

Amyloid- β deposition in basal frontotemporal cortex is associated with selective disruption of temporal mnemonic discrimination

Casey R. Vanderlip¹, Lisa Taylor¹, Soyun Kim¹, Alyssa L. Harris¹, Nandita Tuteja¹,
Novelle Meza¹, Yuritza Y. Escalante¹, Liv McMillan¹, Michael A. Yassa¹, Jenna N. Adams^{1*}

¹ Department of Neurobiology and Behavior and Center for the Neurobiology of Learning and Memory, University of California, Irvine, Irvine, California 92697 USA

*Corresponding author: jnadams@uci.edu

Author contributions:

Conceptualization, C.R.V., J.N.A., & M.A.Y.; Data Acquisition, A.L.H., N.T., N.M., Y.Y.E., S.K.; Project administration, L.M.; Methodology & Software, C.R.V., L.T., J.N.A; Formal Analysis, C.R.V.; Writing – Original Draft, C.R.V. & J.N.A.; Writing – Reviewing and Editing, all authors; Funding Acquisition and Supervision, M.A.Y. & J.N.A.

Acknowledgments:

This research was supported by the National Institute on Aging R01AG053555 to M.A.Y. and F32AG074621 to J.N.A.

Conflict of interest:

M.A.Y. is Co-founder and Chief Scientific Officer of Augnition Labs, LLC. The authors declare no other competing financial interests.

Abstract:

Cerebral amyloid-beta ($A\beta$) accumulation, a hallmark pathology of Alzheimer's disease (AD), precedes clinical impairment by two to three decades. However, it is unclear whether $A\beta$ contributes to subtle memory deficits observed during the preclinical stage. The heterogeneous emergence of $A\beta$ deposition may selectively impact certain memory domains, which rely on distinct underlying neural circuits. In this context, we tested whether specific domains of mnemonic discrimination, a neural computation essential for episodic memory, exhibit specific deficits related to early $A\beta$ deposition. We tested 108 cognitively unimpaired human older adults (66% female) who underwent 18F-florbetapir positron emission tomography ($A\beta$ -PET), and a control group of 35 young adults, on a suite of mnemonic discrimination tasks taxing object, spatial, and temporal domains. We hypothesized that $A\beta$ pathology would be selectively associated with temporal discrimination performance due to $A\beta$'s propensity to accumulate in the basal frontotemporal cortex, which supports temporal processing. Consistent with this hypothesis, we found a dissociation in which generalized age-related deficits were found for object and spatial mnemonic discrimination, while $A\beta$ -PET levels were selectively associated with deficits in temporal mnemonic discrimination. Further, we found that higher $A\beta$ -PET levels in medial orbitofrontal and inferior temporal cortex, regions supporting temporal processing, were associated with greater temporal mnemonic discrimination deficits, pointing to the selective vulnerability of circuits related to temporal processing early in AD progression. These results suggest that $A\beta$ accumulation within basal frontotemporal regions may disrupt temporal mnemonic discrimination in preclinical AD, and may serve as a sensitive behavioral biomarker of emerging AD progression.

Introduction:

In Alzheimer's disease (AD), amyloid-beta (A β) pathology begins to accumulate within the posteromedial and basal frontotemporal cortex (Braak & Braak, 1991; Thal et al., 2002) decades prior to clinical impairment (Jack et al., 2018). Given the early role of A β in AD pathogenesis, identifying subtle cognitive deficits that reflect emerging A β accumulation could enable early detection of AD and sensitively assess clinical intervention outcomes for A β -lowering therapeutics.

Previous research has demonstrated small and inconsistent associations between A β pathology and concurrent cognitive ability during preclinical AD (Adams et al., 2023; Baker et al., 2017; Chételat et al., 2013; Hedden et al., 2013), inspiring debate on whether A β impacts cognition during the preclinical stage compared to the larger effects observed for tau or neurodegeneration (Maass et al., 2019; Mattsson-Carlgrén et al., 2023). However, most previous studies have used dichotomous or global measures of A β (Donohue et al., 2014, 2017; Insel et al., 2020; Landau et al., 2012), which may miss the contribution of heterogeneous A β accumulation patterns. Further, many studies have used composite memory measures from neuropsychological batteries (Donohue et al., 2014) which may preclude identifying subtle impacts of A β on episodic memory deficits. Therefore, a regionally-based investigation of A β pathology's effects on specific mechanisms underlying episodic memory is needed to elucidate its potential role in early, subtle memory deficits.

One critical aspect of episodic memory is pattern separation, a neural computation performed in the hippocampus which reduces interference among similar representations to enable discrimination of overlapping experiences (Bakker et al., 2008; Berron et al., 2016; Yassa & Stark, 2011). Pattern separation occurs across various domains, including object stimuli (Yassa et al., 2010), spatial relationships (Reagh & Yassa, 2014), and temporal ordering (Roberts et al., 2014). While the hippocampus is crucial for pattern separation across domains, cortical regions outside the hippocampus preferentially process specific stimuli and relay this domain-specific information to the hippocampus (Ranganath & Ritchey, 2012).

Extensive research has investigated how aging and AD affect object and spatial mnemonic discrimination and associated neural circuits (Adams et al., 2022; Maass et al., 2019; Reagh et al., 2018; Stark et al., 2010). Older adults demonstrate mnemonic discrimination for object prior to spatial stimuli (Güsten et al., 2021; Holden et al., 2012; Reagh et al., 2016, 2018). Anterior-temporal cortical systems supporting object processing and posterior-medial cortical systems supporting spatial processing are differently vulnerable to tau and A β pathology, respectively (Maass et al., 2019; Ranganath & Ritchey, 2012). While A β 's propensity to deposit within posteromedial cortex has motivated work investigating A β -related spatial mnemonic discrimination deficits, evidence for a direct association between A β and spatial mnemonic discrimination performance in older adults is weak (Adams et al., 2022; Webb et al., 2020), suggesting it may not be a sensitive marker of A β pathology in the preclinical stage.

Conversely, temporal processing engages basal frontotemporal regions (Duarte et al., 2010; E. L. Johnson et al., 2022) that are also highly susceptible to early A β accumulation (Braak & Braak, 1991; Grothe et al., 2017), yet temporal mnemonic discrimination has not been studied in the context of emerging AD. Neurons in medial orbitofrontal cortex (mOFC) track sequences of events (Jafarpour et al., 2023), and lesions in mOFC cause impairments in temporal memory even when object and spatial memory remain unaffected (Shimamura et al., 1990). Further, the inferior temporal (IT) cortex integrates items within a temporal framework (Kulkarni & Lega, 2023; Naya et al., 2017; Naya & Suzuki, 2011), without which temporal discrimination within the hippocampus would be impaired.

The involvement of basal frontotemporal regions in temporal processing and their vulnerability to early A β deposition suggest that temporal mnemonic discrimination performance could reflect underlying A β pathology. Here, we tested whether A β deposition contributes to deficits in temporal mnemonic discrimination in cognitively unimpaired older adults. We hypothesized that A β pathology would be selectively associated with temporal mnemonic discrimination performance, rather than with object or spatial, particularly when measured in basal frontotemporal regions supporting temporal processing.

Materials and Methods

Participants

35 young adults (18 to 35 years of age; mean 23.34 ± 4.42 years old; 71.4% female) and 108 cognitively unimpaired older adults (over 60 years of age; mean 71.22 ± 6.25 years old; 65.7% female) from the Biomarker Exploration in Aging, Cognition, and Neurodegeneration (BEACoN) study at the University of California, Irvine with assessment of mnemonic discrimination performance were included in this analysis (**Table 1**). Older adults additionally received magnetic resonance imaging (MRI) and positron emission tomography (PET) to assess A β pathology. All older adults were within their age-adjusted normal range in cognitive function based on neuropsychological testing. Further, all participants had no major health issues, and no history of significant neurological or psychiatric disorders. All participants provided written informed consent in accordance with the University of California, Irvine Institutional Review Board.

Mnemonic Discrimination Tasks

Young and older adult participants performed a suite of Mnemonic Discrimination Tasks (MDT), with distinct assessments of object, spatial, and temporal mnemonic discrimination.

Object and Spatial: The object and spatial MDT (**Figure 1A-B**) have been extensively described in previous research (Adams et al., 2022; Kim et al., 2023; Reagh et al., 2018). Briefly, both the object and spatial domain MDT included an encoding phase where participants viewed a series of 120 images, making indoor/outdoor judgments for each image (presented for 2 s; interstimulus interval, 0.5 s). Participants had up to two seconds to respond after the stimulus was removed from the screen. In the object domain test phase, participants viewed a series of images

classified as repetitions (identical to those seen during encoding), foils (completely new), or lures (similar but not identical to an image from encoding). These lures are particularly critical as they are known to require hippocampal pattern separation. In the object task, participants were asked to make “old”/“new” judgments based on whether they had seen the images during the encoding phase. Conversely, in the spatial domain test phase, participants viewed the same images as in the encoding phase but had to determine if the image's location on the screen had changed (“same”/“different” judgment). The images were either in the same location (repetition) or had moved slightly (within the same screen quadrant) or significantly (to a different quadrant). This setup was designed to tax spatial pattern separation capacity. For both the object and spatial versions of the MDT, we calculated the response bias-corrected Lure Discrimination Index (LDI), quantified as $p(\text{“New or Different”} \mid \text{Lure}) - p(\text{“New or Different”} \mid \text{Target})$. To remove individuals with contaminant behavior, we excluded subjects (object: $n = 5$, spatial: $n = 2$) who responded greater than 2 standard deviations faster than the group average.

