

Amyloid deposition in younger adults is linked to episodic memory performance

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ABSTRACT

Objective: To examine the relationship of β -amyloid ($A\beta$) deposition to episodic memory in younger (30–49 years), middle-older (50–69 years), and older adults (70–89 years). We hypothesized that subclinical levels of amyloid would be linked to memory in adults across the lifespan in a dose-dependent fashion. Of great interest was whether, within the younger group, a relationship between amyloid level and memory performance could be established.

Methods: A total of 147 participants from the Dallas Lifespan Brain Study, aged 30–89, underwent PET imaging with ^{18}F -florbetapir and cognitive assessment. We assessed the relationship between age group and amyloid and tested whether $A\beta$ differentially affected memory performance across the 3 age groups.

Results: We report a significant association of age to amyloid burden for younger and middle-older adults ($r = 0.57$ and 0.28 , respectively), but not for the oldest group, although absolute level of amyloid increased across the age groups. Importantly, the youngest group showed a significant decrease in recall ($r = -0.47$, $p = 0.004$) and recognition memory ($r = -0.48$, $p = 0.003$) as a function of increases in $A\beta$ burden, whereas this relationship was absent in the middle-older and oldest group (all $p > 0.23$).

Conclusions: These results indicate that variance in subclinical levels of $A\beta$ in younger adults is meaningful, and suggest that higher SUVRs relative to one's peers at a younger age is not entirely benign. *Neurology*® 2016;87:2562–2566

GLOSSARY

$A\beta$ = β -amyloid; **AD** = Alzheimer disease; **CANTAB** = Cambridge Neuropsychological Test Automated Battery; **DLBS** = Dallas Lifespan Brain Study; **MMSE** = Mini-Mental State Examination; **NS** = not significant; **SUVR** = standardized uptake value ratio.

Recent models of Alzheimer disease (AD) suggest that amyloid deposition may become abnormal as much as 20 years before clinical symptoms appear.¹ Despite the availability of in vivo molecular imaging of amyloid deposition, few studies have included individuals younger than 60.² Thus we know little about the earliest disease stage. In an effort to understand AD at its earliest stages, we collected measures of β -amyloid ($A\beta$) burden in 147 cognitively normal adults from age 30–89 years. We divided these participants into 3 age groups (younger: age 30–49, $n = 36$; middle-older: age 50–69, $n = 47$; and oldest: age 70–89, $n = 63$) and addressed 2 questions. First, within each age group, did $A\beta$ show systematic age-related increases, reflecting reliable accrual of the protein? Second, within each age group, was magnitude of $A\beta$ deposition related to memory performance? There is growing evidence that $A\beta$ is associated with subtle differences in episodic memory performance in cognitively normal adults harboring high levels of amyloid.³ Although adults age 30–49 years would normally have low levels of $A\beta$, we hypothesized that younger adults (who likely had yet to experience age-related neurodegeneration) might be sensitive to even low levels of amyloid accumulation and would exhibit an amyloid dose/response relationship to memory.

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METHODS Standard protocol approvals, registrations, and patient consents. This study was approved by the University of Texas at Dallas and University of Texas Southwestern Medical Center human investigations committees. All participants provided written informed consent prior to enrollment and were debriefed in accord with university human investigations committee guidelines.

Participants were 147 cognitively normal adults (91 female) from the Dallas Lifespan Brain Study (DLBS), aged 30–89 years (data from 137 participants were presented previously⁴). All participants underwent a comprehensive neuropsychological assessment and PET using ¹⁸F-florbetapir (Avid Radiopharmaceuticals, Philadelphia, PA) to image fibrillar amyloid burden.⁴ *APOE* status was also collected.

Measurement of amyloid burden. Using the Avid florbetapir template,⁵ amyloid counts were obtained from 8 standard regions of interest and were normalized by the nonspecific binding counts in the cerebellar gray matter to produce standardized uptake value ratios (SUVR).⁴ The mean SUVR of the 8 regions was used for analysis.

