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Beta-amyloid burden predicts poorer mnemonic discrimination in cognitively normal older adults

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Abstract

One of the earliest indicators of Alzheimer's disease pathology is the presence of beta-amyloid (Aβ) protein deposition. Significant amyloid deposition is evident even in older adults who exhibit little or no overt cognitive or memory impairment. Hippocampal-based processes that help distinguish between highly similar memory representations may be the most susceptible to early disease pathology. Amyloid associations with memory have been difficult to establish, possibly because typical memory assessments do not tax hippocampal operations sufficiently. Thus, the present study utilized a spatial mnemonic discrimination task designed to tax hippocampal pattern separation/completion processes in a sample of cognitively normal middle-aged and older adults (53–98 years old) who underwent PET ^{18}F-Florbetapir Aβ scanning. The degree of interference between studied and new information varied, allowing for an examination of mnemonic discrimination as a function of mnemonic similarity. Results indicated that greater beta-amyloid burden was associated with poorer discrimination across decreasing levels of interference, suggesting that even subtle elevation of beta-amyloid in cognitively normal adults is associated with impoverished performance on a hippocampally demanding memory task. The present study demonstrates that degree of amyloid burden negatively impacts the ability of aging adults to accurately distinguish old from increasingly distinct new information, providing novel insight into the cognitive expression of beta-amyloid neuropathology

Keywords

Beta-amyloid; Mnemonic discrimination; Memory; Cognitive aging; Preclinical Alzheimer's disease

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Data availability statement

The data and relevant analysis code have been made publicly available via the Open Science Framework and can be accessed at https://osf.io/nu7zs/.

1. Introduction

Beta-amyloid (Aβ) protein deposition is regarded as one of the earliest indicators of Alzheimer's disease pathology, with pathological changes preceding clinical symptomology by several decades (Jack et al., 2009, 2013; Price and Morris, 1999). Despite great interest in investigating associations between memory performance and amyloid in preclinical older populations, studies suggest Aβ exhibits only weak-to-moderate associations with traditional measures of memory in normal aging (Hedden et al., 2013; Rodrigue et al., 2009). However, it is plausible that healthy older adults harboring Aβ deposits experience changes to memory not captured by these general memory assessments. Understanding the specific facets of memory processing that are most susceptible to early disease pathology would provide critical insight into the cognitive expression of preclinical neuropathology (Bischof and Jacobs, 2019).

Given that Alzheimer's disease is known to affect the medial temporal lobes early in the disease process, hippocampal-based pattern separation/completion processes that help discriminate highly similar memory representations may show greater susceptibility to pathological insult. Typical memory assessments may not sufficiently tax hippocampal operations, thus measures that are specifically designed to test hippocampal-based functioning may provide key insight into memory changes associated with an early hallmark of Alzheimer's disease. Pattern separation and completion processes are often examined using variants of a mnemonic discrimination task (Kirwan and Stark, 2007; Stark et al., 2019) in which participants study various images (e.g., objects). Participants are then tested on their memory for studied objects, as well as non-studied lure objects that are highly perceptually or conceptually similar to studied information. Lure discrimination performance is then calculated based on one's ability to accurately identify mnemonically similar lures. Erroneous endorsement of similar lures is thought to indicate failed separation of mnemonic information and a tendency toward greater generalization across similar memory representations (Berron et al., 2016; Yassa and Stark, 2011). In these tasks, the degree of mnemonic similarity can be varied across a continuum (i.e., low similarity varying to high similarity), allowing for a systematic measure of discrimination as a function of mnemonic overlap between studied and new information. In fact, Liu et al. (2016) suggest that manipulating the degree of similarity may allow for greater sensitivity to detect age or other pathological differences. Older adults often show reduced mnemonic discrimination ability relative to younger adults, especially across a continuum of similar lures (for review, see Liu et al., 2016; Stark et al., 2019), yet less is known about the biological factors that influence memory discrimination beyond age.