Temporal. The temporal MDT is designed to assess temporal mnemonic discrimination abilities (**Figure 1C**). The task was divided into 6 blocks, each comprising an encoding phase followed by a test phase. During the encoding phase, participants viewed a series of 30 images, making indoor/outdoor judgments for each (presented for 2 s; interstimulus interval, 0.5 s). Subsequently, in the test phase, they were presented with two images previously seen during encoding side by side, and asked to determine which image had appeared first during the encoding phase by making a “left”/ “right” judgment. Each image was displayed only once during the encoding phase and once during the test phase for each block, ensuring no repetitions within the context of the task. The majority (75%) of test phase trials assessed temporal lags between stimuli ranging from zero to 16 images during encoding. Additionally, a subset of trials (25%) featured images from the first and last positions of the encoding phase, assessing lags of 27 to 29 (Primacy/Recency trials). However, due to the potential influence of attentional rather than purely mnemonic demands on these Primacy/Recency trials (Morrison et al., 2014), we excluded them from our analysis. Consequently, we calculated temporal discrimination performance based on the accuracy of trials with lags of 16 or fewer across all blocks for each participant. Similar to the analysis of the object and spatial MDT, we excluded subjects ($n = 4$) who responded greater than 2 standard deviations faster than the group average.

Structural MRI Acquisition and Processing

Older adults underwent MRI at the Facility for Imaging Brain Research (FIBRE) at UC Irvine on a 3T Prisma scanner (Siemens Medical System, Munich, Germany) equipped with a 32-channel head coil. A whole brain, high resolution T1-weighted volumetric magnetization prepared rapid gradient echo images (MPRAGE) was acquired for structural analyses (voxel size = 0.8mm^3 resolution, TR/TE/TI = 2300/2.38/902 ms, flip angle = 8° , 240 slices acquired sagittally).

T1-weighted images were processed through FreeSurfer v.6.0.2 to obtain cortical native-space regions of interest for FBP normalization and quantification. T1-weighted images were also processed using Statistical Parametric Mapping 12 (SPM12) software, in which they were

segmented into gray, white, and CSF components and warped to MNI152 2mm standard space. All FreeSurfer segmentation images and resulting MNI-template space T1-weighted images were quality checked by trained researchers, and FreeSurfer segmentations were manually edited when necessary.

PET Acquisition and Processing

To assess A β pathology in older adult participants, 18F-florbetapir (FBP) PET was conducted using an ECAT High-Resolution Research Tomograph (CTI/Siemens) at the University of California, Irvine. A dose of 10 millicuries of the tracer was administered, followed by the acquisition of four 5-minute frames between 50 and 70 minutes post-injection. FBP images underwent attenuation correction, scatter correction, and 2 mm³ Gaussian smoothing. FBP images were then processed using SPM12 software. FBP images were realigned and coregistered to each participant's T1-weighted MRI, and normalized with a whole cerebellum reference region to generate standardized uptake value ratio (SUVR) images. Next, additional 6 mm³ Gaussian smoothing was applied, resulting in an effective resolution of 8 mm³. The mean SUVR from a cortical composite region previously validated for assessing global A β (Landau et al., 2012) was calculated to quantify overall A β burden. A β ⁺ status was determined based on a threshold of >1.11 SUVR (Landau et al., 2012).

In addition to global measures, mean SUVR values were calculated for three composite regions representing stages of early, intermediate, and late A β vulnerability, as identified in prior work (Mattsson et al., 2019). For early-stage A β accumulation, the composite region encompassed the precuneus, posterior cingulate, isthmus cingulate, insula, and both medial and lateral orbitofrontal cortices. The late-stage region was composed of the lingual, pericalcarine, paracentral, precentral, and postcentral cortices. Lastly, the intermediate stage region was defined as the remaining cortical areas. Furthermore, specific regional SUVRs for the mOFC, IT, posterior cingulate cortex, and a combined control region of the primary motor and sensory cortices were also quantified.

We also conducted voxelwise FBP-PET analyses to determine spatially specific relationships between temporal mnemonic discrimination performance and FBP SUVR. Native space FBP images were warped to 2mm MNI space with SPM12, using deformation parameters generated from warping the T1-weighted image to MNI. Voxelwise associations between temporal discrimination performance and FBP SUVR were performed in SPM12, using a linear regression approach. A voxelwise threshold of $p_{unc} < 0.005$ and a cluster extent of greater than 25 voxels was used to determine significant clusters.

Experimental Design and Statistical Analyses

Data was analyzed using Python. Shapiro-Wilk tests for normality revealed that the data were normally distributed, and so parametric statistical analyses were performed. Associations between two variables were assessed using Pearson correlations and linear regressions. Two-way analysis of variance (ANOVA) tests were used to assess two factor interactions. One-way

ANOVAs with Tukey's HSD post-hoc tests were used to identify within-factor differences. Independent samples t-test were used to assess differences between two groups based on A β status. Proportional shared effects of FBP SUVR within A β stages were performed with commonality analysis (Lindenberger & Pötter, 1998) using the "yhat" package in R, which conducts commonality analyses based upon all-possible-subsets regression. $P < 0.05$ was considered significant.

Table 1. Demographic information for study participants

	YA	Aβ- OA	Aβ+ OA
N	35	70	38
Age (years) M (SD)	23.34 (4.42)	70.29 (5.75)	72.20 (6.86)
Education (Years) M (SD)	14.46 (2.70)	16.57 (2.41)	15.21 (2.22)
Female N (%)	25 (71.42%)	42 (60.00%)	29 (76.32%)
Race			
White N (%)	26.47%	51 (72.86%)	35 (92.11%)
Asian N (%)	52.94%	14 (20.00%)	3 (7.89%)
Black N (%)	2.94%	1 (1.43%)	n/a
More than one N (%)	5.88%	2 (2.86%)	n/a
Other	11.76%	2 (2.86%)	n/a
MMSE M (SD)	n/a	28.41 (1.35)	28.62 (1.83)

A β - amyloid- β , YA - Younger adults, OA - Older adults, MMSE - Mini-Mental State Examination, M - mean, SD - standard deviation

RESULTS

Age-related impairments in object and spatial mnemonic discrimination

To first investigate associations between behavioral performance on the object, spatial, and temporal domains of mnemonic discrimination, we correlated performance across the three tasks in young and older adults. Consistent with previous work, we found a strong positive association between object and spatial mnemonic discrimination ($r_p = 0.401$, $p < 0.0001$; **Figure 1D**). Further, we observed significant positive correlations between temporal mnemonic discrimination with both object ($r_p = 0.276$, $p = 0.002$; **Figure 1E**) and spatial mnemonic discrimination ($r_p = 0.372$, p

< 0.0001; **Figure 1F**). These correlations remained significant within just the older adult subsample (temporal vs object: $r_p = 0.271$, $p = 0.009$; temporal vs spatial: $r_p = 0.35$, $p = 0.001$; object vs spatial: $r_p = 0.354$, $p = 0.0004$). These findings align with prior work suggesting that hippocampal pattern separation is domain agnostic (Azab et al., 2014, Yassa & Stark 2011). Critically, however, while statistically correlated, there was variability in the strength of the correlations. This suggests that there may be extra-hippocampal neural mechanisms that are not domain agnostic and therefore likely contribute to differing pattern separation capacities across domains.

We next tested how aging affects performance across object, spatial, and temporal domains by comparing performance between young and older adult groups. Consistent with prior findings (Stark et al., 2013), we observed a large impairment in object mnemonic discrimination in older adults ($t = 5.23$, $p < 0.00001$, Cohen's $d = 1.06$), and a smaller, yet significant impairment in spatial mnemonic discrimination ($t = 2.32$, $p = 0.022$, Cohen's $d = 0.472$) compared to younger adults. In contrast, temporal discrimination capacity did not significantly differ across age groups ($t = 1.39$, $p = 0.17$, Cohen's $d = 0.290$). This aligns with prior work suggesting that, compared to other domains, object mnemonic discrimination is highly vulnerable to the aging process (Reagh et al., 2018), and suggests that temporal discrimination performance does not solely reflect age-related processes.

