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Stronger effect of amyloid load than *APOE* genotype on cognitive decline in healthy older adults

Yen Ying Lim, MPsyCh
Kathryn A. Ellis, PhD
Robert H. Pietrzak, PhD,
MPH
David Ames, MD
David Darby, MBBS,
PhD, FRACP
Karra Harrington, BA
Ralph N. Martins, PhD
Colin L. Masters, MD
Christopher Rowe, MD
Greg Savage, PhD
Cassandra Szoeké, PhD
Victor L. Villemagne,
MD
Paul Maruff, PhD
For the AIBL Research
Group

Correspondence & reprint
requests to Dr. Lim:
y.lim@mhri.edu.au

Supplemental data at
www.neurology.org

Supplemental Data



ABSTRACT

Objective: Although the *APOE* $\epsilon 4$ allele is associated with more rapid decline in memory in healthy older adults, the significance of elevated cerebral β -amyloid ($A\beta$) load for longitudinal changes in cognition is unclear.

Methods: Healthy and cognitively normal older adults ($n = 141$; mean age 76 years) underwent PET neuroimaging for cerebral $A\beta$, *APOE* genotyping, and cognitive assessment as part of their baseline assessment in the Australian Imaging Biomarkers and Lifestyle study. Cognitive function was reassessed 18 months later.

Results: Linear mixed-model analyses adjusted for baseline cognitive function indicated that, relative to individuals with low cerebral $A\beta$, individuals with high cerebral $A\beta$ showed significantly greater decline in working memory and verbal and visual episodic memory at 18 months. Compared with noncarriers, *APOE* $\epsilon 4$ carriers showed a greater decline in visual memory at the 18-month assessment. No interaction between *APOE* $\epsilon 4$ and cerebral $A\beta$ load was observed for any measure of cognitive function.

Conclusions: In this prospective study of healthy older adults, high cerebral $A\beta$ load was associated with greater decline in episodic and working memory over 18 months. The *APOE* $\epsilon 4$ genotype was also associated with a decline in visual memory, although the effect was less than that observed for cerebral $A\beta$ load. *Neurology*® 2012;79:1645-1652

GLOSSARY

$A\beta$ = β -amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **AIBL** = Australian Imaging Biomarkers and Lifestyle; **ANCOVA** = analysis of covariance; **CVLT-II** = California Verbal Learning Test, Second Edition; **DET** = Detection task; **DET-IDN** = Psychomotor-Attention Composite; **IDN** = Identification task; **LMM** = linear mixed model; **MCI** = mild cognitive impairment; **OBK** = One Back task; **OCL** = One Card Learning task; **OCL-OBK** = Working Memory-Learning Composite; **PAL** = Paired Associate Learning task; **PiB** = Pittsburgh compound B; **SUV** = standardized uptake value; **SUVR** = standardized uptake value ratio.

Neuroimaging studies reveal abnormally high cerebral β -amyloid ($A\beta$) loads in a substantial proportion of healthy older adults.¹⁻⁴ However, associations between cerebral $A\beta$ load and cognitive function are generally only small in magnitude, with the strongest relationships found for episodic memory.⁵⁻⁸ Recent cross-sectional studies of healthy older adults reported moderate associations between cerebral $A\beta$ burden and episodic memory when analyses were restricted to carriers of the *APOE* $\epsilon 4$ allele. No such relationships were observed in noncarriers,^{5,6} suggesting that in healthy older adults, elevated cerebral $A\beta$ load may be a more important prognostic factor in individuals genetically at risk for Alzheimer disease (AD). However, the implications of a high cerebral $A\beta$ load for cognitive function should be determined in prospective studies. Further,

From the Mental Health Research Institute (Y.Y.L., K.A.E., D.D., K.H., C.L.M., V.L.V., P.M.), Department of Psychiatry (Y.Y.L.), and Academic Unit for Psychiatry of Old Age, Department of Psychiatry (K.A.E., D.A.), The University of Melbourne, Parkville, Australia; National Ageing Research Institute (K.A.E., D.A., C.S.), Parkville, Australia; Department of Psychiatry (R.H.P.), Yale University School of Medicine, New Haven, CT; Florey Neuroscience Institutes (D.D.), The University of Melbourne, Carlton South, Australia; Centre of Excellence for Alzheimer's Disease Research and Care, School of Exercise, Biomedical and Health Sciences (R.N.M.), Edith Cowan University, Perth, Australia; Department of Nuclear Medicine and Centre for PET (C.R., V.L.V.) and Department of Medicine (C.R.), Austin Health, The University of Melbourne, Heidelberg, Australia; Department of Psychology and ARC Centre of Excellence in Cognition and Its Disorders (G.S.), Macquarie University, Sydney, Australia; and CogState Ltd. (P.M.), Melbourne, Australia.

AIBL Research Group Coinvestigators are listed on the *Neurology*® Web site at www.neurology.org.