Cognitively normal older adult carriers of the *APOE* ε4 allele, a robust genetic risk factor for Alzheimer's disease, show reduced mnemonic discrimination compared to non-carriers (Sheppard et al., 2016; Sinha et al., 2018), and individuals with mild cognitive impairment (MCI) and Alzheimer's disease show poorer discrimination compared to healthy controls (Ally et al., 2013; Stark et al., 2013; Yassa et al., 2010). In relation to pathology, a link between CSF Aβ and memory discrimination has been demonstrated in patients with Alzheimer's disease (Wesnes et al., 2014). However in healthy aging, while one study reported little evidence of a relation between Aβ burden and memory discrimination (Berron

et al., 2019), another study demonstrated that posterior-medial Aβ was specifically associated with reduced scene relative to object lure discrimination (Maass et al., 2019). Thus, studies linking Alzheimer's disease neuropathology and mnemonic discrimination are limited, report mixed results, and warrant further study. The current study sought to advance this literature by investigating associations between PET-measured Aβ deposition (^{18}F-Florbetapir) and memory performance on a spatial mnemonic discrimination task in a sample of cognitively normal middle-aged and older adults. Critically, the present study advances previous research by utilizing a task that systematically manipulates the level of mnemonic similarity between studied and tested information. This controlled approach allows for a more detailed examination of Aβ effects on hippocampal-based discrimination, which may yield new insight into early mnemonic alterations occurring in individuals harboring Alzheimer's disease pathology.

2. Materials and methods

2.1. Participants

Participants included 53 cognitively normal, healthy middle-aged and older adults aged 53–98 (mean age = 70.40 ± 10.61 years), who were part of a larger longitudinal study of 181 healthy adults, of whom 53 had PET, mnemonic discrimination task, and *APOE* genetic data (see Table 1 for demographics). Participants were recruited from the Dallas–Fort Worth metro area and were fluent English speakers, had a minimum of a high school education, and were screened to have normal or corrected-to-normal vision. All participants were also screened at the first wave for any history of metabolic, neurologic or psychiatric conditions, as well as any signs of cognitive impairment using the Mini Mental Status Exam (MMSE < 26), or depression using the Center for Epidemiological Studies Depression Scale (CES-D ≥ 16). PET imaging and genetic samples were obtained at the first wave of longitudinal data collection and the mnemonic discrimination task was conducted at the second wave, with an average of 3.01 years between waves. Demographic information obtained at the second wave of data collection are reported in Table 1. The study was approved by The University of Texas at Dallas and the University of Texas Southwestern Medical Center institutional review boards and all participants provided written informed consent.

2.2. Imaging acquisition

PET images were obtained from a Siemens ECAT HR PET scanner at UT Southwestern Medical Center. Participants were injected with 370 MBq (10mCi) of ^{18}F-Florbetapir (Avid Radiopharmaceuticals/Eli Lilly), and approximately 30 min later were placed in the scanner for imaging. A 2-min scout image was acquired to ensure the brain was in the field of view, then 50 min after injection a 7-min internal rod source transmission scan was acquired. This was followed by a 2-frame by 5-min each dynamic emission acquired image, which was reconstructed using back-projection with a 6mm full width at half maximum Gaussian filter. Emission images were processed by iterative reconstruction with 4 iterations and 14 subsets and a 3 mm ramp filter. High-resolution T1-weighted images were also obtained for each participant on a Philips Achieva 3T whole-body scanner. A T1-weighted MP-RAGE sequence was used to collect the images with the following parameters: 160 sagittal slices, 1 mm^3 voxels; FOV = 256 mm, TE = 3.8 ms, TR = 8.3 ms, 12° FA.

