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Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease

Yen Ying Lim,[1] Paul Maruff,[1,2] Robert H. Pietrzak,[3] David Ames,[4,5] Kathryn A. Ellis,[1,4,5] Karra Harrington,[1] Nicola T. Lautenschlager,[4,6] Cassandra Szoeke,[5,7] Ralph N. Martins,[8] Colin L. Masters,[1] Victor L. Villemagne[1,9,10] and Christopher C. Rowe[9,10], for the AIBL Research Group

1 The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia
2 CogState Ltd., Melbourne, Victoria, Australia
3 Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
4 Academic Unit for Psychiatry of Old Age, St. Vincent's Health, Department of Psychiatry, The University of Melbourne, Kew, Victoria, Australia
5 National Ageing Research Institute, Parkville, Victoria, Australia
6 School of Psychiatry and Clinical Neurosciences and WA Centre for Health and Ageing, The University of Western Australia, Perth, Western Australia, Australia
7 CSIRO Preventative Health Flagship, Parkville, Victoria, Australia
8 Centre of Excellence for Alzheimer's Disease Research and Care, School of Exercise, Biomedical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia
9 Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Victoria, Australia
10 Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia

Correspondence to: Yen Ying Lim
The Florey Institute of Neuroscience and Mental Health,
155 Oak Street, Parkville,
VIC 3052, Australia,
E-mail: yen.lim@florey.edu.au

High amyloid has been associated with substantial episodic memory decline over 18 and 36 months in healthy older adults and individuals with mild cognitive impairment. However, the nature and magnitude of amyloid-related memory and non-memory change from the preclinical to the clinical stages of Alzheimer's disease has not been evaluated over the same time interval. Healthy older adults ($n = 320$), individuals with mild cognitive impairment ($n = 57$) and individuals with Alzheimer's disease ($n = 36$) enrolled in the Australian Imaging, Biomarkers and Lifestyle study underwent at least one positron emission tomography neuroimaging scan for amyloid. Cognitive assessments were conducted at baseline, and 18- and 36-month follow-up assessments. Compared with amyloid-negative healthy older adults, amyloid-positive healthy older adults, and amyloid-positive individuals with mild cognitive impairment and Alzheimer's disease showed moderate and equivalent decline in verbal and visual episodic memory over 36 months (d's = 0.47–0.51). Relative to amyloid-negative healthy older adults, amyloid-positive healthy older adults showed no decline in non-memory functions, but amyloid-positive individuals with mild cognitive impairment showed additional moderate decline in language, attention and visuospatial function (d's = 0.47–1.12), and amyloid-positive individuals with Alzheimer's disease showed large decline in all aspects of memory and non-memory function (d's = 0.73–2.28). Amyloid negative individuals with mild cognitive impairment did not show any cognitive decline over 36 months. When non-demented individuals (i.e. healthy older adults and adults with mild cognitive impairment) were further dichotomized, high amyloid-positive non-demented individuals showed a greater rate of decline in episodic memory and language when compared with low amyloid positive non-demented

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individuals. Memory decline does not plateau with increasing disease severity, and decline in non-memory functions increases in amyloid-positive individuals with mild cognitive impairment and Alzheimer's disease. The combined detection of amyloid positivity and objectively-defined decline in memory are reliable indicators of early Alzheimer's disease, and the detection of decline in non-memory functions in amyloid-positive individuals with mild cognitive impairment may assist in determining the level of disease severity in these individuals. Further, these results suggest that grouping amyloid data into at least two categories of abnormality may be useful in determining the disease risk level in non-demented individuals.

Keywords: beta-amyloid; neuropsychology; mild cognitive impairment; Alzheimer's disease; PET imaging

Abbreviations: AIBL = Australian Imaging, Biomarkers and Lifestyle; AD-Aβ+ = Alzheimer's disease amyloid-β+; HA-Aβ+/− = healthy older adult amyloid-β+/negative; MCI-Aβ+/− = mild cognitive impairment amyloid-β+/negative; SUV = standardized uptake value

Introduction

Recent prospective studies show that amyloid-β positivity, as detected by PET neuroimaging, is associated with substantial decline in episodic memory decline over 18 and 36 months in individuals who meet clinical criteria for mild cognitive impairment (MCI) as well as in otherwise healthy older adults, even in the absence of any change in clinical disease status (Villemagne *et al*., 2011; Doraiswamy *et al*., 2012; Lim *et al*., 2012, 2013*a*, *b*, *c*; Small *et al*., 2012; Ellis *et al*., 2013). In contrast, healthy older adult and MCI groups with low amyloid-β show no deterioration in episodic memory over the same time intervals (Villemagne *et al*., 2011; Lim *et al*., 2012, 2013*a*; Ellis *et al*., 2013). In MCI, the amyloid-β-related memory decline confirms that the clinical abnormalities observed are indicative of incipient Alzheimer's disease (Dubois and Albert, 2004; Albert *et al*., 2011), whereas in healthy older adults, it shows that Alzheimer's disease-related neurodegeneration can be detected years before individuals meet any clinical staging criteria for early Alzheimer's disease (Mintun *et al*., 2006; Aizenstein *et al*., 2008; Rowe *et al*., 2010).