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Table 1 Demographic data for MMSE, CDR-SB, premorbid IQ and HADS scores, and median years of education, for overall, each SUVR group, and each APOE group at baseline assessment

	Overall (n = 141)	SUVR <1.5 (n = 96)	SUVR ≥1.5 (n = 45)	ε4 noncarrier (n = 78)	ε4 carrier (n = 63)
Female sex, %	49.65	50	48.89	51.30	47.60
APOE ε4, n (%)	63 (44.7)	33 (34.4)	30 (66.7)		
Age, y, mean (SD)	76.22 (6.58)	75.52 (6.65)	77.71 (6.22)	76.32 (6.70)	74.94 (7.37)
Education level (category), y, range	13–15	13–15	13–15	13–15	13–15
SUVR neocortex, mean (SD)	1.42 (0.42)	1.16 (0.08)	1.98 (0.27)	1.29 (0.32)	1.58 (0.48)
MMSE score, mean (SD) ^a	28.78 (1.21)	28.84 (1.20)	28.64 (1.25)	28.83 (1.25)	28.71 (1.17)
CDR-SB score, mean (SD)	0.03 (0.16)	0.04 (0.18)	0.02 (0.11)	0.03 (0.18)	0.03 (0.12)
Premorbid IQ, mean (SD)	109.11 (7.31)	108.35 (7.91)	110.73 (5.63)	110.09 (7.14)	108.48 (7.40)
HADS-D score, mean (SD)	2.86 (2.20)	2.79 (1.92)	3.02 (2.73)	2.71 (1.91)	3.05 (2.52)
HADS-A score, mean (SD)	4.26 (2.86)	4.22 (2.61)	4.33 (3.38)	4.04 (2.48)	4.53 (3.29)

Abbreviations: CDR-SB = Clinical Dementia Rating Scale, Sum of Boxes; HADS-A = Hospital Anxiety and Depression Scale, Anxiety Subscale; HADS-D = Hospital Anxiety and Depression Scale, Depression Subscale; MMSE = Mini-Mental State Examination; SUVR = standardized uptake value ratio.

^a None of the variables shown in the table differed by SUVR or APOE status; all $p > 0.05$.

whereas it is well known that healthy older adults who carry the *APOE* ε4 allele show accelerated cognitive decline,^{9,10} it is not clear whether this allele may also moderate the relation between cerebral Aβ level and cognitive decline.

Two prospective Pittsburgh compound B (PiB) PET neuroimaging studies have reported no differences between healthy older adults with high and low cerebral Aβ on the rate of cognitive change over 24 months. However, in both studies, the samples were small ($n \leq 30$), and neither examined the effect of the *APOE* genotype.^{8,11} The aim of the current study was to examine associations between cerebral Aβ load, *APOE* genotype, and cognitive change over 18 months in a large group of healthy older adults. We hypothesized that increased cerebral Aβ load and *APOE* ε4 genotype would be associated with episodic memory decline over 18 months.

METHODS Participants. Participants were recruited from the healthy control group enrolled in the Australian Imaging Biomarkers and Lifestyle (AIBL) flagship study of aging.^{3,12} The process of recruitment and diagnostic classification of healthy older adults enrolled in the AIBL cohort has been described in detail elsewhere.¹² Healthy participants who volunteered were excluded from the AIBL study if they had any of the following: schizophrenia; depression (Geriatric Depression Score of 6 or greater); Parkinson disease; cancer (other than basal cell skin carcinoma) within the last 2 years; symptomatic stroke; uncontrolled diabetes; or current regular alcohol use exceeding 2 standard drinks per day for women or 4 per day for men. A clinical review panel chaired by D.A. reviewed all available med-

ical, psychiatric, and neuropsychological information to confirm the cognitive health of individuals enrolled in the healthy control group. In this study, only the subgroup of healthy older adults who had undergone PiB neuroimaging and who had completed the cognitive battery at baseline and 18-month assessment ($n = 141$) were included. Demographic and clinical characteristics of the healthy control subjects are shown in table 1. The clinical status of all participants did not change at 18 months.

Standard protocol approvals, registrations, and patient consents. The study was approved by and complied with the regulations of 3 institutional research and ethics committees,¹² and all participants provided written informed consent before participating in the study.

Measures. PiB PET neuroimaging and APOE ε4 genotyping. PiB PET imaging methodology has been outlined in detail previously.^{3,13} PET standardized uptake value (SUV) data acquired 40–70 minutes after PiB injection were summed and normalized to the cerebellar cortex SUV, resulting in a region/cerebellar ratio termed the standardized uptake value ratio (SUVR). An 80-mL blood sample was also taken from each participant, 0.5 mL of which was forwarded for *APOE* genotyping at a clinical pathology laboratory.

Cognitive assessments. All participants were assessed with the clinical rating scales and neuropsychological battery from the AIBL study (table 2). These have all been described in detail elsewhere and were administered according to standard protocols by trained research assistants.^{7,12,14} The clinical status of participants was determined by data that included the Mini-Mental State Examination¹⁵ and Clinical Dementia Rating Scale.¹⁶ Premorbid intelligence was estimated using the Wechsler Test of Adult Reading,¹⁷ and levels of depressive and anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale.¹⁸ Verbal learning and verbal episodic memory were measured using the California Verbal Learning Test, Second Edition (CVLT-II),¹⁹ and visual episodic memory was measured using the visual Paired Associate Learning (PAL) task.²⁰ All individuals also performed a set of computerized cognitive tests, which included measures of visual learning (One Card Learning task [OCL]), working memory (One Back task [OBK]), attention

Table 2 Summary of tasks, associated outcome measures, and scores at baseline and 18-month assessment for healthy older adults^a

