



Research Report

Delayed primacy recall in AVLT is associated with medial temporal tau PET burden in cognitively unimpaired adults

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ABSTRACT

Background: Alzheimer's disease (AD) can be diagnosed by *in vivo* abnormalities of amyloid- β plaques (A) and tau accumulation (T) biomarkers. Previous studies have shown that analyses of serial position performance in episodic memory tests, and especially, delayed primacy, are associated with AD pathology even in individuals who are cognitively unimpaired. The earliest signs of cortical tau pathology are observed in medial temporal lobe (MTL) regions, yet it is unknown if serial position markers are also associated with early tau load in these regions. This study of cognitively unimpaired older individuals examined whether serial position scores in word-list recall cross-sectionally predicted tau PET load in the MTL, and were able to discriminate between biomarker profiles, based on AT classification.

Methods: Data from 490 participants (mean age = 68.8 ± 7.2) were extracted from two cohorts, which were merged into one sample. Linear regression analyses were carried out with regional volume-controlled tau (18F-MK-6240) PET SUVR of the entorhinal cortex (EC), parahippocampal cortex (PHC) and hippocampus (H) as outcomes, cross-sectional memory scores from the Rey Auditory Verbal Learning Test as predictors (total and delayed recall, along with serial position scores) and control variables, in separate analyses for each outcome and predictor. The sample was then stratified by biomarker profile and ANCOVAs

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were conducted with the strongest scores from the regression analyses, AT groups as fixed factor and the covariates.

Results: Higher delayed primacy significantly predicted lower tau PET in EC, PHC, and H, cross-sectionally. Higher total recall scores predicted lower EC tau, but delayed primacy showed the best model fit, as indicated by AICs. ANCOVAs showed that AVLT metrics did not significantly discriminate between A–T– and A+T+, after correcting for multiple comparisons.

Conclusions: Serial position analysis of word-list recall, particularly delayed primacy, may be a valuable tool for identifying *in vivo* tau pathology in cognitively unimpaired individuals.

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1. Introduction

Alzheimer's disease (AD) is characterised by the presence of amyloid- β (A β) plaques and the accumulation of tau into neurofibrillary tangles (Maass et al., 2018). According to the research framework published by the National Institute on Aging and the Alzheimer's Association (NIA-AA), AD can be measured and/or staged by *in vivo* abnormalities of core biomarkers (Jack et al., 2024), using positron emission tomography (PET) scans or cerebrospinal fluid (CSF) tests (Cummings, Lee, et al., 2019).

Although most disease-modifying drugs target amyloid (Cummings, Lee, et al., 2019), interventions focusing on tau accumulation are a promising therapeutic approach (Cummings, Blennow, et al., 2019; Jack et al., 2018; 2020; Jadhav et al., 2019; Leuzy et al., 2019; Long & Holtzman, 2019; McDade & Bateman, 2018; Ossenkoppele et al., 2018). Biomarkers of tau include elevated CSF phosphorylated tau and increased cortical tau PET ligand binding (Jack et al., 2024). Among them, the PET ligand 18F-MK-6240 (Hostetler et al., 2016) has been shown to be sensitive to neurofibrillary tangles and detect early tau pathology in preclinical AD (Betthausen et al., 2020), which is first observed in the entorhinal cortex (EC; Adams et al., 2019; Mecca et al., 2022). Tau PET load in medial temporal lobe (MTL) regions, and especially the EC, has been found to be associated with memory performance in cognitively unimpaired individuals (Lowe et al., 2019; Maass et al., 2018). Moreover, previous studies that also included individuals with mild cognitive impairment (MCI) and AD have reported associations between episodic memory performance and tau-tracer uptake in the MTL (Cho et al., 2016; Maass et al., 2017; Ossenkoppele et al., 2016). These findings are in line with the idea that the MTL is essential in memory consolidation, and that episodic memory loss is a key characteristic of AD (Albert et al., 2011; De Simone et al., 2017; De Tollis et al., 2021; Dubois et al., 2007).

While biomarker-based screening is crucial, it often requires access to highly specialised clinical settings (Manera et al., 2023), and with over 60% of people with dementia living in low-to-middle income countries (World Health Organization, 2023), there is an urgent need for accurate, accessible, and cost-effective screening tools. One potential

solution is the use of neuropsychological assessments, which are non-invasive, relatively inexpensive, and require minimal training. However, as biomarkers continue to advance, it is necessary that neuropsychological assessments evolve concurrently, especially to detect subtle changes in underlying pathology (Mueller et al., 2022).