2.3. PET image processing

A rigid affine registration was used to register each participant's PET scan to their T1-weighted MRI image using Advanced Normalization Tools (Avants et al., 2009) scripts, and were visually inspected for registration quality. Freesurfer (Fischl, 2012) parcellations corresponding to seven regions of interest (ROI) traditionally used when measuring Aβ deposition (i.e., anterior and posterior cingulate, precuneus, lateral temporal, lateral parietal, middle and inferior frontal) were also registered to each individual's T1-weighted image. Uptake counts were extracted from each ROI and normalized to whole cerebellar counts to obtain Aβ standardized uptake value ratios (SUVR) in each ROI, and then averaged across ROI to create a mean cortical index of Aβ burden (Rodrigue et al., 2012).

2.4. Genetic sequencing

The genetic sequencing protocol involved collection of saliva samples using Oragene kits. *APOE* genetic information (rs429358 and rs7412) was acquired using TaqMan SNP genotyping assays (Applied Biosystems), and all DNA extraction and genotyping was conducted at The University of Texas Southwestern Medical Center Microarray Core Facility. For more details regarding the genetic sequencing protocol used see (Kennedy et al., 2015). *APOE* ε4 positivity was defined as any participant who was either homozygous or heterozygous for *APOE* ε4 + (i.e., ε 2/ ε 4, ε 3/ ε 4, ε 4/ ε 4, n = 12), as individuals with any copy of an ε 4 allele are at greater risk for Alzheimer's disease than those without ε 4 alleles (Liu et al., 2013). Participants with no ε 4 allele were characterized as *APOE* ε4 negative (i.e., ε 2/ ε 3, ε 3/ ε 3, n = 41).

2.5. Mnemonic discrimination task

A spatial mnemonic discrimination task was used in which participants studied unique pairs of pictures that varied in their spatial location on the screen and were then tested on their memory for the correct spatial location (see Fig. 1 for a depiction of the task). Stimuli consisted of images of everyday objects obtained from the Amsterdam Library of Object Images (Geusebroek et al., 2005) presented against a black background. In each trial of the four alternating study-test runs, two images were presented on the screen in various locations. During each intentional study phase, participants were instructed to remember both the presented objects and their locations. A total of 120 pairs of objects were studied for 3.5 s each, separated by a 0.5 s fixation. At each self-paced test phase, participants were again presented with object pairs and instructed to indicate using a key press whether the pair was 1) 'Same' – same two studied objects in the same studied location, 2) 'Different' – same two studied objects, but at least one in a different location from study, or 3) 'New' – a never before seen, novel pair of objects. Of presented object pairs, 60 were exact repetitions of a studied pair in the same studied location and 60 object pairs were entirely novel. Critically, as a manipulation of mnemonic similarity, 60 of the object pairs were identical to the studied pair, but the location of one of the objects was moved either 5, 10, or 15 cm (i.e., lure pairs; 20 pairs in each similarity condition). Ordering and presentation of pairs of images were randomized across participants and across trial conditions.

2.6. Standard memory measures

Several neuropsychological memory measures were also evaluated to test the specificity of the hypothesized association between beta-amyloid and mnemonic discrimination. Specifically, we included both immediate and delayed free recall measures from the California Verbal Learning Test (CVLT; Delis et al., 2000) and Wechsler Memory Scale (WMS) Logical Memory Test (Wechsler, 1997). All tests were administered by trained personnel using the standard administrations detailed in each test manual.

The CVLT Total Immediate Recall measure was defined as the total number of words correctly recalled immediately after each of five presentations of the word list (maximum score of 80). The CVLT Long Delay Recall was measured as the total number of list words correctly recalled in the long delay free recall subtest (maximum score of 16). Logical Memory Immediate Recall was defined as the score on the immediate portion of story recall (summed across story B and C; maximum score of 50). Logical Memory Delayed Recall was defined as the story recall score on the delayed recall subtest (maximum score of 50).