Task	Measure	Baseline, mean (SD)					18 mo, overall (n = 141), mean (SD)
		Overall (n = 141)	SUVR <1.5 (n = 96)	SUVR ≥1.5 (n = 45)	ε4 noncarrier (n = 78)	ε4 carrier (n = 63)	
DET	Speed, log ₁₀ ms	2.52 (0.12)	2.52 (0.13)	2.52 (0.09)	2.53 (0.11)	2.52 (0.12)	2.53 (0.11)
IDN	Speed, log ₁₀ ms	2.72 (0.07)	2.72 (0.07)	2.73 (0.07)	2.73 (0.07)	2.72 (0.08)	2.72 (0.06)
OCL	Accuracy, arcsine proportion correct	0.96 (0.11)	0.97 (0.10)	0.95 (0.11)	0.96 (0.11)	0.96 (0.11)	0.98 (0.11)
OBK	Accuracy, arcsine proportion correct	1.30 (0.18)	1.32 (0.18)	1.29 (0.18)	1.31 (0.19)	1.30 (0.17)	1.29 (0.18)
PAL	Total errors	43.09 (27.16)	38.35 (25.51)	47.82 (30.63)	40.99 (21.96)	45.18 (32.27)	48.10 (25.97)
CVLT-II Total	Total words recalled	59.13 (10.45)	60.96 (10.22)	57.31 (11.71)	59.59 (10.37)	58.68 (11.23)	54.07 (10.70)
CVLT-II Delayed	Total words recalled	11.23 (3.11)	11.73 (3.04)	10.73 (3.18)	11.38 (2.98)	11.07 (3.22)	10.76 (3.35)
OCL-OBK	Accuracy, arcsine proportion correct	1.15 (0.13)	1.16 (0.11)	1.14 (0.12)	1.15 (0.12)	1.15 (0.11)	1.14 (0.12)
DET-IDN	Speed, ms	2.63 (0.08)	2.62 (0.09)	2.63 (0.07)	2.63 (0.08)	2.62 (0.09)	2.63 (0.08)

Abbreviations: CVLT-II = California Verbal Learning Test, Second Edition; DET = Detection task; IDN = Identification task; DET-IDN = Psychomotor-Attention Composite; OCL = One Card Learning task; OBK = One Back task; OCL-OBK = Working Memory-Learning Composite; PAL = Paired Associate Learning task; SUVR = standardized uptake value ratio.

^a 18-month means for each SUVR group are provided in table 3.

(Identification task [IDN]), and psychomotor (Detection task [DET]) function from the CogState battery.^{14,21,22} Performance on the tests from the CogState battery was not used to classify individuals' clinical status.

Procedure. All healthy participants in this study underwent an extensive medical, psychiatric, and neuropsychological assessment upon enrollment into the AIBL study. The same assessments were repeated 18 months later. In this study, we report PiB neuroimaging and *APOE* ε4 genotyping data obtained at baseline and neuropsychological data obtained at baseline and 18 months to examine the rate of cognitive change in relation to cerebral Aβ load and *APOE* ε4 status.

Data analysis. Each cognitive task provided a single performance score (table 2). A Working Memory-Learning Composite (OCL-OBK) score was generated by standardizing the OCL and OBK scores and then averaging them. A Psychomotor-Attention Composite (DET-IDN) score was generated by standardizing the DET and IDN scores and then averaging them. Consistent with observations from other studies,^{5,8} the distribution of PiB SUVR data was skewed negatively and could not be normalized with data transformations. Thus, SUVR was classified dichotomously as either low (SUVR <1.50) or high (SUVR ≥1.50) in accordance with established criteria.^{8,23}

There were no statistically significant differences between SUVR and *APOE* groups for any of the demographic characteristics (table 1). A series of linear mixed-model (LMM) analyses of covariance (ANCOVA) was conducted to examine the relationship between SUVR status (SUVR <1.5 vs SUVR ≥1.5), *APOE* ε4 status (*APOE* ε4 carrier vs *APOE* ε4 noncarrier), and cognitive change between baseline and 18-month assessment. The LMM procedure was used because of its ability to model both fixed and random effects, which accounts for various sources of variability, and because it provides improved estimates of within-subject coefficients (i.e., random effects) in longitudinal studies.^{24,25} For each task, an LMM ANCOVA with SUVR status, *APOE* ε4 status, and the SUVR × *APOE* ε4 status interaction were entered as fixed factors, participant as a random factor,

baseline cognitive test score as the only covariate, and cognitive test score at the 18-month assessment as a dependent variable. For each performance measure, the magnitude of the difference in adjusted means between low and high SUVR groups and between *APOE* ε4 carrier and noncarrier groups at the 18-month assessment was expressed using the Cohen *d*.²⁶ To assist with interpretation of the LMM, group mean and SD change scores for each SUVR and *APOE* group, as well as for SUVR high and low groups averaged over *APOE* ε4 status and *APOE* ε4 carriers and noncarriers averaged over SUVR status, were calculated. Although estimates of premorbid intelligence were not different between the study groups (table 1), analyses were recomputed with age and premorbid intelligence included as covariates to examine the extent to which cognitive reserve may affect the relationship between cerebral Aβ level, genotype, and change in cognition.²⁷

RESULTS Of the total sample, there was one non-completion for DET and PAL, 2 non-completions for OCL, and 2 non-completions for OBK at the 18-month assessment. Complete baseline and 18-month data were available for all other tasks. LMM analyses indicated that, relative to older adults with SUVR <1.5 at baseline, older adults with SUVR ≥1.5 showed significantly greater decline at the 18-month assessment on all measures of verbal and visual episodic memory as well as working memory (table 3). No decline at the 18-month assessment was observed for measures of psychomotor or attentional function in either SUVR group. The magnitudes of the differences in baseline-adjusted performance between the low and high SUVR groups at the 18-month assessment are shown in the figure. Inspection of group mean raw change scores also indicate that when averaged across *APOE* ε4 status, individuals in the high SUVR group showed greater decline on tasks of ver-

Table 3 Results of linear mixed-model analyses examining change in cognitive performance over 18 months as a function of SUVR and *APOE* $\epsilon 4$ status in healthy older adults^a