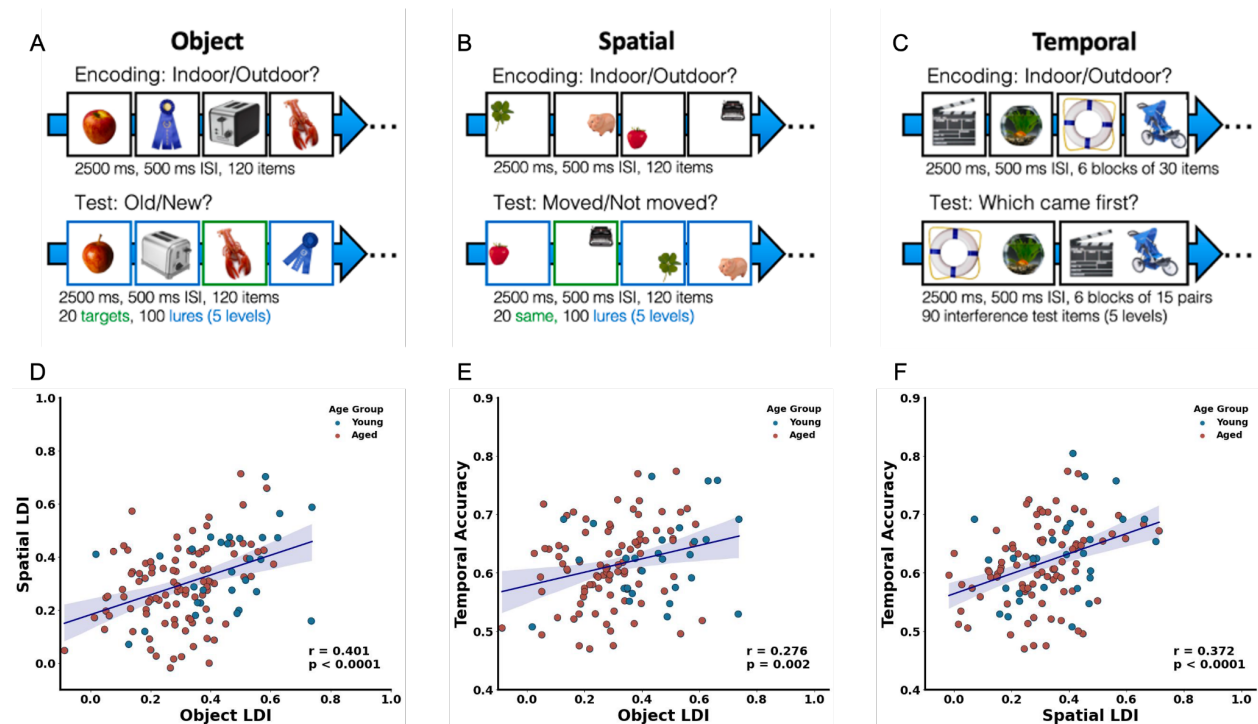


Figure 1. Mnemonic discrimination performance is positively correlated across domains. Schematic of (A) Object, (B) Spatial, and (C) Temporal mnemonic discrimination tasks. (D) Object and Spatial mnemonic discrimination are positively correlated. (E) Significant positive association between object mnemonic discrimination and temporal discrimination. (F) Strong positive association between spatial mnemonic discrimination and temporal discrimination. For D-F, Young adults are in blue and older adults are in red. Linear regression models were used to determine 95% confidence intervals shaded in gray.

Temporal mnemonic discrimination ability is selectively associated with elevated A β levels

While all older adults within this sample were cognitively unimpaired, a subset of individuals (n=38, 35%) were classified as A β + based on their global 18F-florbetapir uptake (see **Methods**). We hypothesized that A β deposition would selectively disrupt temporal mnemonic discrimination and therefore first assessed whether performance on the mnemonic discrimination tasks varied according to A β status. To control for age-related changes and standardize measures across tasks, we z-scored performance of all older adults to the performance of young adults within each domain.

We found no significant difference in performance between A β - and A β + older adults on either object or spatial mnemonic discrimination (object: $t(87) = 0.80$, $p = 0.43$; spatial: $t(84) = 0.34$, $p = 0.74$; **Figure 2A-B**). In contrast, in the temporal domain, A β + older adults exhibited poorer performance compared to their A β - counterparts ($t(85) = 2.03$, $p = 0.047$; **Figure 2C**). Further, an analysis of continuous global A β levels demonstrated a significant negative correlation between global FBP SUVR and temporal mnemonic discrimination (temporal: $r_p = -0.217$, $p = 0.043$; **Figure 2F**), while no such association was found for object or spatial discrimination (object: $r_p = -0.079$, $p = 0.460$, spatial: $r_p = -0.048$, $p = 0.658$; **Figure 2D-E**). These findings collectively indicate a susceptibility of temporal discrimination to A β pathology, supporting our hypothesis that it may serve as a sensitive marker for early A β deposition in the absence of clinical symptoms. Given that A β was selectively related to temporal performance, our subsequent analyses sought to more closely examine the relationship between temporal discrimination and regional patterns of A β deposition to determine the underlying basis of this relationship.

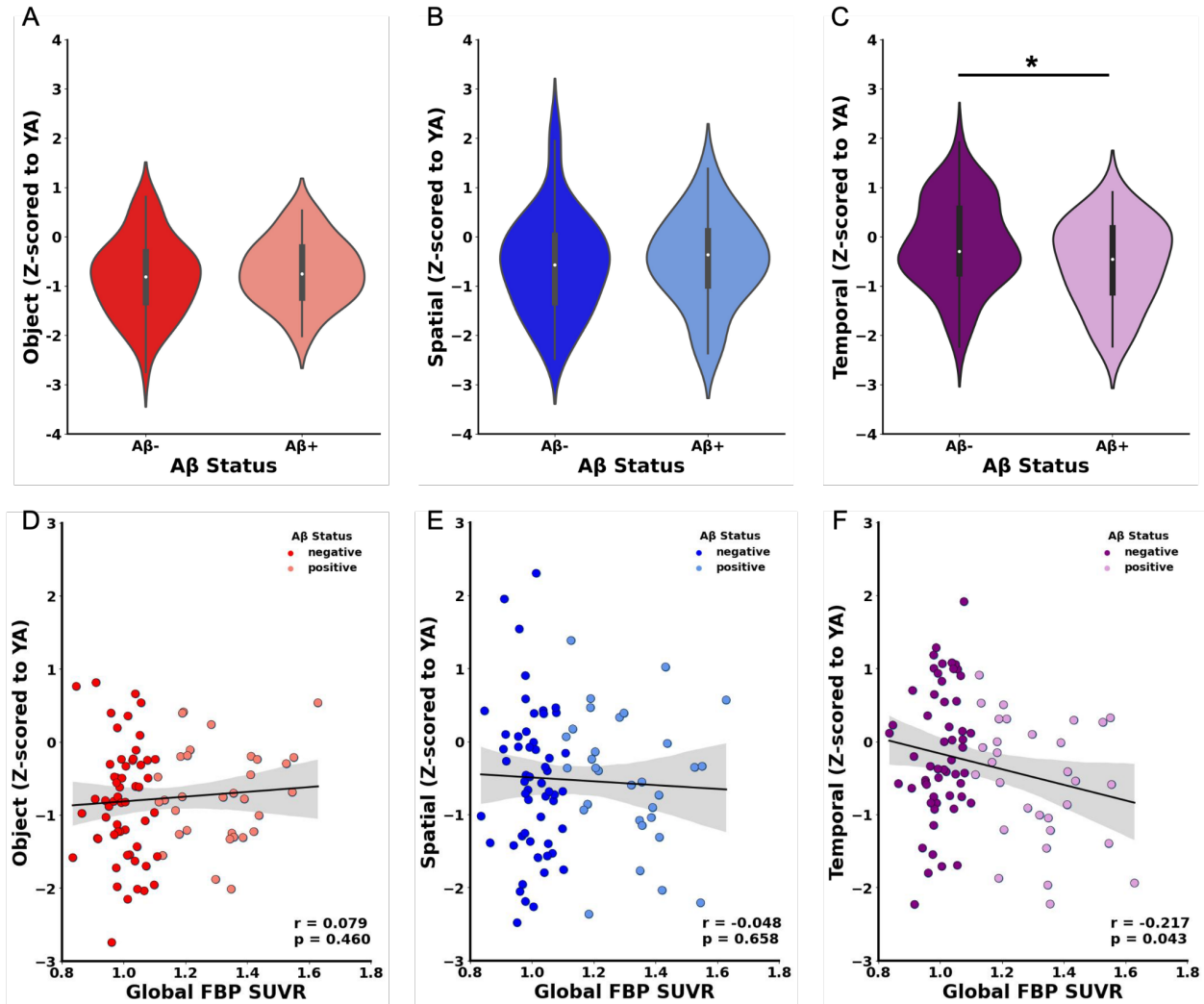


Figure 2. Global Aβ is selectively related to temporal discrimination performance in cognitively unimpaired older adults. Violin plots demonstrating that Aβ+ individuals performed similarly to Aβ- older adults on (A) object mnemonic discrimination and (B) spatial mnemonic discrimination. (C) Aβ+ older adults had impaired temporal discrimination compared to Aβ- individuals. There was no significant correlation between global SUVR and object (D) or spatial (E) mnemonic discrimination. (F) Increased global FBP SUVR was significantly associated with decreased temporal mnemonic discrimination. Linear regression models were used to determine 95% confidence intervals shaded in gray.

