Rates of regional tau accumulation in ageing and across the Alzheimer's disease continuum: an AIBL ^{18}F-MK6240 PET study

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Summary

Background Tau positron emission tomography (PET) imaging enables longitudinal observation of tau accumulation in Alzheimer's disease (AD). ^{18}F-MK6240 is a high affinity tracer for the paired helical filaments of tau in AD, widely used in clinical trials, despite sparse longitudinal natural history data. We aimed to evaluate the natural history of tau accumulation, and the impact of disease stage and reference region on the magnitude and effect size of regional change.

Methods One hundred and eighty-four participants: 89 cognitively unimpaired (CU) beta-amyloid negative (Aβ–), 44 CU Aβ+, 51 cognitively impaired Aβ+ (26 with mild cognitive impairment [MCI] and 25 with dementia) had follow-up ^{18}F-MK6240 PET for one to four years (median 1.48). Regional standardised uptake value ratios (SUVR) were generated. Two reference regions were examined: cerebellar cortex and eroded subcortical white matter.

Findings CU Aβ– participants had very low rates of tau accumulation in the mesial temporal lobe (MTL). In CU Aβ+, significantly higher rate of accumulation was seen in the MTL (particularly the amygdala), extending into the inferior temporal lobes. In MCI Aβ+, the rate of accumulation was greatest in the lateral temporal, parietal and lateral occipital cortex, and plateaued in the MTL. Accumulation was global in AD Aβ+, except for a plateau in the MTL. The eroded subcortical white matter reference region showed no significant advantage over the cerebellar cortex and appeared prone to spill-over in AD participants. Data fitting suggested approximately 15–20 years to accumulate tau to typical AD levels.

Interpretation Tau accumulation occurs slowly. Rates vary according to brain region, disease stage and tend to plateau at high levels. Rates of tau accumulation are best measured in the MTL and inferior temporal cortex in preclinical AD and in large neocortical areas, in MCI and AD.

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Keywords: Tau; ^{18}F-MK6240; Positron emission tomography (PET); Alzheimer's disease; Longitudinal

Introduction

Intracellular tau neurofibrillary tangles (NFT), along with extracellular amyloid-β (Aβ) plaques, are two pathological hallmarks of Alzheimer's disease (AD). In AD, the spatial distribution of brain tau aggregates is linked with cognitive impairment in a domain-specific manner.[1–3] Tau is also closely linked with the development of neurodegeneration.[3–7] Longitudinal *in vivo* tracking of tau can facilitate our understanding of the natural trajectory of tau, its interactivity with Aβ, and

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Research in context

Evidence before this study

The authors systematically reviewed the literature using PubMed (with search terms, 'longitudinal tau' and 'tau positron emission tomography/PET'), as well as conference abstracts and references from full-text articles available prior to February 2022. Prior studies, predominantly using tau PET tracer ^{18}F-flortaucipir, have demonstrated that regional rates of tau accumulation vary by clinical disease stage, and highlight the utility of serial tau PET imaging as a potential outcome measure for Alzheimer's disease (AD) clinical trials.

Added value of this study

Tau tracer ^{18}F-MK6240 is widely used in AD clinical trials, despite sparse longitudinal natural history data. This study investigated the impact of disease stage and reference region selection, thus providing context for the interpretation of estimates of regional rates of tau accumulation in clinical trials using ^{18}F-MK6240. Data fitting was also used to estimate the spatiotemporal trajectory of tau accumulation, enhancing our understanding of the natural history of tau accumulation in AD.

Implications of all the available evidence

Tau accumulation appears to be a protracted process. Rates of tau accumulation in this study varied according to brain region and disease stage, confirming previous reports. Tau accumulation tends to plateau at high levels occurring first in the medial temporal lobe. Clinical trials aimed at slowing tau accumulation measured by PET need to tailor the analysis region to the clinical disease stage and avoid or account for the plateau seen at very high tau levels. Either cerebellar cortex or eroded subcortical white matter may be used as the reference region.

associations with the clinical features of AD. Serial tau positron emission tomography (PET) has also been proposed as a surrogate marker for disease progression in AD clinical trials,[8] and has been included as an outcome measure in trial sub-analyses aiming to evaluate the impact of anti-Aβ therapies on tau burden.[9,10]

Tau tracer ^{18}F-MK6240 has high affinity and selectivity for tau NFT in AD.[11,12] Serial imaging with ^{18}F-MK6240 has reported detectable rates of tau accumulation in both preclinical and symptomatic AD stages.[13] Detection of tau accumulation in preclinical AD is advantageous for clinical trials that are aiming to target this earlier stage of disease.[14] The main aim of this study was to evaluate the rates of tau accumulation in ageing (cognitively unimpaired [CU] Aβ–), preclinical AD (CU Aβ+), and symptomatic disease stages (Aβ+ mild cognitive impairment [MCI] and Alzheimer's disease dementia [AD]) using ^{18}F-MK6240. The second aim was to investigate the impact of two reference regions (cerebellar cortex and eroded subcortical white matter) on the magnitude and effect size of regional change.