	Linear mixed-model results			
	Baseline F	SUVR F	<i>APOE</i> F	SUVR \times <i>APOE</i> F
DET	27.73 ^b	0.42	0.13	0.30
IDN	62.51 ^b	0.47	0.94	0.80
OCL	9.43 ^b	5.36 ^c	5.35 ^c	0.20
OBK	4.50 ^c	6.68 ^c	0.22	0.85
PAL	35.18 ^b	5.69 ^c	0.07	2.93
CVLT-II Total	56.91 ^b	6.01 ^c	3.52	0.33
CVLT-II Delayed	99.31 ^b	9.23 ^b	0.05	2.05
OCL-OBK	10.47 ^b	3.54 ^c	3.46	0.66
DET-IDN	49.09 ^b	0.002	0.14	1.27

Abbreviations: CVLT-II = California Verbal Learning Test, Second Edition; DET = Detection task; IDN = Identification task; DET-IDN = Psychomotor-Attention Composite; OCL = One Card Learning task; OBK = One Back task; OCL-OBK = Working Memory-Learning Composite; PAL = Paired Associate Learning task; SUVR = standardized uptake value ratio.

^a Baseline = effect of baseline cognitive score on performance at the 18-month assessment; SUVR \times *APOE* = interaction between SUVR and *APOE* on performance at the 18-month assessment. Degrees of freedom for OCL-OBK are (1,138), for OCL and OBK tasks are (1,139), for DET and PAL tasks are (1,140), and for IDN, CVLT-II Total, CVLT-II Delayed, and DET-IDN are (1,141).

^b $p < 0.05$.

^c $p < 0.001$.

bal and visual episodic memory, as well as working memory, at the 18-month assessment (table 4).

When *APOE* $\epsilon 4$ status was added to the LMM analyses, no statistically significant interaction between SUVR status and *APOE* $\epsilon 4$ status was observed for any cognitive measure. However, when considered by itself, the presence of the *APOE* $\epsilon 4$ allele was associated with a greater decline in visual memory after 18 months. Magnitudes of differences in baseline-adjusted performance between *APOE* $\epsilon 4$ carriers and noncarriers at the 18-month assessment are shown in the figure (light green bars). The greater decline in performance on memory scores in the *APOE* $\epsilon 4$ carriers, averaged over SUVR groups, is also shown in table 4.

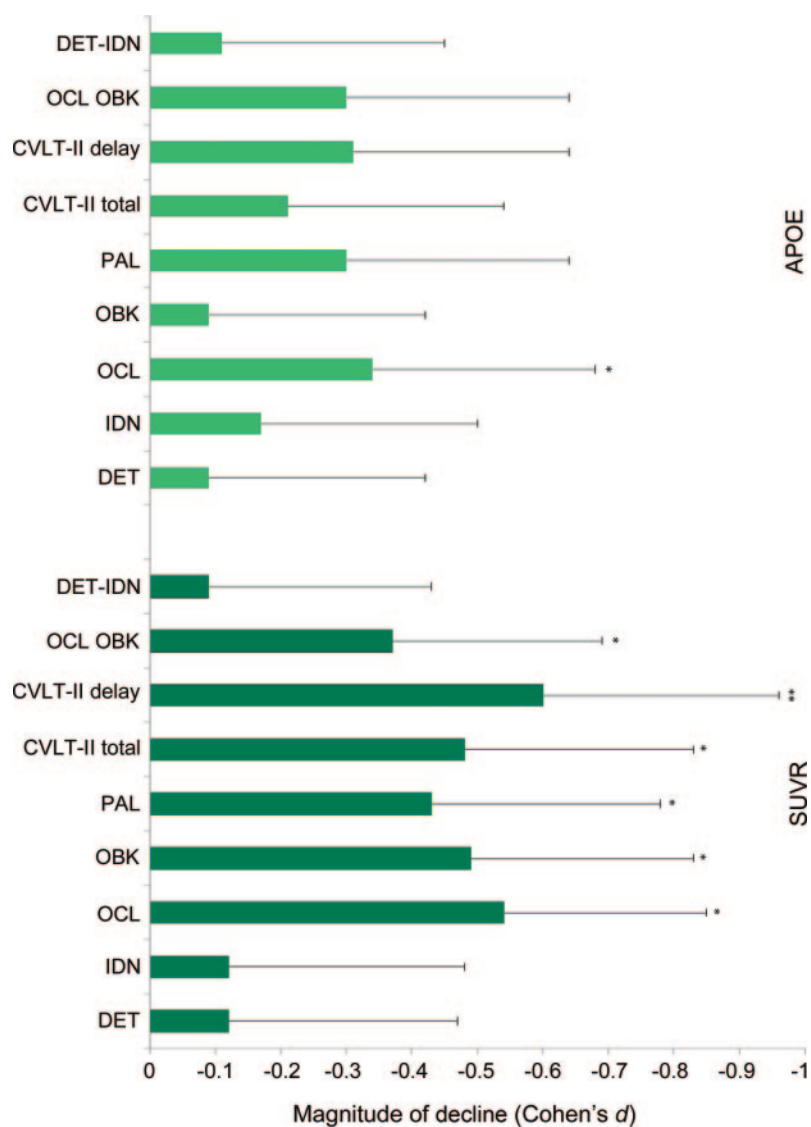
Reanalysis of the data with age and premorbid intelligence included as covariates did not change the pattern of results. No interactions between SUVR and *APOE* $\epsilon 4$ status were observed (all $p > 0.5$). However, statistically significant main effects of SUVR were observed for the OCL, OBK, PAL, CVLT-II Total and Delayed Recall, and OCL-OBK

(all $p < 0.05$). Statistically significant main effects of *APOE* $\epsilon 4$ status were observed for the OCL ($p < 0.05$).

