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The relationship between recall of recently versus remotely encoded famous faces and amyloidosis in clinically normal older adults

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Abstract

Introduction: Alzheimer's disease (AD) patients exhibit temporally graded memory loss with remote memories remaining more intact than recent memories. It is unclear whether this temporal pattern is observable in clinically normal adults with amyloid pathology (i.e. preclinical AD).

Methods: Participants were asked to recall the names of famous figures most prominent recently (famous after 1990) and remotely (famous from 1960–1980) and were provided with a phonemic cue to ensure that memory failure was not purely due to verbal retrieval weaknesses. In addition, participants identified line drawings of objects. Clinically normal older adults (n = 125) were identified as amyloid β positive or negative (Aβ+/−) using Pittsburgh compound B positron emission tomography. The relationship between Aβ+/− and recall of remote and recent famous face-names and objects was examined using repeated measures analyses and general linear models controlling for demographics and media usage.

Results: When provided with a phonemic cue, Aβ+ participants recalled the names of fewer recent famous faces compared with Aβ− participants. However, recall of remote famous face-names and objects did not differ by Aβ group.

Discussion: Relative sparing of remotely learned information compared with recently learned information is (1) detectable in the preclinical stages of AD and (2) related to amyloid pathology. Both this temporal gradient and assessment of person-centered rather than object-centered semantic information may be particularly meaningful for tracking early memory changes in the AD trajectory.

Keywords: Memory; Semantic; Preclinical AD; Naming; Amyloid

1. Introduction

Memory decline is a core feature of prodromal Alzheimer's disease (AD) and AD dementia. Episodic memory, a temporally and context-dependent memory system comprised of explicit autobiographical events [1], is impacted early and preferentially [2,3]. However, semantic

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memory, a long-term memory system that is vital to the integrity of knowledge for facts, objects, and world concepts [1,4], also declines relatively early in the AD trajectory. While semantic memory is generally enriched with age [5], decline in this domain is a known feature of the AD dementia cognitive phenotype [6]. Furthermore, semantic memory may be declining concurrently with episodic memory [7] and even in the preclinical stages of AD [8]. Failure to retrieve proper nouns is the most common complaint of older adults [9], and these failures may, in some cases, represent worrisome semantic memory decline. Therefore, further characterizing changes in semantic memory may be instrumental to the early detection and tracking of AD-related cognitive decline.

A historical body of literature suggests a temporal gradient for memory loss in AD dementia, such that newly learned information is thought to be more vulnerable to disease pathology, with relative preservation of early or remote memories. This is known as Ribot's Law [10]. Famous face identification, traditionally a measure of remote semantic memory [11], is a particularly useful paradigm for exploring the temporal gradient originally described by Ribot. Task-specific demands allow for the examination of stimuli that were presumably encoded earlier versus later in life based on the period during which a famous person was prominent in the media. This paradigm has been exceptionally useful in identifying changes due to age- and disease-related memory loss for person-centered information in patients with semantic dementia [12,13], AD due to dementia [14,15], and temporal lobe epilepsy [16]. Furthermore, there is evidence that recall of famous faces is impaired in AD dementia [14], and naming of famous people is preferentially worse than naming landmarks and objects [17], in patients who satisfy diagnostic criteria for a precursor to AD dementia, mild cognitive impairment. However, it remains unclear whether this pattern is also observed at the preclinical stages of AD, where individuals show biomarker evidence of AD pathology but are otherwise clinically normal.

Therefore, the purpose of this study was two-fold. We aimed to determine whether temporally variant semantic stimuli, particularly semantic information learned relatively recently, was differentially impacted by positron emission tomography (PET) amyloid burden. In addition, we aimed to better understand whether famous face naming exhibited a similar relationship with PET amyloid outcomes compared with a traditional measure of semantic memory (i.e. object naming).

2. Methods

2.1. Sample characteristics

Our sample consisted of 125 clinically normal older adults who completed the famous face paradigm at year 6 of the Harvard Aging Brain Study. The study visit was conducted at Massachusetts General Hospital using protocols and informed consent procedures approved by the Partners Human Research Committee and Internal Review Board. Participants were deemed clinically normal at baseline on criteria including a global Clinical Dementia Rating score of 0 [18], normal Mini–Mental State Examination [19], and scores above age and education adjusted cutoffs on the 20-minute delayed recall of the Logical Memory Story [20]. None of the participants had a history of alcoholism, drug abuse, head trauma, or current serious medical or psychiatric illness. While a subset of individuals in the present study (n = 12) did obtain a global Clinical Dementia Rating score of 0.5 at their year 5 visit, none were given a research diagnosis of mild cognitive impairment at multidisciplinary diagnostic consensus meetings.