Methods

Participants

Participants from the Australian Imaging Biomarkers and Lifestyle flagship study of ageing (AIBL)[15] and the Australian Dementia Network (ADNeT) who completed baseline and one or more follow-up tau ^{18}F-MK6240 PET scans before September 2022 were included in this study if they met the following criteria: 1) ≥50 years of age; 2) were fluent in English; 3) had completed at least seven years of education; and 4) did not have any history of neurological or psychiatric disorders, drug or alcohol abuse or dependence, or any other unstable medical condition. All participants completed neuropsychology assessments every 12–18 months, as previously described.[15] Based on available clinical information and neuropsychology assessments, a multi-disciplinary clinical review panel, blind to Aβ and tau PET results, determines each participants' clinical classification. Participants were deemed to be cognitively unimpaired (CU) if their performance on neuropsychology assessments was within 1.5 standard deviations of published normative data for their age group. Participants were assigned a diagnosis of mild cognitive impairment (MCI) by Winblad et al.[16] and Petersen et al.[17] criteria and Alzheimer's disease dementia (AD) by NINCDS-ADRDA criteria.

Ethics

This study has been approved by the Human Research Ethics Committee at Austin Hospital, Melbourne, Australia (HREC/18/Austin/201), and all participants signed an informed consent form.

Image acquisition

Tau PET imaging involved the intravenous administration of 185MBq (±10%) of ^{18}F-MK6240 with a 20-min acquisition commencing 90-min post-injection. Aβ PET imaging involved the intravenous administration of 200MBq (±10%) of ^{18}F-NAV4694 with a 20-min acquisition time commencing 50-min post-injection. PET scans were acquired on either a Philips TF64 PET/CT or a Siemens Biograph mCT. PET scans for each participant were performed on the same scanner at baseline and follow-up. Low dose CT was obtained for attenuation correction.

Image analysis

Tau ^{18}F-MK6240 PET scans were spatially normalised using the MR-less Computational Analysis of PET from

AIBL (CapAIBL) PCA-based approach,[18] and scaled using two reference regions: 1) cerebellar cortex; and 2) manually-eroded subcortical white matter, modified from a previously described reference region.[19] A grey matter inclusion mask and a meninges exclusion mask were applied. ^{18}F-MK6240 standardised uptake value ratio (SUVR) was estimated for three in-house unweighted composite ROI: i) mesial temporal, Me (comprising entorhinal cortex, amygdala, hippocampus, and parahippocampus); ii) temporoparietal, Te (comprising inferior and middle temporal, fusiform, supramarginal and angular gyri, posterior cingulate/precuneus, superior and inferior parietal, and lateral occipital cortex); and iii) rest of neocortex, R (comprising dorsolateral and ventrolateral prefrontal, orbitofrontal cortex, gyrus rectus, superior temporal, and anterior cingulate), as previously described.[20] Tau ^{18}F-MK6240 SUVR was also estimated in a meta-temporal composite, MT (comprising Free-Surfer derived entorhinal cortex, parahippocampus, amygdala, inferior temporal, fusiform, and middle temporal cortex ROI).[21]

Aβ PET scans were spatially normalised using the MR-less CapAIBL approach (https://milxcloud.csiro.au/tools/capaibl), and the CapAIBL calibrated Centiloid method was applied for quantification.[22] A Centiloid value of 25 was used to discriminate high (Aβ+) and low (Aβ–) Aβ scans.

Vertex-based surface analysis

All ^{18}F-MK6240 scans were in the same standard space. The mean annual rate of tau accumulation (change in SUVR/year) was estimated for each of the clinical groups, scaled using two reference regions: 1) cerebellar cortex; and 2) eroded subcortical white matter, and CapAIBL[18,23] was used to generate surface projections to visualize these changes.