DISCUSSION Results of this study support the hypothesis that in healthy older adults high cerebral $A\beta$ load is associated with a decline in episodic memory over 18 months. Compared with the cognitive performance of healthy older adults with normal cerebral $A\beta$ load, older adults with high cerebral $A\beta$ load showed greater decline across each aspect of episodic memory assessed and the magnitudes of these were by convention moderate²⁶ (i.e., Cohen $d = 0.40$ – 0.60). A decline of comparable magnitude was observed for visual working memory (figure). Because the 95% confidence intervals for these different effect sizes showed substantial overlap, the current data are interpreted most parsimoniously as showing that high cerebral $A\beta$ load gave rise to equivalent decline across all aspects of episodic and working memory. In contrast to memory, no effect of cerebral $A\beta$ load was observed for psychomotor function or visual attention. Hence, the decline in episodic memory observed could not have been due to changes in arousal or attention.

Consistent with previous reports,^{1,4,11,28} we observed no differences between the low and high cerebral $A\beta$ load groups or between *APOE* $\epsilon 4$ carriers and noncarriers, in performance on any of the cognitive tests at the time of neuroimaging (table 2). Healthy older adults with low and high cerebral $A\beta$ load who were *APOE* $\epsilon 4$ carriers and noncarriers were also equivalent on each demographic characteristic (table 1). Furthermore, when the healthy adults were considered as a single group, no decline from the baseline to the 18-month assessment was observed in any aspect of cognition (table 2), and review at 18 months confirmed that their clinical status had not changed. The relatively high estimated premorbid intelligence of the control group in the AIBL cohort has been noted previously,¹² and this was also evident in the current subsample. It has been suggested the high premorbid intelligence could protect against cerebral amyloid-related cognitive decline.²⁷ However, in the current sample, there was no difference between high and low SUVR groups in estimated premorbid intelligence. Furthermore, the effects of cerebral $A\beta$ load and *APOE* $\epsilon 4$ on decline in episodic and working memory did not change when age and estimated premorbid intelligence were controlled for statistically in the analyses. These aspects of the results support the conclusion that the decline in memory and working memory observed after 18 months in healthy older adults was related specifically to high cerebral $A\beta$ load.

Figure Magnitudes of the decline in baseline-adjusted performance between low and high standardized uptake value ratio (SUVR) groups, and *APOE* $\epsilon 4$ carriers and noncarriers, at the 18-month assessment



Magnitude of decline between healthy older adults with SUVR <1.5 and SUVR ≥ 1.5 (dark green bars; 0 line represents SUVR <1.5 group) and between healthy older adults who are *APOE* $\epsilon 4$ carriers and noncarriers (light green bars; 0 line represents *APOE* $\epsilon 4$ noncarriers) for each performance measure, from baseline to 18-month assessment (* $p < 0.05$; ** $p < 0.001$). Error bars represent 95% confidence intervals. CVLT-II = California Verbal Learning Test, Second Edition; DET = Detection task; IDN = Identification task; DET-IDN = Psychomotor-Attention Composite; OCL = One Card Learning task; OBK = One Back task; OCL-OBK = Working Memory-Learning Composite; PAL = Paired Associate Learning task.

The decline in episodic and working memory associated with high cerebral $A\beta$ load was not moderated at all by the *APOE* $\epsilon 4$ status of the healthy older adults. However, when considered by itself, the *APOE* $\epsilon 4$ allele was associated with statistically significant decline over 18 months in visual memory, although the magnitude of this decline was slightly less than that related to differences in cerebral $A\beta$ load. Inspection of the magnitudes of differences between *APOE* $\epsilon 4$ carrier and noncarrier groups for the

other cognitive functions indicated moderate²⁶ (i.e., Cohen $d = 0.24$ – 0.38) but nonsignificant decline for visual episodic memory, for verbal learning, and for the OCL-OBK (figure). This consistency suggests that these effect sizes did reflect true differences in the level of cognitive decline between *APOE* $\epsilon 4$ carriers and noncarriers, although the magnitudes of these differences were not sufficient to be rendered statistically significant in the current study. The presence of an *APOE* $\epsilon 4$ allele-related decline in memory in healthy older adults is consistent with previous observations,^{9,10} although the more subtle effect of *APOE* $\epsilon 4$ positivity observed here could reflect the fact that the current sample was younger than some samples studied recently¹⁰ and studied over a shorter interval than that in the benchmark study of this issue.⁹ Thus, although these data do suggest that both cerebral $A\beta$ load and *APOE* $\epsilon 4$ status predict decline in episodic memory over 18 months, the magnitude of the effect of cerebral $A\beta$ load was greater than that of *APOE* $\epsilon 4$ status. More important, though, LMM analyses and inspection of the group mean change scores (table 4) suggest strongly that the presence of the *APOE* $\epsilon 4$ allele did not moderate cerebral $A\beta$ -related decline in memory in healthy older adults.

