Salthouse, 2004, 2009, 2019; Stern et al., 2014), and our main interest was in investigating the cognitive domains with evidence of decline over time, such as fluid reasoning ("reasoning"), processing speed ("speed"), and episodic memory ("memory") (Gazes et al., 2023; Habeck et al., 2016; Salthouse, 2004, 2009, 2019; Stern et al., 2014). However, for the sample description, we used the baseline scores on the American National Adult Reading Test (Grober and Sliwinski, 1991), a vocabulary measure, to estimate the participant's intelligence quotient. Each of the cognitive domains investigated longitudinally (reasoning, memory, and speed) was estimated through 6 measures each, three were from the neuropsychological battery (out-of-scanner), and three were completed during the MRI exam (in-scanner) (Gazes et al., 2023; Habeck et al., 2016) (Fig. 2).

In order to combine the 6 cognitive measures in each domain and create a more robust measurement, we used a multiple indicator latent change score model (Kievit et al., 2018) to model change in the latent score rather than in the observed scores and generate cognitive scores at

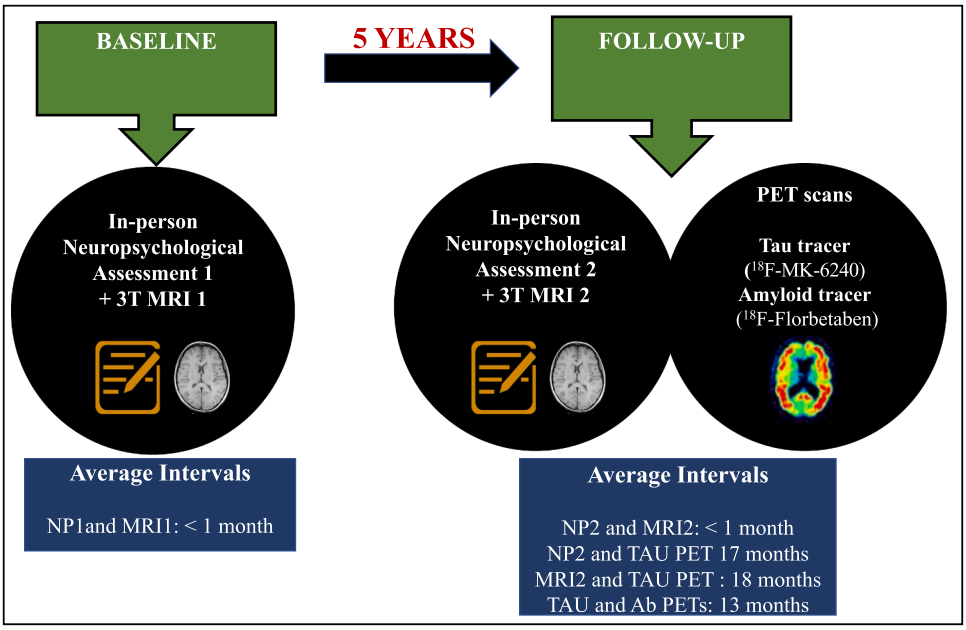

Fig. 1. Illustration of data collection.

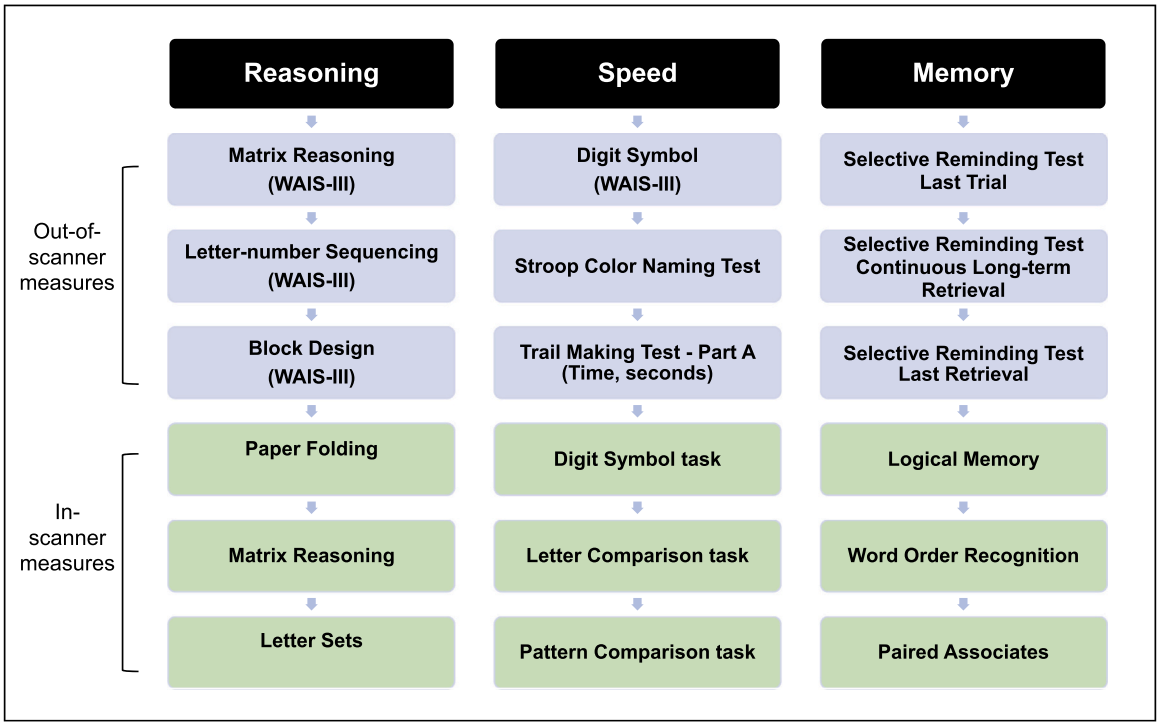

Fig. 2. Summary of cognitive measures used to calculate the latent scores reflecting episodic memory, processing speed, and reasoning. In blue: out-of-scanner measures; in green: in-scanner measures. Abbreviations: WAIS-III: Wechsler Adult Intelligence Scale, 3rd edition.

baseline and follow-up, as detailed in previous studies from our group (Gazes et al., 2023; Simon et al., 2022).

In brief, we modeled the changes in cognitive measures representing the 3 domains (reasoning, speed, and memory), each based on the out-of-scanner and in-scanner tests, using a traditional confirmatory factor analysis as described in our previous studies (Salthouse et al., 2015). Factor loadings were constrained such that the baseline and follow-up loadings were the same. The cognitive change was calculated as a follow-up score minus the baseline score resulting from the latent change score model, with positive values indicating increases in cognitive performance over time and negative values indicating declines in performance over time. We also established the measurement invariance across 2-time points, resulting in an acceptable fit statistic: comparative fit index (CFI) = 0.85, Tucker–Lewis index (TLI) = 0.84, and Root Mean Squared Error of Approximation (RMSEA)= 0.069 (95% Confidence Interval (CI)= 0.065–0.072, $p < 0.001$) (Simon et al., 2022).

2.4. Imaging protocol

2.4.1. Magnetic resonance imaging

All MR images were acquired on a 3.0T Philips Achieva magnet. There were 2 2-hour MR imaging sessions to accommodate several imaging modalities. Relevant to the current study, T1-weighted Magnetization-Prepared Rapid Acquisition Gradient Echo (MPRAGE) scan was acquired to determine cortical thickness (parameters: TE/TR of 3/6.5 ms and flip angle of 8°, in-plane resolution of 256 × 256, field of view of 25.4 × 25.4 cm, and 165–180 slices in axial direction with slice-thickness/gap of 1/0 mm). In addition, Blood Oxygen Level Dependent (BOLD) fMRI for 12 tasks, Fluid Attenuated Inversion Recovery (FLAIR), Diffusion Tensor Imaging (DTI), Arterial Spin Labeling (ASL), and a 9.5-minute resting BOLD scan were acquired but not reported in the current study. A neuroradiologist reviewed each subject's scans; any significant findings were conveyed to the subject's primary care physician.

Each subject's structural T1 scan was reconstructed using FreeSurfer v5.1 (http://surfer.nmr.mgh.harvard.edu/). We used this older version to maintain consistency in data processing. The accuracy of FreeSurfer's subcortical segmentation and cortical parcellation (Fischl et al., 2002; Fischl et al., 2004) has been reported to be comparable to manual labeling. Each subject's white and gray matter boundaries as well as gray matter and cerebral spinal fluid boundaries were visually inspected slice by slice, manual control points were added when any visible discrepancy was found, and reconstruction was repeated until we reached satisfactory results within every subject. The subcortical structure borders were plotted by TkMedit visualization tools and compared against the actual brain regions. In case of discrepancies, they were corrected manually.

2.4.2. PET imaging

2.4.2.1. Amyloid-β PET. Participants underwent ^{18}F-florbetaben PET scans to assess amyloid-β burden. Participant preparation consists of intravenous catheterization followed by the bolus injection (over 10–20 seconds) of the tracer. The PET scans were acquired on the same MCT PET/CT scanner (Siemens) in dynamic, 3D imaging mode beginning 50 minutes after injection. Brain images were acquired in 4 × 5-minute frames over a period of 20 minutes. The images were immediately assessed for technical validity. If considered inadequate, the participant had an additional 20 minutes of continuous imaging. Transmission scans were done prior to the scan. If there was a repeat scan, transmission was done after the scan.

