Decline in Cognitive Function over 18 Months in Healthy Older Adults with High Amyloid- β

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Abstract. We aimed to characterize the nature and magnitude of cognitive decline in a group of healthy older adults with high and low levels of amyloid- β (A β) and who were *APOE* ϵ 4 carriers and non-carriers. Healthy older adults underwent positron emission tomography neuroimaging for A β , *APOE* genotyping, and cognitive and clinical assessment as part of their baseline assessment in the Australian Imaging, Biomarker, and Lifestyle study. Cognitive function and clinical ratings were reassessed 18 months later. Linear mixed model analyses adjusted for baseline cognitive function indicated that relative to healthy older adults with low A β , healthy older adults with high A β showed greater decline in episodic memory and language at 18 months. No decline on any measure of executive function, attention, or clinical rating was observed for healthy older adults with high A β levels. Compared to non-carriers, *APOE* ϵ 4 carriers showed a greater decline only on the task of visual memory at the 18 month assessment. Importantly though, no interaction between *APOE* ϵ 4 and A β was observed on any measure of cognitive function. The results of this study suggest that high A β load was associated with greater decline in episodic memory and language, that the magnitude of this decline was moderate and equivalent across both domains, and that *APOE* ϵ 4 carriage did not moderate the relationship between A β and decline in memory and language functions.

Keywords: Alzheimer's disease, amyloid- β , apolipoprotein E ϵ 4, cognitive change, cognitive neuropsychology, healthy older adults

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INTRODUCTION

Levels of amyloid- β (A β) detected using positron emission tomography (PET) neuroimaging agents show that the majority of patients with clinically diagnosed Alzheimer's disease (AD) have abnormally high levels of A β by some validated criterion (e.g., standardized uptake value ratio [SUVR] of greater than 1.5 on PET imaging using Pittsburgh Compound B [PiB]). However, while A β neuroimaging biomarkers are abnormal in approximately 95% of people with AD, the significance of abnormal A β as a biomarker of AD has been questioned as approximately 20–30% of healthy older adults also show abnormally high A β levels [1, 2]. Most cross-sectional studies in healthy older adults show only small differences, if any, in cognitive function or clinical ratings between groups with high and low A β [1, 3–5]. Furthermore, in healthy older adults, A β levels are associated only weakly (e.g., r ranging from 0.18–0.30) with cognitive function, mainly in episodic memory, although these associations become stronger when samples are restricted to those who carry the apolipoprotein E (*APOE*) ϵ 4 allele [6–9]. Thus, the importance of high A β levels in healthy older adults is still unclear.

The weak and inconsistent associations between A β and cognitive function in healthy older adults may be due to the cross-sectional study designs. As AD is a progressive neurodegenerative disease, prospective longitudinal studies should facilitate understanding of the importance of high A β levels in cognitively normal older adults. Previous prospective studies of healthy older adults suggest that high A β levels are associated with some decline in cognitive and clinical status, at least over 18 months [10–13], with one reporting that episodic memory decline in healthy older adults with high A β levels can be detected over 6 months, albeit on the basis of very frequent re-assessments [14]. While the majority of these studies were conducted using small samples (e.g., $n = 19$ –32) [12, 15], a recent study of a subset of the Australian Imaging, Biomarkers and Lifestyle (AIBL) healthy control cohort ($n = 141$) reported substantial decline in measures of episodic memory from the CogState brief battery in healthy older adults who had undergone PiB-PET neuroimaging at baseline and cognitive and clinical assessment at baseline and 18 months later [10, 16]. This decline occurred despite there being no change in the clinical status of the group. This study also found that while the presence of the *APOE* ϵ 4 allele was associated with decline in visual memory over 18 months, it did not moderate the rate of A β -related memory decline

[10]. This A β -related cognitive decline in healthy older adults was replicated, in part, by a prospective study following healthy older adults for 18 months after neuroimaging with florbetapir F-18. In this study, a smaller group of healthy older adults with high A β showed a decline in performance on the ADAS-Cog [4] although not on any of the other neuropsychological measures.