The Boston process approach to neuropsychological assessment (Libon et al., 2013; Milberg, Hebben & Kaplan, 2009) emphasises the analysis of distinct cognitive processes that influence test performance, providing deeper insights than traditional composite scores. Applied to episodic memory tests, such as list-learning and story recall, this approach includes the analysis of serial position effects, where patterns of recall are considered alongside “traditional” scores (Bruno et al., 2013; Diaz-Orueta et al., 2018; Grant & Adams, 2009; Talamonti et al., 2020). The serial position curve is a common pattern observed in memory tests, where individuals often recall items from the beginning (primacy) and/or end (recency) of a list better than those in the middle, creating an U-shaped curve (e.g., Murdock, 1962). This pattern has been consistently replicated and has proven effective in enhancing the detection of AD pathology. For example, delayed primacy from a word-list test, which measures recall of items from the primacy region in the delayed trial, has been found to be associated with global AD pathology and neuritic plaques linked to amyloid- β aggregation (Bruno, Gicas, et al., 2024), while loss of recency in both word-lists and stories is associated with higher levels of CSF tau levels (Bruno et al., 2023a; Bruno et al., 2023b).

Although past studies have reported an association between tau PET load and episodic memory performance (Cho et al., 2016; Maass et al., 2017; Ossenkoppele et al., 2016), whether process-based scores, and more specifically serial position scores (SPs), are also linked to tau in MTL regions is unknown. Considering the sensitivity shown by SPs to *in vivo* AD pathology, e.g., tau and amyloid in CSF (Bruno et al., 2023a; Bruno et al., 2023b) or amyloid in PET (Bruno et al., 2021), the examination of potential associations with tau PET is promising.

This study aimed to examine whether serial position markers in word-list recall were associated with 18F-MK-6240 PET tau load in the MTL, specifically the EC, parahippocampal cortex (PHC) and hippocampus (H), in cognitively unimpaired

older individuals, and whether serial position scores outperformed traditional test metrics in predicting tau PET burden in these regions. We also explored if serial position metrics discriminated between individuals based on their amyloid (A; with 11C-PiB) and tau (T; with 18F-MK-6240) PET load classifications. Based on previous findings, we hypothesised that serial position scores would be associated with tau PET load, outperforming traditional scores, and discriminate between AT profiles.

2. Methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. No part of the study procedures was pre-registered prior to the research being conducted and no part of the study analyses was pre-registered prior to the research being conducted.

2.1. Participants

Data were drawn from the Wisconsin Alzheimer's Disease Research Center (ADRC) of the University of Wisconsin–Madison, and the Wisconsin Registry for Alzheimer's Prevention (WRAP). To be included in the analysis, participants had to have measures of both Pittsburgh compound-B (11C-PiB) PET, to assess amyloid distribution volume ratios (DVR), and 18F-MK-6240 PET for tau standardized uptake value ratio (SUVR), alongside word-list recall data, derived from the Rey Auditory Verbal Learning Test (AVLT; Rey, 1958). Cognitive assessments, 18F-MK-6240 PET scans, and 11C-PiB PET scans had to be acquired within a two-year period for each participant. When possible, the most recent data were analysed. In addition, participants had to be classified as cognitively unimpaired at 18F-MK-6240 PET visit, as assessed by a multi-disciplinary consensus conference review that was blind to AD biomarkers statuses (e.g., PET or CSF data). In WRAP, a two-tiered consensus conference approach was used (for details, see Johnson et al., 2018; Langhough Koscik et al., 2021). For both WRAP and ADRC, cognitive statuses were determined by teams that included physicians, clinical neuropsychologists, and clinical nurse practitioners, and based on core clinical criteria developed by the National Institute on Aging and the Alzheimer's Association (Albert et al., 2011; McKhann et al., 2011). After applying the inclusion criteria above, the sample comprised 490 individuals, 367 from WRAP and 123 from ADRC, whose average age at 18F-MK-6240 PET was 68.8 (7.2). Of these, 12 (2.45 %) reported their race as American Indian or Alaska Native, one (.20 %) as Asian, 21 (4.29 %) as Black or African American, 453 (92.45 %) as White, one (.20 %) as other and two (.41 %) as unknown. Table 1 reports all the variables included in this study. All activities for this study were approved by the ethics committees of the authors' universities and competed in accordance with the Declaration of Helsinki. All participants provided informed consent prior to testing.

2.2. Memory assessment

Word-list recall performance was assessed with the Rey Auditory Verbal Learning Test (AVLT; Rey, 1958). The AVLT is a copyrighted instrument and can be obtained from Western Psychological Services (<https://www.wpspublish.com>). In this test, participants are read a list of 15 unrelated nouns a total of five times and are asked to recall these words freely after each presentation, in any order. Then a new 15-word list is tested (interference), followed by a subsequent recall of the originally presented list. Finally, after about 20–30 min, subjects are asked to recall the original list once again, ending with a recognition test. To evaluate episodic memory, we scored total recall (sum of all the correctly recalled items across all five initial trials), and delayed recall (number of words recalled correctly after the 20–30 min delay), which represent the typical test scores extracted from the AVLT. Primacy was defined as the first four words, middle was defined as the next seven, and recency was defined as the final four words, as per prior investigations (e.g., Bruno et al., 2013). Participants' cognitive data were taken from whichever visit was closest to the 18F-MK-6240 PET scan visit.