Image processing followed a previous established procedure (Tahmi et al., 2019). The standardized uptake value, defined as the decay-corrected brain radioactivity concentration normalized for injected dose and body weight, is then calculated. The standardized uptake value is normalized to cerebellum gray matter to derive the standardized uptake value ratio (SUVR). The SUVR was determined at both the voxel and ROI level. We used K-means clustering of log-transformed SUVR values to classify each participant's overall scan as "amyloid positive" or "amyloid negative" (Villemagne et al., 2012), considering a threshold of 1.25 for 18F-florbetaben tracer (Bullich et al., 2021). In addition, 2 trained radiologists classified the generated static PET images as amyloid-β positive or negative.

2.4.2.2. Tau PET. Tau PET images were acquired using a Siemens Biograph64 mCT/PET scanner in dynamic 3D imaging mode. We used ^{18}F-MK-6240 tracer to assess tau burden, which was synthesized and administered onsite. An intravenous bolus injection (target dose: 5 mCi) of the ^{18}F-MK-6240 tracer was administered 80–100 minutes prior to the image acquisition. Six dynamic frames were acquired within 30 minutes (6 × 5 minutes) of scanning. An iterative reconstruction algorithm was used to generate dynamic PET volumes with 1 × 1 × 2 mm voxel size. The process started by aligning 4 dynamic PET frames to the first frame using rigid-body registration and generating a static PET image by averaging the 4 registered frames.

The static PET volume was then registered with the CT and merged to generate a composite image. Each participant's structural T1 scan, after being reconstructed with FreeSurfer, was registered directly to the static Tau PET volume using an intermodal and intrasubject registration technique (rigid-body registration: 6 degrees of freedom, mutual information). FreeSurfer regional masks were then used to extract regional uptake values. Regional and voxel-wise Tau PET SUVRs were obtained by normalizing the regional and voxel-wise uptake value with the average uptake value in the cerebellar gray matter region. In addition, to classify the sample according to Braak I-VI stages (Braak and Braak, 1991), we calculated the volume-weighted mean SUVR for composite regions representing each stage (Scholl et al., 2016) (for details, see Supplementary Table S1).

As our primary interest was to investigate the association between cognitive changes and early elevation in tau PET uptake in AD-vulnerable regions, we created meta-ROIs that included 16 subregions selected a priori based on previous work (Insel et al., 2020). The tau SUVR of each subregion was averaged to create 4 meta-ROIs, as described below and illustrated in Fig. 3: (1) total-AD ROI comprising all 16 areas; (2) medial temporal lobe-ROI (MTL-ROI), including the entorhinal cortex, hippocampus, parahippocampal gyrus and amygdala; (3) lateral temporal lobe-ROI (LTL-ROI), comprised of the banks of the superior temporal sulcus, transverse temporal lobe, temporal pole, inferior, middle, and superior temporal lobe, and fusiform; and (4) cingulate/parietal lobe ROI (C/P-ROI), including inferior and superior parietal lobe, isthmus cingulate, precuneus, and supramarginal gyrus. The regional tau SUVRs of the left and right hemispheres were then averaged to create a mean measure of tau SUVR for each region.

2.5. Statistical analysis

We report the demographic characteristics, cognitive performance, amyloid-β status, and ^{18}F-MK-6240 SUVR using means and standard deviation for the continuous variables, and frequency and percentage for the categorical variables.

We assessed factors potentially associated with cognitive change (memory, speed, and reasoning) or regional tau deposition in the meta-ROIs (Total-AD, MTL, LCL, and C/P) using regression analysis. Those factors were age, biological sex, race, education, and amyloid-β level, which were considered independent variables in the models. Each regression included a measure of cognitive change or regional tau as a dependent variable. To assess the associations between tau burden ([^{18}F]-MK-6240 SUVR) and retrospective cognitive change, we used separate multiple regression models for each meta-ROI (total-AD, MTL, LCL, and C/P) and each cognitive domain (i.e., memory, speed, and reasoning).

Our primary analysis focused on tau deposition in the total-AD-ROI, and secondary analyses focused on each regional ROI (MTL, LCL, and C/P). Age, sex, years of education, and baseline cognitive performance were included as covariates in the models since those may influence cognitive functioning or tau levels. As an exploratory analysis, we conducted multiple regression models for each of the 34 brain areas in the "Desikan-Killiany-Tourville" atlas (Klein and Tourville, 2012) plus hippocampus and amygdala with available data on tau deposition. Furthermore, we used the Bonferroni method (Armstrong, 2014) to account for multiple comparison corrections in this exploratory analysis.

Considering that our sample is mostly amyloid-β negative (82%), the primary analysis did not adjust for amyloid-β levels. As a sensitivity analysis, we reran the primary regression models including amyloid-β level (continuous variable) as a covariate. In addition, to assess whether the time interval between PET scan and cognitive/MRI exams moderated the significant associations between tau deposition and cognitive change, we reran the regressions by adding the interval as a covariate and interaction term. Analyses were performed using R and SPSS 26, and a priori significance levels were set to 0.05.

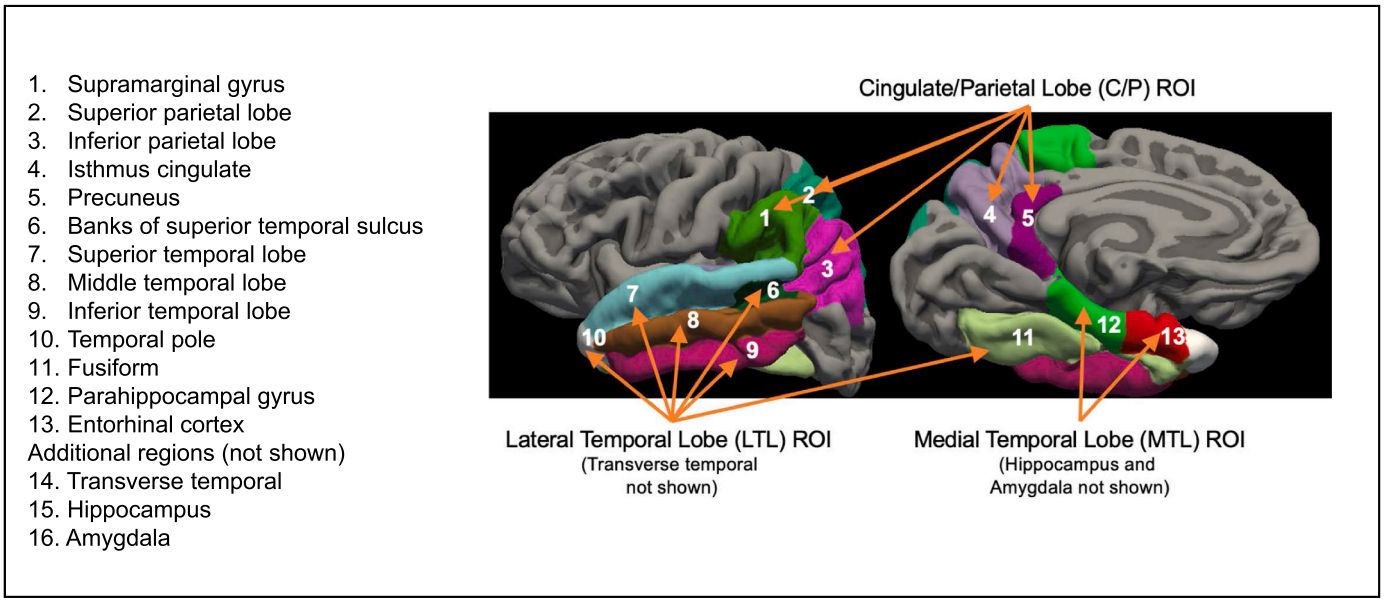

Fig. 3. Illustrations of regions of interest. Abbreviations: ROI, region of interest.

3. Results

3.1. Sample characteristics

Table 1 describes the demographic features of the study sample, including age, sex, race/ethnicity, education, and data on cognitive performance and tau deposition ([^{18}F]-MK-6240 SUVR). In addition, time intervals between cognitive assessments and imaging acquisitions (MRI and PET scan) are provided.

Participants were, on average, 67.5 ± 5.8 (mean ± SD) years old at the time of the follow-up MRI and cognitive assessment, which generally occurred within 1 month of each other. Overall, the sample was highly educated (16.20 ± 2.26), mostly White (White = 63.4%; Black = 26.1%; Latinx = 7.3%), and had high intelligence quotient scores (118.97 ± 7.76). All participants were cognitively healthy at both baseline and follow-up and showed a significant cognitive decline over 5 years in all 3 cognitive domains for the larger samples from the 2 studies (n > 230) (Gazes et al., 2023; Simon et al., 2022). For the subset examined in this manuscript (N = 41), this pattern remained similar, as we observed cognitive decline in reasoning [t(40) = 7.904, $p < 0.001$] and speed [t(40) = 9.220, $p < 0.001$]. However, the change in memory was not significant [t(40) = 0.723, $p = 0.47$]. Most participants were classified as Braak stage 0 (82.9%), some as Braak stage 1 (14.6%), and 1 participant as Braak stage 2 (2.4%). Regarding amyloid-β status, 82% of the sample (N = 39, 2 missing data) were classified as negative for amyloid-β when using a threshold of 1.25 for 18F-florbetaben tracer (Bullich et al., 2021).