Statistics

Demographic data were analysed using an independent samples t-test for continuous data, and Chi-square test of independence for categorical data, with a threshold of significance of $p < 0.05$. Effect size was reported as Cohen's *d*. Based on central limit theorem, parametric statistics were used. Annual change in ^{18}F-MK6240 SUVR in each composite ROI was estimated as the slope obtained from linear regression of SUVR (independent variable) by Δtime (dependent variable). Annual percentage change in ^{18}F-MK6240 SUVR in each composite was estimated as follows:

$$\left(\frac{\text{Annual tau SUVR change}}{\text{Mean (baseline, follow–up SUVR)}} \times 100\right)$$

The progression of tau, assessed by ^{18}F-MK240, was evaluated using a four-step procedure, as previously described[24,25] using all participants. The procedure estimates the mean and slope of each individual's ^{18}F-MK6240 SUVR for each region, fits a polynomial to the estimated means and slopes across the individuals, integrates the polynomial fits over time, and inverts this relationship to get the single variable mean trajectory curves as a function of disease time. In general terms, this procedure is a description of the resolution of an ordinary differential equation, where F is the fitted polynomial:

$$\frac{d\,SUVR}{dt} = F(SUVR)$$

Role of the funding source

The funding sources for this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Cerveau Technologies, who supplied the ^{18}F-MK6240 tau tracer precursor for research use, approved the manuscript prior to submission for publication.

Results

Participants

The cohort comprised 184 participants: 89 CU Aβ–, 44 CU Aβ+, and 51 cognitively impaired Aβ+ (26 with MCI and 25 with AD dementia). Table 1 shows the demographic characteristics of the cohort at baseline.

Vertex-based surface projections of tau accumulation

Vertex-based surface projections were used to demonstrate the spatial distribution and rate of ^{18}F-MK6240 accumulation (mean SUVR/year) for the clinical groups, normalised to the cerebellar cortex (Fig. 1). Minimal tau accumulation was observed in the CU Aβ– group. CU Aβ+ individuals showed highest mean tau accumulation in the mesial temporal cortex, inferior and lateral temporal gyri, and clusters of tau accumulation in the precuneus and angular gyri. MCI Aβ+ individuals were observed to have the highest mean tau accumulation in the superior and lateral temporal, occipital and parietal cortices, with lower rates in the precuneus and prefrontal cortices. AD Aβ+ individuals were observed to have tau accumulation globally, across the cortex, with lower rates in the mesial temporal cortex and sensorimotor cortex. Surface projections were also generated using $SUVR_{WM}$ (Supplementary Fig. S1). With this reference region, CU Aβ– individuals had a higher, though still low, mean rate of tau accumulation in the mesial temporal region. The spatial distribution of tau observed in the CU Aβ+, MCI Aβ+ and AD Aβ+ groups was similar, irrespective of the reference region.

	CU Aβ– n = 89	CU Aβ+ n = 44	MCI Aβ+ n = 26	AD Aβ+ n = 25
Age (yrs)	74.1 ± 4.5	78.8 ± 6.3**	74.7 ± 7.8	69.4 ± 8.1**
Sex, F (%)	42 (47.2%)	24 (54.5%)	9 (34.6%)	12 (48.0%)
APOE ε4+ (%)[a]	26 (29.9%)	24 (55.8%)*	11 (61.1%)*	10 (62.5%)*
Centiloid	4.3 ± 9.0	83.1 ± 40.7**	94.3 ± 45.3**	110.7 ± 32.8**
Baseline MMSE	28.6 ± 1.2	28.1 ± 1.5*	26.4 ± 1.6**	22.1 ± 3.4**
Duration of follow-up (yrs) [Median (range)]	1.56 (0.97, 3.62)	2.22 (0.96, 3.58)	1.26 (1.00, 3.53)	1.32 (0.93, 3.83)*

Mean (SD), unless otherwise specified. T-test (one-tailed): *p ≤ 0.05, **p ≤ 0.001 compared to CU Aβ–. Abbreviations: CU = cognitively unimpaired; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia; *APOE* = apolipoprotein E gene; MMSE = Mini-Mental State Examination. [a]*APOE* genotype only available for 164/184 participants.

Table 1: **Cohort demographic characteristics at baseline.**

Tau accumulation in composite brain regions of interest

Baseline SUVR, annual tau SUVR change, and annual tau SUVR percentage change were estimated in each composite ROI for the clinical groups. Results are shown for the two reference regions: a) cerebellar cortex (Fig. 2; Table 2 and Supplementary Table S2); and b) eroded subcortical white matter (Fig. 2; Supplementary Tables S1 and S3). Tau accumulation was also estimated across individual brain regions, for each of the clinical groups (Supplementary Figs S2a and S2b), demonstrating a similar regional distribution of tau accumulation as observed for the vertex-based surface projections for both reference regions.