Elevated Aβ levels in regions impacted early in AD is associated with impaired temporal mnemonic discrimination

Given the overall association between temporal mnemonic discrimination and Aβ levels, we aimed to determine how early this Aβ effect may begin, hypothesizing Aβ levels in regions known to accumulate Aβ early would be related to performance. There are multiple proposed staging methods for identifying which areas are affected earliest by Aβ deposition, and there is not complete consensus on which regions should be included in each stage. Here we used one proposed staging scheme which categorized cortical regions into early, intermediate, and late stages based

on the timing of A β accumulation as a testbed (Mattsson et al., 2019). We quantified mean FBP SUVR in early, intermediate, and late-stage regions (Mattsson et al., 2019; see **Methods**) and correlated these stage-specific FBP values with temporal discrimination accuracy. Our analyses revealed significant negative correlations between FBP SUVR with temporal mnemonic discrimination performance in both early ($r_p = -0.240$, $p = 0.025$; **Figure 3A**) and intermediate ($r_p = -0.228$, $p = 0.034$; **Figure 3B**) stages. However, A β levels in late-stage areas showed a marginal, but not significant, relationship with temporal discrimination ($r_p = -0.170$, $p = 0.107$; **Figure 3C**).

To further investigate if A β in vulnerable regions are selectively related to temporal mnemonic discrimination, we conducted a commonality analysis to determine the unique versus shared variance of FBP SUVR within each stage on temporal mnemonic discrimination performance. This analysis demonstrated that the majority of variance (45.2%; coefficient = 0.035) of temporal mnemonic discrimination performance is explained by shared variance of early and intermediate stage A β . Shared variance across all three stages (21.4%; coefficient = 0.017) and unique variance of early (8.2%; coefficient = 0.006), intermediate (7.5%; coefficient = 0.006) and late stage FBP SUVR (25.1%; coefficient = 0.019) contributed to a lesser extent. These results suggest a notable link between increased A β deposition in areas vulnerable early in AD and poorer temporal discrimination. However, more importantly, this indicates that A β accumulation in specific brain regions, particularly those affected in the early and intermediate stages, may contribute to the deficits observed in temporal discrimination, rather than just global A β accumulation.

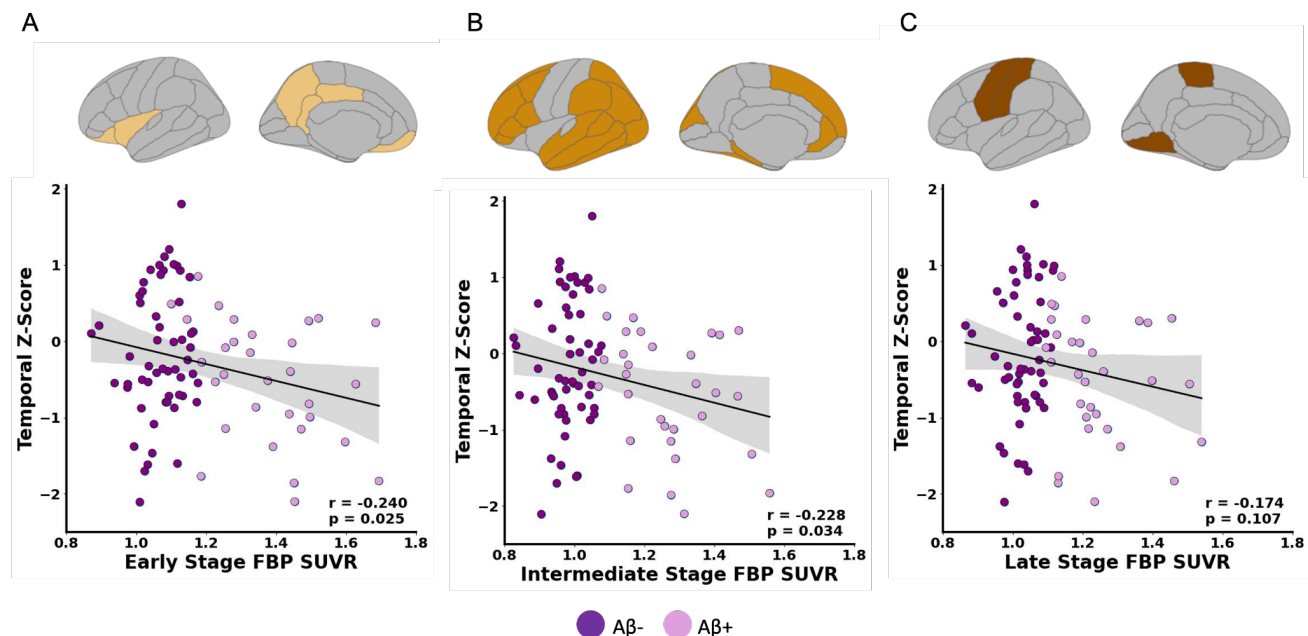


Figure 3. A β deposition in areas vulnerable to early accumulation is related to temporal discrimination. A) Significant negative association between FBP SUVR in early composite region composite and temporal mnemonic discrimination. **B)** Significant negative association between FBP SUVR in intermediate composite region and temporal mnemonic discrimination. **C)** No significant relationship between FBP SUVR in regions affected later in A β progression and temporal mnemonic discrimination.

A β deposition in cortical regions supporting temporal memory are specifically associated with impairment in temporal discrimination

One plausible explanation for the link between A β deposition and impaired temporal discrimination is the involvement of specific brain circuits that are particularly susceptible to A β pathology. To test this hypothesis, we examined the relationship between temporal discrimination performance and A β levels in key cortical regions supporting temporal processing that are also known to accumulate A β (i.e. mOFC and IT). As control regions, we included the posterior cingulate cortex (PCC) as an early A β -accumulating posteromedial region that is not particularly involved in temporal processing, and primary sensory/motor cortex as a region that neither accumulates A β early nor contributes to temporal processing.

Consistent with this hypothesis, our analyses revealed a strong correlation between diminished temporal mnemonic discrimination with increased FBP SUVR in the mOFC ($r_p = -0.281$, $p = 0.008$; **Figure 4A**) and IT ($r_p = -0.325$, $p = 0.002$; **Figure 4B**). In contrast, A β levels in the PCC, an area associated with A β deposition early in disease progression, but not temporal processing, was not significantly associated with temporal discrimination performance ($r_p = -0.176$, $p = 0.103$; **Figure 4C**). Similarly, FBP SUVR in areas not traditionally associated with temporal processing or A β deposition, such as the primary motor and sensory cortices, showed no correlation with temporal mnemonic discrimination ($r_p = -0.127$, $p = 0.243$; **Figure 4D**). This lack of association in regions not implicated in temporal processing further supports the notion that A β -related impairments in temporal mnemonic discrimination are specifically linked to its deposition in brain areas integral to temporal processing and episodic memory.

Previous research indicates a complex relationship between A β deposition and cognitive deficits, suggesting that while A β may be associated with cognitive deficits, its levels do not consistently correlate with cognitive function beyond a certain threshold. Given this, we aimed to determine whether, within A β + individuals, heightened regional A β levels were associated with worsening temporal discrimination deficits. We again found strong significant correlations between higher FBP SUVR in the mOFC and IT and deficits in temporal mnemonic discrimination when restricting analyses to A β + individuals (mOFC: $r_p = -0.470$, $p = 0.008$, IT: $r_p = -0.487$, $p = 0.005$; **Figure 4A-B**). Conversely, we again observed no significant correlation between temporal mnemonic discrimination deficits and FBP SUVR in PCC ($r_p = -0.226$, $p = 0.221$; **Figure 4C**) and the primary motor and sensory cortices ($r_p = -0.157$, $p = 0.399$; **Figure 4D**) when restricting analyses to A β + individuals. These results indicate that the degree of A β deposition in basal frontotemporal cortical regions is associated with worsening temporal mnemonic discrimination, suggesting that regional A β plays a direct role in the disruption of this cognitive function and is not just an incidental marker of preclinical AD.