On average, there was an interval of approximately 17–18 months between tau PET scan and follow-up MRI/cognitive exams, with a wide range (1–49 months). Of note, both the PET scans (tau and amyloid-β) occurred after the follow-up MRI/cognitive exams. Despite that, most of the sample (73%) presented an interval within 2 years between PET and MRI/cognitive exams. Reasons for this interval discrepancy included tau data collection beginning later in the study, scheduling challenges, and the temporary interruption of data collection due to the local onset of the COVID-19 pandemic in 2020. In addition, PET amyloid-β and tau PET scans occurred, on average, 13 months apart.

Regarding the sample differences in amyloid-β status, participants with positive amyloid-β (N = 7) presented higher levels of tau deposition, particularly on the meta MTL-ROI. Moreover, the interval between tau scan and MRI/cognitive exams was shorter for those with positive amyloid-β, as we prioritize collecting tau data on those with higher amyloid-β burden.

3.2. Factors associated with tau deposition and cognitive change

The amyloid-β level was associated with higher levels of tau, above and beyond age, sex, race/ethnicity, and education (Table 2). We did not observe age, race/ethnicity, and years of education to be associated with tau, although sex was associated with tau levels, as females presented a higher tax burden than males in most meta-ROIs. Regarding cognition, there was no association between cognitive change and demographics such as age, sex, race/ethnicity, and education, as well as the amyloid-β level (Supplementary Table S2). This observation was consistent when we combined these factors in 1 model or explored bivariate associations between these factors and cognitive change.

3.3. Tau deposition and retrospective change in episodic memory

After controlling for age, sex, education, and baseline memory performance, steeper decline in memory was associated with greater [^{18}F]MK-6240 SUVR in the total-AD meta-ROI ($\beta = -1.81$, $p = 0.03$), in the meta-ROIs LCL ($\beta = -1.79$, $p = 0.03$), and C/P ($\beta = -1.75$, $p = 0.02$) and, at a trend level, in the MTL ($\beta = -0.99$, $p = 0.05$) (Table 3, Fig. 4A–D). When we controlled for amyloid-β level in our models (N = 39), the pattern remained similar, but the significance of the findings was marginal, as observed for total-AD meta-ROI ($\beta = -1.64$, $p = 0.08$), and in the meta-ROIs LCL ($\beta = -1.64$, $p = 0.08$), C/P ($\beta = -1.65$, $p = 0.08$), and MTL ($\beta = -0.84$, $p = 0.14$).

In the exploratory analysis, we investigated which brain areas contributed to the significant findings (Fig. 4E). In the MTL, we observed that memory change was associated with tau deposition in the amygdala ($\beta = -1.23$, $p = 0.004$) and hippocampus ($\beta = -1.07$, $p = 0.03$), but not in the entorhinal cortex ($\beta = -0.42$, $p = 0.27$) and parahippocampal gyrus ($\beta = -0.46$, $p = 0.49$). The remaining temporo-parietal regions with significant associations with memory decline included the posterior cingulate ($\beta = -2.06$, $p = 0.01$), superior parietal lobe ($\beta = -1.89$, $p = 0.01$), inferior parietal lobe ($\beta = -1.85$, $p = 0.04$), supramarginal gyrus ($\beta = -1.12$, $p = 0.04$), temporal pole ($\beta = -0.90$, $p = 0.04$), and superior temporal lobe ($\beta = -1.65$, $p = 0.04$). Nevertheless, these findings did not survive correction for multiple comparisons ($p < 0.001$).

Table 1
Sample characteristics

	Overall sample (n = 41)	Aβ− (n = 32)	Aβ+ (n = 7)	*p*-value
Age, years at follow-up M (SD) [min, max]	67.39 (5.80) [55, 77]	67.15 (5.79) [55, 77]	70.57 (4.42) [64, 75]	0.15
Sex/Gender, female n(%)	19 (46.2%)	15 (46.9%)	2 (28.6%)	0.43
Race/Ethnicity n(%)	White 26 (63.4%) Black 11 (26.1%) Pacific Island 1 (2.4%) Other 3 (7.3%)	White 22 (68.8%) Black 8 (25%) Pacific Island 1 (3.1%) Other 1 (3.1%)	White 3 (42.9%) Black 3 (42.9%) Pacific Island 0 Other 1 (14.3%)	0.41
	Latinx 3 (7.3%)	Latinx 2 (6.3%)	Latinx 0	0.10
Education (years) M(SD) [min, max]	16.20 (2.26) [12, 21]	16.34 (2.39) [12, 21]	15.86 (1.86) [14, 18]	0.61
Dementia Rating Scale[b] M(SD) [min, max]	139.15 (4.82) [124, 144]			
Estimated IQ (at baseline) M(SD) [min, max]	118.97 (7.76) [102, 128.64]	119.73 (7.09) [104.40, 128.56]	116.25 (11.04) [102, 128.64]	0.15
Speed change M(SD) [min, max]	−0.18 (0.14) [−0.62, 0.11]	−0.16 (0.13) [−0.42, 0.11]	−0.27 (0.18) [−0.62, −0.03]	0.10
Reasoning change M(SD) [min, max]	−0.16 (0.11) [−0.57, 0.07]	−0.15 (0.10) [−0.44, 0.07]	−0.22 (0.16) [−0.57, −0.09]	0.17
Memory change M(SD) [min, max]	−0.05 (0.53) [−1.51, 0.99]	−0.01 (0.49) [−1.5, 0.99]	−0.32 (0.68) [−1.14, 0.68]	0.17
Amyloid uptake (^{18}F-Florbetaben)[a] [min, max]	1.14 (0.19) [0.90, 1.78]	1.07 (0.06) [0.90, 1.20]	1.49 (0.20) [1.28, 1.78]	<0.001
Tau uptake ([^{18}F]-MK-6240) by ROIs				
Total-AD-ROI M(SD)	0.92 (0.09) [0.73, 1.16]	0.91 (0.08) [0.73, 1.06]	0.98 (0.12) [0.79, 1.16]	0.05
Medial temporal lobe meta-ROI M(SD)	0.91 (0.15) [0.73, 1.56]	0.89 (0.10) [0.73, 1.07]	1.03 (0.27) [0.75, 1.56]	**0.02**
Lateral temporal lobe meta-ROI M(SD)	0.96 (0.09) [0.76, 1.19]	0.95 (0.08) [0.73, 1.10]	1.02 (0.12) [0.83, 1.19]	0.06
Cingulate/Parietal meta-ROI M(SD)	0.87 (0.09) [0.68, 1.18]	0.86 (0.08) [0.68, 1.00]	0.94 (0.12) [0.78, 1.18]	**0.03**
Braak stages n(%)	Braak 0: 34 (82.9%) Braak I: 6 (14.6%) Braak II: 1 (2.4%)	Braak 0: 27 Braak I: 5 Braak II: 0	Braak 0: 5 Braak I: 1 Braak II: 1	0.09
Months between cog and tau scan M(SD) [min, max]	17.56 (12.87) [0.0, 49.0]	19.53 (13.46) [0.0, 49.0]	8.00 (5.41) [1.0, 18.0]	**0.03**
Months between MRI and tau scan M(SD) [min, max]	18.26 (13.52) [1.0, 48.0]	20.00 (12.87) [1.0, 49.0]	7.85 (5.78) [2.0, 18.0]	**0.03**

Key: AD, Alzheimer's disease; IQ, intelligence quotient; ROI, region of interest; SD, standard deviation.
[a] Missing amyloid data for 2 participants.

3.4. Tau deposition and retrospective change in processing speed

Steeper decline in speed was also associated with greater [^{18}F]MK-6240 SUVR in the total-AD meta-ROI ($\beta = -0.53, p = 0.04$), in the meta-ROIs MTL ($\beta = -0.36$, $p = 0.02$), LCL ($\beta = -0.55$, $p = 0.04$), and at trend level, C/P ($\beta = -0.52$, $p = 0.05$) (Table 4, Fig. 5A–D). When controlling for amyloid-β level in our models (N = 39), the results remained significant for MTL meta-ROI ($\beta = -0.37, p = 0.04$), but were marginal for the remaining meta-ROIs, such as total-AD ($\beta = -0.53$, $p = 0.09$), LCL ($\beta = -0.55, p = 0.07$), and C/P ($\beta = -0.51, p = 0.10$).

In our exploratory analysis we observed 10 areas that presented significant associations with speed decline (Fig. 5E): lateral occipital ($\beta = -0.63$, $p = 0.01$), entorhinal cortex ($\beta = -0.27$, $p = 0.01$), fusiform gyrus ($\beta = -0.55$, $p = 0.02$), lingual ($\beta = -0.58$, $p = 0.02$), inferior parietal ($\beta = -0.60$, $p = 0.03$), amygdala ($\beta = -0.28$, $p = 0.03$), superior parietal ($\beta = -0.52$, $p = 0.03$), inferior temporal ($\beta = -0.60$, $p = 0.03$), temporal pole ($\beta = -0.28$, $p = 0.04$), and hippocampus ($\beta = -0.31, p = 0.04$). However, these findings did not survive correction for multiple comparisons ($p < 0.001$).

Despite the pattern observed for memory and speed, no associations between tau levels and reasoning change were observed (Supplementary Table S2).