The failure to find any decline on neuropsychological tests of memory [10] was unexpected, especially as the ADAS-Cog has been reported to be insensitive to true cognitive change in groups other than those with moderate AD [17, 18]. One possible explanation arises from a *post-hoc* analysis of the rate of change over time detected in this study which indicates that, despite being non-significant, the magnitude of decline in performance detected on the test of verbal memory (auditory verbal learning task) was equivalent to that detected on the ADAS-Cog (i.e., both $ds \sim 0.90$) [4]. Therefore, the absence of statistically significant differences in memory decline between high and low A β groups could have reflected that the study was underpowered to address this issue in healthy older adults. Further investigations with a larger sample size and neuropsychological battery are required. In addition to the CogState brief battery, the AIBL study uses a large neuropsychological test battery to define cognitive performance [19]. Examination of the extent to which performance on different aspects of cognitive function may provide a chance for replication of our previous report with an independent set of tests, also provides an opportunity to determine whether A β -related changes in cognition extend beyond episodic memory. While the AIBL study does not include the ADAS-Cog, clinical ratings of disease severity are characterized using the Clinical Dementia Rating (CDR) scale. Therefore, the extent to which clinical ratings change over time in healthy older adults with high A β can also be determined using the sum of boxes score from the CDR (i.e., CDR-SB) [20].

The aim of the current study was therefore to determine the effect of A β on cognitive change over 18 months in a large group of healthy older adults from the AIBL study, who have been assessed with an extensive neuropsychological battery. The overarching hypothesis was that high A β at baseline would be associated with greater decline in cognition, particularly in the domain of episodic memory. We explored the extent to which increased A β at baseline was associated with decline in cognitive domains other than memory and in clinical disease rating scales. We also explored the extent to which decline in any cognitive domain was moderated by the presence of the *APOE* ϵ 4 allele.

METHODS

Participants

All participants in the current study were recruited from the healthy control group enrolled in the AIBL Flagship Study of Ageing. The process of recruitment and diagnostic classification of healthy older adults enrolled in the AIBL cohort has been described in detail previously [19, 21]. Healthy adults (HA) who volunteered were excluded from the AIBL study if they had any of the following: schizophrenia; depression (Geriatric Depression Score (GDS) of 6 or greater); Parkinson's disease; cancer (other than basal cell skin carcinoma) within the last two years; symptomatic stroke; uncontrolled diabetes; or current regular alcohol use exceeding two standard drinks per day for women or four per day for men. A clinical review panel chaired by DA reviewed all available medical, psychiatric, and neuropsychological information to confirm the cognitive health of individuals enrolled in the healthy controls group. In this study, only HA who had undergone PiB-PET neuroimaging and who had completed the AIBL neuropsychological battery at baseline and 18-month assessment ($n = 178$) were included. Demographic and clinical characteristics of the HA are shown in Table 1. The clinical status of all participants did not change at 18 months. The study was approved by and complied with the regulations of three institutional research and ethics committees [19],

and all participants provided written informed consent prior to participating in the study.

Measures

PiB-PET neuroimaging and APOE $\epsilon 4$ genotyping

PiB-PET imaging methodology has been outlined in detail previously [13, 21]. Each subject received ~ 370 MBq 11-C PiB intravenously over 1 minute. A 30-minute acquisition of PET standardized uptake value (SUV) data in 3-dimensional mode, consisting of 6 frames each of 5 minutes, acquired 40–70 minutes post-PiB injection were summed and normalized to the cerebellar cortex SUV, resulting in a region-to-cerebellar ratio termed SUV ratio (SUVR). Neocortical A β burden was expressed as the average SUVR of the area-weighted mean of frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions [13, 21]. 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 and clinical assessments

All participants were assessed with the clinical rating scales and neuropsychological battery from the AIBL study. These have all been described in detail elsewhere and were administered according to standard protocols by trained research assistants [9, 19, 22]. The clinical status of participants was determined by data

Table 1

Demographic means (SD) for MMSE, CDR-SB, premorbid IQ, and HADS scores, and median years of education, for overall and each SUVR group at baseline assessment