2.2. Amyloid imaging acquisition

Amyloid β (Aβ) burden was assessed using Pittsburgh compound B (PiB), a compound that binds to fibrillar amyloid, N-methyl-[11C]-2- (4-methylaminophenyl)-6-hydroxybenzothiazole [21], at baseline, year 4, and year 6. A PET scan was acquired at Massachusetts General Hospital using a Siemens ECAT EXACT HR + PET scanner. A dose of 8.5–15 mCi PiB was injected following a 10-minute transmission scan for attenuation correction. Sixty minutes of data were acquired in 3D acquisition mode following injection. PiB-PET data were processed as a distribution of volume ratio images (40 to 60-minute interval, gray matter cerebellar reference region). Mean PiB distribution volume ratio values were extracted from an aggregate of cortical regions susceptible to amyloid burden in AD including frontal, lateral temporal and parietal, and retrosplenial (FLR) cortices [22]. Participants were dichotomized on this FLR measure into Aβ+ and Aβ− groups using a Gaussian mixture modeling approach with a cutoff value of 1.2 distribution volume ratio [23]. Amyloid status was determined for majority of the participants (67%) at the time of novel semantic memory measure administration (year 6). Given slow Aβ accumulation rates, particularly in Aβ− participants [24], a subset of participants with previously acquired PiB-PET scans was classified as Aβ+/− using data from a year 4 PiB-PET scan (24%) and a baseline scan (9%).

2.3. Semantic memory measures

The famous face naming task involved selection of 24 target photographs of prominent public figures who were actively present in the media (television, sports, radio, and cinema). These faces were piloted previously on a group of healthy and cognitively normal older adults who were not enrolled in the present study, to ensure that chosen faces were familiar and well known [25]. Faces were selected based on a time period of prominence and dichotomized into remote (famous from 1960–1980) and recent time periods (1990 to present). Images of remote faces were chosen from their approximate time of prominence to ensure temporal relevance, whereas pictures of recent faces comprised images within the last three decades. All faces were presented

on a computer tablet in color on a white background in a PowerPoint format. Performance for each face is provided in Supplementary Fig. 2.

A famous face was presented one at a time for a maximum of 20 seconds. Participants were asked to recall the name and occupation of each face. Participants were first prompted to recall the names spontaneously. However, to ensure that the inability to access a name was not purely attributed to word retrieval difficulties, we provided a phonemic cue. More specifically, we included the "with cue" recall outcome to isolate predominantly storage-based semantic memory loss. Phonemic cues were provided by giving the sound of the first two letters of the famous figure's first name. Scores were obtained for an overall total of correctly recalled remote and recent famous faces without and with a phonemic cue. A response was quantified as correct if the participant recalled the first or last name of the famous face. Given our primary interest in the integrity of the semantic memory system rather than age-related difficulties in retrieval monitoring, analyses were focused on recall with a phonemic cue; however, we also examined free recall (i.e. recall without a cue).

Our comparative measure of semantic processing included confrontation naming (Boston Naming Test [BNT]) [26]. Performance on the BNT included both the number of items freely recalled and number of items recalled with a phonemic cue.

2.4. Cognitive factor scores

To compare famous face naming with other cognitive domains, composite scores of memory, processing speed, and executive function were generated. Confirmatory factor analyses were conducted using the lavaan R package [27], to construct longitudinal factors for these three domains. The hypothesized factor structure was modeled after a previously reported cross-sectional analysis [22] and adapted to include cognitive measures with repeated administration across all time points (see Supplementary Material). These include the executive function composite which consists of the Wechsler Adult Intelligence Scale-III Letter-Number Sequencing (the number of trials correctly completed) [28], phonemic fluency (the sum of the words produced in response to the letters F, A, and S, each over 60 sec) [29], and the Trail Making Test (time to complete Form B minus Form A) [30]. Episodic memory was assessed using Logical Memory delayed recall [20], the free recall score from the Free and Cued Selective Reminding Test [31], and the delayed recall score from Six-Trial Selective Reminding Test [32]. Processing speed was assessed by the Wechsler Adult Intelligence Scale-Revised Digit-Symbol Coding [33], and the Trail Making Test (time to complete Form A) [30].