Scans normalised to the cerebellar cortex reference region showed that CU Aβ– individuals had low rates of change (SUVR/year) in Me and MT (Fig. 2, Table 2). Compared to the CU Aβ– group, CU Aβ+ individuals had significantly higher rates of tau accumulation in Me (d = 0.90), MT (d = 0.93), Te (d = 0.73) and R (d = 0.52) (Table 2). Compared to the CU Aβ– group, MCI Aβ+ individuals had significantly higher rates of tau accumulation in Te (d = 0.70) and R (d = 0.71) (Table 2). Compared to the CU Aβ– group, AD Aβ+ individuals had significantly higher rates of tau accumulation in Te (d = 0.93) and R (d = 1.32). The regional annual percentage change in tau $SUVR_{Cb}$ is reported in Supplementary Table S2.

Rates of change (SUVR/year) for scans normalised to the eroded subcortical white matter are reported in Supplementary Table S1, while the regional annual percentage change in tau $SUVR_{WM}$ is reported in Supplementary Table S3.

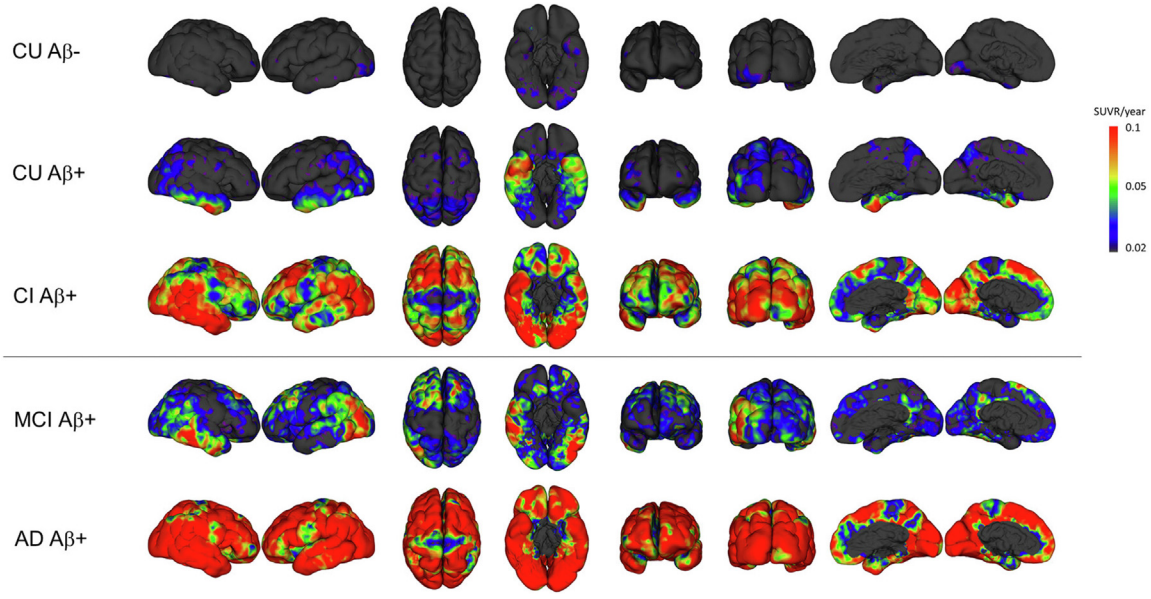

Fig. 1: **Annual rate of ^{18}F-MK6240 accumulation across the clinical groups (cerebellar cortex reference region).** Vertex-based surface projections demonstrating the spatial distribution and rate of ^{18}F-MK6240 accumulation (mean SUVR/year) for each clinical group, normalised to the cerebellar cortex. CU Aβ–: n = 89; CU Aβ+: n = 44; MCI Aβ+: n = 26; AD Aβ+: n = 25. Abbreviations: CU = cognitively unimpaired; CI = cognitively impaired; MCI = mild cognitive impairment; and AD = Alzheimer's disease dementia.