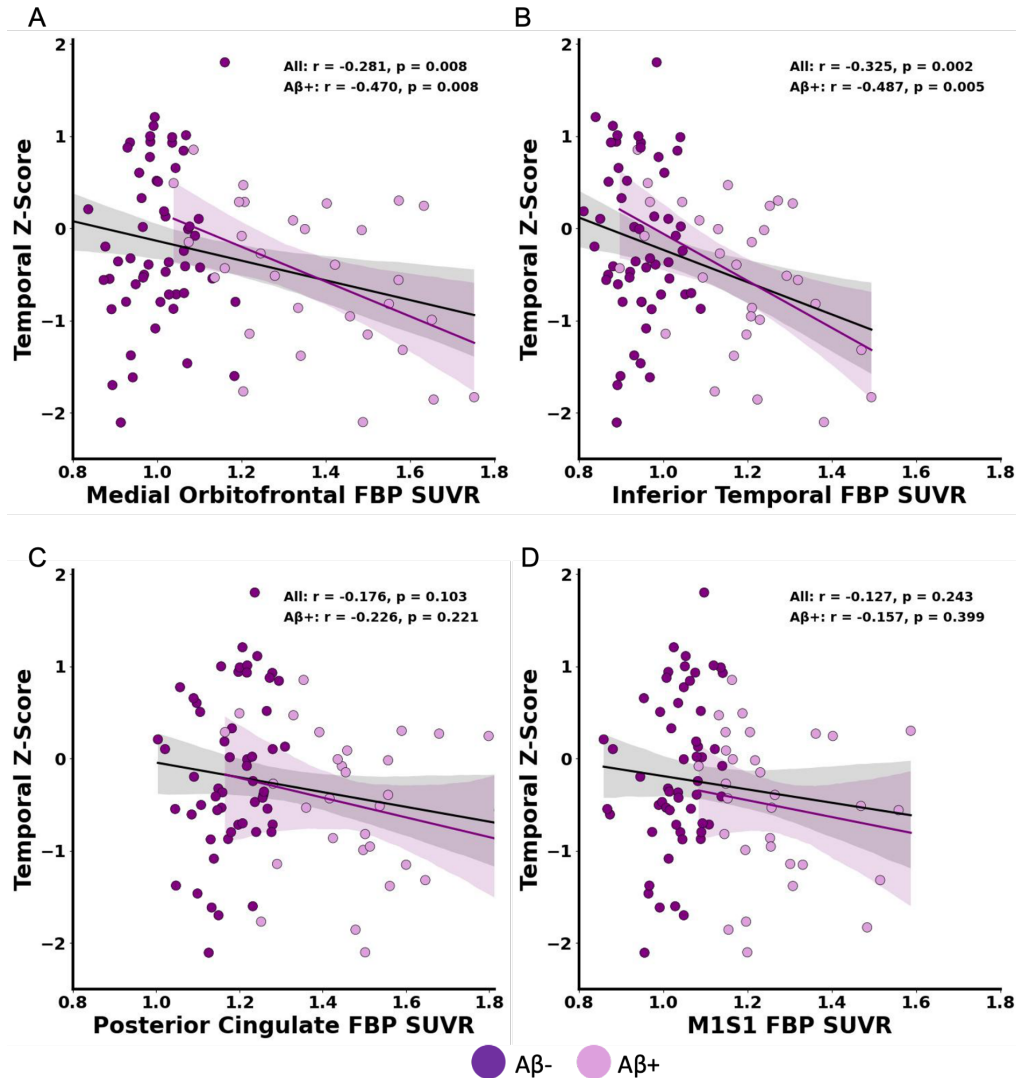


Figure 4. Selective relationship between Aβ deposition in regions related to temporal processing and temporal mnemonic discrimination performance. (A) Significant negative association between medial orbitofrontal cortex FBP SUVR and temporal mnemonic discrimination across all older adults (black line) and within the Aβ+ older adults (purple line). (B) Significant negative correlation between FBP SUVR in inferior temporal cortex and temporal discrimination across all older adults (black line) and within Aβ+ older adults (purple line). (C) Despite the posterior cingulate cortex being vulnerable to Aβ pathology, FBP SUVR did not significantly correlate with temporal mnemonic discrimination. (D) There was no relationship between FBP SUVR in primary motor/primary sensory cortex (M1S1) and temporal mnemonic discrimination.

To further validate the spatial specificity of this relationship, we employed a voxelwise approach to analyze the association between voxelwise FBP SUVR levels and temporal mnemonic discrimination performance. Our voxelwise analysis confirmed selective associations between worse temporal mnemonic discrimination performance with an increase in voxelwise FBP SUVR within clusters of the bilateral mOFC and bilateral IT (**Figure 5**; $p_{unc} < 0.005, k > 25$), reinforcing our *a priori* hypothesis driven ROI-based results. Additional data-driven clusters included bilateral ventral visual cortex and fusiform cortex. Critically, this voxelwise association was again absent

in regions known to be susceptible to A β deposition but not directly involved in temporal processing (i.e. posteromedial cortex regions such as PCC). This absence of association in areas unrelated to temporal processing further affirms the specificity of the link between A β pathology in regions supporting temporal processing, such as mOFC and IT, with temporal mnemonic discrimination deficits.

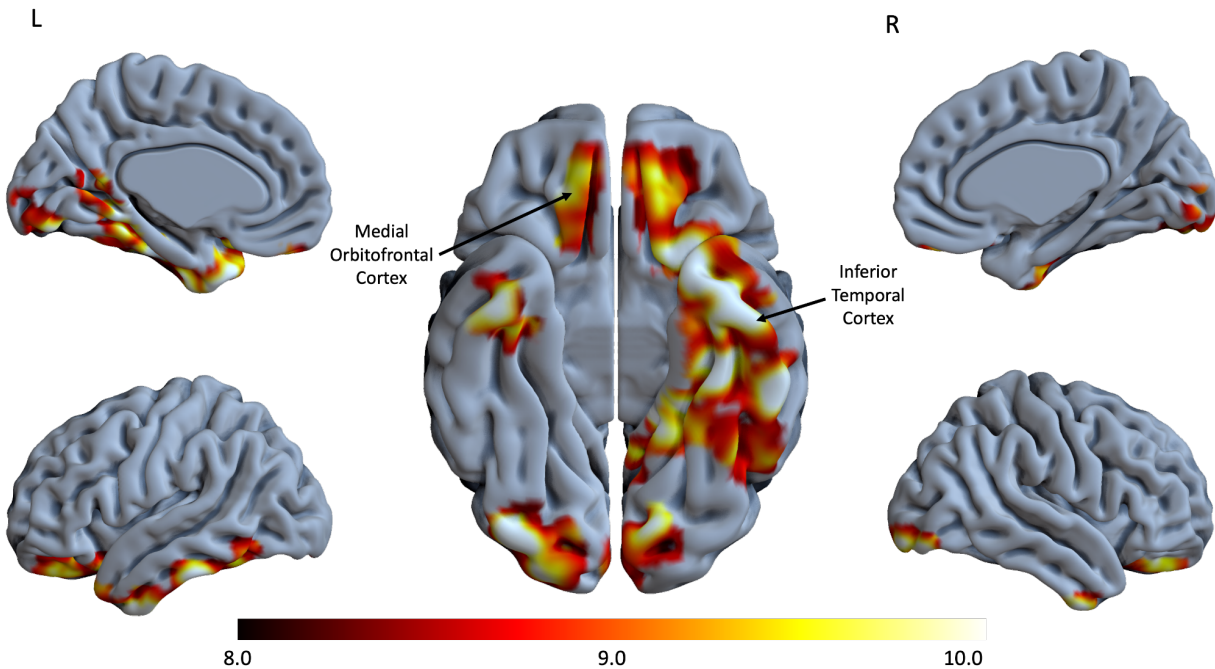


Figure 5. Voxelwise analysis of the association between FBP SUVR and temporal mnemonic discrimination. Medial and lateral view of both left and right hemispheres and inferior view of the whole brain. Increased FBP SUVR in basal frontotemporal regions such as medial orbitofrontal cortex and inferior temporal cortex is associated with temporal mnemonic discrimination deficits.

Discussion

We demonstrate that A β deposition in the basal frontotemporal cortex is related to temporal mnemonic discrimination deficits in cognitively unimpaired older adults. We utilized distinct domains of mnemonic discrimination tasks to separately tax object, spatial, and temporal pattern separation in older adults who underwent A β -PET and young adult control participants. We found that older adults with elevated A β levels were selectively impaired on temporal, but not object or spatial, mnemonic discrimination. This temporal mnemonic discrimination deficit was driven by deposition of A β within cortical regions previously shown to support temporal processing such as mOFC and IT (Jafarpour et al., 2023; Naya et al., 2017), which are also regions proposed to have early vulnerability to A β deposition (Braak & Braak, 1991; Grothe et al., 2017). Our results suggest that temporal mnemonic discrimination deficits are a sensitive marker of early A β deposition in the preclinical stage of AD, and may be a useful domain to predict future disease progression and cognitive decline.

Previous investigations between A β and mnemonic discrimination have been restricted to the object or spatial domains (Adams et al., 2022; Berron et al., 2024; Jutten et al., 2022; Maass et al., 2019; Papp et al., 2020; Vanderlip et al., 2024). This work shows that while A β may have subtle relationships with object discrimination (Berron et al., 2024; Papp et al., 2020), especially in large studies powered to detect small effects (Papp et al., 2020; Young et al., 2023), these effects may be mediated through tau pathology in anterior-temporal cortical networks (Berron et al., 2019, 2024; Maass et al., 2019), suggesting an indirect relationship with A β . In the spatial domain, many studies have failed to observe a direct relationship between A β and performance (Adams et al., 2022; Berron et al., 2024; Kim et al., 2023), even though A β accumulates within posteromedial cortical regions that support spatial processing (Berron et al., 2018; Maass et al., 2019). However, it is important to note that one study which employed a mnemonic discrimination task varying both spatial location and object identity simultaneously did observe an association with global A β levels (Webb et al., 2020). Finally, studies using various features from mnemonic discrimination tasks to predict A β status have found features such as recognition memory or response biases had more predictive power than the actual mnemonic component of these tasks (Kim et al., 2023; Vanderlip et al., 2024), further supporting an indirect relationship with A β in object and spatial domains.