2.5. Media usage

A self-administered 10-item media usage questionnaire (Supplementary Fig. 1) was administered to all participants following completion of the famous face-naming task. The survey was designed using closed questions quantifying both objective and subjective use of media. Questions were further designed to account for variability in interest of media modalities as well as time-based usage of these modalities, as measured by the time spent on social media, watching television and movies, and staying engaged in political and social culture. Overall media usage was computed as an average of all items with a higher score reflecting more usage.

2.6. Statistical analysis

Statistical analyses were completed using R 3.3 (http://CRAN.R-project.org/doc). Means and standard deviations for demographic and apolipoprotein E (*APOE*) ε4 differences in Aβ+/− groups were reported using t-tests and chi-squared tests for linear and categorical variables, respectively. Performance on the famous face paradigm was reported using means and standard error scores for recall of famous faces with and without a phonemic cue across recent, remote, and all faces. Independent samples t-tests were completed to distinguish differences in overall recall for recent versus remote famous faces and recall without and with a cue, regardless of Aβ status. Pearson's r correlations were used to compare performance on famous face-name recall with other measures of semantic memory (i.e., BNT, category fluency) and cognitive factor scores to better characterize neuropsychological domains specific to famous face-naming.

A repeated measures analysis of variance was completed to first explore the interaction of time period (cued recent vs. cued remote) and amyloid status after controlling for demographic factors and media usage. Secondary group comparison analyses were then completed to further assess and characterize performance between cued recent and cued remote famous face-names recalled within the Aβ+ versus the Aβ− groups. Effects of age, sex, education, and media usage were modeled as covariates. Although our main outcome of interest was recall with a cue, we were also interested in whether performance diverged between Aβ groups and time period condition without cued recall. As such, an identical repeated measures analysis of variance was completed with the exception that performance without cued recall on recent versus remote faces was examined. Given the non-normally distributed responses for famous face recall, Mann–Whitney U testing was completed post hoc to verify the accuracy of parametric results.

3. Results

3.1. Demographics

There were no differences between Aβ− and Aβ+ groups in sex distribution, age, or years of education (Table 1). No group differences were observed on Logical Memory delayed recall. However, the Aβ+ group exhibited

slightly lower Mini–Mental State Examination scores compared with the Aβ− group. Moreover, Aβ+ participants were significantly more likely to be *APOE* ε4+. There were no significant differences between the groups on media usage, t(123) = 0.257, $P = .797$.

3.2. Famous face test performance and relationship to other cognitive variables

Participants generally recalled more remote famous faces compared with recent famous faces regardless of the cueing condition [without cue: t(124) = 6.144, $P < .001$; with cue: t(124) = 8.398, $P < .001$]. Not unexpectedly, performance improved from the noncueing to the cueing conditions [t(124) = 15.74, $P < .001$]. Improved performance following a cue persisted regardless of whether stimuli were remote [t(124) = 12.50, $P < .001$] or recent [t(113) = 12.88, $P < .001$] (Supplementary Table 1).

As can be observed in Fig. 1, correlations among recall for recent and remote famous faces, without a phonemic cue, r = 0.738, $P < .001$ and with a phonemic cue, r = 0.598, $P < .001$ suggest a moderate positive relationship between recent and remote naming. In our condition with no phonemic cuing, slightly more variance (54.5%) in recent recall is explained by remote recall. In the phonemic cue condition, 35.7% of the variance in recent recall is explained by remote recall. When comparing famous face naming to performance on the BNT, correlations were positive but relatively weak, ranging from r = 0.327 to 0.429 (Table 2). In addition, correlations across noncueing and cueing conditions were comparable. Small to moderate relationships between both recent and remote recall for famous faces (with a phonemic cue) and all three composites of memory, speed, and executive functioning were observed (Table 2). Moreover, a similar relationship was observed for composite scores and remote and recent recall without a phonemic cue, though these relationships were slightly weaker when compared to the cueing condition.