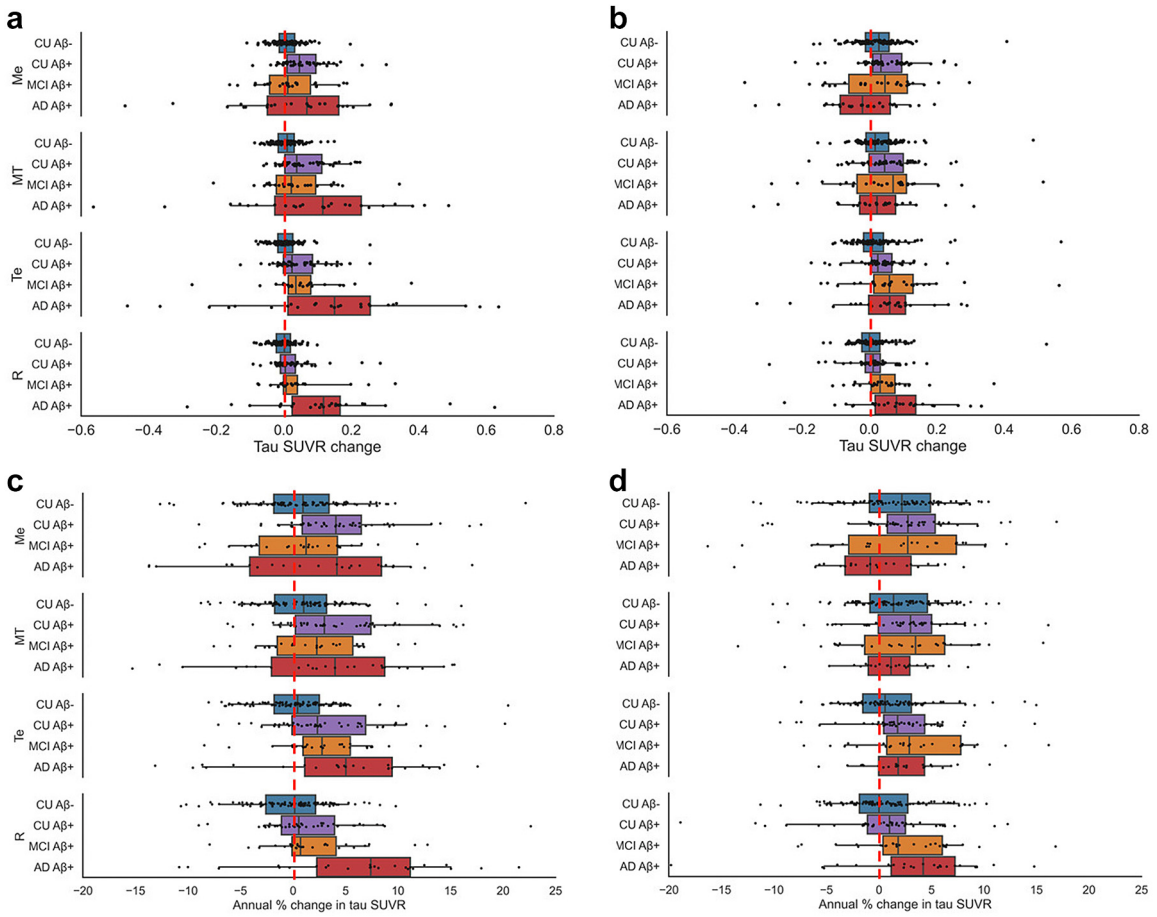

Fig. 2: **Annual rate of tau SUVR change and annual percentage change in composite ROI.** Boxplots showing annual tau SUVR change in composite ROI for the clinical groups, normalised to a) cerebellar cortex reference region; and b) eroded subcortical white matter reference region. Boxplots showing annual tau SUVR percentage change in composite ROI for the clinical groups normalised to c) cerebellar cortex reference region; and d) eroded subcortical white matter reference region. The red dashed vertical line represents zero change. Within the boxes, the line represents the median value. The whiskers extend from the 5th to the 95th percentile. CU Aβ–: n = 89; CU Aβ+: n = 44; MCI Aβ+: n = 26; AD Aβ+: n = 25. Abbreviations: CU = cognitively unimpaired; MCI = mild cognitive impairment; AD = Alzheimer's disease dementia.

The effect size for annual change in tau SUVR was higher for the $SUVR_{Cb}$ than the $SUVR_{WM}$ (Table 2, Supplementary Table S1) across all composite ROI, when comparing the Aβ+ groups to the CU Aβ–. The 95% confidence intervals for all estimates were wide, particularly for the MCI Aβ+ and AD Aβ+ groups, with greater variability than the CU groups.

Change in reference region SUV

The rate of SUV change per year in the cerebellar cortex (Supplementary Fig. S3a) was not significantly different when comparing the Aβ+ groups to the CU Aβ–group. The AD Aβ+ and CU Aβ+ groups had significantly higher rate of SUV change in the eroded subcortical white matter reference regions than the Aβ– CU group (Supplementary Fig. S3b). Supplementary Fig. S4 shows plots of SUV change by age for the two reference regions. A subset of AD Aβ+ participants under the age of 65 were observed to have an increase in SUV in the eroded subcortical white matter reference region; a finding that was not observed for the cerebellar cortex reference region.