2.7. Statistical analysis

Memory accuracy was calculated for each condition as the proportion of correct responses subtracted by the proportion of incorrect responses to repeated or entirely novel trials. This correction accounts for potential individual biases in memory responding (Ally et al., 2013). Specifically, for the repeated trials, accuracy was calculated as the proportion of repeated trials accurately identified as ‘Same’ minus the proportion of novel trials misidentified as ‘Same’ [pSame|Same – pSame|New]. For each of the similar lure conditions, lure discrimination accuracy was calculated as the proportion of lure trials accurately identified as ‘Different’ minus the proportion of novel trials misidentified as ‘Different’ [pDifferent|Different – pDifferent|New]. Lastly, for the novel trials, accuracy was calculated as the proportion of novel trials accurately identified as ‘New’ minus the proportion of repeated trials misidentified as ‘New’ [pNew|New – pNew|Same].

To investigate effects of amyloid on mnemonic similarity task performance, a linear mixed effects model was estimated predicting lure discrimination accuracy. The model included a fixed effect of continuous SUVR, with a random intercept on participant and random slope on the within-subject measure of lure similarity (coded 0, 1, 2 across the three increasingly distinct distance conditions), and an SUVR by similarity interaction. This accounts for individual variability in both level of mnemonic discrimination, as well as individual variability in the effect of decreasing similarity on mnemonic discrimination. Covariates included age and years of education at the time of memory assessment (as continuous variables), and *APOE ε*4 status and sex (as dichotomous variables). Interactions between each of these covariates and slope of lure similarity were also included.

To explore whether an SUVR effect was present for standard memory measures in our sample, as opposed to being selective to mnemonic discrimination, we estimated four separate linear regressions with SUVR predicting CVLT Immediate and Long Delay Recall, and Logical Memory Immediate and Delayed Recall, along with covariates of age, sex, education, and *APOE ε*4 status. All continuous variables were mean-centered in all models.

All statistical analyses were conducted in R (R Core Team, 2018), and $\alpha = 0.05$ indicated statistical significance.

3. Results

See Table 1 for mean mnemonic discrimination task accuracy and performance on the standard memory measures. Results of the linear mixed model showed conditional effects of similarity on lure discrimination accuracy [*Est.(SE)* = 0.07(0.02), $t(47) = 4.23$, $p < .001$], with accurate discrimination generally increasing as lures became more distinct from studied information. There were also conditional effects of age [*Est.(SE)* = −0.007(0.003), $t(47) = -2.81$, $p = .007$] and sex [*Est.(SE)* = −0.13(0.05), $t(47) = -2.53$, $p = .015$] on lure discrimination, such that discrimination accuracy generally decreased with increasing age and men showed poorer general discrimination accuracy than women. There was no conditional effect of SUVR on general lure discrimination [*Est.(SE)* = −0.01(0.18), $t(47) = -0.05$, $p = 0.96$]. Critically, the model showed an independent association between SUVR and the slope of lure discrimination across levels of lure similarity, beyond effects of age, *APOE* ε4 status, sex, and education [*Est.(SE)* = −0.20(0.09) , $t(47) = -2.18$, $p = .035$, Fig. 2]. Individuals with lower SUVR could more accurately distinguish lures that were more distinct from studied information, while those with higher SUVR showed little discrimination difference across the three similarity levels. This suggests that greater beta-amyloid burden is accompanied by a diminished ability to detect differences in mnemonic information even as similarity is reduced.

The SUVR effect on change in lure discrimination as a function of similarity remained after controlling for time between PET scanning and completion of the mnemonic discrimination task [*Est.(SE)* = −0.21(0.09), $t(46) = -2.25$, $p = .03$]. Linear regressions predicting standard measures of memory revealed no significant SUVR effect on any memory measure [CVLT Immediate Recall: *Est.(SE)* = −8.29(9.84), $t(47) = -0.84$, $p = .40$; CVLT Long Delay Recall: *Est.(SE)* = −3.21(3.30), $t(47) = -0.97$, $p = .34$; Logical Memory Immediate Recall: *Est.(SE)* = −0.74(6.14), $t(47) = -0.12$, $p = .91$; Logical Memory Delayed Recall: *Est.(SE)* = 2.58(6.9), $t(47) = 0.37$, $p = .71$], providing evidence that more global measures of memory may not be as sensitive to the effects of amyloid, at least in cognitively normal adults, in line with previous research (e.g., Hedden et al., 2013). Instead, we found that amyloid deposition was related to mnemonic discrimination processes required to distinguish increasingly similar information.