3.3. Effect of amyloid status on face-name performance–with phonemic cue

There was a significant interaction for the effect of amyloid status on recent/remote recall with a phonemic cue, F(1, 119) = 5.768, $P = .018$ (Table 3). Group comparisons did not reveal a significant effect of amyloid status on remote famous face recall (Table 3). By contrast, amyloid status significantly impacted the recall of recent famous faces, such that the Aβ+ group recalled fewer recent famous face names compared with the Aβ− group (Table 3, Fig. 2). On average, Aβ+ participants recalled 8.03 recent famous faces, as opposed to their Aβ− counterparts, who recalled an average of 9.60 recent famous faces (Supplementary Table 1). In addition to Aβ status, older age and less media usage were significant predictors for performance on recent famous face recall.

3.4. Removing the phonemic cue: Effect of amyloid status on face-name performance–without phonemic cues

A significant interaction was not observed for the effect of amyloid status on recent/remote recall without a phonemic cue, F(1, 119) = 0.753, $P = .387$. When examining performance between Aβ+ and Aβ− groups and recent versus remote naming without a cue, the Aβ+'s recalled both fewer remote, F(1, 119) = 6.046, $P = .015$ and fewer recent, F(1,119) = 10.343, $P = .002$ names.

3.5. Effect of amyloid status on other semantic measures

There were no differences in performance on the BNT by Aβ group for either total score F(1,110) = 0.854, $P = .358$ or total score + items recalled with a phonemic cue F(1,110) = 0.248, $P = .620$.

4. Discussion

Our study findings suggest that (1) recall for temporally variant pieces of semantic information are differentially related to amyloidosis such that a relative vulnerability for recently over remotely encoded semantic memory is observed and (2) famous face naming as a semantic measure may be more related to amyloidosis in clinically normal older adults compared with object naming.

Our results are consistent with previous research suggesting a decline in semantic memory along the AD trajectory during the prodromal [6,34–36] and preclinical stages [7,8] of the disease. Furthermore, several studies suggest preferential decline for famous face-name recall over more global measures of semantic memory, such as object

Table 1
Descriptive characteristics of the Harvard Aging Brain Study subsample, by Aβ+/− status

Demographic	All	Aβ−	Aβ+	Significance testing
N (%)	125	90 (72%)	35 (28%)	
Age (years)	78.82 ± 6.12	78.46 ± 6.41	79.74 ± 5.27	t(123) = −1.143, $P = .257$
Female (%)	58%	60%	54%	$\chi^2(1, 124) = 0.339$, $P = .686$
APOE ε4+ (%)	29%	15%	63%	$\chi^2(1, 124) = 27.50$, $P < .001$
Education	16.04 ± 3.02	16.00 ± 2.93	16.14 ± 3.29	t(123) = −0.237, $P = .813$
MMSE	29.09 ± 1.171	29.24 ± 1.02	28.69 ± 1.43	t(123) = 2.112, $P = .040$
Log Mem-II	16.86 ± 3.470	16.94 ± 3.14	16.66 ± 4.24	t(123) = 0.413, $P = .681$

Abbreviations: *APOE* ε4+, *APOE* ε4 allele positive; MMSE, Mini–Mental Status Examination; Log Mem-II, Logical Memory delayed recall.
NOTE. Mean and standard deviations are reported unless otherwise noted.