Age, baseline tau, and the spatiotemporal trajectory of tau accumulation

Plots showing the relationship between tau accumulation and age (Supplementary Fig. S5a and S5b), highlight that the greatest tau burden in SUVR across the composite brain regions is observed in young cognitively impaired individuals less than 75 years of age and that at high baseline SUVR (Me > 2, MT > 3, Te > 3.5), rates of change in some individuals may be negative, and therefore contribute substantial variance to the rates of change in the MCI and AD groups. This relationship

ROI	CU Aβ− (n = 89)		CU Aβ+ (n = 44)					MCI Aβ+ (n = 26)					AD Aβ+ (n = 25)				
	Baseline SUVR	Δ SUVR/yr	Baseline SUVR	T stat	d	Δ SUVR/yr	T stat	d	Baseline SUVR	T stat	d	Δ SUVR/yr	T stat	d	Baseline SUVR	T stat	d	Δ SUVR/yr	T stat	d
Me	0.89 ± 0.16	0.0088 ± 0.0444	1.18 ± 0.29***	6.33	1.34 [1.00–1.80]	0.0587 ± 0.0727***	4.19	0.90 [0.52, 1.28]	1.53 ± 0.60***	5.39	2.03 [1.51–2.53]	0.0169 ± 0.0884	0.45	0.14 [−0.30, 0.58]	1.90 ± 0.69***	7.25	2.89 [2.30–3.46]	0.0313 ± 0.1885	0.59	0.24 [−0.21, 0.68]
MT	0.96 ± 0.14	0.0100 ± 0.0417	1.25 ± 0.29***	6.20	1.41 [1.00–1.80]	0.0615 ± 0.0766***	4.17	0.93 [0.55, 1.30]	1.70 ± 0.76***	4.97	1.196 [1.45–2.46]	0.0393 ± 0.1068	1.37	0.47 [0.03, 0.91]	2.33 ± 0.86***	7.94	3.28 [2.66–3.90]	0.0817 ± 0.2371	1.51	0.62 [0.17, 1.07]
Te	1.02 ± 0.13	0.0061 ± 0.0460	1.18 ± 0.24***	4.16	0.92 [0.54–1.30]	0.0484 ± 0.0771***	3.36	0.73 [0.36, 1.10]	1.62 ± 0.73***	4.14	1.64 [1.15–2.12]	0.0523 ± 0.1111*	2.07	0.70 [0.25, 1.14]	2.74 ± 1.36***	6.34	2.70 [2.13–3.26]	0.1274 ± 0.2690*	2.24	0.93 [0.46, 1.38]
R	0.88 ± 0.11	−0.0007 ± 0.0337	0.94 ± 0.14**	2.44	0.45 [0.08–0.82]	0.0235 ± 0.0661*	2.29	0.52 [0.15, 0.88]	1.21 ± 0.57**	2.85	1.12 [0.66–1.58]	0.0365 ± 0.0911*	2.04	0.71 [0.27, 1.16]	1.71 ± 0.91***	4.53	1.91 [1.39–2.41]	0.1194 ± 0.1854**	3.23	1.32 [0.84–1.80]

Baseline tau SUVR and annual tau SUVR change per year (Δ SUVR/year), normalised to the cerebellar cortex. T stat = t statistic from a one-tailed t-test comparing the Aβ+ clinical groups against the CU Aβ− group, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001. Effect size = Cohen's *d*, point estimate [95% confidence interval]. Abbreviations: Me = mesial temporal; MT = meta-temporal; Te = temporoparietal; R = rest of neocortex.

Table 2: **Baseline and annual tau SUVR change (cerebellar cortex reference region).**

between baseline tau and tau accumulation in composite ROI is also shown in Supplementary Fig. S6. The spatiotemporal trajectory of tau accumulation over several decades is shown for the Mesial temporal, Temporoparietal, and Rest of brain regions in Fig. 3.

Discussion

Serial tau imaging with ^{18}F-MK6240 was able to detect tau accumulation in both cognitively unimpaired (CU) and cognitively impaired participants (MCI and AD) who were Aβ+ at baseline. Accumulation of tau was predominantly observed in mesial temporal and inferior temporal regions in CU Aβ+, in lateral temporoparietal regions in MCI Aβ+, and all cortical regions in AD Aβ+ except for the mesial temporal lobe.