Critically, the tau-cognition associations remained similar after controlling for intervals between tau and MRI/cognitive exams. None of the associations observed between tau levels and memory or speed change were moderated by the interval between the PET scan and MRI/cognitive exams ($p > 0.05$). In addition, it is relevant to note that the associations observed are unique to tau and not β-amyloid, as we did not observe any association between amyloid levels and cognition (for details, see Supplementary Table S6).

3.5. Sensitivity analysis: the influence of tau levels

We ran a sensitivity analysis to assess the influence of the outlier in tau values in the data. First, we reran the primary analysis removing the subject classified as Braak stage 2, which has the highest tau uptake values. The results were no longer significant, although some results were marginal (for details, see Supplementary Tables S4–S5). Nevertheless, when we reran the primary analysis by randomly removing 1 subject classified as Braak stage 1 or Braak stage 0, we also observed a lack of significant results (Supplementary Tables S4–S5). This demonstrated that the removal of any data point reduced enough statistical power to render the results nonsignificant.

4. Discussion

In this study, we investigated how in vivo measures of regional tau are associated with 5-year cognitive change in cognitively unimpaired older adults. We found that higher tau-tracer ^{18}F-MK-6240 SUVR in AD-related ROIs was associated with steeper decline in episodic memory and processing speed, but not with reasoning. This pattern was observed beyond critical demographics (age, sex, and education), baseline cognitive performance, and amyloid-β status. Our findings suggest regional specificity of tau-cognition relationships, particularly involving the MTL, cingulate, and parietal regions.

These findings extend the previous literature that episodic memory is a key domain associated with early tau deposition, even in cognitively unimpaired older adults and lower levels of amyloid-β (Chen et al., 2021b; Insel et al., 2020; Jack et al., 2020; Maass et al., 2018; Marks et al., 2017; Sperling et al., 2019; Vogel et al., 2020; Ziontz et al., 2019). In our study, memory decline was associated with higher tau uptake (^{18}F-MK-6240) in the total-AD meta-ROI but also in more specific

Table 2
Associations between participant's demographics, amyloid status, and regional ^{18}F-MK-6240 SUVR

	Total AD-ROI	MTL-ROI	LTL-ROI	C/P-ROI
Intercept	0.885 (0.205)	0.361 (0.340)	0.963 (0.209)	0.885 (0.205)
	***p* < 0.001**	*p* = 0.29	***p* < 0.001**	***p* < 0.001**
Age (follow-up)	−0.001 (0.003)	−0.000 (0.004)	−0.001 (0.003)	−0.001 (0.003)
	p = 0.59	*p* = 0.94	*p* = 0.64	*p* = 0.59
Sex/Gender[a]	−0.075 (0.029)	−0.026 (0.048)	−0.076 (0.030)	−0.075 (0.029)
	***p* = 0.01**	*p* = 0.58	***p* = 0.01**	***p* = 0.01**
Race	−0.014 (0.016)	0.027 (0.026)	−0.017 (0.016)	−0.014 (0.016)
	p = 0.37	*p* = 0.33	*p* = 0.30	*p* = 0.37
Education	0.004 (0.006)	0.011 (0.011)	0.003 (0.006)	0.004 (0.006)
	p = 0.51	*p* = 0.29	*p* = 0.65	*p* = 0.51
Amyloid level	0.189 (0.075)	0.339 (0.123)	0.167 (0.076)	0.189 (0.075)
	***p* = 0.01**	***p* = 0.01**	***p* = 0.03**	***p* = 0.01**

Estimated fixed effects are reported along with their standard errors in parentheses.
Key: AD, Alzheimer's disease; C/P, cingulate/parietal lobe; LTL, lateral temporal lobe; MTL, medial temporal lobe; ROI, region of interest.
[a] Reference values: 0 = women; 1 = men.

Table 3
Associations between tau uptake ([^{18}F]MK-6240 SUVR) with change in memory as outcome

Models: N = 41		Global tau uptake	MLT tau uptake	LTL tau uptake	C/P tau uptake
Age	β	−0.01	−0.01	−0.01	−0.01
	p-value	0.31	0.28	0.31	0.31
Sex/Gender	β	−0.20	−0.11	−0.20	−0.22
	p-value	0.21	0.48	0.22	0.17
Education	β	0.01	0.02	0.01	0.01
	p-value	0.66	0.55	0.68	0.70
Memory Baseline	β	−0.25	−0.26	−0.25	−0.23
	p-value	**0.01**	0.01	0.01	0.02
Tau uptake	β	−1.81	−0.99	−1.79	−1.75
	p-value	**0.03**	**0.05**	**0.03**	**0.02**
R^2		0.31	0.29	0.30	0.31
F(5,40)		3.14	2.93	3.12	3.27

Memory change = follow-up minus baseline, the more negative, the greater the decline. Each column represents a separate model.
Key: C/P, cingulate/parietal lobe; LTL, lateral temporal lobe; MTL, medial temporal lobe.

meta-ROIs reflecting MTL, LTL, and cingulate/parietal regions. Our exploratory analysis indicates that this pattern was particularly strong in MTL areas typically associated with memory, such as the hippocampus and amygdala (Buffalo et al., 2006; Dolcos et al., 2005; Insel et al., 2020). Surprisingly, we did not observe a significant association between memory decline and tau uptake in the entorhinal cortex. This finding contradicts observations from previous literature (Insel et al., 2020; Scholl et al., 2016) and suggests that our small sample size may have limited statistical power.

Our finding also supports the relevance of tau burden in other non-MTL brain areas previously linked to memory and attention, including regions on the cingulate cortex, parietal, and temporal lobes (Insel et al., 2020). For instance, the posterior cingulate cortex has been previously associated with autobiographic memory and attention regulation (Leech and Sharp, 2014), and the superior parietal lobe linked to attention control and working memory (Shomstein, 2012). Higher tau uptake in other regions such as temporal pole, inferior parietal lobe, and supramarginal gyrus seems to have contributed to our findings on memory decline. Some of these areas have been associated with memory (e.g., temporal pole) (Chadwick et al., 2016) but also with social cognition and semantic processing (Chadwick et al., 2016; Pulvermuller, 2013; Tso et al., 2018). It is possible that the relevance of these areas in our findings is related to the nature of the memory tasks used in the study, which were all highly dependent on verbal or semantic content (e.g., word list, story, word pairs).

The novelty of our study is that early tau deposition (^{18}F-MK-6240) was associated with processing speed decline when accounting for critical covariates, including amyloid-β level (particularly in MTL). Therefore, processing speed decline was associated with higher tau uptake in the total-AD meta-ROI, and in ROIs reflecting MTL and LTL, and some parietal regions. When exploring the regions that could potentially be driving this pattern, we identified similar regions to those described in the tau-memory associations, such as the hippocampus, amygdala, and inferior and superior parietal lobes. Critically, entorhinal emerged as a relevant ROI for the tau-speed associations, even when we controlled for memory change in our speed models. These findings suggest that early tau deposition in AD-related regions on MTL and parietal lobe may also hinder the performance on timed tasks, resulting in a speed decline. This finding has clinical relevance as processing speed is critical in complex everyday-life tasks when the information needed is often available within a limited time frame. In addition, processing speed decline was also associated with higher tau uptake in regions relevant to the processing of visual information, such as the lateral occipital cortex, lingual gyrus, and fusiform gyrus. These areas have been linked with the visual recognition of objects, letters, words, and patterns (Grill-Spector et al., 2001; Lingnau and Downing, 2015; Mechelli et al., 2000). It is worth mentioning that our finding is consistent with the visual timed tasks used in the study, which demanded participants to quickly identify patterns of letters, numbers, colors, shapes, and lines.

Our observations are in line with longitudinal studies of cognitively unimpaired older adults that show tau deposition to be associated with a decline in global cognition (Aschenbrenner et al., 2018; Biel et al., 2021; Pontecorvo et al., 2019), verbal fluency (Ziontz et al., 2019), and in composite scores including memory, executive function, speed, and language (Hanseeuw et al., 2019; Ossenkoppele et al., 2022). It is possible that these nonmemory findings are based on timed tests (e.g., fluency), and that decline in processing speed influences changes in other cognitive domains. Despite that, the contribution of tau burden to nonmemory cognitive decline in cognitively healthy older adults remains inconsistent, as other reports indicate that tau deposition was not associated with a decline in executive functions, including speed-demanding tasks (e.g., Trail Making Test B) (Sperling et al., 2019).