	Overall ($n = 178$)	SUVR < 1.5 ($n = 123$)	SUVR ≥ 1.5 ($n = 55$)	$\epsilon 4$ non-carrier ($n = 102$)	$\epsilon 4$ carrier ($n = 76$)
n (%) female	89 (50%)	61 (50%)	28 (51%)	50 (49.02%)	39 (51.32%)
n (%) APOE $\epsilon 4$	76 (42.70%)	40 (32.52%)	36 (65.45%)	—	—
Age (years)	71.55 (7.45)	69.92 (6.99)	75.20 (7.19)	72.66 (7.52)	70.07 (7.13)
Education level (category)	13–15 years	13–15 years	13–15 years	13–15 years	13–15 years
SUVR Neocortex	1.41 (0.40)	1.16 (0.09)	1.95 (0.26)	1.30 (0.31)	1.55 (0.45)
MMSE	28.74 (1.23)	28.81 (1.23)	28.58 (1.23)	28.77 (1.26)	28.70 (1.20)
CDR-SB	0.00 (0.19)	0.00 (0.21)	0.00 (0.12)	0.28 (0.21)	0.04 (0.16)
Premorbid IQ	111.72 (6.67)	111.25 (7.10)	112.78 (5.52)	112.44 (6.57)	110.76 (6.73)
HADS-D	2.00 (2.31)	2.00 (2.17)	2.00 (2.60)	2.69 (2.20)	2.94 (2.45)
HADS-A	4.00 (2.84)	4.00 (2.64)	4.00 (3.26)	3.78 (2.52)	4.63 (3.17)
Cardiovascular risk factors					
Body mass index	26.29 (3.93)	26.32 (4.46)	26.28 (3.68)	26.30 (3.91)	26.23 (3.97)
Abdominal circumference	92.53 (12.29)	92.70 (12.12)	92.17 (12.78)	92.66 (13.03)	92.37 (11.35)
n (%) past smokers	90 (51%)	59 (48%)	31 (56%)	52 (51%)	38 (50%)
n (%) current smokers	6 (3%)	6 (5%)	0 (0%)	5 (5%)	1 (1%)
n (%) hypertension history	76 (43%)	51 (41%)	25 (45%)	47 (46%)	29 (38%)
n (%) angina history	14 (8%)	12 (10%)	2 (4%)	9 (9%)	5 (7%)
n (%) diabetes history	13 (7%)	8 (7%)	5 (9%)	9 (9%)	4 (5%)

Age was the only variable that differed by SUVR status, $p < 0.001$, and by APOE status, $p < 0.05$. SUVR, Standardized Uptake Value Ratio; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating Scale, Sum of Boxes Score, HADS-D, Hospital Anxiety and Depression Scale, Depression Subscale; HADS-A, Hospital Anxiety and Depression Scale, Anxiety Subscale.

Table 2
Summary of tasks, and mean (SD) scores at baseline and 18 month assessment for healthy older adults, and age-adjusted baseline mean (SD) for SUVR < 1.5 and SUVR $\geq$ 1.5 groups

Task	Baseline mean (SD)					18 months mean(SD)
	Overall	SUVR < 1.5	SUVR $\geq$ 1.5	ϵ 4 non-carrier	ϵ 4 carrier	Overall
CDR SB	0.04 (0.19)	0.05 (0.21)	0.03 (0.11)	0.05 (0.21)	0.04 (0.16)	0.06 (0.26)
Logical memory 1	12.85 (3.82)	13.13 (3.82)	12.22 (3.92)	12.78 (3.78)	12.94 (3.78)	12.11 (3.49)
Logical memory 2	11.24 (4.04)	11.43 (4.10)	10.80 (4.25)	11.19 (4.03)	11.30 (4.04)	11.05 (3.86)
CVLT-II total learning	51.11 (10.56)	51.02 (10.51)	51.33 (10.74)	51.17 (10.38)	51.04 (10.41)	49.31 (10.75)
CVLT-II short delay	11.05 (2.29)	11.10 (2.81)	10.94 (3.27)	10.93 (2.99)	11.21 (2.90)	10.68 (3.14)
CVLT-II long delay	11.63 (3.10)	11.59 (3.08)	11.72 (3.15)	11.51 (3.05)	11.79 (3.05)	11.58 (3.25)
RCFT 3 minute recall	17.15 (6.50)	17.65 (6.52)	16.06 (6.67)	18.03 (6.40)	16.01 (6.43)	17.87 (5.96)
RCFT 30 minute recall	16.63 (5.63)	16.80 (5.53)	16.23 (5.71)	17.21 (5.43)	15.83 (5.45)	17.52 (5.77)
Stroop colours	33.39 (10.53)	33.83 (10.47)	32.39 (10.69)	33.38 (10.41)	33.41 (10.43)	33.31 (10.17)
Stroop C/D	2.29 (0.73)	2.35 (0.76)	2.15 (0.66)	2.29 (0.75)	2.28 (0.71)	2.38 (0.61)
RCFT copy	31.42 (3.29)	31.44 (3.26)	31.39 (3.33)	31.50 (3.22)	31.32 (3.23)	29.33 (4.01)
Letter fluency	40.75 (11.87)	39.64 (10.95)	43.24 (10.97)	40.89 (12.01)	40.57 (12.04)	41.70 (12.23)
Category switching accuracy	12.46 (3.16)	12.74 (3.09)	11.81 (3.26)	12.51 (3.16)	12.39 (3.18)	11.81 (3.08)
Digit span	17.85 (3.73)	17.80 (3.57)	17.96 (4.11)	17.90 (3.56)	17.78 (3.98)	17.22 (3.32)
Digit symbol	57.79 (13.09)	57.72 (12.11)	57.94 (12.39)	58.61 (11.94)	56.68 (11.96)	57.54 (13.18)
Stroop dots	14.60 (3.90)	14.52 (3.88)	14.81 (3.97)	14.30 (3.84)	14.99 (3.85)	14.16 (3.00)
Category fluency	39.11 (8.06)	38.79 (8.07)	39.80 (8.25)	39.23 (8.00)	38.95 (8.02)	38.49 (8.26)
BNT	28.26 (1.82)	28.19 (1.84)	28.41 (1.88)	28.29 (1.82)	28.22 (1.83)	28.19 (2.02)