4. Discussion

Across the present sample of cognitively normal middle-aged through older adults, mnemonic lure discrimination decreased as a function of increasing spatial similarity. This finding is consistent with a wealth of previous research examining mnemonic similarity effects in aging (Holden et al., 2012; Liu et al., 2016; Stark et al., 2010, 2019), which together demonstrate that discriminating old from new memory representations becomes more difficult when similarity between the two is greater, especially for older adults. Importantly, we extend this previous work by demonstrating that Aβ deposition, an early biomarker of Alzheimer's disease, negatively influenced the degree to which participants

were able to accurately distinguish old from increasingly distinct, new information. Individuals exhibiting higher amyloid burden showed reduced mnemonic discrimination across levels of similarity, suggesting that greater Aβ pathology contributes to a diminished ability to separate memory representations even as they become less similar (i.e., greater generalization across representations). Individuals with lower Aβ, however, were better able to capitalize on subtle differences between old and new information to increase accurate lure discrimination as a function of decreasing similarity. Importantly, we observed evidence of an association between Aβ and mnemonic discrimination across the continuum of amyloid values, in contrast to prior work comparing groups of Aβ+ and Aβ− individuals according to a selected cutoff value. The present results are in accord with research using rodent models of Alzheimer's disease which indicate that episodic memory networks that help distinguish overlapping patterns of mnemonic information are disrupted in rodents that express human amyloid precursor protein (Palmer and Good, 2011). Here, we observe that in humans even subtle deposition of Aβ appears to be related to hippocampal-based pattern separation/completion processes, providing key insight into the impact of early Alzheimer's disease related pathology on memory function in cognitively normal middle-aged and older adults.

Our findings identify an important aspect of hippocampal-based memory function in humans where individuals at higher risk for developing Alzheimer's disease exhibit subtle cognitive deficits in comparison to individuals at lower risk for Alzheimer's disease. Prior work suggests that carriers of an *APOE* ε4 allele show poorer discrimination of studied from similar lure items compared to those without the allele (Sheppard et al., 2016; Sinha et al., 2018), and similarly, individuals with MCI show impaired mnemonic discrimination compared to cognitively normal older adults (Ally et al., 2013; Stark et al., 2013; Yassa et al., 2010). Studies relating amyloid biomarkers with mnemonic performance in healthy aging indicate mixed results (Berron et al., 2019; Maass et al., 2019); however, none of these prior studies report manipulations of target-lure similarity. Thus, the current findings suggest that varying the degree of similarity better captures the subtle cognitive differences occurring in individuals harboring early indicators of potential disease pathology. Indeed, we identified associations between a continuous measure of Aβ and change in lure discrimination accuracy as a function of similarity, beyond any effect on general lure discrimination. Additionally, we found no association between amyloid and performance on any standard measure of general memory function examined, however it will be important for future research to provide a more direct test of this hypothesis. The present results relate amyloid, a biological indicator of Alzheimer's pathology, to mnemonic discrimination in cognitively normal middle-aged to older adults, and suggest that greater amyloid burden reduces an individual's sensitivity to detect differences in mnemonic information as a function of similarity between previously encountered and new information. These findings underscore the importance of investigating beta-amyloid effects on memory measures designed to tax complex hippocampal processes in cognitively normal adults in order to capture cognitive alterations that could be indicative of later clinical trajectories.