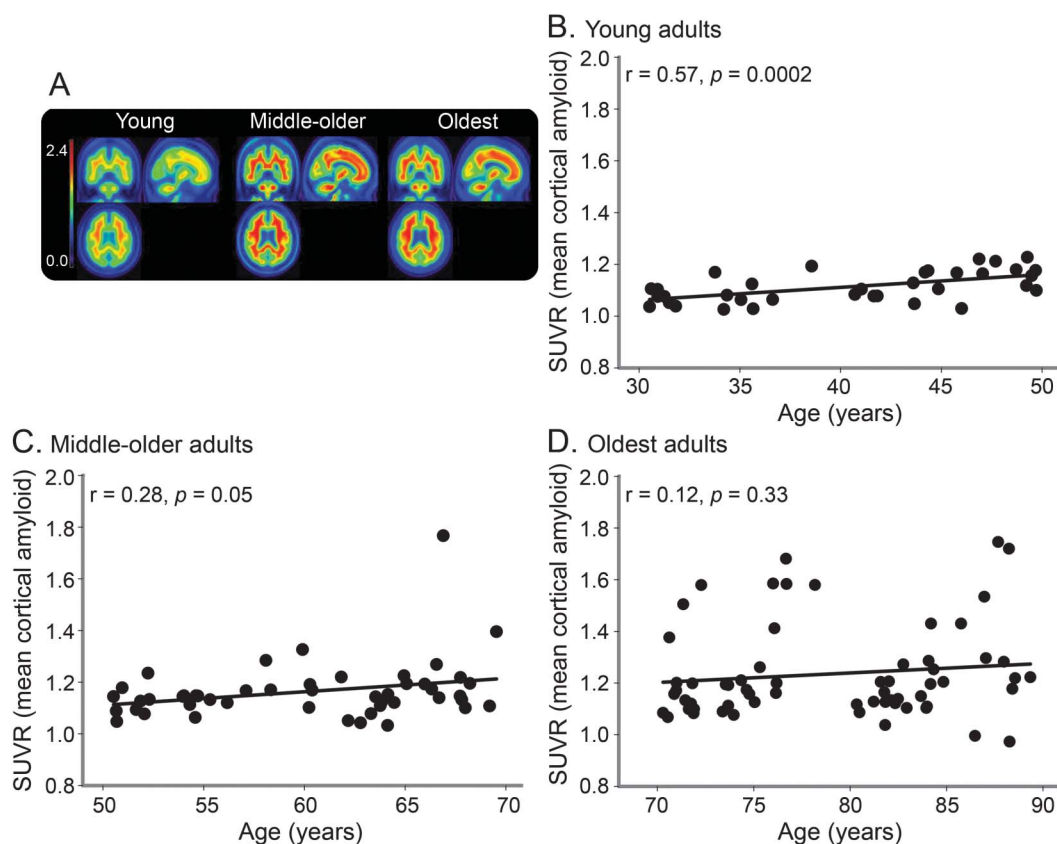
Episodic memory measures. Participants received 2 memory tests: The Hopkins Verbal Learning Test, which provided measures of immediate recall, delayed recall, and recognition of a list of words; and the Cambridge Neuropsychological Test Automated Battery (CANTAB) Verbal Recognition Test, which yielded memory scores of immediate recall and recognition and delayed recognition. Each set of scores was transformed to *z* scores across the whole sample, and used to derive recall and recognition

constructs. The recall construct was created by combining *z* scores for delayed recall, Hopkins immediate recall, and CANTAB immediate recall (Cronbach $\alpha = 0.78$). The recognition construct was similarly created from Hopkins immediate recognition and CANTAB immediate and delayed recognition (Cronbach $\alpha = 0.71$).

RESULTS Age and A β . Figure 1A depicts the mean SUVR image for each age group, separately. Within each age group, we then assessed whether the SUVR increased with age, using a one-way analysis of variance. As shown in figure 1B, amyloid increased significantly with age in the younger group ($F [2] = 9.60, p = 0.01, r = 0.57, p < 0.0002$) (table). In the middle-older group, this association was less pronounced ($r = 0.28, p = 0.05$), with greater dispersion of SUVR values. Finally, in the oldest group, amyloid was considerably elevated relative to the other 2 age groups, but age and amyloid burden were unrelated ($r = 0.12, p = 0.33$).