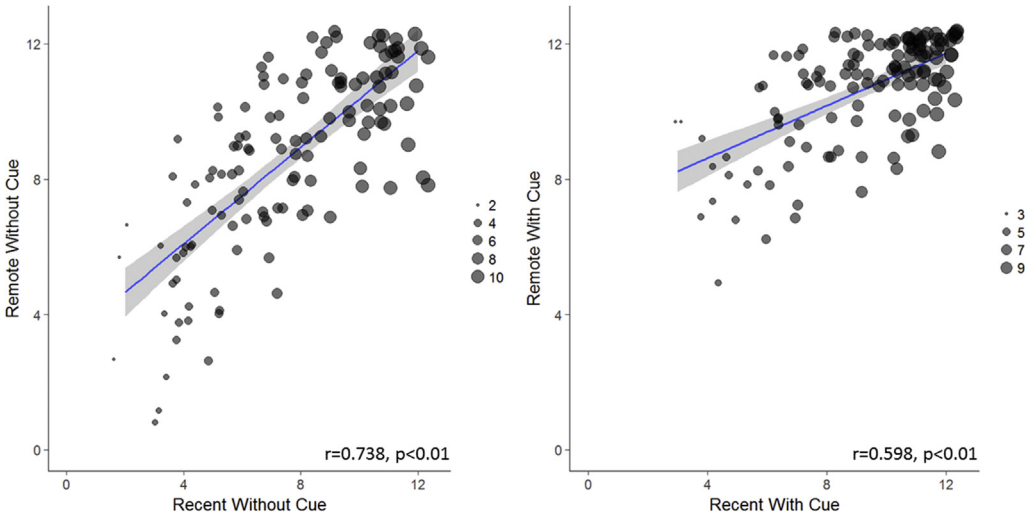

Fig. 1. Relationship between recent and remote recall by cue type. Scatterplots showing the correlation between recent and remote famous face naming without a cue (left) and with a cue (right). A jitter was applied to individual data points, to minimize overlap and visualize the approximate density of individual performance for recent and remote recall. The size of each data point was scaled by frequency of participant performance. Nonjittered scatterplots can be viewed in Supplementary Fig. 3.

naming, in patients with mild cognitive impairment [14,17]. This finding was consistent in our sample, as participants performed similarly on a test of object naming regardless of amyloid status.

Previous research on the temporal gradient of famous face-name recall is varied. For example, Greene et al [14] found a relatively greater impairment of recent over remote face-name memory in patients with AD; however, Thompson et al. [37] found the contrary. Study findings replicated a deficit in recall of famous-faces over objects; however, only an insignificant benefit for remote over recent famous name recognition was observed, failing to support Ribot's law. It is important to consider the task-dependent manipulation of stimuli in the latter; participants were probed to select a famous name among four famous names presented on a card, which partially eliminated semantic features of famous face recognition and name recall, and conversely encouraged the use of a lexically motivated retrieval process. Similarly, in our paradigm, we found stronger signal in our phonemic cue condition for amyloid-related outcomes, than our condition without a phonemic cue. Thus, variability in task design may contribute to variability in observed results.

The greater impact of amyloid on recent versus remote memory may be explained by a few key factors. In both normal aging and AD, hippocampal regions are impacted preferentially [38,39]. However, Huijbers et al. [40] found that neocortical amyloid deposition was associated with functional changes in the medial temporal lobe (MTL) and most

Table 2
Correlation matrix of semantic and other measures of cognition

	Famous face recall								
	Remote	Recent	Remote	Recent					
Task	Without cue		With cue		BNT	CAT	Mem	Speed	EF
BNT	0.397*	0.327*	0.429*	0.423*	1				
CAT	0.392*	0.367*	0.384*	0.406*	0.422*	1			
Mem	0.417*	0.364*	0.333*	0.463*	0.244†	0.529*	1		
Speed	0.343*	0.357*	0.347*	0.456*	0.445*	0.594*	0.443*	1	
EF	0.328*	0.294†	0.379*	0.406*	0.545*	0.598*	0.282†	0.523*	1

Abbreviations: BNT, Boston Naming Test; CAT, category fluency; Mem = memory composite; EF, executive function composite.

NOTE. Cross sectional relationship (Pearson's r) between recent and remote recall, measures of semantic processing, and composites of executive function, memory, and processing speed.

*$P < .001$.

†$P < .01$.

Table 3
Repeated measures analysis of recency by amyloid status and group comparisons of recent and remote recall with phonemic cue by amyloid status

Recency by Aβ interaction				
	F(1, 119) = 5.768, $P = .018$, $\eta_p^2 = 0.046$			
	Remote and recent recall with cue			
Overall model	Sum of squares	F	*P* value	η_p^2
Remote famous face name recall				
Age	55.25	28.06	<.001	0.191
Education	2.28	1.16	.285	0.010
Sex	1.29	0.66	.419	0.005
Media	6.83	3.47	.065	0.028
Aβ	5.08	2.58	.111	0.021
Error	234.30			
Recent famous face name recall				
Age	122.45	30.22	<.001	0.203
Education	7.46	1.84	.177	0.015
Sex	0.42	0.10	.747	0.001
Media	69.87	17.25	<.001	0.127
Aβ	44.50	10.98	.001	0.085
Error	482.09			

Abbreviation: Aβ, amyloid β.

NOTE. Model covaries for age, education, sex, and media usage.