2.3. Positron emission tomography

All participants underwent T1-weighted MRI (3 T GE Signa 750) and amyloid and tau PET (Siemens EXACT HR+) imaging with [C-11]Pittsburgh Compound-B (11C-PiB) and 18F-MK-6240, respectively, according to previously published methods (Betthausen et al., 2019; Johnson et al., 2014). Briefly, PET time-series were coregistered to T1-weighted MRI that were tissue-class and ROI-segmented in subject space using SPM12. Amyloid burden was assessed as a global cortical average 11C-PiB distribution volume ratio (DVR; Logan graphical analysis, Logan et al., 1996; cerebellum GM reference region; $k_2' = .169 \text{ min}^{-1}$) across eight bi-lateral ROIs (angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus) with amyloid positivity determined using a previously established threshold (cortical 11C-PiB DVR ≥ 1.19) based on ROC analysis with visual ratings (Racine et al., 2016). Tau burden was assessed as 18F-MK-6240 standard uptake value ratio (SUVR; inferior cerebellum reference region) 70–90 min post-injection in the entorhinal cortex using a previously published tau positivity threshold based on the mean plus two standard deviations of a PiB(-) control group (entorhinal 18F-MK-6240 SUVR > 1.27 ; see Betthausen et al., 2020). For detailed image processing methods see Betthausen et al. (2019; 2020) and Johnson et al. (2014).

2.4. Genotyping

DNA was extracted from whole blood samples using the PUREGENE® DNA Isolation Kit (Gentra Systems, Inc., Minneapolis, MN) and DNA concentrations were quantified using UV spectrophotometry (DU® 530 Spectrophotometer, Beckman Coulter, Fullerton, CA), for further details, see Darst et al.,

Table 1 – Means (percentages or standard deviations, and ranges) of the demographic variables, tau PET load in the EC, PHC and H, PiB DVR, elapsed times, and memory scores, for the whole sample and by AT groups.

	Total (N = 490)	A–T– (N = 355)	A+T– (N = 64)	A–T+ (N = 25)	A+T+ (N = 46)
Sample (WRAP)	367 (74.9 %)	260 (73.2 %)	52 (81.3 %)	19 (76.0 %)	36 (78.3 %)
Gender (Fem)	333 (68.0 %)	234 (65.9 %)	45 (70.3 %)	22 (88 %)	32 (69.6 %)
APOE risk score	1.14 (.74; .00–3.25)	.97 (.61; .00–3.25)	1.57 (.86; .32–3.25)	1.15 (.81; .32–3.25)	1.81 (.89; .70–3.25)
Education (y)	16.52 (2.66; 8.00–29.00)	16.47 (2.68; 8.00–29.00)	16.39 (2.63; 12.00–25.00)	16.48 (2.29; 12.00–21.00)	17.15 (2.73; 12.00–23.00)
Age at tau PET scan	68.81 (7.17; 48.53–87.72)	67.68 (7.35; 48.53–87.72)	70.72 (5.48; 54.37–81.91)	73.74 (6.18; 62.30–85.01)	72.26 (5.51; 58.54–82.95)
Elapsed time Tau – AVLT	.29 (.64; –1.78–2.00)	.29 (.63; –1.78–2.00)	.29 (.74; –1.54–1.98)	.13 (.63; –.92–1.37)	.29 (.63; –1.51–2.00)
Number of AVLT visits	6.07 (1.81; 1.00–13.00)	5.94 (1.88; 1.00–13.00)	6.33 (1.71; 2.00–11.00)	6.44 (1.29; 3.00–9.00)	6.48 (1.46; 1.00–10.00)
EC SUVR	1.09 (.25; .65–2.79)	1.01 (.12; .65–1.26)	1.04 (.13; .74–1.27)	1.45 (.22; 1.27–2.15)	1.66 (.30; 1.28–2.79)
PHC SUVR	1.02 (.16; .63–2.31)	.98 (.10; .63–1.25)	1.01 (.12; .75–1.40)	1.19 (.11; 1.01–1.48)	1.29 (.24; 1.01–2.31)
H SUVR	.95 (.17; .59–1.93)	.90 (.11; .59–1.23)	.92 (.11; .66–1.21)	1.13 (.14; .91–1.50)	1.25 (.20; .93–1.93)
PiB DVR	1.16 (.20; .86–2.05)	1.06 (.06; .86–1.19)	1.40 (.18; 1.19–1.97)	1.09 (.05; 1.01–1.18)	1.56 (.21; 1.24–2.05)
Elapsed time Tau – Amyloid	.01 (.13; –1.00–.94)	.00 (.12; –1.00–.94)	.03 (.16; –.29–.94)	.01 (.19; –.61–.67)	.00 (.02; –.40–.10)
Total recall	53.89 (11.50; 23.00–90.00)	54.40 (11.93; 23.00–90.00)	55.17 (10.35; 27.00–85.00)	50.04 (7.98; 32.00–65.00)	50.20 (10.34; 29.00–78.00)
Total delayed	10.50 (2.88; 2.00–15.00)	10.56 (2.89; 2.00–15.00)	10.92 (2.59; 4.00–15.00)	10.04 (2.62; 6.00–15.00)	9.72 (3.20; 3.00–15.00)
Imm primacy	1.87 (1.16; .00–4.00)	1.90 (1.20; .00–4.00)	1.98 (1.06; .00–4.00)	1.56 (1.00; .00–4.00)	1.63 (1.04; .00–4.00)
Imm middle	2.20 (1.51; .00–7.00)	2.24 (1.55; .00–7.00)	2.39 (1.51; .00–7.00)	1.64 (1.11; .00–4.00)	2.00 (1.37; .00–5.00)
Imm recency	2.70 (.97; .00–4.00)	2.73 (.94; .00–4.00)	2.58 (.99; .00–4.00)	2.80 (1.00; 1.00–4.00)	2.54 (1.17; .00–4.00)
Del primacy	3.17 (.95; .00–4.00)	3.23 (.93; .00–4.00)	3.20 (.76; 1.00–4.00)	2.84 (1.03; 1.00–4.00)	2.83 (1.16; .00–4.00)
Del middle	4.97 (1.62; .00–7.00)	4.98 (1.63; .00–7.00)	5.27 (1.56; 1.00–7.00)	4.80 (1.47; 2.00–7.00)	4.61 (1.71; 1.00–7.00)
Del recency	2.36 (1.16; .00–4.00)	2.35 (1.15; .00–4.00)	2.44 (1.13; .00–4.00)	2.40 (1.29; .00–4.00)	2.28 (1.22; .00–4.00)