To our knowledge, temporal mnemonic discrimination has not previously been studied in the preclinical stage of AD. Our results substantiate previous work demonstrating robust age-group differences in object and spatial mnemonic discrimination (Leal & Yassa, 2018; Reagh et al., 2016; Stark et al., 2013, 2019). Critically, we provide a novel dissociation between temporal mnemonic discrimination, which we found to differ by A β status but not age, compared to object and spatial mnemonic discrimination, which we found to differ by age but not by A β status. However, previous work has shown age effects in temporal mnemonic discrimination at longer temporal lags, though A β biomarker information was unavailable (Roberts et al., 2014; Tolentino et al., 2012). Beyond A β positivity, our results extended to associations with continuous global FBP

SUVR as well as FBP SUVR within early and intermediate stages of A β deposition (Mattsson et al., 2019), supporting the sensitivity of the temporal domain to A β pathology. Based on our current work and the previous literature, we propose that age-related changes in hippocampal integrity and medial temporal lobe tau may drive initial age-related deficits in object (and to a lesser extent, spatial) mnemonic discrimination (Berron et al., 2019, 2024; Stark & Stark, 2017). Conversely, temporal mnemonic discrimination may be disrupted in preclinical AD due to early A β deposition in basal frontotemporal cortex (Braak & Braak, 1991; Grothe et al., 2017; Thal et al., 2002), as these cortical regions support temporal processing. Finally, deficits in spatial mnemonic discrimination may emerge with symptomatic stages of mild cognitive impairment or AD, when failures of spatial processing are well established (Kim et al., 2023; Paleja & Spaniol, 2013).

Our primary mechanistic hypothesis was that A β accumulation affects temporal mnemonic discrimination because basal frontotemporal regions vulnerable to A β are also involved in temporal processing. Temporal mnemonic discrimination, which involves both the memory of sequences and items, as well as the capacity to bind items in sequence, depends on connections between the prefrontal cortex, hippocampus, and IT (Naya et al., 2017). Specifically, the mOFC contributes to temporal processing (Zhou et al., 2019) and has strong connections to IT, feeding input into the hippocampus through the perirhinal and entorhinal cortices (Heather Hsu et al., 2020; Huang et al., 2021; Saleem et al., 2008). IT is critical for item representation, with evidence underscoring its role in recognition memory (Easton & Gaffan, 2001; Miller et al., 1991; Naya & Suzuki, 2011). Both mOFC and IT have extensive connections to the medial temporal lobe, therefore we hypothesize that A β deposition could alter temporal mnemonic discrimination by degrading cortical input into the hippocampus, thus leading to weakened hippocampal representations. Indeed, we found strong associations between temporal mnemonic discrimination and A β in both regions. Importantly, these correlations persisted when assessing this association within only A β ⁺ individuals. This critically supports that not only the presence, but the severity of A β , in these regions impacts temporal mnemonic discrimination in a dose-dependent manner.

To confirm the spatial specificity of associations between regional A β and temporal mnemonic discrimination, we conducted regional control and voxelwise analyses. We first contrasted the effect found in mOFC and IT with two control areas to provide a dissociation - one highly vulnerable to A β , but not directly involved in temporal processing (PCC) and one unaffected by A β and not involved in temporal processing (primary sensory/motor cortex). Consistent with our initial hypothesis, we did not observe a significant association between temporal mnemonic discrimination and A β levels in either region, which is notable given the high susceptibility of the PCC to A β accumulation (Leech & Sharp, 2014; Scheff et al., 2014). Remarkably, our voxelwise analyses also confirmed that A β within basal frontotemporal regions, but not posteromedial regions, was related to temporal mnemonic discrimination. The voxelwise spatial pattern of A β that was associated with temporal mnemonic discrimination strikingly resembles “Stage A” of the neuropathologically-driven A β accumulation model as described by Braak and colleagues (Braak & Braak, 1991), which similarly implicates medial frontal, basal temporal, and ventral visual cortex. Our voxelwise results are also consistent with the first stage

of other PET-based staging studies of A β , which specifically include IT and orbitofrontal cortex (Cho et al., 2016; Grothe et al., 2017). This specificity highlights the importance of considering regional vulnerability and functional relevance when investigating the impacts of A β deposition on cognitive abilities, consistent with previous studies demonstrating stronger relationships between regional or voxelwise A β and cognition than global levels (Farrell et al., 2018; Sperling et al., 2019; Tideman et al., 2022).

A compelling future extension of this work is to explore the potential synergistic effects of tau pathology in the association between A β and temporal mnemonic discrimination (Ossenkoppele et al., 2022; Sperling et al., 2019). We suspect that tau deposition is also related to temporal mnemonic discrimination given previous work demonstrating anterolateral entorhinal cortex involvement in temporal processing (Montchal et al., 2019). Further, mOFC and IT are regions thought to reflect a transition between “age-related” medial temporal lobe tau and the widespread cortical tauopathy characteristic of AD (K. A. Johnson et al., 2016; Schöll et al., 2016), and regions concurrently expressing both pathologies may lead to greater deficits in neuronal processing. In the current study, we could not assess tau deposition due to a lack of tau-PET data, and therefore future work will investigate the important role tau may play in temporal mnemonic discrimination.

Limitations include the highly educated sample consisting of primarily non-Hispanic white individuals. Future work in more diverse populations will aid in the generalizability of these results. Further, it is possible that other mechanisms such as synaptic dysfunction or hyperactivity may mediate the relationship between A β and performance. Thus, future work needs to investigate other potential mechanisms that give rise to deficits in temporal mnemonic discrimination. Lastly, longitudinal data will be needed to directly assess whether temporal mnemonic discrimination deficits are predictive of future cognitive decline, as previous work demonstrates that longitudinal relationships between A β and cognitive decline may be stronger than cross-sectional effects (Donohue et al., 2017; Ossenkoppele et al., 2022; Sperling et al., 2019).

We identified a selective relationship between temporal mnemonic discrimination and A β pathology in cognitively unimpaired older adults. We demonstrate that this relationship is due to A β deposition in basal frontotemporal regions supporting temporal processing, which may preclude these regions from sending proper information to the hippocampus for temporal pattern separation computations. Our work suggests that deficits in temporal mnemonic discrimination may serve as an early marker for A β accumulation. In light of this, cognitive batteries could be expanded to include tasks taxing temporal discrimination to enhance early detection of individuals at high risk for cognitive decline and to better assess the efficacy of A β -lowering therapeutics.

References

- Adams, J. N., Kim, S., Rizvi, B., Sathishkumar, M., Taylor, L., Harris, A. L., Mikhail, A., Keator, D. B., McMillan, L., & Yassa, M. A. (2022). Entorhinal–Hippocampal Circuit Integrity Is Related to Mnemonic Discrimination and Amyloid- β Pathology in Older Adults. *The Journal of Neuroscience*, *42*(46), 8742–8753. <https://doi.org/10.1523/JNEUROSCI.1165-22.2022>
- Adams, J. N., Márquez, F., Larson, M. S., Janecek, J. T., Miranda, B. A., Noche, J. A., Taylor, L., Hollearn, M. K., McMillan, L., Keator, D. B., Head, E., Rissman, R. A., & Yassa, M. A. (2023). Differential involvement of hippocampal subfields in the relationship between Alzheimer’s pathology and memory interference in older adults. *Alzheimer’s & Dementia: Diagnosis, Assessment & Disease Monitoring*, *15*(2), e12419. <https://doi.org/10.1002/dad2.12419>
- Baker, J. E., Lim, Y. Y., Pietrzak, R. H., Hassenstab, J., Snyder, P. J., Masters, C. L., & Maruff, P. (2017). Cognitive impairment and decline in cognitively normal older adults with high amyloid- β : A meta-analysis. *Alzheimer’s & Dementia: Diagnosis, Assessment & Disease Monitoring*, *6*(1), 108–121. <https://doi.org/10.1016/j.dadm.2016.09.002>
- Bakker, A., Kirwan, C. B., Miller, N. I., & Stark, C. E. L. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science*, *319*, 1640–1642.
- Berron, D., Cardenas-Blanco, A., Bittner, D., Metzger, C. D., Spottke, A., Heneka, M. T., Fliessbach, K., Schneider, A., Teipel, S. J., Wagner, M., Speck, O., Jessen, F., & Düzel, E. (2019). Higher CSF Tau Levels Are Related to Hippocampal Hyperactivity and Object Mnemonic Discrimination in Older Adults. *The Journal of Neuroscience*, *39*(44), 8788–8797. <https://doi.org/10.1523/JNEUROSCI.1279-19.2019>
- Berron, D., Neumann, K., Maass, A., Schütze, H., Fliessbach, K., Kiven, V., Jessen, F., Sauvage, M., Kumaran, D., & Düzel, E. (2018). Age-related functional changes in

domain-specific medial temporal lobe pathways. *Neurobiology of Aging*, 65, 86–97.

<https://doi.org/10.1016/j.neurobiolaging.2017.12.030>

Berron, D., Olsson, E., Andersson, F., Janelidze, S., Tideman, P., Düzel, E., Palmqvist, S., Stomrud, E., & Hansson, O. (2024). Remote and unsupervised digital memory assessments can reliably detect cognitive impairment in Alzheimer's disease.