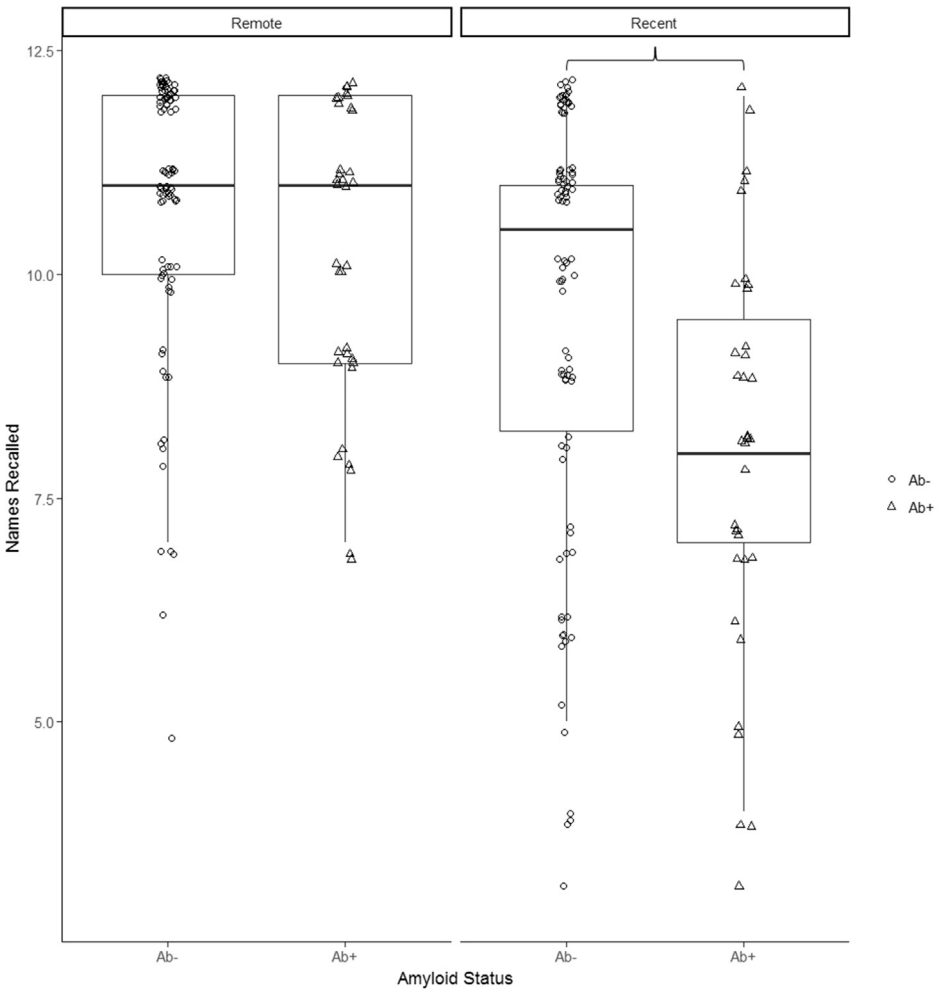

Fig. 2. Boxplot of unadjusted mean recent and remote names recalled with a cue by amyloid status. The Aβ+ group recalled fewer recent famous face names despite phonemic cueing compared with the Aβ− group. A jitter was applied to individual raw data points.

notably the entorhinal cortex. The entorhinal cortex is critical for the integrity of communication between the hippocampus and neocortical regions [41] and is implicated in theories of memory consolidation [42,43]. If medial temporal regions are particularly susceptible to amyloid-related functional changes early in disease trajectory, recent memories may degrade first due to aberrant entorhinal activity, and consequentially, compromised communication between neocortical traces and the hippocampus. This interpretation is consistent with frameworks for the Cortical Reallocation and Multiple Trace Theories [44,45].

Alternatively, it is arguable that our task is not purely semantic but perhaps shares features with episodic processes. The hippocampus is implicated both in the recognition of remote and recent famous faces [25,46]. Furthermore, it is thought that the hippocampus mediates access to memory traces of semantic representations stored in long-term memory [47,48]. However, the inherent encoding of these representations begins as an episode. For example, names are fragile episodic memories, initially [49]. Given the age-related loss of activation in the hippocampus, a region integral to encoding during tasks of episodic memory (Sperling et al., 2003), one potential interpretation for our temporal gradient may be an initial deficit of episodic encoding developing concurrently with very early AD pathology. This encoding deficit has been supported further in functional magnetic resonance imaging findings of healthy older adults [50].