Note: APOE: apolipoprotein; Education in years; Elapsed time Tau – AVLT: Elapsed time between tau PET scan and cognitive test visit in which AVLT scores were collected, in years; EC: entorhinal cortex; PHC: parahippocampal cortex; H: hippocampus; SUVR: standard uptake value ratio; PiB: Pittsburgh compound-B; DVR: distribution volume ratio; Elapsed time Tau – Amyloid: elapsed time between 18F-MK-6240 PET and 11C-PiB PET scans, in years. Imm: immediate; Del: delayed.

2017. Samples were aliquoted on 96-well plates for determination of APOE genotypes. An APOE risk score was calculated based on the odds ratios of the e2/e3/e4 genotype, as previously reported (Darst et al., 2017).

2.5. Statistical analysis

Assumptions of normality and homoscedasticity were checked, along with Q–Q plots. Volume-controlled entorhinal cortex (EC), parahippocampal cortex (PHC), and hippocampus (H) tau PET SUVRs, were log₁₀ transformed due to non-normal distributions. To explore the relationships between the AVLT scores and log-transformed EC, PHC and H tau PET SUVRs, partial correlations, controlling for gender, years of education, APOE risk score, age at tau PET scan, visit number to account for practice effects, elapsed time between cognitive assessment and tau PET scan, PiB DVR, elapsed time between 18F-MK-6240 PET and 11C-PiB PET scans, and sample (WRAP or ADRC), were conducted.

Linear regression analyses were conducted with AVLT scores that were found to be significantly associated with regional tau PET SUVRs, as predictors, in separate models. Gender, years of education, APOE risk score, age at tau PET scan, visit number to account for practice effects, elapsed time between cognitive assessment and tau PET scan, PiB DVR, elapsed time between 18F-MK-6240 PET and 11C-PiB PET scans, and sample (WRAP or ADRC), were used as control variables. Volume-controlled and log-transformed EC, PHC and H tau PET SUVRs represented the outcomes in separate analyses. We adjusted for multiple testing using a false discovery rate-based approach (FDR; Benjamini & Hochberg, 1995) for all the predictors, corrected across EC, PHC and H tau PET SUVRs. To determine which AVLT score is the best predictor of EC, PHC and H tau PET SUVRs, we compared AIC fit statistics (Aiken, West, & Reno, 1991) across otherwise parallel models, lower AIC values indicate a better fit, and a model with a delta-AIC (i.e., the difference between the two AIC values being compared) greater than 2 is considered significantly better than the model it is being compared to (Burnham & Anderson, 2004).

Lastly, to examine the effect of biomarker group classification (A–T–, A–T+, A+T–, A+T+) on AVLT metrics, analyses of covariance (ANCOVA) were conducted. AT classification was the independent variable and the same covariates except PiB DVR were included. The AVLT metrics identified as significant in prior linear regression analyses were used as dependent variables in separate ANCOVA models. Analyses were conducted using JASP (.18.3; <https://jasp-stats.org/>) and the R code used in JASP for the analyses can be accessed from a public repository: <https://doi.org/10.17605/OSF.IO/7TWJ6>.