The current study extends a growing literature on mnemonic discrimination by providing evidence that beta-amyloid burden may underlie the modulation of hippocampal discrimination operations in otherwise cognitively normal aging. The current study, however, identifies merely one biological factor that influences mnemonic discrimination

ability, and future studies with larger sample sizes that examine possible interactions between multiple biological or lifestyle markers (e.g., genetic risk factors, neurofibrillary tau tangles, cardiovascular health) are needed. For example, medial temporal lobe tau has been associated with reduced lure discrimination in healthy older adults with high amyloid burden, suggesting potential synergistic effects of Alzheimer's disease-related pathologies on mnemonic discrimination (Leal et al., 2019; Maass et al., 2019). Functional neuroimaging may provide additional insight into the effect of amyloid on activation related to mnemonic lure discrimination in both hippocampal and extra-hippocampal regions (Marks et al., 2017). Lastly, examination of longitudinal change in these types of memory processes will be critical in relating early memory discrimination deficits with later diagnostic outcomes.

5. Conclusions

The present study demonstrated that greater beta-amyloid protein deposition is predictive of poorer memory discrimination in a cognitively normal sample of healthy middle-aged and older adults. Beta-amyloid deposition is regarded as one of the earliest indicators of Alzheimer's disease, and the present study suggests that even in cognitively normal adults, beta-amyloid burden may negatively impact hippocampal-based discrimination processes in memory performance. These results highlight the utility of a more fine-grained approach to quantifying memory performance in the study of AD biomarkers within cognitively normal aging. Capturing these subtle cognitive alterations may help better identify those at risk for future memory decline.

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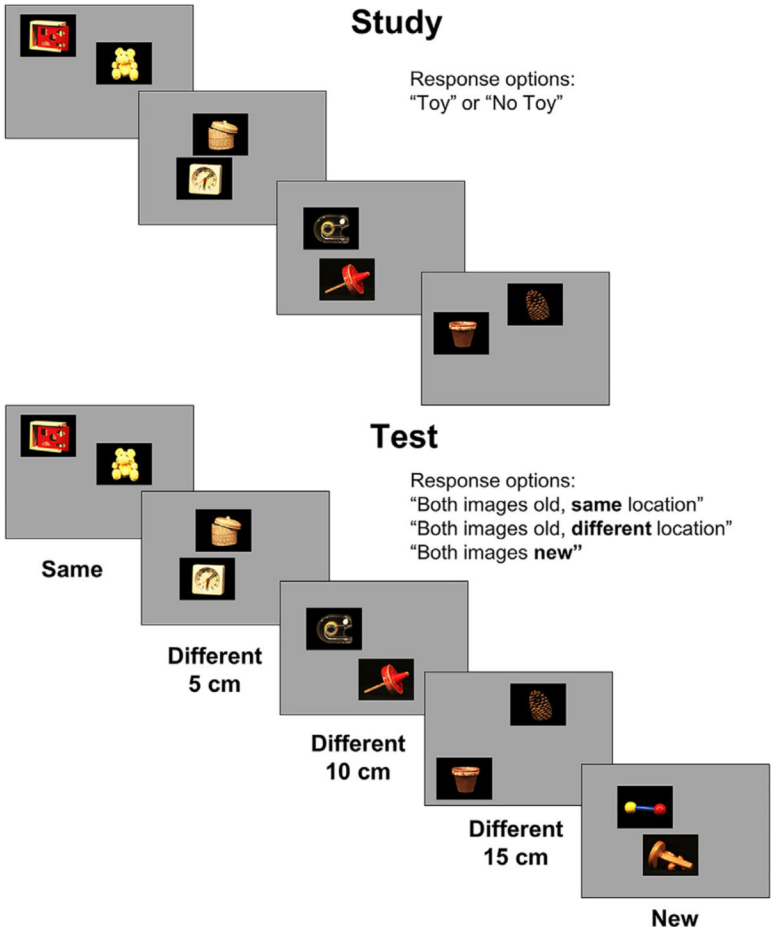

Fig. 1. Mnemonic discrimination task paradigm.

During the study phase participants studied object pairs and made a judgment on whether either of the objects was a toy or not. During the test phase participants made "Same ", "Different ", or "New " judgments about object pairs that were either repeated from study (Same), similar to studied pairs but in a different, systematically varied location (Different 5, 10, 15 cm), or entirely new (New).