With rehearsal and continued retrieval over time, it is thought that episodes lose their temporal and spatial context, enduring a process of semanticization [14]. Therefore, a potential second interpretation of our findings may reflect deficits in processes of memory consolidation and retrieval. It is possible that recently acquired semantic information is re-encoded poorly and relies on hippocampally mediated consolidation for longer periods of time. As memory traces endure age-related lesions to hippocampally mediated neocortical connections, recent memories still dependent on the hippocampus are lost preferentially [44]. Conversely, a failure of degrading MTL structures, such as the entorhinal cortex, hinder the linking of semantic information to disparate neocortical regions implicated in memory retrieval

[51], resulting in a temporal gradient for recent information that has failed to undergo a process of semanticization. In the case of our findings, it is possible that participants are experiencing a combination of all three outcomes, such that there are deficits to encoding, consolidation, and retrieval, though we attempt to diminish retrieval based inefficiencies.

In consideration of semantic and episodic memory processes, our findings of a weak correlation between recent and remote famous face-name recall and our episodic memory composite (Table 2) suggest that a portion of the variance in performance may be attributed to episodic features of the test. A similarly weak correlation with object naming suggests that there is a partial global semantic feature to this assessment. Taken together, these findings may indicate an intersection between these two memory systems. It is, however, not intuitive that recent and remote famous face recall were related to our executive function and processing speed composites to the same magnitude as our memory composite, given that a memory paradigm would share the highest variance with a memory composite. This may be attributed to the distributed functional localization of semantic memory, which integrates multiple cognitive domains for successful processing and recall [52].

A limitation of using famous face paradigms is that knowledge of famous faces may be confounded by differences in media usage. Moreover, while our questionnaire tracks interest in media and time-based usage of related modalities, this is specific to recent rather than remote media usage and does not reflect objective quantification of remote media exposure. However, when incorporating this score as a covariate, we found that it did not differ across our Aβ+/− groups, and our findings were consistent for a vulnerability of recent over remote recall, when controlling for this factor in our models. Future studies using famous face learning may benefit from tracking longitudinal changes in media usage from mid to late adulthood, as interest in media and quantifiable media usage may change over time.

A second limitation of our study is our knowledge for when individuals presumably encoded the famous faces used in our paradigm, and furthermore, how frequently these memories were retrieved. This has an implication for our findings. While we aim to reduce retrieval-based failures by providing a phonemic cue, it is alternatively possible that the process of consolidation is interrupted at encoding and much earlier along the course of memory consolidation, as discussed above. If individuals are failing to encode famous faces and names initially, our phonemic condition fails to account for our observed outcomes. Our paradigm may therefore benefit from the addition of multiple choice famous face-name recognition to account for famous face familiarity within our cohort.

Taken together, our findings converge with various studies on the utility of famous face name paradigms in detecting temporal nuances in encoding and recall, as well as detection of changes in memory early in the AD trajectory. Future research may benefit from investigating hippocampal activation patterns for the functional distinction between episodic versus semantic features of this task. For example, a finding by Bernard et al. [46] describes a specialization of the anterior hippocampus for incidental episodic encoding, whereas the role of the posterior hippocampus is thought to be involved in retrieval of semantic information, regardless of temporal context. Investigating this distinction further in the scope of famous face-name recall may result in functional specificity of semantic retrieval.

While much is left to be understood about the nature of this task, our results demonstrate a vulnerability of recently encoded semantic information that further supports theories of the static role of the MTL in memory consolidation. In addition, these results highlight the potential utility of famous face naming measures in identifying early changes in AD. Finally, we present the first finding of associations between decline in temporally variant semantic information and amyloid burden in a clinically normal population.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2017.11.003.

RESEARCH IN CONTEXT

1. Systematic review: We comprehensively reviewed the literature examining semantic memory, the use of famous face naming paradigms, and the temporal gradient of long-term memory in healthy older adults and those with prodromal Alzheimer's disease (AD) and AD dementia.
2. Interpretation: Our study suggests that semantic memory for recently encoded information is more vulnerable compared with remotely encoded information, in individuals who are clinically normal, but show biomarker evidence of AD pathology. The relative sparing of remote over recent semantic memory retention may develop many years prior to diagnosis of AD, at the stage of preclinical AD.
3. Future directions: Further exploration of the temporal gradient observed in semantic memory will determine whether this cognitive signature is a sensitive marker for early detection of AD-related cognitive decline.

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