which included the Mini-Mental Status Examination [23] and CDR scale [20]. Premorbid intelligence was estimated using the Wechsler Test of Adult Reading [24] and levels of depressive and anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale [25]. Attention and processing speed was measured using the Digit Span and Digit Symbol-Coding tasks (Wechsler Adult Intelligence Scale-Third edition) [26] and visuoconstruction was measured using the Rey-Osterrieth Complex Figure Test (RCFT) copy trial [27]. Language was assessed using a 30-item version of the Boston naming Test (BNT) [28]. Verbal learning and episodic memory was measured using the California Verbal Learning Test-Second edition (CVLT-II) [29] and Logical Memory Recall 1 and 2 (Wechsler Memory Scale, Story A only) [30]. Visual episodic memory was measured using the RCFT 3-minute and 30-minute delayed recall trials. Executive function was measured using D-KEFS fluency [31] and Stroop colour naming (Victoria version) [32].

Procedure

All of the HA in this study underwent an extensive medical, psychiatric, and neuropsychological assessment upon enrolment into the AIBL study. The same assessments were repeated 18 months later. In this study, we report PiB neuroimaging and *APOE* ϵ 4 genotyping data obtained at baseline, and neuropsychological data obtained at baseline and 18 months in

order to examine the rate of cognitive change in relation to A β load and *APOE* ϵ 4 status.

Data analysis

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 $\geq$ 1.50) in accordance with established criteria [5, 21].

A one-way analysis of variance (ANOVA) showed a significant difference in age between the high and low SUVR groups, $F(1,176)=21.30$, $p < 0.001$ (see Table 1). An analysis of covariance (ANCOVA) with age as a covariate was conducted to compare performance of low and high SUVR groups at baseline (see Table 2). Finally, a series of linear mixed model (LMM) ANCOVA were conducted to examine the relationship between SUVR status (SUVR < 1.5 versus SUVR $\geq$ 1.5), *APOE* ϵ 4 status (ϵ 4 carrier versus ϵ 4 non-carrier), and cognitive and clinical change between baseline and 18-month assessment. For each task, an LMM ANCOVA with SUVR status, *APOE* ϵ 4 status, and the SUVR $\times$ *APOE* ϵ 4 interaction were entered as fixed factors; baseline cognitive or clinical test score, and age as covariates; participant as a random factor, 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

Table 3

Linear Mixed Model with SUVR and *APOE* $\epsilon 4$ status as fixed factors, baseline cognitive score and age as covariate, and participants as random factor in healthy controls