Our study has several strengths that advance previous research. We approached tau-cognition associations based on a priori AD-ROIs (Insel et al., 2020) and used cognitive domains well established to change in aging (Gazes et al., 2023; Habeck et al., 2016; Salthouse, 2004, 2009, 2019; Stern et al., 2014). Critically, cognitive change was measured based on multiple tasks (i.e., 6 per domain), using a robust measurement-latent change approach (Kievit et al., 2018). In addition,

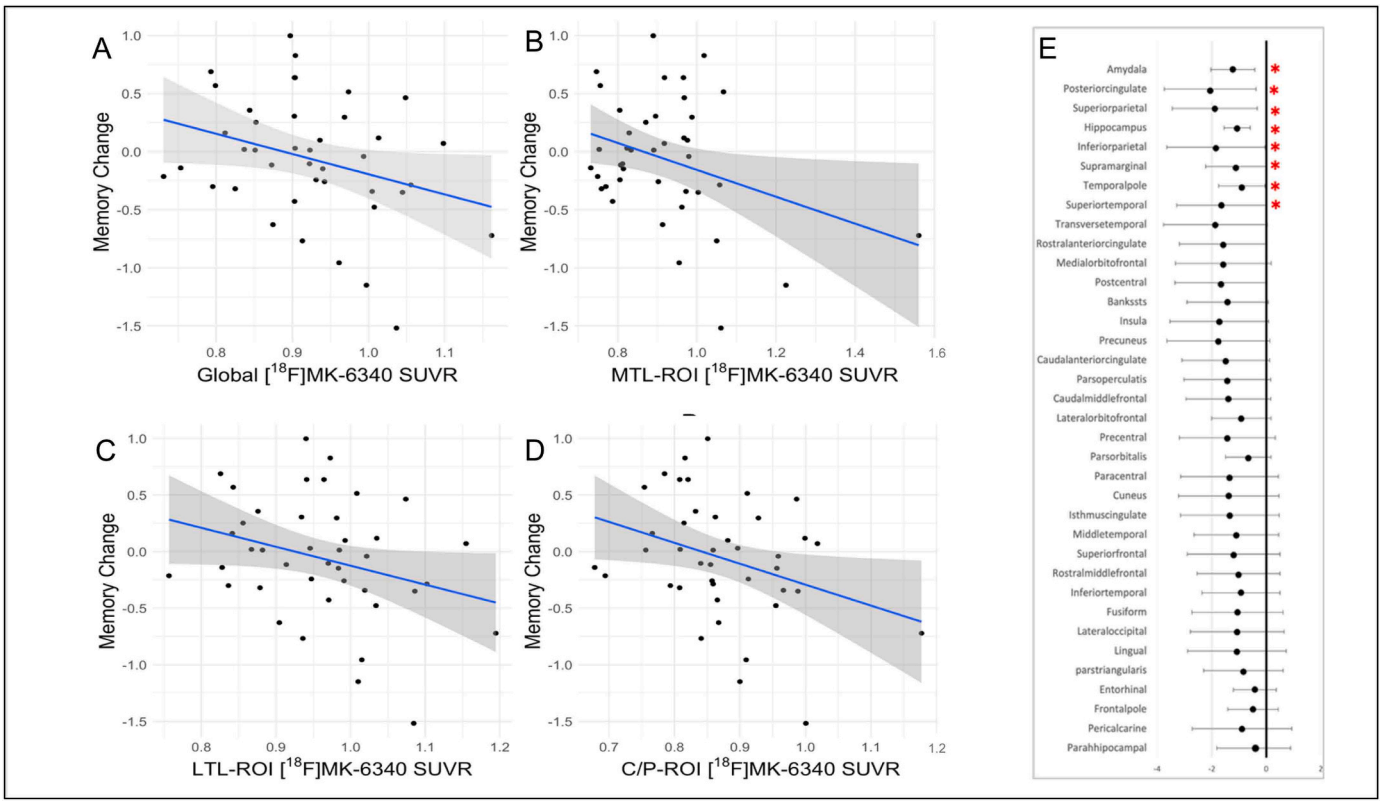

Fig. 4. Scatterplot diagrams illustrating the relationship between tau PET uptake [^{18}F-MK-6240] and memory change across brain regions. (A–D) The associations considering regional tau uptake (meta-ROIs). (E) A forest plot representing the unstandardized betas and 95% interval confidence for each linear regression considering 36 brain areas. The results highlighted (*) are not corrected for multiple comparisons. All regressions accounted for age at follow-up, sex/gender, education, and baseline memory performance. Abbreviations: C/P, cingulate/parietal lobe; LTL, lateral temporal lobe; MTL, medial temporal lobe; ROI, region of interest; SUVR, standardized uptake value ratio.

Table 4
Association of tau uptake ([^{18}F]MK-6240 SUVR) with change in speed as outcome

Models: N = 41		Global tau uptake	MLT tau uptake	LTL tau uptake	C/P tau uptake
Age	β	−0.006	−0.006	−0.006	−0.006
	p-value	0.17	0.22	0.18	0.18
Sex/Gender	β	−0.04	−0.01	−0.04	−0.04
	p-value	0.40	0.70	0.38	0.37
Education	β	0.007	0.008	0.007	0.007
	p-value	0.52	0.47	0.55	0.54
Speed Baseline	β	−0.004	0.01	−0.003	0.003
	p-value	0.93	0.73	0.94	0.94
Tau uptake	β	−0.53	−0.36	−0.55	−0.52
	p-value	**0.04**	**0.02**	**0.04**	**0.05**
R^2		0.17	0.20	0.17	0.16
F(5,40)		1.43	1.78	1.52	1.40

Speed change = follow-up minus baseline, the more negative, the greater the decline. Each column represents a separate model.
Key: C/P, cingulate/parietal lobe; LTL, lateral temporal lobe; MTL, medial temporal lobe; SUVR, standardized uptake value ratio.

we used the PET tracer ^{18}F-MK-6240, shown to be sensitive to cognitive decline in cognitively intact older adults (Betthauser et al., 2020; Kwan et al., 2023). Moreover, the associations observed were unique to tau and not β-amyloid, which strengthens the value of specifically investigating tau levels and cognitive decline.

This study has several limitations that may limit the generalizability of the findings. We assessed the relationships between tau tracer retention and cognitive decline retrospectively rather than prospectively because of the more recent implementation of tau PET in our studies. Although consideration of the time interval between PET tau scan and MRI/cognitive exams did not significantly change our results or moderate the association between tau and cognitive change, the intervals were large for some participants, especially for those who were amyloid-β negative. It is worth mentioning that our studies (RANN/CR) were originally designed to investigate cognitive aging and not AD pathology, and therefore our sample size was limited, particularly for amyloid-β positive individuals. In addition, while we observed the influence of the higher tau values in our results, the sensitivity analysis suggests that this issue was difficult to disentangle from our overall low power due to the relatively small sample size. Although we took advantage of the available amyloid-β data to better describe our sample, the fact that most participants were amyloid-β negative made it difficult to have a balanced sample and enough power to detect amyloid-β moderation effects on the findings. Therefore, the observation that tau deposition was associated with memory and speed decline regardless of amyloid-β levels should be considered with caution, although it is consistent with previous reports (Maass et al., 2018; Sperling et al., 2019). Furthermore, although our exploratory analysis provides more specific information regarding relevant brain areas for tau-cognition associations and may better inform future studies, the observed pattern did not survive multiple comparisons and should be interpreted with caution. Lastly, the present results need to be confirmed with larger and more diverse samples.

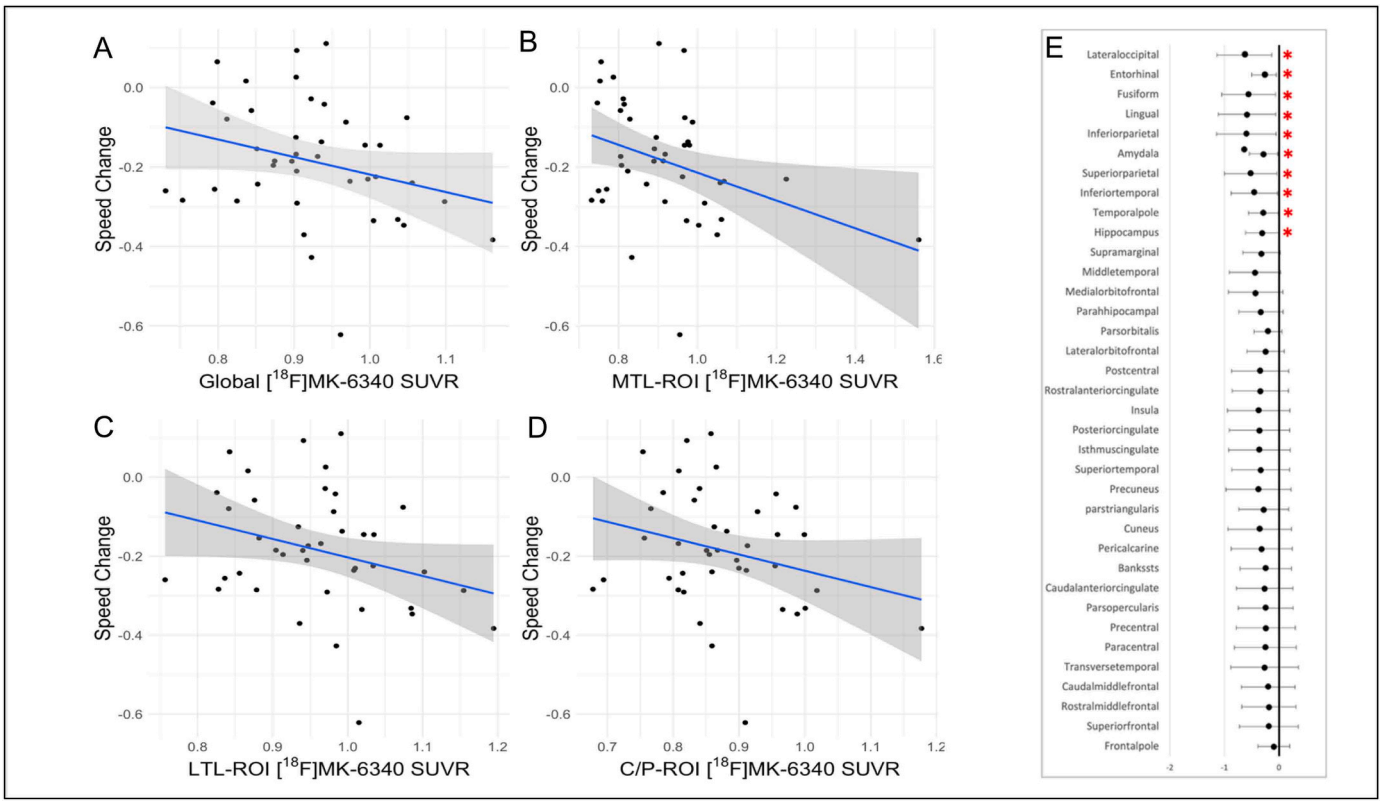

Fig. 5. Scatterplot diagrams illustrating the relationship between tau PET [^{18}F-MK-6240] and processing speed change across brain regions. (A–D) The associations considering regional tau uptakes (meta-ROIs). (E) A forest plot representing the unstandardized betas and 95% interval confidence for each linear regression considering different 36 brain areas. The results highlighted (*) are not corrected for multiple comparisons. All regressions accounted for age at follow-up, sex/gender, education, and baseline memory performance. Abbreviations: C/P, cingulate/parietal lobe; LTL, lateral temporal lobe; MTL, medial temporal lobe; ROI, region of interest; SUVR, standardized uptake value ratio.