Effect sizes for annual rates of tau accumulation compared to CU Aβ− trended lower with $SUVR_{WM}$ than $SUVR_{Cb}$, particularly in AD. A subset of young (<65 years of age) AD Aβ+ individuals were observed to have a SUV increase in the eroded subcortical white matter reference region, due to either tau accumulation or spill-over of the ^{18}F-MK6240 signal into the eroded subcortical white matter mask for the $SUVR_{WM}$ reference region, which lowered the estimated $SUVR_{WM}$ and thus, the yearly rate of change for these individuals.

As observed with the tau PET tracer flortaucipir, the regional rates of tau accumulation were dependent on baseline tau burden, as has been reported previously.[21,26] The proportion of AD Aβ+ that showed longitudinal decline in tau SUVR was higher in those with very high levels of baseline tau. This was most apparent in mesial temporal and temporoparietal regions. Plots of regional tau SUVR and age showed that participants with very high baseline tau were young (<75 years of age) and cognitively impaired (AD Aβ+ > MCI Aβ+). This contribution to the variance in the rates of tau accumulation by PET will substantially increase the cohort size required for clinical trials aimed at slowing the rate of tau accumulation.

This study also estimated the spatiotemporal trajectory of tau accumulation. While tau starts accumulating early in the mesial temporal lobe (Me) (reaching the threshold for abnormality ~6 and ~7 years earlier than in Te and R, respectively), it then slows in this region as the disease progresses. It takes about 16 years to get from the levels of CU Aβ− SUVR to the SUVR observed in AD patients, and about 10 years after crossing the threshold of abnormality. Conversely, tau accumulation in the lateral temporoparietal cortex (Te) accelerates, then tending to plateau later in the disease course, at very high tau levels, while tau starts accumulating later in the R composite region with less tendency to plateau at very high levels. In Te, it takes about 17 years to get from the levels of CU Aβ− SUVR to the SUVR observed in AD patients, and about 14 years after crossing the threshold of abnormality. In R, where tau starts

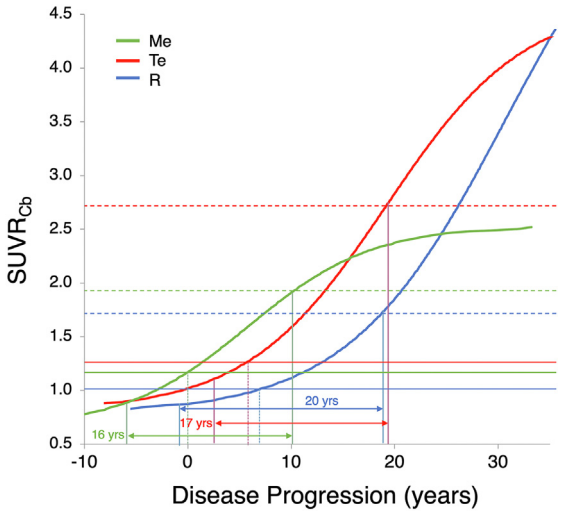

***Fig. 3:* Spatiotemporal trajectory of tau accumulation.** Fig. 3 shows the natural history of regional tau accumulation measured as ^{18}F-MK6240 SUVR normalised to the cerebellar cortex reference region, as fitted from the data. The first three solid vertical lines represent mean CU Aβ– $SUVR_{Cb}$ values for the composite ROI (Me: 0.89, Te: 1.02; R: 0.88). The next three solid vertical lines and the dashed horizontal lines represent the mean AD Aβ+ $SUVR_{Cb}$ values for the composite ROI (Me: 1.90, Te: 2.74, R: 1.71). The dashed vertical lines and solid horizontal lines represent the threshold for abnormality (95th percentile of CU Aβ–). To reach the mean $SUVR_{Cb}$ observed in AD from the mean $SUVR_{Cb}$ observed in CU Aβ–, it takes approximately 16 years in Me, 17 years in Te, and 20 years in R. Abbreviations: Me = mesial temporal (green), Te = temporoparietal (red), and R = rest of neocortex (blue).

accumulating much later, it takes about 20 years to get from the levels of CU Aβ– SUVR to the SUVR observed in AD patients, and about 12 years after crossing the threshold of abnormality. In contrast, we have reported a 30-year trajectory for Aβ accumulation.[24]

Minimal tau accumulation in CU Aβ– is consistent with prior longitudinal analyses,[13,21,26–28] and consistent with observations that tau accumulation is accelerated in the context of Aβ.[8,21,29] The low rates of tau accumulation in CU Aβ– confined to mesial temporal and temporal regions may be consistent with primary age-related tauopathy (PART).[30] Cognitively impaired Aβ+ younger individuals have been observed to have a higher baseline cortical tau burden, and more rapid accumulation in longitudinal tau than cognitively impaired Aβ+ older individuals in ^{18}F-flortaucipir PET analyses.[21,27,31] For cognitively impaired individuals, younger age has also been associated with more rapid tau accumulation,[29] independent of baseline tau in a meta-temporal region of interest.[27] Few cognitively impaired participants in this study were under 65 years of age (10/51), which may have impacted the group-level rate of tau accumulation.