3. Results

In Table 1, means, standard deviations and ranges are described for all the variables included in the current study, for the whole sample and by AT groups.

Table 2 – Partial correlations between AVLT scores and EC, PHC, and H tau PET SUVRs.

	EC	PHC	H
Total recall	–.124**	–.060	–.043
Delayed recall	–.082	–.051	–.036
Immediate primacy	–.089	–.056	–.065
Immediate middle	–.060	–.032	–.019
Immediate recency	–.037	–.042	–.029
Delayed primacy	–.156***	–.125**	–.103*
Delayed middle	–.029	–.010	–.001
Delayed recency	–.027	–.004	.002

Note: N = 490. Partial correlations, controlling for gender, years of education, APOE risk score, age at tau PET scan, visit number to account for practice effects, elapsed time between cognitive assessment and tau PET scan, PiB DVR, elapsed time between 18F-MK-6240 PET and 11C-PiB PET scans, and sample (WRAP or ADRC), between memory scores and log-transformed EC, PHC and H tau PET SUVRs. EC: Entorhinal cortex; PHC: Parahippocampal cortex; H: Hippocampus. **p* < .05; ***p* < .01; ****p* < .001. Bold: indicates significant partial coefficients.

3.1. Correlations

As shown in Table 2, partial correlations indicated that not all memory scores were significantly correlated with tau PET SUVRs. Specifically, only total recall and delayed primacy were significantly correlated with EC tau PET SUVRs, while only delayed primacy was significant associated with PHC and H tau PET SUVRs. See Figure S1 in Supplementary materials for partial plots between AVLT Total and Delayed primacy recall and EC, PHC and H tau PET SUVRs, while controlling for the covariates.

3.2. Linear regression

Separate linear regression analyses were conducted for each outcome with total recall and delayed primacy, separately. Table 3 reports the full models for each outcome.

Entorhinal cortex (EC) tau PET SUVRs. Linear regression analyses showed that the separate model fits with total recall and delayed primacy were significant; as were their coefficients, see Table 3 for details. More total and delayed primacy recall were significantly associated with lower EC tau PET SUVRs (Total recall: $\beta = -.13$, SE = .00, unadjusted-*p* = .006, adjusted-*p* = .018; CIs $-.002$ to -2.746×10^{-4} ; Delayed primacy: $\beta = -.14$, SE = .00, unadjusted-*p* = .001, adjusted-*p* = .006; CIs $-.020$ to $-.005$). Delta-AIC between the model with delayed primacy model and the model with total recall was greater than two, indicating the delayed primacy model was significantly better.

Parahippocampal cortex (PHC) tau PET SUVRs. Linear regression analyses showed that the model fit with total recall was not significant, yet the model fit with delayed primacy recall was significant, as was the delayed primacy coefficient. More delayed primacy recall was significantly associated with lower PHC tau PET SUVRs ($\beta = -.12$, SE = .00, unadjusted-*p* = .006, adjusted-*p* = .012; CIs $-.013$ to $-.002$).

Table 3 – Linear regression models predicting volume-controlled EC, PHC, and H tau PET SUVRs (log-transformed).

Predictor	Outcome	Total recall model ¹		Delayed primacy model ²	
		β	p	B	p
Gender	EC	.07	.084	.07	.079
	PHC	-.02	.585	-.02	.726
	H	-.01	.842	.00	1.000
APOE risk score	EC	.07	.110	.07	.101
	PHC	.01	.794	.01	.771
	H	.03	.517	.03	.501
Education years	EC	.05	.176	.06	.153
	PHC	.05	.222	.06	.169
	H	.06	.139	.07	.105
Age at PET	EC	.14	.003	.15	<.001
	PHC	.08	.117	.08	.114
	H	.08	.101	.08	.107
Elapsed time Tau - AVLT	EC	-.02	.583	-.02	.569
	PHC	.01	.834	.01	.811
Visit number	EC	-.02	.715	-.03	.466
	PHC	-.02	.731	-.02	.627
	H	-.02	.740	-.02	.672
PiB DVR	EC	.46	<.001	.45	<.001
	PHC	.38	<.001	.38	<.001
	H	.39	<.001	.39	<.001
Elapsed time Tau–PiB	EC	.02	.670	.02	.598
	PHC	.01	.772	.02	.713
	H	.00	.959	.00	.992
Sample	EC	-.16	<.001	-.12	.003
	PHC	-.13	.006	-.11	.007
	H	-.10	.031	-.09	.028
AVLT score	EC	-.13	.006*	-.14	.001*
	PHC	-.07	.186	-.12	.006*
	H	-.05	.347	-.10	.024*
AIC	EC	-2548.45		-2552.83	
	PHC	-2809.98		-2815.90	
	H	-2667.89		-2672.22	
Adjusted R ²	EC	.293		.299	
	PHC	.168		.178	
	H	.174		.182	