Recent pathophysiological models of Alzheimer's disease show that amyloid-β accumulation slows once individuals meet clinical criteria for Alzheimer's disease (Jack *et al*., 2010, 2013; Bateman *et al*., 2012; Villemagne *et al*., 2013). Further, although cross-sectional studies report robust negative associations between amyloid-β and memory in MCI, no such associations are observed in Alzheimer's disease (Pike *et al*., 2007; Mormino *et al*., 2008). It is possible, therefore, that when compared to the rate of amyloid-β accumulation observed in non-demented individuals, the rate of cognitive decline may also decrease once clinical criteria for Alzheimer's disease are met (Jack *et al*., 2010; Bateman *et al*., 2012). However, as yet, the nature and magnitude of amyloid-β-related cognitive change in the preclinical and clinical stages of Alzheimer's disease have not been compared directly. Further, in the majority of studies from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study cohort, amyloid-β-related memory decline has been characterized using a single neuropsychological test of episodic memory (e.g. verbal list learning; Ellis *et al*., 2013), an episodic memory composite score (Villemagne *et al*., 2011, 2013), or with a brief computerized cognitive test battery (i.e. CogState brief battery; Lim *et al*., 2012, 2013*a*, *b*). Although these data provide converging evidence that in non-demented individuals, amyloid-β positivity is associated with episodic memory decline, there has been no thorough investigation of the extent to which any amyloid-β-related decline extends to other aspects of cognition (e.g. attention, language and executive function). Further, as decline in cognition is the hallmark of clinically diagnosed Alzheimer's disease (Almkvist, 1996; Mohs *et al*., 2000; Minati *et al*., 2009), it provides a strong basis for comparison of the nature and magnitude of cognitive decline in the preclinical and prodromal stages of the disease.

The aim of this study was to investigate the nature and magnitude of change in a comprehensive range of neuropsychological outcomes over 36 months in individuals with Alzheimer's disease, patients with amnestic MCI and in healthy older adults with a positive and negative amyloid-β scan. The first hypothesis was that all aspects of cognition would remain stable over 36 months in healthy older adults and in individuals with amnestic MCI who are amyloid-β−. The second hypothesis was that amyloid-β positivity in healthy older adults and in individuals with MCI or Alzheimer's disease would be associated with a significant decline in memory over 36 months. We then explored the extent to which changes in other aspects of cognition were associated with amyloid-β positivity and whether these changes differed according to clinical group. Further, as previous studies have reported an effect of apolipoprotein (*APOE*) ε4 carriage on cognitive decline (Caselli *et al*., 2009; Lim *et al*., 2012; Ellis *et al*., 2013), we explored whether *APOE* ε4 moderated any cognitive decline associated with amyloid-β positivity. Finally, as we have shown previously that non-demented individuals who have high amyloid-β positivity [e.g. standardized uptake value (SUV) ratio ⩾ 1.9] progress to MCI or Alzheimer's disease at a faster rate than non-demented individuals who have low amyloid-β positivity (e.g. SUV ratio 1.5–1.9) (Rowe *et al*., 2013*a*), we explored the extent to which the level of amyloid-β positivity affects rates of cognitive decline over 36 months.

Materials and methods

Participants

All participants in the current study were recruited from the AIBL Study of Ageing (Ellis *et al*., 2009; Rowe *et al*., 2010). The process of recruitment and diagnosis classification has been described in detail previously (Ellis *et al*., 2009). In this study, only healthy older adults and individuals with MCI or Alzheimer's disease who had undergone

amyloid-β imaging with PET and who had completed the AIBL neuropsychological battery at baseline and at 18-month and 36-month follow-up were included. Demographic characteristics of each participant group are shown in Table 1.