5. Conclusion

Overall, our findings reinforce the notion that pathological tau in areas of early deposition may influence cognitive changes known to be affected in AD even in a sample of cognitively unimpaired older adults and low amyloid-β level. In addition, our data suggest that tau burden may, in part, underlie memory and speed decline typically seen in normal aging. Critically, the present results highlight the relevance of investigating longitudinal tau-cognition relationships beyond memory, and processing speed seems to be a promising marker of tau burden. This path of research may contribute to a better understanding of the differences between AD, primary age-related tauopathy (Crary et al., 2014), and normal aging, with the impact of future interventions.

Verification

The present manuscript has not been published previously (except in the form of an abstract), and it is not under consideration for publication elsewhere. The publication is approved by all authors and by the responsible authorities where the work was carried out. If accepted, the manuscript will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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CRediT authorship contribution statement

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Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.10.001.

References

Armstrong, R.A., 2014. When to use the Bonferroni correction. Ophthalmic Physiol. Opt. 34 (5), 502–508. https://doi.org/10.1111/opo.12131.

Aschenbrenner, A.J., Gordon, B.A., Benzinger, T.L.S., Morris, J.C., Hassenstab, J.J., 2018. Influence of tau PET, amyloid PET, and hippocampal volume on cognition in

Alzheimer disease. Neurology 91 (9), e859–e866. https://doi.org/10.1212/WNL.0000000000006075.
Betthauser, T.J., Cody, K.A., Zammit, M.D., Murali, D., Converse, A.K., Barnhart, T.E., Stone, C.K., Rowley, H.A., Johnson, S.C., Christian, B.T., 2019. In vivo characterization and quantification of neurofibrillary tau PET radioligand (18)F-MK-6240 in humans from Alzheimer disease dementia to young controls. J. Nucl. Med. 60 (1), 93–99. https://doi.org/10.2967/jnumed.118.209650.
Betthauser, T.J., Koscik, R.L., Jonaitis, E.M., Allison, S.L., Cody, K.A., Erickson, C.M., Rowley, H.A., Stone, C.K., Mueller, K.D., Clark, L.R., Carlsson, C.M., Chin, N.A., Asthana, S., Christian, B.T., Johnson, S.C., 2020. Amyloid and tau imaging biomarkers explain cognitive decline from late middle-age. Brain 143 (1), 320–335. https://doi.org/10.1093/brain/awz378.
Biel, D., Brendel, M., Rubinski, A., Buerger, K., Janowitz, D., Dichgans, M., Franzmeier, N., Alzheimer's Disease Neuroimaging, I, 2021. Tau-PET and in vivo Braak-staging as prognostic markers of future cognitive decline in cognitively normal to demented individuals. Alzheimers Res. Ther. 13 (1), 137. https://doi.org/10.1186/s13195-021-00880-x.
Blessed, G., Tomlinson, B.E., Roth, M., 1968. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br. J. Psychiatry 114 (512), 797–811. https://doi.org/10.1192/bjp.114.512.797.
Braak, H., Braak, E., 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol. 82 (4), 239–259. https://doi.org/10.1007/BF00308809.
Braak, H., Thal, D.R., Ghebremedhin, E., Del Tredici, K., 2011. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J. Neuropathol. Exp. Neurol. 70 (11), 960–969. https://doi.org/10.1097/NEN.0b013e318232a379.
Brier, M.R., Gordon, B., Friedrichsen, K., McCarthy, J., Stern, A., Christensen, J., Owen, C., Aldea, P., Su, Y., Hassenstab, J., Cairns, N.J., Holtzman, D.M., Fagan, A. M., Morris, J.C., Benzinger, T.L., Ances, B.M., 2016. Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. Sci. Transl. Med. 8 (338), 338ra366. https://doi.org/10.1126/scitranslmed.aaf2362.
Buffalo, E.A., Bellgowan, P.S., Martin, A., 2006. Distinct roles for medial temporal lobe structures in memory for objects and their locations. Learn. Mem. 13 (5), 638–643. https://doi.org/10.1101/lm.251906.
Bullich, S., Roe-Vellve, N., Marquie, M., Landau, S.M., Barthel, H., Villemagne, V.L., Sanabria, A., Tartari, J.P., Sotolongo-Grau, O., Dore, V., Koglin, N., Muller, A., Perrotin, A., Jovalekic, A., De Santi, S., Tarraga, L., Stephens, A.W., Rowe, C.C., Sabri, O., Seibyl, J.P., Boada, M., 2021. Early detection of amyloid load using (18)F-florbetaben PET. Alzheimers Res. Ther. 13 (1), 67. https://doi.org/10.1186/s13195-021-00807-6.
Chadwick, M.J., Anjum, R.S., Kumaran, D., Schacter, D.L., Spiers, H.J., Hassabis, D., 2016. Semantic representations in the temporal pole predict false memories. Proc. Natl. Acad. Sci. U. S. A. 113 (36), 10180–10185. https://doi.org/10.1073/pnas.1610686113.
Chen, S.D., Lu, J.Y., Li, H.Q., Yang, Y.X., Jiang, J.H., Cui, M., Zuo, C.T., Tan, L., Dong, Q., Yu, J.T., Alzheimer's Disease Neuroimaging, I, 2021a. Staging tau pathology with tau PET in Alzheimer's disease: a longitudinal study. Transl. Psychiatry 11 (1), 483. https://doi.org/10.1038/s41398-021-01602-5.
Chen, X., Cassady, K.E., Adams, J.N., Harrison, T.M., Baker, S.L., Jagust, W.J., 2021b. Regional tau effects on prospective cognitive change in cognitively normal older adults. J. Neurosci. 41 (2), 366–375. https://doi.org/10.1523/JNEUROSCI.2111-20.2020.
Crary, J.F., Trojanowski, J.Q., Schneider, J.A., Abisambra, J.F., Abner, E.L., Alafuzoff, I., Arnold, S.E., Attems, J., Beach, T.G., Bigio, E.H., Cairns, N.J., Dickson, D.W., Gearing, M., Grinberg, L.T., Hof, P.R., Hyman, B.T., Jellinger, K., Jicha, G.A., Kovacs, G.G., Knopman, D.S., Kofler, J., Kukull, W.A., Mackenzie, I.R., Masliah, E., McKee, A., Montine, T.J., Murray, M.E., Neltner, J.H., Santa-Maria, I., Seeley, W.W., Serrano-Pozo, A., Shelanski, M.L., Stein, T., Takao, M., Thal, D.R., Toledo, J.B., Troncoso, J.C., Vonsattel, J.P., White 3rd, C.L., Wisniewski, T., Woltjer, R.L., Yamada, M., Nelson, P.T., 2014. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol. 128 (6), 755–766. https://doi.org/10.1007/s00401-014-1349-0.
Dolcos, F., LaBar, K.S., Cabeza, R., 2005. Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. Proc. Natl. Acad. Sci. U. S. A. 102 (7), 2626–2631. https://doi.org/10.1073/pnas.0409848102.
Duyckaerts, C., Braak, H., Brion, J.P., Buee, L., Del Tredici, K., Goedert, M., Halliday, G., Neumann, M., Spillantini, M.G., Tolnay, M., Uchihara, T., 2015. PART is part of Alzheimer disease. Acta Neuropathol. 129 (5), 749–756. https://doi.org/10.1007/s00401-015-1390-7.
Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33 (3), 341–355. https://doi.org/10.1016/s0896-6273(02)00569-x.
Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D.H., Busa, E., Seidman, L.J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., Dale, A. M., 2004. Automatically parcellating the human cerebral cortex. Cereb Cortex 14 (1), 11–22. https://doi.org/10.1093/cercor/bhg087.
Gazes, Y., Lee, S., Fang, Z., Mensing, A., Noofoory, D., Hidalgo Nazario, G., Babukutty, R., Chen, B.B., Habeck, C., Stern, Y., 2023. Effects of brain maintenance and cognitive reserve on age-related decline in three cognitive abilities. J. Gerontol. B Psychol. Sci. Soc. Sci. 78 (8), 1284–1293. https://doi.org/10.1093/geronb/gbad044.
Grill-Spector, K., Kourtzi, Z., Kanwisher, N., 2001. The lateral occipital complex and its role in object recognition. Vision Res. 41 (10–11), 1409–1422. https://doi.org/10.1016/s0042-6989(01)00073-6.
Grober, E., Sliwinski, M., 1991. Development and validation of a model for estimating premorbid verbal intelligence in the elderly. J. Clin. Exp. Neuropsychol. 13 (6), 933–949. https://doi.org/10.1080/01688639108405109.
Habeck, C., Gazes, Y., Razlighi, Q., Steffener, J., Brickman, A., Barulli, D., Salthouse, T., Stern, Y., 2016. The Reference Ability Neural Network Study: Life-time stability of reference-ability neural networks derived from task maps of young adults. Neuroimage 125, 693–704. https://doi.org/10.1016/j.neuroimage.2015.10.077.
Hanseeuw, B.J., Betensky, R.A., Jacobs, H.I.L., Schultz, A.P., Sepulcre, J., Becker, J.A., Cosio, D.M.O., Farrell, M., Quiroz, Y.T., Mormino, E.C., Buckley, R.F., Papp, K.V., Amariglio, R.A., Dewachter, I., Ivanoiu, A., Huijbers, W., Hedden, T., Marshall, G.A., Chhatwal, J.P., Rentz, D.M., Sperling, R.A., Johnson, K., 2019. Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. JAMA Neurol. 76 (8), 915–924. https://doi.org/10.1001/jamaneurol.2019.1424.
Hostetler, E.D., Walji, A.M., Zeng, Z., Miller, P., Bennacef, I., Salinas, C., Connolly, B., Gantert, L., Haley, H., Holahan, M., Purcell, M., Riffel, K., Lohith, T.G., Coleman, P., Soriano, A., Ogawa, A., Xu, S., Zhang, X., Joshi, E., Della Rocca, J., Hesk, D., Schenk, D.J., Evelhoch, J.L., 2016. Preclinical characterization of 18F-MK-6240, a promising PET tracer for in vivo quantification of human neurofibrillary tangles. J. Nucl. Med. 57 (10), 1599–1606. https://doi.org/10.2967/jnumed.115.171678.
Insel, P.S., Mormino, E.C., Aisen, P.S., Thompson, W.K., Donohue, M.C., 2020. Neuroanatomical spread of amyloid beta and tau in Alzheimer's disease: implications for primary prevention. Brain Commun. 2 (1), fcaa007. https://doi.org/10.1093/braincomms/fcaa007.
Jack Jr., C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12 (2), 207–216. https://doi.org/10.1016/S1474-4422(12)70291-0.
Jack, C.R., Wiste, H.J., Weigand, S.D., Therneau, T.M., Lowe, V.J., Knopman, D.S., Botha, H., Graff-Radford, J., Jones, D.T., Ferman, T.J., Boeve, B.F., Kantarci, K., Vemuri, P., Mielke, M.M., Whitwell, J., Josephs, K., Schwarz, C.G., Senjem, M.L., Gunter, J.L., Petersen, R.C., 2020. Predicting future rates of tau accumulation on PET. Brain 143 (10), 3136–3150. https://doi.org/10.1093/brain/awaa248.
Jellinger, K.A., Alafuzoff, I., Attems, J., Beach, T.G., Cairns, N.J., Crary, J.F., Dickson, D. W., Hof, P.R., Hyman, B.T., Jack Jr., C.R., Jicha, G.A., Knopman, D.S., Kovacs, G.G., Mackenzie, I.R., Masliah, E., Montine, T.J., Nelson, P.T., Schmitt, F., Schneider, J.A., Serrano-Pozo, A., Thal, D.R., Toledo, J.B., Trojanowski, J.Q., Troncoso, J.C., Vonsattel, J.P., Wisniewski, T., 2015. PART, a distinct tauopathy, different from classical sporadic Alzheimer disease. Acta Neuropathol. 129 (5), 757–762. https://doi.org/10.1007/s00401-015-1407-2.
Johnson, K.A., Schultz, A., Betensky, R.A., Becker, J.A., Sepulcre, J., Rentz, D., Mormino, E., Chhatwal, J., Amariglio, R., Papp, K., Marshall, G., Albers, M., Mauro, S., Pepin, L., Alverio, J., Judge, K., Philiossaint, M., Shoup, T., Yokell, D., Dickerson, B., Gomez-Isla, T., Hyman, B., Vasdev, N., Sperling, R., 2016. Tau positron emission tomographic imaging in aging and early Alzheimer disease. Ann. Neurol. 79 (1), 110–119. https://doi.org/10.1002/ana.24546.
Kievit, R.A., Brandmaier, A.M., Ziegler, G., van Harmelen, A.L., de Mooij, S.M.M., Moutoussis, M., Goodyer, I.M., Bullmore, E., Jones, P.B., Fonagy, P., Consortium, N., Lindenberger, U., Dolan, R.J., 2018. Developmental cognitive neuroscience using latent change score models: a tutorial and applications. Dev. Cogn. Neurosci. 33, 99–117. https://doi.org/10.1016/j.dcn.2017.11.007.
Klein, A., Tourville, J., 2012. 101 labeled brain images and a consistent human cortical labeling protocol. Front. Neurosci. 6, 171. https://doi.org/10.3389/fnins.2012.00171.
Kwan, A.T.H., Arfaie, S., Therriault, J., Azizi, Z., Lussier, F.Z., Tissot, C., Chamoun, M., Bezgin, G., Servaes, S., Stevenon, J., Rahmouni, N., Pallen, V., Gauthier, S., Rosa-Neto, P., 2023. Medial temporal tau predicts memory decline in cognitively unimpaired elderly. Brain Commun. 5 (1), fcac325. https://doi.org/10.1093/braincomms/fcac325.
Lee, W.J., Brown, J.A., Kim, H.R., La Joie, R., Cho, H., Lyoo, C.H., Rabinovici, G.D., Seong, J.K., Seeley, W.W., Alzheimer's Disease Neuroimaging, I, 2022. Regional Abeta-tau interactions promote onset and acceleration of Alzheimer's disease tau spreading. Neuron 110 (12), 1932–1943 e1935. https://doi.org/10.1016/j.neuron.2022.03.034.
Leech, R., Sharp, D.J., 2014. The role of the posterior cingulate cortex in cognition and disease. Brain 137 (Pt 1), 12–32. https://doi.org/10.1093/brain/awt162.
Lingnau, A., Downing, P.E., 2015. The lateral occipitotemporal cortex in action. Trends Cogn. Sci. 19 (5), 268–277. https://doi.org/10.1016/j.tics.2015.03.006.
Lohith, T.G., Bennacef, I., Vandenberghe, R., Vandenbulcke, M., Salinas, C.A., Declercq, R., Reynders, T., Telan-Choing, N.F., Riffel, K., Celen, S., Serdons, K., Bormans, G., Tsai, K., Walji, A., Hostetler, E.D., Evelhoch, J.L., Van Laere, K., Forman, M., Stoch, A., Sur, C., Struyk, A., 2019. Brain imaging of Alzheimer dementia patients and elderly controls with (18)F-MK-6240, a PET tracer targeting neurofibrillary tangles. J. Nucl. Med. 60 (1), 107–114. https://doi.org/10.2967/jnumed.118.208215.
Maass, A., Lockhart, S.N., Harrison, T.M., Bell, R.K., Mellinger, T., Swinnerton, K., Baker, S.L., Rabinovici, G.D., Jagust, W.J., 2018. Entorhinal tau pathology, episodic memory decline, and neurodegeneration in aging. J. Neurosci. 38 (3), 530–543. https://doi.org/10.1523/JNEUROSCI.2028-17.2017.
Marks, S.M., Lockhart, S.N., Baker, S.L., Jagust, W.J., 2017. Tau and beta-amyloid are associated with medial temporal lobe structure, function, and memory encoding in