	Linear mixed model results			
	Baseline (df) F	SUVR (df) F	<i>APOE</i> (df) F	SUVR $\times$ <i>APOE</i> (df) F
CDR SB	(1,163) 94.59**	(1,163) 0.67	(1,163) 2.41	(1,163) 3.25
Logical memory 1	(1,168) 62.77**	(1,168) 0.79	(1,168) 3.68	(1,168) 0.02
Logical memory 2	(1,164) 117.77**	(1,164) 3.48*	(1,164) 2.54	(1,164) 0.76
CVLT-II total recall	(1,170) 109.95**	(1,170) 0.72	(1,170) 1.51	(1,170) 0.84
CVLT-II short delay	(1,167) 85.39**	(1,167) 3.78*	(1,167) 0.73	(1,167) 0.003
CVLT-II long delay	(1,169) 98.47**	(1,169) 7.04**	(1,169) 0.02	(1,169) 3.28
RCFT 3 min recall	(1,167) 68.14**	(1,167) 0.19	(1,167) 6.03*	(1,167) 0.65
RCFT 30 min recall	(1,166) 42.13**	(1,166) 0.13	(1,166) 8.87**	(1,166) 0.62
Stroop colours	(1,161) 144.46**	(1,161) 0.66	(1,161) 2.32	(1,161) 0.002
Stroop C/D	(1,161) 34.66**	(1,161) 0.72	(1,161) 1.80	(1,161) 0.18
RCFT copy	(1,168) 38.51**	(1,168) 1.98	(1,168) 6.11*	(1,168) 2.55
Letter fluency	(1,170) 282.16**	(1,170) 0.58	(1,170) 1.56	(1,170) 1.02
Category switching	(1,166) 16.87**	(1,166) 5.50*	(1,166) 1.57	(1,166) 0.06
Accuracy				
Digit span	(1,164) 158.03**	(1,164) 2.53	(1,164) 0.15	(1,164) 0.03
Digit symbol	(1,169) 160.73**	(1,169) 0.23	(1,169) 0.04	(1,169) 2.33
Stroop dots	(1,162) 36.03**	(1,162) 0.17	(1,162) 0.003	(1,162) 0.17
Category fluency	(1,168) 165.16**	(1,168) 3.62*	(1,168) 2.58	(1,168) 0.02
BNT	(1,146) 105.51**	(1,146) 4.31*	(1,146) 4.12*	(1,146) 0.25

* $p < 0.05$, ** $p < 0.001$. SUVR, Standardized Uptake Value Ratio; CDR-SB, Clinical Dementia Rating Scale, Sum of Boxes Score; CVLT-II, California Verbal Learning Task-Second edition; RCFT, Rey-Osterrieth Complex Figure Test; Stroop C/D = Stroop (Colours/Dots); BNT, Boston Naming Test.

and between *APOE* $\epsilon 4$ carriers and non-carriers at the 18-month assessment was expressed using Cohen's d [33].

The criterion for statistical significance for all comparisons or correlations was set to $p < 0.01$. This was done to balance the risk of false positive findings against identification of important relationships when a) performance on the neuropsychological outcome measures was likely to be highly correlated, especially for tests that assess the same cognitive domain, b) this is an exploratory investigation in a relatively new area of neuropsychology in which an important clinical issue has been identified, and c) measures of effect size were used to guide interpretation about the meaningfulness of results. Specifically, Type I errors were suspected where comparisons were statistically significant at the corrected level but where effect sizes were very small (e.g., $d < 0.20$).

RESULTS

LMM analyses indicated that compared to HA with SUVR < 1.5 at baseline, HA with baseline SUVR ≥ 1.5 showed significantly greater decline at the 18-month assessment for Logical Memory Recall 2, CVLT-II short and long delayed recall, Clock drawing, Category Fluency, and BNT (Table 3). No decline at the 18-month assessment was observed for measures

of psychomotor function, or short-term memory in either SUVR group. Magnitudes of the differences in baseline-adjusted performance between the low and high SUVR groups at the 18-month assessment are shown in Fig. 1.

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 neuropsychological measure or the clinical rating scale. When considered by itself, the presence of the *APOE* $\epsilon 4$ allele was associated with a greater decline in visual episodic memory and visuoconstruction after 18 months (Table 3). Magnitudes of differences in baseline-adjusted performance between *APOE* $\epsilon 4$ carriers and non-carriers at the 18-month assessment are shown in Fig. 2.