Alzheimer's & Dementia, alz.13919. <https://doi.org/10.1002/alz.13919>

Berron, D., Schütze, H., Maass, A., Cardenas-Blanco, A., Kuijf, H. J., Kumaran, D., & Düzel, E. (2016). Strong Evidence for Pattern Separation in Human Dentate Gyrus. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 36(29), 7569–7579.

<https://doi.org/10.1523/JNEUROSCI.0518-16.2016>

Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berl)*, 82(4), 239–259.

Chételat, G., La Joie, R., Villain, N., Perrotin, A., De La Sayette, V., Eustache, F., & Vandenberghe, R. (2013). Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. *NeuroImage: Clinical*, 2, 356–365.

<https://doi.org/10.1016/j.nicl.2013.02.006>

Cho, H., Choi, J. Y., Hwang, M. S., Kim, Y. J., Lee, H. M., Lee, H. S., Lee, J. H., Ryu, Y. H., Lee, M. S., & Lyoo, C. H. (2016). In vivo cortical spreading pattern of tau and amyloid in the Alzheimer disease spectrum. *Annals of Neurology*, 80(2), 247–258.

<https://doi.org/10.1002/ana.24711>

Donohue, M. C., Sperling, R. A., Petersen, R., Sun, C.-K., Weiner, M. W., Aisen, P. S., & for the Alzheimer's Disease Neuroimaging Initiative. (2017). Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline Among Cognitively Normal Persons.

JAMA, 317(22), 2305. <https://doi.org/10.1001/jama.2017.6669>

Donohue, M. C., Sperling, R. A., Salmon, D. P., Rentz, D. M., Raman, R., Thomas, R. G., Weiner, M., & Aisen, P. S. (2014). The Preclinical Alzheimer Cognitive Composite:

Measuring Amyloid-Related Decline. *JAMA Neurology*, 71(8), 961.

<https://doi.org/10.1001/jamaneurol.2014.803>

Duarte, A., Henson, R. N., Knight, R. T., Emery, T., & Graham, K. S. (2010). Orbito-frontal Cortex is Necessary for Temporal Context Memory. *Journal of Cognitive Neuroscience*, 22(8), 1819–1831. <https://doi.org/10.1162/jocn.2009.21316>

Easton, A., & Gaffan, D. (2001). Crossed unilateral lesions of the medial forebrain bundle and either inferior temporal or frontal cortex impair object–reward association learning in Rhesus monkeys. *Neuropsychologia*, 39(1), 71–82. [https://doi.org/10.1016/S0028-3932\(00\)00098-1](https://doi.org/10.1016/S0028-3932(00)00098-1)

Farrell, M. E., Chen, X., Rundle, M. M., Chan, M. Y., Wig, G. S., & Park, D. C. (2018). Regional amyloid accumulation and cognitive decline in initially amyloid-negative adults. *Neurology*, 91(19). <https://doi.org/10.1212/WNL.0000000000006469>

Grothe, M. J., Barthel, H., Sepulcre, J., Dyrba, M., Sabri, O., Teipel, S. J., For the Alzheimer's Disease Neuroimaging Initiative, Alzheimer's Disease Neuroimaging Initiative, Weiner, M., Aisen, P., Weiner, M., Aisen, P., Petersen, R., Jack, C. R., Jagust, W., Trojanowki, J. Q., Toga, A. W., Beckett, L., Green, R. C., ... Raj, B. A. (2017). In vivo staging of regional amyloid deposition. *Neurology*, 89(20), 2031–2038. <https://doi.org/10.1212/WNL.0000000000004643>

Güsten, J., Ziegler, G., Düzel, E., & Berron, D. (2021). Age impairs mnemonic discrimination of objects more than scenes: A web-based, large-scale approach across the lifespan. *Cortex*, 137, 138–148. <https://doi.org/10.1016/j.cortex.2020.12.017>

Heather Hsu, C.-C., Rolls, E. T., Huang, C.-C., Chong, S. T., Zac Lo, C.-Y., Feng, J., & Lin, C.-P. (2020). Connections of the Human Orbitofrontal Cortex and Inferior Frontal Gyrus. *Cerebral Cortex*, 30(11), 5830–5843. <https://doi.org/10.1093/cercor/bhaa160>

Hedden, T., Oh, H., Younger, A. P., & Patel, T. A. (2013). Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*, 80(14), 1341–1348.

<https://doi.org/10.1212/WNL.0b013e31828ab35d>

Holden, H. M., Hoebel, C., Loftis, K., & Gilbert, P. E. (2012). Spatial pattern separation in cognitively normal young and older adults. *Hippocampus*.

<https://doi.org/10.1002/hipo.22017>

Huang, C.-C., Rolls, E. T., Hsu, C.-C. H., Feng, J., & Lin, C.-P. (2021). Extensive Cortical Connectivity of the Human Hippocampal Memory System: Beyond the “What” and “Where” Dual Stream Model. *Cerebral Cortex*, 31(10), 4652–4669.

<https://doi.org/10.1093/cercor/bhab113>

Insel, P. S., Donohue, M. C., Sperling, R., Hansson, O., & Mattsson-Carlsson, N. (2020). The A4 study: β -amyloid and cognition in 4432 cognitively unimpaired adults. *Annals of Clinical and Translational Neurology*, 7(5), 776–785. <https://doi.org/10.1002/acn3.51048>

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M., & Sperling, R. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer’s disease. *Alzheimer’s & Dementia : The Journal of the Alzheimer’s Association*, 14(4), 535–562. <https://doi.org/10.1016/j.jalz.2018.02.018>

Jafarpour, A., Lin, J. J., Knight, R. T., & Buffalo, E. A. (2023). Multiple memory systems for efficient temporal order memory. *Hippocampus*, 33(10), 1154–1157.

<https://doi.org/10.1002/hipo.23550>

Johnson, E. L., Chang, W. K., Dewar, C. D., Sorensen, D., Lin, J. J., Solbakk, A.-K., Endestad, T., Larsson, P. G., Ivanovic, J., Meling, T. R., Scabini, D., & Knight, R. T. (2022). Orbitofrontal cortex governs working memory for temporal order. *Current Biology*, 32(9), R410–R411. <https://doi.org/10.1016/j.cub.2022.03.074>

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., ... Sperling, R. (2016). Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Annals of Neurology*, 79(1), 110–119. <https://doi.org/10.1002/ana.24546>
- Jutten, R. J., Rentz, D. M., Fu, J. F., Mayblyum, D. V., Amariglio, R. E., Buckley, R. F., Properzi, M. J., Maruff, P., Stark, C. E., Yassa, M. A., Johnson, K. A., Sperling, R. A., & Papp, K. V. (2022). Monthly At-Home Computerized Cognitive Testing to Detect Diminished Practice Effects in Preclinical Alzheimer's Disease. *Frontiers in Aging Neuroscience*, 13, 800126. <https://doi.org/10.3389/fnagi.2021.800126>
- Kim, S., Adams, J. N., Chappel-Farley, M. G., Keator, D., Janecek, J., Taylor, L., Mikhail, A., Hollearn, M., McMillan, L., Rapp, P., & Yassa, M. A. (2023). Examining the diagnostic value of the mnemonic discrimination task for classification of cognitive status and amyloid-beta burden. *Neuropsychologia*, 191, 108727. <https://doi.org/10.1016/j.neuropsychologia.2023.108727>
- Kulkarni, N., & Lega, B. C. (2023). *Episodic boundaries affect neural features of representational drift in humans*. <https://doi.org/10.1101/2023.08.20.553078>
- Landau, S. M., Mintun, M. A., Joshi, A. D., Koeppe, R. A., Petersen, R. C., Aisen, P. S., Weiner, M. W., Jagust, W. J., & for the Alzheimer's Disease Neuroimaging Initiative. (2012). Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Annals of Neurology*, 72(4), 578–586. <https://doi.org/10.1002/ana.23650>
- Leal, S. L., & Yassa, M. A. (2018). Integrating new findings and examining clinical applications of pattern separation. *Nature Neuroscience*, 21(2), 163–173. <https://doi.org/10.1038/s41593-017-0065-1>
- Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain: A Journal of Neurology*, 137(Pt 1), 12–32. <https://doi.org/10.1093/brain/awt162>
- Lindenberger, U., & Pötter, U. (1998). The complex nature of unique and shared effects in