A β and memory by age group. Next, to assess the effects of age group and amyloid on episodic memory, we conducted general linear models separately on the recall and recognition construct. Age was treated as a group factor, mean cortical SUVR was treated as a continuous predictor, and the age \times SUVR

Figure 1 Association of amyloid burden and age in 3 age groups



(A) Mean amyloid in young, middle-older, and oldest adults of the sample. (B–D) Amyloid burden reliably increases within the younger age group, but was not associated with age in the oldest group. SUVR = standardized uptake value ratio.

Table	Demographics and memory performance		
	Younger adults (n = 36)	Middle-older adults (n = 48)	Oldest adults (n = 63)
Age, y	40.21 (6.89)	60.2 (6.14)	79.02 (6.05)
MMSE	29.5 (0.7)	29.4 (0.7)	29.0 (1.09)
MMSE range	27-30	27-30	26-30
Years of education	16.63 (2.88)	16.91 (2.27)	15.76 (2.63)
Cortical amyloid	1.11 (0.05)	1.16 (0.11)	1.23 (0.18)
Hopkins immediate recall	7.83 (1.90)	6.95 (2.0)	6.41 (1.56)
Hopkins delayed recall	5.52 (2.88)	5.41 (2.61)	4.5 (2.42)
CANTAB immediate recall	8.16 (1.92)	7.75 (1.87)	6.30 (1.82)
Recall memory z scores	0.372 (0.83)	0.135 (0.85)	-0.315 (0.71)
CANTAB immediate recognition	22.9 (1.06)	23.14 (1.07)	22.27 (2.01)
CANTAB delayed recognition	22.55 (1.68)	22.85 (1.35)	21.58 (2.16)
Hopkins immediate recognition	21.22 (2.25)	20.36 (2.34)	20.44 (2.48)
Recognition memory performance	0.187 (0.70)	0.167 (0.58)	-0.234 (0.92)
APOE % (ε4 carrier)	27.7	23.4	15.8

Abbreviations: CANTAB = Cambridge Neuropsychological Test Automated Battery; MMSE = Mini-Mental State Examination. Values are mean (SD) unless otherwise noted.

interaction was modeled. *APOE* status was a covariate. To obtain the most parsimonious model, we reduced each model after nonsignificant interactions ($p > 0.10$).

For episodic recall, we found a main effect of age ($F [2] = 4.38, p = 0.01; \eta^2 = 0.06$) and SUVR ($F [1] = 10.56, p = 0.001; \eta^2 = 0.07$), qualified by an age \times SUVR interaction ($F [2] = 3.70, p = 0.02; \eta^2 = 0.051$). Figure 2A shows that in younger adults, higher amyloid was associated with diminished recall ($r = -0.47, p = 0.004$), whereas neither middle-older ($r = -0.19$, not significant [NS]) nor oldest adults ($r = -0.05$, NS) showed this association.

The recognition memory analysis yielded the same 2 main effects: age ($F [2] = 3.32, p = 0.03; \eta^2 = 0.04$) and cortical SUVR ($F [1] = 7.16, p < 0.01; \eta^2 = 0.05$), as well as a significant age \times SUVR interaction ($F [2] = 2.94, p = 0.05; \eta^2 = 0.041$). Figure 2B shows the interaction was of the same pattern as described above for recall (younger: $r = -0.48, p = 0.003$; middle-older: $r = -0.17$, NS; oldest: $r = -0.01$, NS). *APOE* status was not associated with any effects on recall or recognition. Of note, some participants in the youngest group showed low memory performance without high levels of amyloid. These individuals tended to have low verbal ability as measured by the Shipley Verbal Learning and the Educational Testing Service Advanced Vocabulary Task. Further, Mini-Mental State Examination (MMSE) scores were high for all groups and the 2 lowest participants (MMSE = 26) were not among the outliers for memory performance.