DISCUSSION

The results of this study support the hypothesis that in healthy older adults, high A β is associated with greater decline over 18 months in episodic memory and this decline also extended to language function. With neuropsychological performance at baseline controlled statistically, a larger decline over 18 months was observed for paragraph recall and verbal recall, over short and long delays, in healthy older adults with high A β than in healthy older adults with low A β (Fig. 1).

Table 4
Linear Mixed Model 18 month estimated marginal means, and Cohen's d of difference in magnitude of decline between SUVR < 1.5 and SUVR $\geq$ 1.5 groups, and between APOE ϵ 4 carriers, and non-carriers

	18 month EM mean (SD)		18 month EM mean (SD)	
	SUVR < 1.5 (n = 123)	SUVR $\geq$ 1.5 (n = 55)	ϵ 4 non-carrier (n = 102)	ϵ 4 carrier (n = 76)
CDR-SB	0.05 (0.23)	0.08 (0.24)	0.04 (0.28)	0.10 (0.22)
Logical memory 1	12.24 (3.26)	11.74 (3.32)	12.49 (3.93)	11.48 (3.03)
Logical memory 2	11.42 (3.22)	10.39 (3.29)	11.32 (3.87)	10.49 (3.00)
CVLT-II total learning	49.62 (9.03)	48.32 (9.16)	48.07 (10.91)	49.87 (8.34)
CVLT-II short delay	11.02 (2.84)	10.07 (2.89)	10.35 (3.45)	10.74 (2.61)
CVLT-II long delay	11.82 (2.81)	10.60 (2.84)	11.22 (3.38)	11.16 (2.59)
RCFT 3 min recall	17.93 (5.16)	17.54 (5.34)	18.79 (6.37)	16.69 (4.85)
RCFT 30 min recall	17.57 (5.28)	17.25 (5.49)	18.71 (6.52)	16.11 (4.98)
Stroop colours	33.06 (7.83)	34.17 (8.42)	32.60 (10.17)	34.63 (7.35)
Stroop C/D	2.37 (0.60)	2.46 (0.64)	2.35 (0.77)	2.48 (0.56)
RCFT copy	29.09 (3.94)	30.04 (4.07)	30.37 (4.88)	28.76 (3.68)
Letter fluency	42.40 (8.43)	41.30 (8.59)	41.00 (10.13)	42.69 (7.72)
Category switching accuracy	11.36 (3.23)	12.68 (3.38)	12.35 (4.07)	11.68 (2.98)
Digit span	17.01 (2.68)	17.73 (2.72)	17.45 (3.23)	17.29 (2.48)
Digit symbol	58.19 (9.49)	57.42 (9.63)	57.64 (11.52)	57.96 (8.78)
Stroop dots	14.18 (3.04)	13.96 (3.27)	14.08 (3.97)	14.06 (2.87)
Category fluency	39.13 (6.49)	37.04 (6.55)	37.25 (7.81)	38.93 (5.96)
BNT	28.40 (1.86)	27.75 (1.88)	27.77 (2.25)	28.38 (1.69)

SUVR, Standardized Uptake Value Ratio; CDR-SB, Clinical Dementia Rating Scale, Sum of Boxes Score; CVLT-II, California Verbal Learning Task-Second edition; RCFT, Rey-Osterrieth Complex Fig Test; Stroop C/D=Stroop (Colours/Dots); BNT, Boston Naming Test.

Fig. 1. Magnitude of decline between healthy older adults with SUVR < 1.5 and SUVR $\geq$ 1.5 ("0" line represents SUVR < 1.5 group, negative values indicate decline) for each neuropsychological measure from baseline to 18-month assessment (* p < 0.05; ** p < 0.001); error bars represent 95% confidence intervals.

Fig. 2. Magnitude of decline between healthy older adults who are *APOE* $\epsilon 4$ carriers and non-carriers (“0” line represents *APOE* $\epsilon 4$ non-carriers, negative values indicate decline), for each neuropsychological measure, from baseline to 18 month assessment (* $p < 0.05$; ** $p < 0.001$); error bars represent 95% confidence intervals.

These differences were, by convention, small to moderate in magnitude (i.e., $d = 0.35$ to 0.40). Although healthy older adults with high $A\beta$ also showed a greater decline in performance on other measures of verbal memory (e.g., Logical Memory 1 and CVLT-II total learning), the magnitudes of these were not large enough to reach statistical significance ($d < 0.20$).