Two small prospective studies have investigated the extent to which cerebral $A\beta$ load, measured using PiB PET neuroimaging, is related to change in cognitive function in healthy older adults.^{8,11} As in the current study, the entire group of healthy older adults from the Melbourne Healthy Aging Study cohort showed no change in memory or nonmemory composite scores 18 or 36 months after a baseline PiB PET scan. However, when adults in this group were classified as having high or low cerebral $A\beta$ load, using the same criterion as that used in the current study, healthy older adults with high cerebral $A\beta$ load showed statistically significant decline of a moderate magnitude on both memory and nonmemory composite scores 36 months after PET scanning.⁸ However, by the 36-month assessment, 25% of healthy older adults with high cerebral $A\beta$ load met the clinical criteria for mild cognitive impairment (MCI). Thus, the general decline in cognition observed at 36 months postscan reflected this change in clinical status. Conversely, in a subset of healthy control subjects recruited from the Alzheimer's Disease Neuroimaging Initiative (ADNI), individuals with low or high cerebral $A\beta$ load did not differ in the rate at which their global cognitive ability and verbal episodic memory deteriorated over 15 months. Given the magnitudes of the effects observed here, the sample studied in the ADNI cohort was probably too small to allow for the detection of any subtle decline in memory.¹¹ Taken together, the

Table 4 Group raw change scores of cognitive performance over 18 months of healthy older adults in each SUVR and APOE group

	SUVR <1.5 change, mean (SD)	SUVR ≥1.5 change, mean (SD)	ε4 averaged across SUVR, mean (SD)
DET speed			
ε4 noncarrier	0.02 (0.01)	-0.01 (0.01)	0.01 (0.01)
ε4 carrier	-0.02 (0.01)	0.02 (0.02)	0.00 (0.02)
SUVR averaged across ε4	0.01 (0.03)	0.01 (0.01)	
IDN speed			
ε4 noncarrier	0.00 (0.01)	-0.03 (0.03)	-0.02 (0.03)
ε4 carrier	-0.01 (0.01)	0.02 (0.01)	0.00 (0.01)
SUVR averaged across ε4	0.00 (0.01)	0.02 (0.03)	
OCL accuracy			
ε4 noncarrier	0.04 (0.03)	0.02 (0.02)	-0.01 (0.03)
ε4 carrier	0.02 (0.01)	-0.01 (0.01)	-0.03 (0.01)
SUVR averaged across ε4	0.03 (0.03)	0.01 (0.01)	
OBK accuracy			
ε4 noncarrier	0.01 (0.01)	-0.03 (0.02)	-0.01 (0.02)
ε4 carrier	-0.02 (0.02)	-0.05 (0.02)	-0.03 (0.01)
SUVR averaged across ε4	-0.01 (0.02)	-0.04 (0.01)	
PAL no. of errors			
ε4 noncarrier	6.08 (4.30)	5.94 (3.64)	5.62 (4.82)
ε4 carrier	5.81 (4.11)	8.47 (5.99)	7.14 (5.99)
SUVR averaged across ε4	5.95 (4.21)	7.21 (3.88)	
CVLT-II Total			
ε4 noncarrier	-4.26 (3.01)	-6.23 (4.41)	-5.25 (4.05)
ε4 carrier	-5.23 (3.70)	-5.22 (3.69)	-5.23 (3.69)
SUVR averaged across ε4	-4.75 (3.36)	-5.73 (4.05)	
CVLT-II Delayed			
ε4 noncarrier	0.01 (0.01)	-1.75 (1.23)	-0.87 (0.80)
ε4 carrier	-1.41 (0.99)	0.51 (0.36)	-0.45 (0.36)
SUVR averaged across ε4	-0.70 (0.50)	-0.62 (1.11)	
OCL-OBK accuracy			
ε4 noncarrier	0.00 (0.00)	-0.03 (0.02)	-0.02 (0.02)
ε4 carrier	-0.02 (0.01)	-0.05 (0.03)	-0.03 (0.02)
SUVR averaged across ε4	-0.01 (0.01)	-0.04 (0.01)	
DET-IDN speed			
ε4 noncarrier	0.02 (0.01)	0.00 (0.00)	0.01 (0.01)
ε4 carrier	-0.01 (0.01)	0.02 (0.01)	0.01 (0.02)
SUVR averaged across ε4	0.01 (0.02)	0.01 (0.01)	

Abbreviations: CVLT-II = California Verbal Learning Test, Second Edition; DET = Detection task; IDN = Identification task; DET-IDN = Psychomotor-Attention Composite; OCL = One Card Learning task; OBK = One Back task; OCL-OBK = Working Memory-Learning Composite; PAL = Paired Associate Learning task; SUVR = standardized uptake value ratio.

results from these 2 previous prospective studies and the current study suggest that in healthy older adults, high cerebral Aβ does increase the risk of progression to MCI and that the subtle decline in memory that characterizes such progression can be detected over relatively short time intervals (i.e., 18 months), even in the absence of any change in clinical status. Our

results are consistent with prospective studies of healthy older adults with increased cerebral amyloid determined from analysis of CSF.^{29,30} These studies also report that pathologic levels of CSF Aβ42 are associated with increased rates of cognitive decline, although like the neuroimaging studies, these changes were observed over much longer intervals than those observed here (e.g., 4–10 years).^{29,30} In the current cohort of individuals with high cerebral Aβ, we expect that the decline in memory will continue until it reaches levels that would be considered as reflecting cognitive impairment (compared with normative data) and the clinical status of individuals changes from cognitively normal to indicative of MCI.

The finding that cerebral Aβ-related decline in memory can occur without a change in clinical status also raises an important issue about the methods for classifying levels of cognitive function in healthy older adults. Our group has suggested that the earliest stages of AD may be most accurately detected through objective evidence for decline in cognitive function, in particular memory function, rather than from the detection of impairment in cognition.^{31–33} Recent recommendations for the definition of the preclinical stage of AD have also recommended that the identification of objectively defined cognitive decline may assist in the detection of preclinical AD.^{34,35} Thus, the combination of objectively defined cognitive decline with putative AD biomarkers should considerably strengthen the ability to detect preclinical AD.³⁴