Note: $N = 490$. β = Standardised regression coefficient; AVLT = Auditory Verbal Learning Test; EC: entorhinal cortex; PHC: parahippocampal cortex; H: hippocampus; SUVR: standard uptake value ratio; PiB: Pittsburgh compound-B; DVR: distribution volume ratio; $p = p$ -value; * significant after adjusting p -value for multiple comparisons. In all models, variables showed a Variation Inflation Factor (VIF) < 2; AIC = Akaike Information Criterion; Adjusted R² = adjusted proportion of explained variance. Bold: model with significantly best model fit, as per delta-AIC. Models with EC as outcome: ¹Model with Total recall: $F(10,479) = 21.26, p < .001$; ²Model with Delayed primacy: $F(10,479) = 21.88, p < .001$. Models with PHC as outcome: ¹Model with Total recall: $F(10,479) = 10.85, p < .001$; ²Model with Delayed primacy: $F(10,479) = 11.56, p < .001$. Models with H as outcome: ¹Model with Total recall: $F(10,479) = 11.32, p < .001$; ²Model with Delayed primacy $F(10,479) = 11.84, p < .001$.

Hippocampus (H) tau PET SUVRs. Linear regression analyses showed that while the model fit with delayed primacy was significant, as was the delayed primacy coefficient, the model fit with total recall was not. More delayed primacy recall was significantly associated with lower H tau PET SUVRs ($\beta = -.10$, $SE = .00$, unadjusted- $p = .024$, adjusted- $p = .036$; CIs $-.014$ to $-.001$).

3.3. ANCOVAs

Fig. 1 reports the means and error variance for total and delayed primacy recall scores by AT group. We carried out two separate ANCOVAs with total and delayed primacy recall as dependent variables, separately. After adjusting for the covariates, there was a statistically significant effect of

biomarker group classification on delayed primacy recall ($F(3, 478) = 2.91, p = .034$, partial $\eta^2 = .02$) and total recall scores ($F(3, 478) = 3.35, p = .019$, partial $\eta^2 = .02$).

Post hoc comparisons of the estimated marginal means indicated that the A+T+ group ($M = 2.84, SE = .15$) had significantly lower delayed primacy recall scores than the A–T– group ($M = 3.21, SE = .06$, unadjusted- $p = .017$) and the A+T– group ($M = 3.22, SE = .12$, unadjusted- $p = .030$), yet these comparisons were no longer significant when correcting with Tukey's HSD test (adjusted- $p = .081$, adjusted- $p = .131$, respectively), the A+T+ group had similar mean scores to the A–T+ group ($M = 2.86, SE = .19$, unadjusted- $p = 1.000$, adjusted- $p = .935$); no other significant differences between groups were found (all $p > .05$). For total recall, significantly higher scores were observed in the A+T– group ($M = 58.46$,

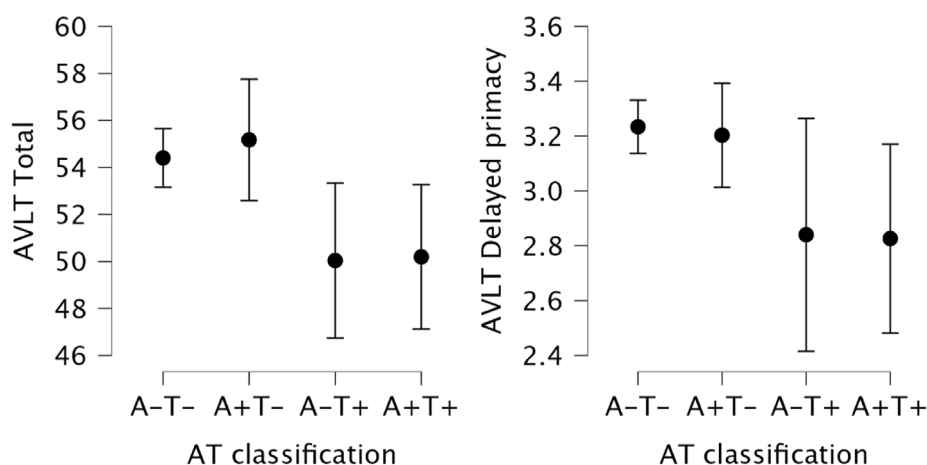


Fig. 1 – Means and error variance of Total recall (left) and Delayed primacy (right) scores by AT classification.