Healthy older adults with high $A\beta$ also showed greater decline in language function (Category Fluency and BNT). As for verbal memory, decline on these tasks was moderate in magnitude ($d \sim 0.30$). Subtle decline in language in healthy older adults who have high levels of $A\beta$ determined by PiB-PET imaging has not previously been observed, however, impairment in language is known to occur early in AD and MCI [34, 35]. In the AIBL study, language was assessed using tests of confrontation naming, letter and category fluency. The absence of any $A\beta$ -related cognitive decline on letter fluency is consistent with the absence of any effects observed for fluency measures with a greater executive function load (i.e., Category Switching Accuracy) or on measures of executive function (i.e., RCFT Copy).

No differences between the high and low $A\beta$ groups were detected for the rate of decline for visual memory, executive function, and attention or for the clinical rating of disease severity (CDR-SB, Fig. 1). For these aspects of cognitive and clinical function, the small magnitudes for the differences in change between the groups (Fig. 1), as well as the large study sample, suggests strongly that in each case, the absence of statistically significant differences was not due to insufficient power. Interestingly, the high $A\beta$ group showed some improvement from baseline on one aspect of executive function (Category Switching). The meaning of this $A\beta$ -related improvement is unclear but the statistical significance is likely to be Type I error as we performed many comparisons and performance on no other measure of executive function or language improved significantly over the 18 months. No differences in change over time were found between high and low $A\beta$ groups on any measure of attention.

When considered together, the results of this study suggest that the cognitive decline in healthy older adults with high $A\beta$ is moderate in magnitude, extends beyond episodic memory to language and is equivalent

across these two cognitive domains. In contrast, A β load was not associated with decline in any aspect of executive or attentional function, or with changes in clinical ratings of disease severity. The decline in episodic memory observed in this study is consistent with the results of a recent prospective study of a subgroup of the current sample using a brief computerized battery, which also found that in healthy older adults, high A β was associated with moderate to large decline in verbal and visual episodic memory [10]. However, in another recent study of A β -related cognitive change in healthy older adults enrolled in the AV45-A11 study, no evidence of cognitive decline in healthy adults with high A β was observed for episodic memory when these older adults were assessed using the same Logical Memory test as was used in the current study [4]. Given the consistency and magnitude of memory decline in healthy older adults with high A β observed in this and our previous study [10], and that *post-hoc* estimation of effect sizes indicated that the magnitude of decline in episodic memory was relatively large ($d \sim 0.9$), we believe that the absence of any A β -related memory decline observed in the AV45-A11 study was a consequence of the small sample size (healthy older adults with high A β , $n = 10$; total healthy older adults, $n = 69$). Interestingly though, in the AV45-A11 healthy older adults cohort, significant A β -related decline was observed for the ADAS-Cog and the CDR-SB. The ADAS-Cog was not included in the AIBL study because of its known insensitivity to cognitive change, particularly in the very early stages of AD [17, 18]. However, no A β -related change was observed in this study for the CDR-SB. As such, the meaning of the decline in clinical ratings observed in the AV45-A11 cohort is unclear, especially when no statistically significant decline was found for the more sensitive neuropsychological measures of memory.

It is possible that risk factors related to cardiovascular disease may contribute to decline in cognitive function [36, 37]. However, we believe that any changes in cognition are unlikely to reflect any gross cardiovascular changes as individuals with a history of untreated cardiovascular disease were excluded from entry to the AIBL study. Further, there were no differences between the low and high A β groups, and *APOE* $\epsilon 4$ carriers and non-carriers on the frequency of well-established cardiovascular risk factors. Importantly, while some individuals in AIBL have cardiovascular risk factors, a condition of entry into AIBL was that all systemic illness (e.g., hypertension or hyperlipidemia) were controlled medically. Finally, a recent study of cardiovascular changes in the AIBL

neuroimaging cohort reported that the frequency of white matter changes and lacunar infarcts were very low in the healthy older adults group [38].