To examine the reliability of the relationship of mean cortical SUVR and memory across the lifespan, we used a sliding window analysis⁶ with a 20-year age-bin (figure 3) that allowed us to define the age window when the covariance of amyloid and memory is significant. We found that the low memory/high A β effect occurred between ages ~ 35 and ~ 55 , and was no longer reliable at a correlation strength below $r = -0.33, r = -0.31$ for recall and recognition memory, respectively. This large age window suggests that the finding is generalizable and not limited to one specific configuration of subject scores or age groups.

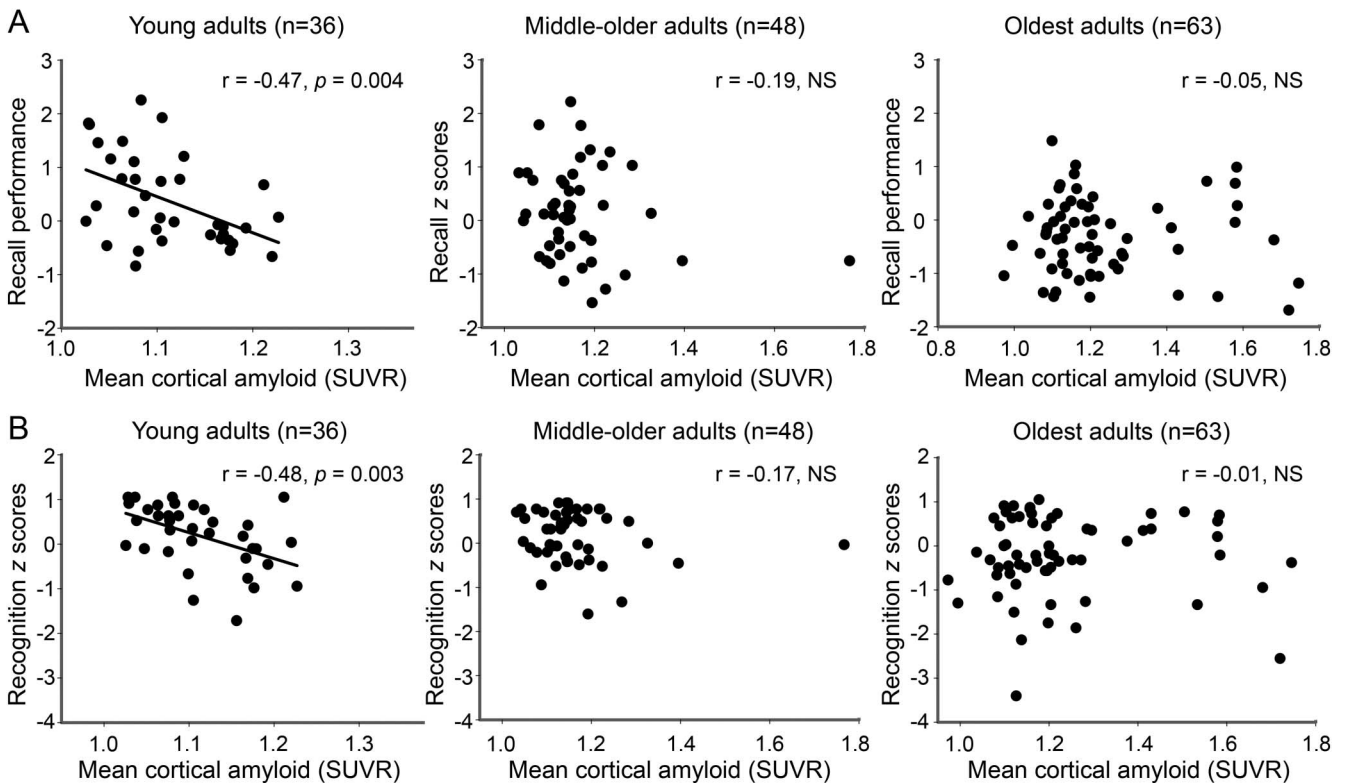
DISCUSSION The results suggest that amyloid levels that are higher than one's age peers may have an influence on memory, particularly at ages 30–55 years.