SE = 1.28) than in the A+T+ group ($M = 53.34$, $SE = 1.54$; unadjusted- $p = .006$, adjusted- $p = .029$) and the A-T+ group ($M = 53.13$, $SE = 1.97$, unadjusted- $p = .019$), yet this last comparison was no longer significant when correcting with Tukey's HSD test (adjusted- $p = .086$), and higher than the A-T- group ($M = 56.01$, $SE = .59$, unadjusted- $p = .075$, adjusted- $p = .281$); no other significant differences between groups were found (all $p > .05$).

4. Discussion

In this study, we examined whether serial position markers in word-list recall were associated with 18F-MK-6240 PET tau load in the MTL, specifically the entorhinal cortex (EC), parahippocampal cortex (PHC) and hippocampus (H), in cognitively unimpaired older individuals, and whether serial position scores outperformed traditional test metrics in predicting tau PET burden in these regions. We also investigated if serial position metrics discriminated between individuals based on their amyloid (A; with 11C-PiB) and tau (T; with 18F-MK-6240) PET load classifications. It was hypothesised that serial position scores of a word-list test would be associated with tau PET load in the EC, PHC and H, outperforming traditional scores, and that these would provide useful clinical information. Current results indicated that delayed primacy was indeed associated with tau PET burden in medial temporal regions, outperforming traditional scores. ANCOVAs showed that the A+T+ group had lower delayed primacy recall scores than the A-T- and A+T- groups, while the A+T- group had higher total recall scores than the A+T+ and A-T+ groups. In this section, the results and their implications will be described in detail and discussed based on previous literature.

Current findings are consistent with past studies reporting that in cognitively unimpaired individuals, tau PET load in MTL is associated with poorer memory performance (Lowe et al., 2019), and specifically, episodic memory (Maass et al., 2018). Moreover, the present study provides novel evidence on the usefulness of serial position markers derived from word-list recall tests, especially delayed primacy, in detecting tau PET burden cross-sectionally across two cohorts.

Specifically, we showed that more delayed primacy recall was associated with lower tau PET load in the three regions of the MTL examined here, EC, PHC and H, when controlling for demographic variables and PiB DVR. One more recalled word from the primacy region in the delayed trial cross-sectionally corresponded to 27 % less tau PET load in the EC, 24 % less in the PHC, and 20 % less in the H. As for traditional scores, total recall significantly predicted tau PET load in the EC, but not in the PHC or H, yet the model fits with delayed primacy were significantly better than with total recall, as shown by AICs. Furthermore, delayed recall was not significantly associated with tau PET burden in any of three MTL regions examined. The partial correlations reported in Table 2 reveal that while there was a weak primacy effect in immediate recall, probably reflecting the learning process, the primacy effect observed in the delayed trial was the strongest of all serial position markers. In particular, the weak correlations observed between delayed middle or recency recall and MTL tau PET load, highlight the relevance of delayed primacy recall, especially, when considering the lack of significant associations found between delayed recall and tau PET burden. Given the importance of MTL, in terms of the early neuropathological changes seen in AD (Adams et al., 2019) and its critical role in long-term episodic memory (De Simone et al., 2017), present findings suggest that delayed primacy in word-list recall might be a valuable tool for the identification of *in vivo* tau pathology in cognitively unimpaired older adults.

The novelty presented by the current study is the use of the 18F-MK-6240 PET ligand (Hostetler et al., 2016), which allows the examination of regional tau-tracer intake. This offers an important advantage over CSF, especially when investigating the earliest changes occurring in cognitively unimpaired individuals, as seen with cortical tau pathology in the EC (Adams et al., 2019). A previous study of the WRAP dataset reported that cognitively unimpaired individuals with elevated EC tau PET levels did not generally have increased tau PET levels in other brain regions, and that those who showed elevations in both amyloid and tau, had a higher amyloid burden than those with elevated amyloid only, which is consistent with the biomarker cascade model (Betthausen et al., 2020). Therefore, it could be argued that current findings expand previous ones,

so that delayed primacy in word-list recall is not only associated with amyloid deposition (Bruno, Gicas, et al., 2024), but it is also associated with tau PET load in the MTL.

The study by Betthausen et al. (2020) also showed that in cognitively unimpaired individuals, the combination of elevated amyloid- β and EC tau, as measured by PET, is associated with faster cognitive decline compared to those with pathological levels of either amyloid- β or tau alone. Considering amyloid- β and tau accumulations begin years before clinical impairment, we believe it is necessary to examine whether these measures of episodic memory also discriminate between cognitively unimpaired older adults with different AT classifications. Only recently, a study of serial position markers derived from story recall tests found that A+T+ classification was best predicted, cross-sectionally, by the recency ratio, which indices how much of the end of the story was forgotten between initial learning and delayed assessment, outperforming traditional scores of the same tests (Bruno, Jauregi-Zinkunegi, et al., 2024). In the current study, we intended to examine whether traditional and serial position scores from the AVLT, which, in contrast to story recall as in the previous study, is a word-list test, discriminated between AT biomarker profiles. Given that delayed primacy emerged as the only significant predictor of PHC and H tau PET load, and appeared to be superior to total recall for EC, as shown by AIC, we ran separate analyses of covariance with each measure as outcome, AT groups as fixed factor. These analyses showed that the A+T+ group had significantly lower delayed primacy scores than the A–T– and A+T– groups, yet these differences were no longer significant after correcting for multiple comparisons. For total recall, the A+T– group had significantly higher scores than the A+T+ and A–T+ groups, but only the difference between A+T– and A+T+ remained significant after correction. Considering that only cognitively unimpaired participants were included in the current study, the group sizes were unequal, especially when compared to the larger A–T– group, and these findings should be taken with caution.