As in our previous study [10], we found that the presence of the *APOE* $\epsilon 4$ allele did not increase the rate of decline in memory and language associated with high levels of A β in healthy older adults. However, when the effect of *APOE* $\epsilon 4$ carriage itself was determined, it was associated with cognitive decline over 18 months, although the decline was greatest and statistically significant for measures of visual episodic memory and visuoconstruction. No *APOE* $\epsilon 4$ -related decline was observed for measures of verbal memory or language. In this context, it is interesting that by itself, high A β was not associated with any decline on the measure of visual memory used in the current study. Thus, the current results raise an intriguing possible dissociation between decline in visual and verbal memory arising either from high A β or *APOE* $\epsilon 4$ carriage. Importantly, in our previous study [10], we observed that cognitive decline, as measured by computerized measures of visual memory (i.e., visual pattern separation, and visual paired associate learning), in healthy older adults with high A β was as large as that observed for verbal memory. Hence, the specificity of the effect of *APOE* $\epsilon 4$ carriage on visual memory observed in the current study may be a reflection of the task used to measure visual episodic memory (i.e., RCFT). Recent carefully designed prospective studies have shown that healthy older adults who carry the *APOE* $\epsilon 4$ allele, but whose A β status was unknown, showed decline over 5 years in both memory and executive function [39–41]. Our studies have shown that the effects of high A β seem to be restricted to episodic memory and language. Thus, the dichotomized effect of high A β and the *APOE* $\epsilon 4$ allele on the RCFT copy and recall tasks may reflect that successful performance on the RCFT may require cognitive processes beyond memory, and may most likely be largely influenced by executive function, which by itself is modulated by the *APOE* $\epsilon 4$ allele but not by A β [39, 41]. However, this hypothesis is speculative and requires replication. More importantly, the results of the current study indicate that *APOE* $\epsilon 4$ carriage did not moderate A β -related cognitive impairment, and that cognitive decline associated with *APOE* $\epsilon 4$ carriage was less robust than that observed for A β .

The results of the current study show that the importance of high levels of A β is better understood from prospective studies than from cross-sectional studies. Several previous studies have observed that increased A β is not associated with impaired cognitive function

in otherwise healthy older adults [1, 3, 42], although when the correlation between A β levels and neuropsychological performance in healthy older adults were studied, these studies have found moderate negative relationships between A β and performance on measures of cognition, and particularly tests of episodic memory [9, 42–45]. When *APOE* genotype was added to the analyses, studies have observed that the relationship between A β and cognitive impairment at a particular assessment time point was moderated by the *APOE* ϵ 4 allele, with individuals who were carriers of the ϵ 4 allele performing worse than non-carriers [6, 7]. These studies converge to suggest that in healthy older adults, elevated A β load is associated with subtle AD-related cognitive impairment, particularly in individuals who are genetically at-risk for the disease. Thus, as AD is a progressive disease and the hallmark of AD is objectively-defined decline in cognitive function, the relationship between A β and cognitive decline in healthy older adults may be best understood from prospective studies. Although still few in number, the data from these prospective studies do converge to suggest that in healthy older adults, high A β does increase the risk of progression to MCI [12], and that the subtle decline in cognition, particularly in episodic memory, that characterizes this progression can be detected in relatively short time intervals (i.e., 18 months) [10], even in the absence of any change in clinical status.

Along with the current study, the findings of these studies are also consistent with previous research that has sought to determine the extent to which decline in cognitive function predicts an increase in A β load. In healthy older adults followed prospectively with brief batteries of computerized cognitive tests, we identified that statistically significant decline in verbal and visual episodic memory was associated with increased risk of high A β load, when tested over 6 years [13], 2 years [46], and even one year [47]. Similarly, other studies have also observed declines in cognition in healthy older adults with high A β load [44, 48, 49]. The results of these previous studies and the current study further reinforce the importance of the detection of objective decline in cognitive function, particularly memory function, rather than cross-sectional detection of cognitive impairment, in the earliest stages of AD. This A β -related decline in memory observed here accords with recent recommendations for the definition of the preclinical stage of AD, where the identification of objectively defined cognitive decline may assist in the more accurate detection of preclinical AD. The findings of the current study, along with previous studies,

reinforce the possibility that the preclinical stage of AD is characterized by high levels of A β , and objective evidence of decline in memory function, thus making this stage of the AD process an important time for anti-amyloid intervention [50, 51].

DISCLOSURE STATEMENT

Authors' disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=1607>).

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