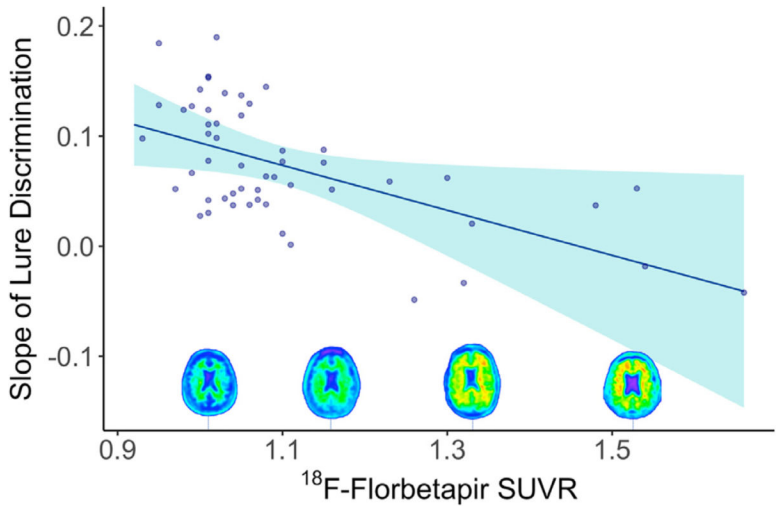

Fig. 2. Greater beta-amyloid deposition is associated with poorer mnemonic discrimination.
The figure depicts the effect of beta-amyloid burden on change in lure discrimination accuracy across decreasing levels of lure similarity. Older adults with lower SUVR display better discrimination across lures as they become more distinct from studied information (i.e., steeper slope of lure discrimination), whereas older adults with greater beta-amyloid deposition showed a reduced ability to capitalize on mnemonic differences across levels of similarity (i.e., a reduced slope of lure discrimination). These results indicate that cognitively normal older adults harboring beta-amyloid deposition experience changes to memory, with even slight elevation of beta-amyloid negatively affecting hippocampal-based discrimination processes. *Note:* Data points represent model-derived subject-specific slope estimates of lure discrimination. Depicted brains represent PET images from four representative participants with estimated SUVR values of 1.00, 1.16, 1.33, 1.52, from left to right. SUVR = standardized uptake value ratio.

Table 1

Participant demographics and task accuracy.

N Men/Women	33/20
*N APOE ε*4+/−	12/41
Mean age (SD)	70.4 (10.61)
Mean education (SD)	16.6 (2.32)
Mean MMSE (SD)	28.57 (1.68)
Mean CES-D (SD)	4.85 (5.38)
Mean SUVR (SD)	1.10 (0.16)
Mean mnemonic discrimination task accuracy (SD)	
Same	0.61 (0.16)
Different – 5 cm	0.14 (0.19)
Different – 10 cm	0.18 (0.22)
Different – 15 cm	0.31 (0.25)
New	0.72 (0.22)
Mean standard memory measure performance (SD)	
CVLT immediate	50.47 (10.75)
CVLT delayed	11.42 (3.46)
WMS logical memory immediate	27.23 (6.50)
WMS logical memory delayed	22.75 (7.29)

Note: SD = standard deviation; MMSE = Mini-mental Status Exam; CES-D = Center for Epidemiological Study-Depression Scale; SUVR = standardized uptake value ratio; Task accuracy reported as mean percent accuracy corrected for response bias; cm indicates distance of lure from studied location as an index of mnemonic similarity; CVLT = California Verbal Learning Test; WMS = Wechsler Memory Scale; CVLT Immediate Recall reported as the total words immediately recalled after each of the five word list presentations; CVLT Long Delay Recall reported as total list words recalled after the delay period; Logical Memory Immediate Recall reported as score on immediate portion of story recall; Logical Memory Delayed Recall reported as story recall score after the delay period.