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.

Neurology 2012;79;1645
DOI 10.1212/WNL.0b013e31826e9ae6

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 Szoeke, PhD
Victor L. Villemagne, MD
Paul Maruff, PhD
For the AIBL Research Group

ABSTRACT

Objective: Although the *APOE ϵ4* allele is associated with more rapid decline in memory in healthy older adults, the significance of elevated cerebral β-amyloid (Aβ) 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 Aβ, *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 Aβ, individuals with high cerebral Aβ showed significantly greater decline in working memory and verbal and visual episodic memory at 18 months. Compared with noncarriers, *APOE ϵ4* carriers showed a greater decline in visual memory at the 18-month assessment. No interaction between *APOE ϵ4* and cerebral Aβ load was observed for any measure of cognitive function.

Conclusions: In this prospective study of healthy older adults, high cerebral Aβ load was associated with greater decline in episodic and working memory over 18 months. The *APOE ϵ4* genotype was also associated with a decline in visual memory, although the effect was less than that observed for cerebral Aβ load. ***Neurology*® 2012;79:1645–1652**

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

GLOSSARY

Aβ = 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 (Aβ) loads in a substantial proportion of healthy older adults.[1–4] However, associations between cerebral Aβ 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 Aβ burden and episodic memory when analyses were restricted to carriers of the *APOE ϵ4* allele. No such relationships were observed in noncarriers,[5,6] suggesting that in healthy older adults, elevated cerebral Aβ load may be a more important prognostic factor in individuals genetically at risk for Alzheimer disease (AD). However, the implications of a high cerebral Aβ load for cognitive function should be determined in prospective studies. Further,

Supplemental data at www.neurology.org

Supplemental Data

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.

Study funding: Funding information is provided at the end of the article.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.

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 ≤ 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 medical, 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 Examination[15] 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 noncompletion for DET and PAL, 2 noncompletions for OCL, and 2 noncompletions 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 ϵ4* status in healthy older adults[a]

	Linear mixed-model results			
	Baseline F	SUVR F	*APOE* F	SUVR × *APOE* 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 × *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).

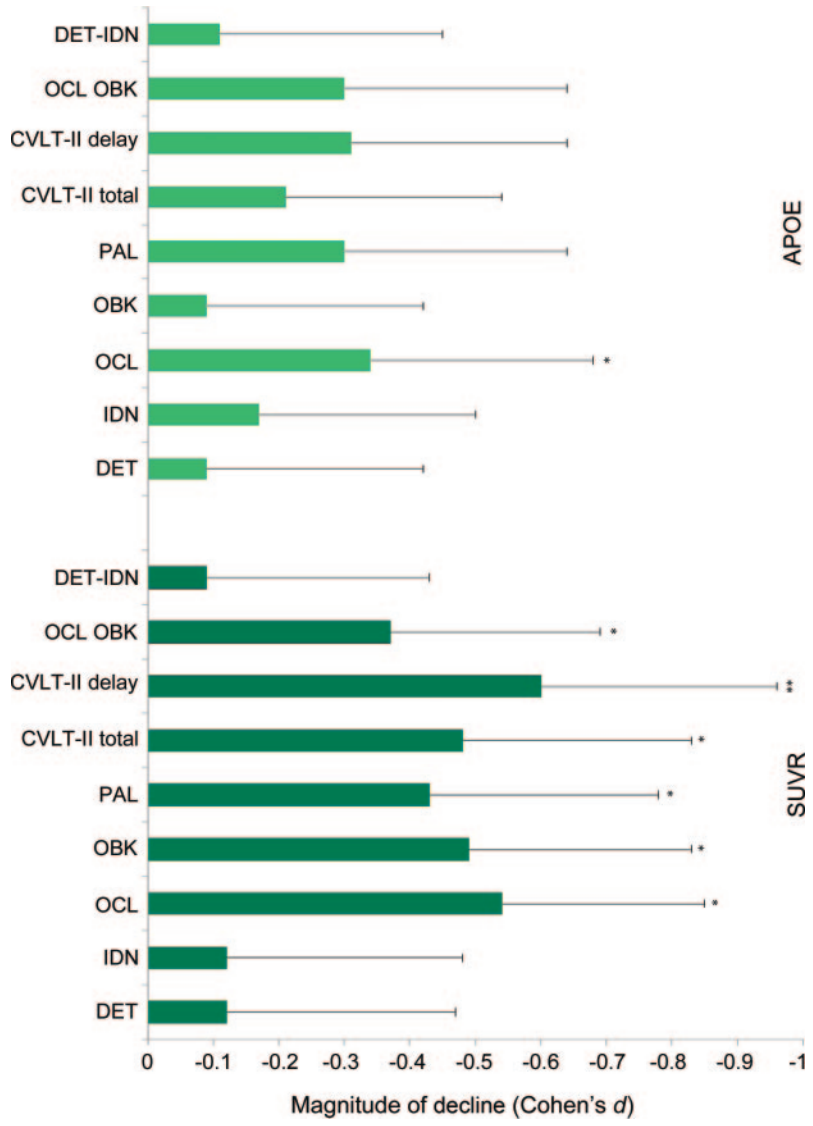
When *APOE ϵ4* status was added to the LMM analyses, no statistically significant interaction between SUVR status and *APOE ϵ4* status was observed for any cognitive measure. However, when considered by itself, the presence of the *APOE ϵ4* allele was associated with a greater decline in visual memory after 18 months. Magnitudes of differences in baseline-adjusted performance between *APOE ϵ4* 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 ϵ4* 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 ϵ4* 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 ϵ4* status were observed for the OCL ($p < 0.05$).