Based on the results in this study, there are a few points of relevance to AD clinical trials that opt to use tau ^{18}F-MK6240 as an outcome measure. Selection of composite ROI for use in a therapy trial should take into consideration that a meta-temporal composite may be ideal for early detection and useful in the assessment of tau accumulation at the preclinical disease stages, while a neocortical composite focusing on temporoparietal regions may be more sensitive to detect changes at the symptomatic stages of disease. The observation of a plateau or decline in the rate of tau accumulation in AD Aβ+ participants with very high levels of baseline tau and the contribution this makes to the variance in the rate of tau accumulation should be considered when designing disease-modifying therapies that are aiming to demonstrate clearance or slowing of tau accumulation. Reference region selection for SUVR calculation appears to have little impact on assessment of change in tau. Overall, this study found that the cerebellar cortex reference region performed well, and the alternate eroded subcortical white matter reference region may be subject to spill-over effect or white matter tau accumulation when cortical tau is high in cognitively impaired persons.

There were a few important limitations to this study. The sample size was relatively small, particularly with low numbers in the Aβ+ cognitively impaired groups. As mentioned earlier, ^{18}F-flortaucipir PET papers have shown that younger age[27,29] and higher baseline tau[21,27,31] are associated with higher rates of tau accumulation, and in one study, both factors have been shown to be independent predictors of the rates of accumulation.[27] Whilst the data shown here suggests this is also seen with ^{18}F-MK6240, the relatively small sample size of the cognitively impaired groups precluded more detailed analyses that may have been able to disentangle the relative contribution of these two factors. Additionally, participants in this study had high levels of education and did not have significant medical or psychiatric comorbidities. AD Aβ+ participants had mild dementia (MMSE 22.1 ± 3.4). While these features may be consistent with characteristics of participants recruited to clinical trials, individuals with more severe disease and medical comorbidities, were not represented in this sample and thus the results may not be widely generalizable. Additionally, the median duration of follow-up in this study was shorter than would typically be expected for a preclinical AD trial. This study was also limited by the lack of a replication cohort to validate these findings.

In summary, longitudinal tau ^{18}F-MK6240 PET detected tau accumulation in both preclinical and symptomatic Alzheimer's disease with a median of 1.48 years follow-up. The regional rate of tau accumulation was influenced by baseline tau burden and clinical disease stage. Fitting of the data suggests that tau accumulation takes approximately 15–20 years to reach the levels observed in AD. The use of tau ^{18}F-MK6240 PET as an outcome measure for clinical trials should take

into consideration the selection of composite ROI, regional baseline tau burden, choice of reference region, and clinical disease stage.

Contributors

NK contributed to formal analysis, investigation, methodology, visualization, and writing the original draft. VD contributed to data curation, formal analysis, investigation, methodology, software, validation, visualization, and writing – review & editing. NK and VD had direct access to the data and verified the data. JR, CF, and JF contributed to project administration. LW contributed to funding acquisition. CLM contributed resources. PB contributed to data curation and formal analysis. VLV contributed to conceptualization, formal analysis, methodology, visualization, writing – review & editing. CCR contributed to conceptualization, funding acquisition, resources, supervision, writing – review & editing. All authors read and approved the final version of the manuscript.

Data sharing statement

Access to the deidentified datasets used and/or analysed during the current study require approval of an expression of interest (EOI) by the AIBL management committee. The EOI form can be requested from the corresponding author.

Declaration of interests

CCR was the recipient of a research grant from Cerveau (institution), who supplied the MK6240 tau tracer precursor for research use. CCR has received consulting fees from Prothera and Merck (scientific advisory panels) and Biogen (for preparation of educational material). CCR has received support for attending meetings and/or travel from Cerveau and the Alzheimer's Association. VLV has received consulting fees from IXICO, Eli Lilly, Life molecular imaging and has received payment/honoraria from ACE Barcelona. VLV has participated on the data safety monitoring/advisory board of Eli Lilly. JF was the recipient of a research grant from the National Health and Medical Research Council (NHMRC), grant numbers APP1132604 and APP1140955. NK, VD, JR, LW, CF, PB, and CLM do not report any disclosures.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2023.104450.

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