normal aging. J. Neurosci. 37 (12), 3192–3201. https://doi.org/10.1523/JNEUROSCI.3769-16.2017.
Mattis, S., 1988. Dementia Rating Scale (DRS). Psychological Assessment Resources.
Mechelli, A., Humphreys, G.W., Mayall, K., Olson, A., Price, C.J., 2000. Differential effects of word length and visual contrast in the fusiform and lingual gyri during reading. Proc. Biol. Sci. 267 (1455), 1909–1913. https://doi.org/10.1098/rspb.2000.1229.
Ossenkoppele, R., Pichet Binette, A., Groot, C., Smith, R., Strandberg, O., Palmqvist, S., Stomrud, E., Tideman, P., Ohlsson, T., Jogi, J., Johnson, K., Sperling, R., Dore, V., Masters, C.L., Rowe, C., Visser, D., van Berckel, B.N.M., van der Flier, W.M., Baker, S., Jagust, W.J., Wiste, H.J., Petersen, R.C., Jack Jr., C.R., Hansson, O., 2022. Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. Nat. Med. 28 (11), 2381–2387. https://doi.org/10.1038/s41591-022-02049-x.
Ossenkoppele, R., Schonhaut, D.R., Scholl, M., Lockhart, S.N., Ayakta, N., Baker, S.L., O'Neil, J.P., Janabi, M., Lazaris, A., Cantwell, A., Vogel, J., Santos, M., Miller, Z.A., Bettcher, B.M., Vossel, K.A., Kramer, J.H., Gorno-Tempini, M.L., Miller, B.L., Jagust, W.J., Rabinovici, G.D., 2016. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 139 (Pt 5), 1551–1567. https://doi.org/10.1093/brain/aww027.
Pascoal, T.A., Shin, M., Kang, M.S., Chamoun, M., Chartrand, D., Mathotaarachchi, S., Bennacef, I., Therriault, J., Ng, K.P., Hopewell, R., Bouhachi, R., Hsiao, H.H., Benedet, A.L., Soucy, J.P., Massarweh, G., Gauthier, S., Rosa-Neto, P., 2018. In vivo quantification of neurofibrillary tangles with [(18)F]MK-6240. Alzheimers Res. Ther. 10 (1), 74. https://doi.org/10.1186/s13195-018-0402-y.
Pontecorvo, M.J., Devous, M.D., Kennedy, I., Navitsky, M., Lu, M., Galante, N., Salloway, S., Doraiswamy, P.M., Southekal, S., Arora, A.K., McGeehan, A., Lim, N.C., Xiong, H., Truocchio, S.P., Joshi, A.D., Shcherbinin, S., Teske, B., Fleisher, A.S., Mintun, M.A., 2019. A multicentre longitudinal study of flortaucipir (18F) in normal ageing, mild cognitive impairment and Alzheimer's disease dementia. Brain 142 (6), 1723–1735. https://doi.org/10.1093/brain/awz090.
Price, J.L., Morris, J.C., 1999. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann. Neurol. 45 (3), 358–368. https://doi.org/10.1002/1531-8249(199903)45:3<358::aid-ana12>3.0.co;2-x.
Pulvermuller, F., 2013. How neurons make meaning: brain mechanisms for embodied and abstract-symbolic semantics. Trends Cogn. Sci. 17 (9), 458–470. https://doi.org/10.1016/j.tics.2013.06.004.
Rowe, C.C., Bourgeat, P., Ellis, K.A., Brown, B., Lim, Y.Y., Mulligan, R., Jones, G., Maruff, P., Woodward, M., Price, R., Robins, P., Tochon-Danguy, H., O'Keefe, G., Pike, K.E., Yates, P., Szoeke, C., Salvado, O., Macaulay, S.L., O'Meara, T., Head, R., Cobiac, L., Savage, G., Martins, R., Masters, C.L., Ames, D., Villemagne, V.L., 2013. Predicting Alzheimer disease with beta-amyloid imaging: results from the Australian imaging, biomarkers, and lifestyle study of ageing. Ann. Neurol. 74 (6), 905–913. https://doi.org/10.1002/ana.24040.
Salthouse, T.A., 2004. What and when of cognitive aging. Curr. Dir. Psychol. Sci. 13 (4), 140–144. https://doi.org/10.1111/j.0963-7214.2004.00293.x.
Salthouse, T.A., 2005. Relations between cognitive abilities and measures of executive functioning. Neuropsychology 19 (4), 532–545. https://doi.org/10.1037/0894-4105.19.4.532.
Salthouse, T.A., 2009. Decomposing age correlations on neuropsychological and cognitive variables. J. Int. Neuropsychol. Soc. 15 (5), 650–661. https://doi.org/10.1017/S1355617709990385.
Salthouse, T.A., 2019. Trajectories of normal cognitive aging. Psychol. Aging 34 (1), 17–24. https://doi.org/10.1037/pag0000288.
Salthouse, T.A., Habeck, C., Razlighi, Q., Barulli, D., Gazes, Y., Stern, Y., 2015. Breadth and age-dependency of relations between cortical thickness and cognition. Neurobiol. Aging 36 (11), 3020–3028. https://doi.org/10.1016/j.neurobiolaging.2015.08.011.
Salthouse, T.A., Pink, J.E., Tucker-Drob, E.M., 2008. Contextual analysis of fluid intelligence. Intelligence 36 (5), 464–486. https://doi.org/10.1016/j.intell.2007.10.003.
Scholl, M., Lockhart, S.N., Schonhaut, D.R., O'Neil, J.P., Janabi, M., Ossenkoppele, R., Baker, S.L., Vogel, J.W., Faria, J., Schwimmer, H.D., Rabinovici, G.D., Jagust, W.J., 2016. PET imaging of tau deposition in the aging human brain. Neuron 89 (5), 971–982. https://doi.org/10.1016/j.neuron.2016.01.028.
Scholl, M., Maass, A., Mattsson, N., Ashton, N.J., Blennow, K., Zetterberg, H., Jagust, W., 2019. Biomarkers for tau pathology. Mol. Cell. Neurosci. 97, 18–33. https://doi.org/10.1016/j.mcn.2018.12.001.
Shomstein, S., 2012. Cognitive functions of the posterior parietal cortex: top-down and bottom-up attentional control. Front. Integr. Neurosci. 6, 38. https://doi.org/10.3389/fnint.2012.00038.
Simon, S.S., Lee, S., Gu, Y., Mensing, A., Noofoory, D., Hidalgo Nazario, G.M., Babukutty, R.S., Stern, Y., 2023. Leisure activity engagement across adulthood predicts cognitive change after five years: do gender and age matter? J. Int. Neuropsychol. Soc. 29 (6), 529–540. https://doi.org/10.1017/S1355617722000510.
Sperling, R.A., Mormino, E.C., Schultz, A.P., Betensky, R.A., Papp, K.V., Amariglio, R.E., Hanseeuw, B.J., Buckley, R., Chhatwal, J., Hedden, T., Marshall, G.A., Quiroz, Y.T., Donovan, N.J., Jackson, J., Gatchel, J.R., Rabin, J.S., Jacobs, H., Yang, H.S., Properzi, M., Kirn, D.R., Rentz, D.M., Johnson, K.A., 2019. The impact of amyloid-beta and tau on prospective cognitive decline in older individuals. Ann. Neurol. 85 (2), 181–193. https://doi.org/10.1002/ana.25395.
Stern, Y., 2012. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 11 (11), 1006–1012. https://doi.org/10.1016/S1474-4422(12)70191-6.
Stern, Y., Arenaza-Urquijo, E.M., Bartres-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W.S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., Reserve, R., Protective Factors, P. I. A. E. D, Conceptual Frameworks, Workgroup, 2020. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement. 16 (9), 1305–1311. https://doi.org/10.1016/j.jalz.2018.07.219.
Stern, Y., Habeck, C., Steffener, J., Barulli, D., Gazes, Y., Razlighi, Q., Shaked, D., Salthouse, T., 2014. The Reference Ability Neural Network Study: motivation, design, and initial feasibility analyses. Neuroimage 103, 139–151. https://doi.org/10.1016/j.neuroimage.2014.09.029.
Tahmi, M., Bou-Zeid, W., Razlighi, Q.R., 2019. A fully automatic technique for precise localization and quantification of amyloid-beta PET scans. J. Nucl. Med. 60 (12), 1771–1779. https://doi.org/10.2967/jnumed.119.228510.
Tso, I.F., Rutherford, S., Fang, Y., Angstadt, M., Taylor, S.F., 2018. The "social brain" is highly sensitive to the mere presence of social information: an automated meta-analysis and an independent study. PLoS One 13 (5), e0196503. https://doi.org/10.1371/journal.pone.0196503.
van Rossum, I.A., Visser, P.J., Knol, D.L., van der Flier, W.M., Teunissen, C.E., Barkhof, F., Blankenstein, M.A., Scheltens, P., 2012. Injury markers but not amyloid markers are associated with rapid progression from mild cognitive impairment to dementia in Alzheimer's disease. J Alzheimers Dis 29 (2), 319–327. https://doi.org/10.3233/JAD-2011-111694.
Villemagne, V.L., Mulligan, R.S., Pejoska, S., Ong, K., Jones, G., O'Keefe, G., Chan, J.G., Young, K., Tochon-Danguy, H., Masters, C.L., Rowe, C.C., 2012. Comparison of 11C-PiB and 18F-florbetaben for Abeta imaging in ageing and Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imaging 39 (6), 983–989. https://doi.org/10.1007/s00259-012-2088-x.
Vogel, J.W., Iturria-Medina, Y., Strandberg, O.T., Smith, R., Levitis, E., Evans, A.C., Hansson, O., Alzheimer's Disease Neuroimaging, I., Swedish BioFinder, S., 2020. Spread of pathological tau proteins through communicating neurons in human Alzheimer's disease. Nat. Commun. 11 (1), 2612. https://doi.org/10.1038/s41467-020-15701-2.
Vogel, J.W., Young, A.L., Oxtoby, N.P., Smith, R., Ossenkoppele, R., Strandberg, O.T., La Joie, R., Aksman, L.M., Grothe, M.J., Iturria-Medina, Y., Alzheimer's Disease Neuroimaging, I, Pontecorvo, M.J., Devous, M.D., Rabinovici, G.D., Alexander, D.C., Lyoo, C.H., Evans, A.C., Hansson, O., 2021. Four distinct trajectories of tau deposition identified in Alzheimer's disease. Nat. Med. 27 (5), 871–881. https://doi.org/10.1038/s41591-021-01309-6.
Ziontz, J., Bilgel, M., Shafer, A.T., Moghekar, A., Elkins, W., Helphrey, J., Gomez, G., June, D., McDonald, M.A., Dannals, R.F., Azad, B.B., Ferrucci, L., Wong, D.F., Resnick, S.M., 2019. Tau pathology in cognitively normal older adults. Alzheimers Dement. (Amst) 11, 637–645. https://doi.org/10.1016/j.dadm.2019.07.007.