We opted to focus on cognitively unimpaired individuals in our analyses based on theoretical considerations. We see the identification of cognitive markers in individuals without evident signs of disease as crucial, especially as these can be implemented even without extensive clinical background information. Although the inclusion of clinically impaired participants would have been informative, the number of participants with MCI with available data across the two cohorts was very low ($n = 44$). We believe future research with larger groups of individuals with cognitive impairment would be necessary to extend current findings and examine the research questions discussed here further.

Strengths of this study include the sample size and that cognitive assessments and tau PET scans were collected within few months of each other for most participants, not exceeding more than two years. Additionally, the 18F-MK-6240 and 11C-PiB PET scans were collected within days of each other for most, with a maximum of one year, reducing the likelihood of progressing to either amyloid or tau positivity between the acquisitions of the two scans. Even though the most recent data were analysed when possible, one participant who was T+ at most recent tau PET scan had progressed to A+ at most recent 11C-PiB PET scan. However, the elapsed

time between the 18F-MK-6240 and 11C-PiB scans, and between cognitive assessment and 11C-PiB scan, was approximately 2.4 years, exceeding the two-year exclusion criteria described in section 2.1. To ensure consistency across participants, in the analyses reported here, this individual was classified as A–T+ based on the best time-matching visits for the three measures, which were collected within 11 days. A *post hoc* analysis analogous to the main analyses was conducted, in which this participant was included in the A+T+ instead, and the main results from the regression analyses and ANCOVAs did not differ from those reported here. One of the study's limitations is that, as described in section 2.1, the sample comprised mostly of individuals who identified as white. Considering the importance of including a more diverse range of ethnicities and backgrounds in AD research (Manly et al., 2021; Morris et al., 2019), future studies should consider exploring whether the findings reported here would also apply to a more diverse sample.

5. Conclusion

In summary, this cross-sectional study showed that in cognitively unimpaired individuals, loss of delayed primacy recall in a word-list is negatively associated with 18F-MK-6240 PET tau load in the MTL, outperforming traditional AVLT scores, such as total and delayed recall. Specifically, when controlling for demographic variables and amyloid burden, results indicated that lower delayed primacy recall was associated with an increase in entorhinal cortex, parahippocampal and hippocampus tau PET SUVR. Although delayed primacy distinguished between AT biomarker profiles, group differences were no longer significant after correcting for multiple comparisons. Considering current findings, we propose that conducting a serial position analysis of word-list data, with a particular focus on delayed primacy, could serve as a valuable tool for identifying *in vivo* tau pathology.

CRediT authorship contribution statement

Ainara Jauregi-Zinkunegi: Writing – original draft, Formal analysis, Conceptualization. **Tobey Betthausen:** Project administration, Funding acquisition. **Cynthia M. Carlsson:** Project administration, Funding acquisition. **Barbara B. Bendlin:** Writing – review & editing, Project administration, Funding acquisition. **Ozioma Okonkwo:** Project administration, Funding acquisition. **Nathaniel A. Chin:** Project administration, Funding acquisition. **Sanjay Asthana:** Project administration, Funding acquisition. **Rebecca E. Langhough:** Project administration, Funding acquisition. **Sterling C. Johnson:** Project administration, Funding acquisition. **Kimberly D. Mueller:** Project administration, Funding acquisition. **Davide Bruno:** Writing – original draft, Project administration, Funding acquisition, Formal analysis.

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Conflicts of interest

No author reports any conflicts of interests or disclosures.

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Scientific transparency statement

DATA: WRAP and ADRC data can be requested from: <https://wrap.wisc.edu/data-requests-2/> and <https://www.adrc.wisc.edu/apply-resources>. Data will be released to internal and external investigators following confirmation of the Institutional Review Board approval together with an evaluation by WRAP and ADRC of scientific merit and resource availability.

CODE: All analysis code supporting this research is publicly available: <https://doi.org/10.17605/OSF.IO/7TWJ6>.

MATERIALS: This research did not make use of any materials to generate or acquire data.

DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.

PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

For full details, see the *Scientific Transparency Report* in the online version of this article.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cortex.2024.12.012>.

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