The finding that A β showed a steady increase with age, even in the younger group, suggests that the accumulation is both reliable and meaningful. Evidence for an age/A β relationship was strongest in the younger group and weak in the middle-older adults and absent in the oldest, suggesting that A β in early and middle adulthood may be particularly important.

Most interesting was the age \times amyloid interaction on both recall and recognition memory. Results showed that amyloid exerted a dose/response relationship at young ages, whereas the effect weakened as people aged and amyloid levels rose.

The younger adults in this study generally had healthy brains and consequently may have been particularly sensitive to the neural insult of a mildly elevated level of A β .

Figure 2 Relationship of episodic memory and amyloid burden in different age groups



(A) Amyloid burden is associated with significant decrease in recall memory performance in younger adults. (B) Amyloid burden is associated with significant decrease in recognition memory performance in younger adults. Removing the outlier from the model of the middle-older adults did not change the findings. NS = not significant; SUVR = standardized uptake value ratio.

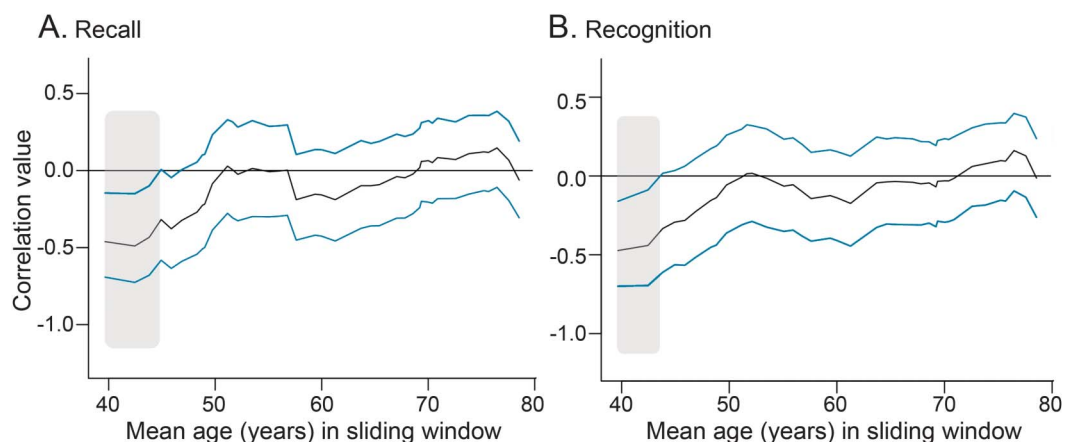
In contrast, the older adults may have already experienced a range of neural insults (i.e., white matter hyperintensities, dopamine depletion, volume loss), and as a result, it could be more difficult to isolate the relatively subtle effect of amyloid in the older groups.

We also recognize that the A β effects we observed could be mediated by tau infiltration in medial

temporal structures, as it has been shown that tau deposition is a stronger predictor of memory performance in older adults compared to A β .⁷ The advent of tau imaging will ultimately clarify this issue.

Our results raise the intriguing possibility that younger individuals with higher cortical SUVR than their peers will also exhibit lower memory

Figure 3 Sliding window analysis across the lifespan on episodic memory and amyloid burden



Sliding window analysis on the relationship of recall (left panel) and recognition memory (right panel) on mean cortical standardized uptake value ratio. Reliable significant associations were detected for the age ranges of ~35 to ~55 years for both memory constructs (shaded area).

performance compared to their peers. Tau imaging may untangle the causal factor of memory difference and longitudinal research is needed to assess whether elevated amyloid at young ages is a harbinger of AD many decades later. Both of these approaches are currently underway in the DLBS.

AUTHOR CONTRIBUTIONS

Study concept and design: Gérard N. Bischof, Denise C. Park. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: Gérard N. Bischof, Denise C. Park. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Gérard N. Bischof. Obtaining funding: Denise C. Park, Karen M. Rodrigue, Kristen M. Kennedy. Administrative, technical, or material support: Gérard N. Bischof, Denise C. Park, Mike Devous. Study supervision: Denise C. Park.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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