Although these are the first studies to investigate the extent to which amyloid imaging biomarkers predict future cognitive decline, previous research has sought to determine the extent to which decline in cognitive function predicts an increase in cerebral Aβ load. For example, in a series of studies of healthy adults followed prospectively with brief batteries of cognitive tests, we identified that statistically reliable decline in aspects of verbal and visual episodic memory tests over 6 years¹³ 2 years,³⁶ and even 1 year³⁷ was associated with increased risk of high cerebral Aβ load. Other studies have observed similar declines in cognition in individuals with high cerebral Aβ load.^{28,38} When considered with the results of the current study, these data suggest that the combination of decline in memory with parameters from amyloid imaging may be useful for the identification of the AD process in individuals who do not meet any clinical criteria for cognitive impairment. In healthy older adults with high cerebral Aβ load, an objectively defined decline in memory may also be a worthy target for anti-amyloid therapies.³⁹

An important methodologic issue needs to be considered when interpreting the current results be-

cause an extensive investigation of cognitive function was not conducted. The tasks used were chosen based on brevity, test-retest reliability, demonstrated sensitivity to change, and ability to be applied repeatedly without the generation of practice effects.^{21,40} Exploration using more detailed neuropsychological tests will be useful in further elucidating the nature of cerebral A β -related decline in cognition.

AUTHOR CONTRIBUTIONS

D. Ames, R.N. Martins, C.L. Masters, K.A. Ellis, V.L. Villemagne, C. Szoek, C. Rowe, G. Savage, and P. Maruff are senior investigators of the AIBL study. C. Rowe and V.L. Villemagne conducted and oversaw neuroimaging for all participants. Y.-Y. Lim and K. Harrington conducted neuropsychological assessments. Y.-Y. Lim, R.H. Pietrzak, and P. Maruff conducted all statistical analyses and interpretation of the data. Y.-Y. Lim and P. Maruff prepared the manuscript. K.A. Ellis, R.H. Pietrzak, D. Ames, D. Darby, K. Harrington, R.N. Martins, C. Rowe, G. Savage, C. Szoek, and V.L. Villemagne drafted and revised the manuscript.

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DISCLOSURE

Y.-Y. Lim and K.A. Ellis report no disclosures. R.H. Pietrzak is a scientific consultant to CogState Ltd., the company that provided the CogState battery of tests used in this study. D. Ames has served on scientific advisory boards for Novartis, Eli Lilly, Janssen, and Pfizer Inc.; has received funding for travel from Janssen and Pfizer Inc.; has received speaker honoraria from Pfizer Inc. and Lundbeck Inc.; and has received research support from Eli Lilly and Company, GlaxoSmithKline, Forest Laboratories Inc., Novartis, and CSIRO. D. Darby is a scientific consultant to CogState Ltd., the company that provided the CogState battery of tests used in this study and is a shareholder of stock in CogState Ltd. K. Harrington reports no disclosures. R. N. Martins serves as consultant to the small biotech company Alzhyme; currently no financial benefits or fees accepted; research support, government entities: CSIRO flagship funding for 3 years at \$1 million per annum; stock/stock options/board of directors compensation: holds stock for the small biotech company Alzhyme, which is not listed. C.L. Masters reports no disclosures. C. Rowe serves on scientific advisory boards for Bayer Schering Pharma, Elan Corporation, and AstraZeneca; has received speaker honoraria from Bayer Schering Pharma; and receives research support from Bayer Schering Pharma, Avid

Radiopharmaceuticals, Inc., CSIRO, and the Alzheimer's Association. G. Savage reports no disclosures. C. Szoek has previously been a clinical consultant and received speaker honoraria from Pfizer, sanofi-aventis, Mayne Pharma, and Lundbeck; has been employed as Commercial Entity Clinical Consultant, Preventive Health, CSIRO Associate Professor, Women's Healthy Ageing, National Ageing Research Institute, University of Melbourne; research support, government entities: NHMRC, chief investigator, 2009, 2010; academic entities: National Ageing Research Institute, University of Melbourne, Melbourne Health; research support, foundations, and societies: ESA, Epilepsy Fellowship, 2007 Bio21, Pharmacogenetics Overseas Training Scholarship, 2008 RACP, PostDoc Scholarship, 2007 Alzheimer's Association of Australia, Research Fellow, 2008–2010, Scobie and Claire McKinnon Foundation, chief investigator, 2009, Collier Foundations, chief investigator, 2009, and Brain Foundation, chief investigator, 2010. V.L. Villemagne serves as a consultant for Bayer Schering Pharma and receives research support from NHMRC and NEDO, Japan. P. Maruff is a full-time employee of CogState Ltd. **Go to Neurology.org for full disclosures.**

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REFERENCES

1. Aizenstein HJ, Nebes RD, Saxton JA, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol* 2008;65:1509–1517.
2. Pike KE, Savage G, Villemagne VL, et al. β -Amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain* 2007;130:2837–2844.
3. Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging* 2010;31:1275–1283.
4. Mintun MA, LaRossa GN, Sheline YI, et al. ¹¹C-PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology* 2006;67:446–452.
5. Kantarci K, Lowe V, Przybelski SA, et al. APOE modifies the association between AB load and cognition in cognitively normal older adults. *Neurology* 2012;78:232–240.
6. Lim YY, Ellis KA, Ames D, et al. AB amyloid, cognition and APOE genotype in the preclinical stages of Alzheimer's disease. *Alzheimers Dement* (in press 2012).
7. Pike KE, Ellis KA, Villemagne VL, et al. Cognition and beta-amyloid in preclinical Alzheimer's disease: data from the AIBL study. *Neuropsychologia* 2011;49:2384–2390.
8. Villemagne VL, Pike KE, Ch  telat G, et al. Longitudinal assessment of A β and cognition in aging and Alzheimer disease. *Ann Neurol* 2011;69:181–192.
9. Caselli RJ, Dueck AC, Osborne D, et al. Longitudinal modeling of age-related memory decline and the APOE E4 effect. *N Engl J Med* 2009;361:255–263.
10. Schiepers OJG, Harris SE, Gow AJ, et al. APOE E4 status predicts age-related cognitive decline in the ninth decade: longitudinal follow-up of the Lothian Birth Cohort 1921. *Mol Psychiatry* 2012;17:315–324.
11. Ewers M, Insel P, Jagust WJ, et al. CSF biomarker and PIB-PET-derived β -amyloid signature predicts metabolic, gray matter, and cognitive changes in nondemented subjects. *Cereb Cortex* 2011;22:1993–2004.
12. Ellis KA, Bush AI, Darby D, et al. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. *Int Psychogeriatr* 2009;21:672–687.
13. Villemagne VL, Pike KE, Darby D, et al. A β deposits in older non-demented individuals with cognitive decline are indicative of preclinical Alzheimer's disease. *Neuropsychologia* 2008;46:1688–1697.