- hierarchical linear regression: Implications for developmental psychology. *Psychological Methods*, 3(2), 218–230. <https://doi.org/10.1037/1082-989X.3.2.218>
- Maass, A., Berron, D., Harrison, T. M., Adams, J. N., La Joie, R., Baker, S., Mellinger, T., Bell, R. K., Swinnerton, K., Inglis, B., Rabinovici, G. D., Düzel, E., & Jagust, W. J. (2019). Alzheimer's pathology targets distinct memory networks in the ageing brain. *Brain*, 142(8), 2492–2509. <https://doi.org/10.1093/brain/awz154>
- Mattsson, N., Palmqvist, S., Stomrud, E., Vogel, J., & Hansson, O. (2019). Staging β -Amyloid Pathology With Amyloid Positron Emission Tomography. *JAMA Neurology*, 76(11), 1319. <https://doi.org/10.1001/jamaneurol.2019.2214>
- Mattsson-Carlgren, N., Salvadó, G., Ashton, N. J., Tideman, P., Stomrud, E., Zetterberg, H., Ossenkoppele, R., Betthausen, T. J., Cody, K. A., Jonaitis, E. M., Langhough, R., Palmqvist, S., Blennow, K., Janelidze, S., Johnson, S. C., & Hansson, O. (2023). Prediction of Longitudinal Cognitive Decline in Preclinical Alzheimer Disease Using Plasma Biomarkers. *JAMA Neurology*. <https://doi.org/10.1001/jamaneurol.2022.5272>
- Miller, E. K., Li, L., & Desimone, R. (1991). A Neural Mechanism for Working and Recognition Memory in Inferior Temporal Cortex. *Science*, 254(5036), 1377–1379. <https://doi.org/10.1126/science.1962197>
- Montchal, M. E., Reagh, Z. M., & Yassa, M. A. (2019). Precise temporal memories are supported by the lateral entorhinal cortex in humans. *Nature Neuroscience*, 22(2), 284–288. <https://doi.org/10.1038/s41593-018-0303-1>
- Morrison, A. B., Conway, A. R. A., & Chein, J. M. (2014). Primacy and recency effects as indices of the focus of attention. *Frontiers in Human Neuroscience*, 8. <https://doi.org/10.3389/fnhum.2014.00006>
- Naya, Y., Chen, H., Yang, C., & Suzuki, W. A. (2017). Contributions of primate prefrontal cortex and medial temporal lobe to temporal-order memory. *Proceedings of the National Academy of Sciences*, 114(51), 13555–13560. <https://doi.org/10.1073/pnas.1712711114>

- Naya, Y., & Suzuki, W. A. (2011). Integrating what and when across the primate medial temporal lobe. *Science (New York, N.Y.)*, 333(6043), 773–776.
<https://doi.org/10.1126/science.1206773>
- Ossenkoppele, R., Pichet Binette, A., Groot, C., Smith, R., Strandberg, O., Palmqvist, S., Stomrud, E., Tideman, P., Ohlsson, T., Jögi, 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., ... Hansson, O. (2022). Amyloid and tau PET-positive cognitively unimpaired individuals are at high risk for future cognitive decline. *Nature Medicine*, 28(11), 2381–2387. <https://doi.org/10.1038/s41591-022-02049-x>
- Paleja, M., & Spaniol, J. (2013). Spatial pattern completion deficits in older adults. *Frontiers in Aging Neuroscience*, 5, 3. <https://doi.org/10.3389/fnagi.2013.00003>
- Papp, K. V., Rentz, D. M., Maruff, P., Sun, C.-K., Raman, R., Donohue, M. C., Schembri, A., Stark, C., Yassa, M. A., Wessels, A. M., Yaari, R., Holdridge, K. C., Aisen, P. S., & Sperling, R. A. (2020). The Computerized Cognitive Composite (C3) in A4, an Alzheimer’s Disease Secondary Prevention Trial. *The Journal of Prevention of Alzheimer’s Disease*, 1–9. <https://doi.org/10.14283/jpad.2020.38>
- Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nat Rev Neurosci*, 13, 713–726. <https://doi.org/10.1038/nrn3338>
- Reagh, Z. M., Ho, H. D., Leal, S. L., Noche, J. A., Chun, A., Murray, E. A., & Yassa, M. A. (2016). Greater loss of object than spatial mnemonic discrimination in aged adults. *Hippocampus*, 26(4), 417–422. <https://doi.org/10.1002/hipo.22562>
- Reagh, Z. M., Noche, J. A., Tustison, N. J., Delisle, D., Murray, E. A., & Yassa, M. A. (2018). Functional Imbalance of Anterolateral Entorhinal Cortex and Hippocampal Dentate/CA3 Underlies Age-Related Object Pattern Separation Deficits. *Neuron*, 97(5), 1187-1198.e4. <https://doi.org/10.1016/j.neuron.2018.01.039>
- Reagh, Z. M., & Yassa, M. A. (2014). Object and spatial mnemonic interference differentially

- engage lateral and medial entorhinal cortex in humans. *Proc Natl Acad Sci U S A*, *111*, E4264-73. <https://doi.org/10.1073/pnas.1411250111>
- Roberts, J. M., Ly, M., Murray, E., & Yassa, M. A. (2014). Temporal discrimination deficits as a function of lag interference in older adults. *Hippocampus*, *24*(10), 1189–1196. <https://doi.org/10.1002/hipo.22303>
- Saleem, K. S., Kondo, H., & Price, J. L. (2008). Complementary circuits connecting the orbital and medial prefrontal networks with the temporal, insular, and opercular cortex in the macaque monkey. *Journal of Comparative Neurology*, *506*(4), 659–693. <https://doi.org/10.1002/cne.21577>
- Scheff, S. W., Price, D. A., Ansari, M. A., Roberts, K. N., Schmitt, F. A., Ikonovic, M. D., & Mufson, E. J. (2014). Synaptic Change in the Posterior Cingulate Gyrus in the Progression of Alzheimer's Disease. *Journal of Alzheimer's Disease*, *43*(3), 1073–1090. <https://doi.org/10.3233/JAD-141518>
- Schöll, 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>
- Shimamura, A. P., Janowsky, J. S., & Squire, L. R. (1990). Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients. *Neuropsychologia*, *28*, 803–813.
- 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., Properzi, M., ... Johnson, K. A. (2019). The impact of amyloid-beta and tau on prospective cognitive decline in older individuals. *Annals of Neurology*, *85*(2), 181–193. <https://doi.org/10.1002/ana.25395>

- Stark, S. M., Kirwan, C. B., & Stark, C. E. L. (2019). Mnemonic Similarity Task: A Tool for Assessing Hippocampal Integrity. *Trends in Cognitive Sciences*, 23(11), 938–951.
<https://doi.org/10.1016/j.tics.2019.08.003>
- Stark, S. M., & Stark, C. E. L. (2017). Age-related deficits in the mnemonic similarity task for objects and scenes. *Behavioural Brain Research*, 333, 109–117.
<https://doi.org/10.1016/j.bbr.2017.06.049>
- Stark, S. M., Yassa, M. A., Lacy, J. W., & Stark, C. E. (2013). A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia*, 51, 2442–2449.
<https://doi.org/10.1016/j.neuropsychologia.2012.12.014>
- Stark, S. M., Yassa, M. A., & Stark, C. E. L. (2010). Individual differences in spatial pattern separation performance associated with healthy aging in humans. *Learning & Memory*, 17(6), 284–288.
- Thal, D. R., Rüb, U., Orantes, M., & Braak, H. (2002). Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology*, 58(12), 1791–1800.
<https://doi.org/10.1212/wnl.58.12.1791>
- Tideman, P., Stomrud, E., Leuzy, A., Mattsson-Carlgen, N., Palmqvist, S., Hansson, O., & for the Alzheimer’s Disease Neuroimaging Initiative. (2022). Association of β -Amyloid Accumulation With Executive Function in Adults With Unimpaired Cognition. *Neurology*, 98(15). <https://doi.org/10.1212/WNL.0000000000013299>
- Tolentino, J. C., Pirogovsky, E., Luu, T., Toner, C. K., & Gilbert, P. E. (2012). The effect of interference on temporal order memory for random and fixed sequences in nondemented older adults. *Learning & Memory*, 19(6), 251–255.
- Vanderlip, C. R., Lee, M., & Craig E.L. (2024). Cognitive modeling of the Mnemonic Similarity Task as a digital biomarker for Alzheimer’s Disease. *bioRxiv*, 2024.03.07.584012.
<https://doi.org/10.1101/2024.03.07.584012>

- Webb, C. E., Foster, C. M., Horn, M. M., Kennedy, K. M., & Rodrigue, K. M. (2020). Beta-amyloid burden predicts poorer mnemonic discrimination in cognitively normal older adults. *NeuroImage*, *221*, 117199. <https://doi.org/10.1016/j.neuroimage.2020.117199>
- Yassa, M. A., & Stark, C. E. (2011). Pattern separation in the hippocampus. *Trends Neurosci*, *34*, 515–525. <https://doi.org/10.1016/j.tins.2011.06.006>
- Yassa, M. A., Stark, S. M., Bakker, A., Albert, M. S., Gallagher, M., & Stark, C. E. L. (2010). High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnesic mild cognitive impairment. *NeuroImage*, *51*(3), 1242–1252.
- Young, C. B., Mormino, E. C., Poston, K. L., Johnson, K. A., Rentz, D. M., Sperling, R. A., & Papp, K. V. (2023). Computerized cognitive practice effects in relation to amyloid and tau in preclinical Alzheimer’s disease: Results from a multi-site cohort. *Alzheimer’s & Dementia: Diagnosis, Assessment & Disease Monitoring*, *15*(1), e12414. <https://doi.org/10.1002/dad2.12414>
- Zhou, J., Montesinos-Cartagena, M., Wikenheiser, A. M., Gardner, M. P. H., Niv, Y., & Schoenbaum, G. (2019). Complementary Task Structure Representations in Hippocampus and Orbitofrontal Cortex during an Odor Sequence Task. *Current Biology*, *29*(20), 3402-3409.e3. <https://doi.org/10.1016/j.cub.2019.08.040>