DISCUSSION Results of this study support the hypothesis that in healthy older adults high cerebral Aβ load is associated with a decline in episodic memory over 18 months. Compared with the cognitive performance of healthy older adults with normal cerebral Aβ load, older adults with high cerebral Aβ load showed greater decline across each aspect of episodic memory assessed and the magnitudes of these were by convention moderate[26] (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 Aβ load gave rise to equivalent decline across all aspects of episodic and working memory. In contrast to memory, no effect of cerebral Aβ 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 Aβ load groups or between *APOE ϵ4* 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 Aβ load who were *APOE ϵ4* 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 Aβ load and *APOE ϵ4* 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 Aβ load.

Figure **Magnitudes of the decline in baseline-adjusted performance between low and high standardized uptake value ratio (SUVR) groups, and *APOE* ε4 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* ε4 carriers and noncarriers (light green bars; 0 line represents *APOE* ε4 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 Aβ load was not moderated at all by the *APOE ϵ4* status of the healthy older adults. However, when considered by itself, the *APOE ϵ4* 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 Aβ load. Inspection of the magnitudes of differences between *APOE ϵ4* carrier and noncarrier groups for the other cognitive functions indicated moderate[26] (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 ϵ4* 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 ϵ4* allele-related decline in memory in healthy older adults is consistent with previous observations,[9,10] although the more subtle effect of *APOE ϵ4* positivity observed here could reflect the fact that the current sample was younger than some samples studied recently[10] 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 Aβ load and *APOE ϵ4* status predict decline in episodic memory over 18 months, the magnitude of the effect of cerebral Aβ load was greater than that of *APOE ϵ4* status. More important, though, LMM analyses and inspection of the group mean change scores (table 4) suggest strongly that the presence of the *APOE ϵ4* allele did not moderate cerebral Aβ-related decline in memory in healthy older adults.

Two small prospective studies have investigated the extent to which cerebral Aβ 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 Aβ load, using the same criterion as that used in the current study, healthy older adults with high cerebral Aβ 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 Aβ 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 Aβ 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 years[13] 2 years,[36] and even 1 year[37] 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 Aβ-related decline in cognition.

AUTHOR CONTRIBUTIONS

D. Ames, R.N. Martins, C.L. Masters, K.A. Ellis, V.L. Villemagne, C. Szoeke, 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. Szoeke, and V.L. Villemagne drafted and revised the manuscript.

ACKNOWLEDGMENT

The AIBL investigators thank Richard Head of Commonwealth Scientific and Industrial Research Organization for initiating and facilitating the AIBL collaboration. Alzheimer's Australia (Victoria and Western Australia) assisted with promotion of the study and the screening of telephone calls from volunteers. The AIBL team thanks the clinicians who referred patients with Alzheimer disease to the study: Associate Professor Brian Chambers, Professor Edmond Chiu, Dr. Roger Clarnette, Dr. Mary Davison, Dr. John Drago, Dr. Peter Drysdale, Dr. Jacqueline Gilbert, Dr. Kwang Lim, Professor Nicola Lautenschlager, Dr. Dina LoGiudice, Dr. Peter McCardle, Dr. Steve McFarlane, Dr. Alastair Mander, Dr. John Merory, Professor Daniel O'Connor, Dr. Ron Scholes, Dr. Mathew Samuel, Dr. Darshan Trivedi, and Associate Professor Michael Woodward. The authors thank all those who participated in the study for their commitment and dedication to helping advance research into the early detection and causation of AD.

STUDY FUNDING

Funding for the study was provided in part by the study partners (Australian Commonwealth Scientific Industrial and Research Organization, Edith Cowan University, Mental Health Research Institute, Alzheimer's Australia, National Ageing Research Institute, Austin Health, CogState Ltd., Hollywood Private Hospital, and Sir Charles Gardner Hospital). The study also received support from the National Health and Medical Research Council and the Dementia Collaborative Research Centres program, as well as ongoing funding from the Science and Industry Endowment Fund.

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. Szoeke 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.**

Received February 22, 2012. Accepted in final form May 29, 2012.

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. ^{11}C-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 Demen (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, Chételat G, et al. Longitudinal assessment of Aβ 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. Aβ 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 amnestic 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 Demen 2011;26:326–333.
23. Jack CR, Lowe VJ, Senjem ML, et al. ^{11}C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic 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 Aβ deposition. Arch Neurol 2009;66:1476–1481.
29. Stomrud E, Hansson O, Zetterberg H, Blennow K, Minthon 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 Demen 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 Demen 2011;27:627−637.
38. Chételat 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.