14. Lim YY, Ellis KA, Harrington K, et al. Use of the CogState Brief Battery in the assessment of Alzheimer's disease related cognitive impairment in the Australian Imaging, Biomarker and Lifestyle (AIBL) study. *J Clin Exp Neuropsychol* 2012;34:345–358.
15. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
16. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1983;43:2412–2414.
17. Wechsler D. Wechsler Test of Adult Reading: Examiner's Manual. San Antonio, TX: Psychological Corporation; 2001.
18. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. *BMJ* 1986;292:344.
19. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test, Second Edition (CVLT-II). San Antonio, TX: Psychological Corporation; 2000.
20. Harel BT, Darby D, Pietrzak RH, Ellis KA, Snyder PJ, Maruff P. Examining the nature of impairment in visual paired associate learning in amnesic mild cognitive impairment. *Neuropsychology* 2011;25:752–762.
21. Fredrickson J, Maruff P, Woodward M, et al. Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. *Neuroepidemiology* 2010;34:65–75.
22. Hammers D, Spurgeon E, Ryan K, et al. Reliability of repeated cognitive assessment of dementia using a brief computerized battery. *Am J Alzheimers Dis Other Dement* 2011;26:326–333.
23. Jack CR, Lowe VJ, Senjem ML, et al. ¹¹C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnesic mild cognitive impairment. *Brain* 2008;131:665–680.
24. Gueorguieva R, Krystal JH. Move over ANOVA: Progress in analyzing repeated-measures data and its reflection in papers published in the *Archives of General Psychiatry*. *Arch Gen Psychiatry* 2004;61:310–317.
25. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data. New York: Springer-Verlag; 2000.
26. Cohen J. A power primer. *Psychol Bull* 1992;112:155–159.
27. Rentz DM, Locascio JJ, Becker JA, et al. Cognition, reserve, and amyloid deposition in normal aging. *Ann Neurol* 2010;67:353–364.
28. Storandt M, Mintun MA, Head D, Morris JC. Cognitive decline and brain volume loss as signatures of cerebral amyloid- β peptide deposition identified with Pittsburgh compound B: cognitive decline associated with A β deposition. *Arch Neurol* 2009;66:1476–1481.
29. Stomrud E, Hansson O, Zetterberg H, Blennow K, Mintun L, Londos E. Correlation of longitudinal cerebrospinal fluid biomarkers with cognitive decline in healthy older adults. *Arch Neurol* 2010;67:217–223.
30. Gustafson DR, Skoog I, Rosengren L, Zetterberg H, Blennow K. Cerebral spinal fluid β -amyloid 1–42 concentration may predict cognitive decline in older women. *J Neurol Neurosurg Psychiatry* 2007;78:461–464.
31. Collie A, Maruff P, Shafiq-Antonacci R, et al. Memory decline in healthy older people: Implications for identifying mild cognitive impairment. *Neurology* 2001;56:1533–1538.
32. Collie A, Maruff P. The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. *Neurosci Biobehav Rev* 2000;24:365–374.
33. Maruff P, Collie A, Darby D, Weaver-Cargin J, Masters C, Currie J. Subtle memory decline over 12 months in mild cognitive impairment. *Dement Geriatr Cogn Disord* 2004;18:342–348.
34. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimers Dement* 2011;7:280–292.
35. Morris JC. Revised criteria for mild cognitive impairment may compromise the diagnosis of Alzheimer disease dementia. *Arch Neurol* 2012;700:700–708.
36. Darby D, Brodtmann A, Pietrzak RH, et al. Episodic memory decline predicts cortical amyloid status in community-dwelling older adults. *J Alzheimers Dis* 2011;27:627–637.
37. Darby D, Pietrzak RH, Fredrickson J, et al. Intra-individual cognitive decline using a brief computerized cognitive screening test. *Alzheimers Dement* 2011;27:627–637.
38. Ch  telat G, Villemagne VL, Pike KE, et al. Independent contribution of temporal β -amyloid deposition to memory decline in the pre-dementia phase of Alzheimer's disease. *Brain* 2010;134:798–807.
39. Darby D, Brodtmann A, Woodward M, Budge M, Maruff P. Using cognitive decline in novel trial designs for primary prevention and early disease-modifying therapy trials of Alzheimer's disease. *Int Psychogeriatr* 2011;1–10.
40. Darby D, Maruff P, Collie A, McStephen M. Mild cognitive impairment can be detected by multiple assessments in a single day. *Neurology* 2002;59:1042–1046.

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Stronger effect of amyloid load than *APOE* genotype on cognitive decline in healthy older adults

Yen Ying Lim, Kathryn A. Ellis, Robert H. Pietrzak, et al.

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