All participants with Alzheimer's disease met NINCDS-ADRDA criteria for Alzheimer's disease (McKhann *et al*., 1984), and in all cases, the clinical review panel (chaired by D.A.) reviewed all available data to ensure that the diagnosis was consistent with these agreed criteria. Similarly, all available data for participants with MCI were reviewed to ensure that their classification was consistent with internationally agreed criteria (Petersen *et al*., 1999; Winblad *et al*., 2004). For participants with Alzheimer's disease, an additional inclusion criterion was a score of 18 to 26 on the Mini-Mental State Examination (Folstein *et al*., 1975). All participants with Alzheimer's disease and MCI received a Clinical Dementia Rating scale sum of boxes score and a total score (Morris, 1983). Exclusion criteria at baseline were: schizophrenia; depression (Geriatric Depression Score of $\geqslant$6); Parkinson's disease; cancer (other than basal cell skin carcinoma) within the past 2 years; symptomatic stroke; uncontrolled diabetes; or current regular alcohol use exceeding two standard drinks per day for women or four per day for men. Clinical classification was blinded to amyloid-β imaging data.

The study was approved by and complied with the regulations of the institutional research and ethics committees of Austin Health, St. Vincent's Health, Hollywood Private Hospital and Edith Cowan University (Ellis *et al*., 2009). All participants provided written informed consent before participating in the study.

Measures

Positron emission tomography neuroimaging and *APOE* ε4 genotyping

Amyloid-β imaging with PET was conducted using either ^{11}C-Pittsburgh compound B (Pittsburgh compound B), ^{18}F-florbetapir or ^{18}F-flutemetamol. PET methodology has been described in detail previously (Rowe *et al*., 2010; Vandenberghe *et al*., 2010; Wong *et al*., 2010). Given the different pharmacokinetic characteristics, a different acquisition protocol was adopted for each tracer. Thirty minute acquisitions were started 40 min after injection of Pittsburgh compound B, 20-min acquisitions were performed 50 min after injection of florbetapir and 90 min after injection of flutemetamol. For Pittsburgh compound B and flutemetamol, PET SUV data were summed and normalized to the cerebellar cortex SUV, resulting in a region-to-cerebellar ratio termed SUV ratio. For florbetapir, the SUV ratio was generated using the whole cerebellum as the reference region (Clark *et al*., 2011). In line with previous studies, the SUV ratio was classified dichotomously as either negative or positive. For Pittsburgh compound B and flutemetamol, a SUV ratio threshold $\geqslant$1.5 was used (Rowe *et al*., 2010; Vandenberghe *et al*., 2010). In the case of florbetapir, based on the results of a phase III study (Clark *et al*., 2011), an SUV ratio threshold of $\geqslant$1.1 was used to discriminate between amyloid-β− and amyloid-β+. As participants were scanned at different follow-up time points (Table 1), we classified participants as amyloid-β− or amyloid-β+ based on the SUV ratio that was obtained closest to their 36 month follow-up time point.

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 which have been described in detail elsewhere (Ellis *et al*., 2009; Rowe *et al*., 2010). The clinical status of participants was determined by data which included the Mini-Mental State Examination (Folstein *et al*., 1975), and the Clinical Dementia Rating scale (Morris, 1983). Premorbid intelligence was estimated using the Wechsler Test of Adult Reading (Wechsler, 2001), and levels of depressive and anxiety symptoms were assessed using the Hospital Anxiety and Depression (Snaith and Zigmond, 1986).

Procedure

Participants underwent an extensive medical, psychiatric, and neuropsychological assessment upon enrolment into the AIBL study. The same

Table 1 Demographic and clinical characteristics of each participant group

	HA-Aβ− (*n* = 244)	HA-Aβ+ (*n* = 76)	MCI-Aβ− (*n* = 16)	MCI-Aβ+ (*n* = 41)	AD-Aβ+ (*n* = 36)	*P*-value
Female, *n* (%)	126 (51.6)	41 (53.9)	9 (56.3)	19 (46.3)	21 (58.3)	0.856
APOE ε4, *n* (%)	59 (24.2)	45 (59.2)	1 (6.3)	28 (68.3)	28 (77.8)	<0.001
Age, mean (SD)	68.62 (6.10)	73.87 (7.32)	77.38 (8.69)	80.41 (6.73)	74.81 (8.46)	<0.001
Premorbid IQ, mean (SD)	108.15 (7.13)	110.00 (6.37)	105.00 (11.70)	109.05 (7.03)	103.47 (8.82)	<0.001
HADS depression, mean (SD)	2.61 (2.21)	2.54 (2.37)	3.47 (1.92)	3.43 (2.38)	3.25 (2.89)	0.096
HADS anxiety, mean (SD)	4.15 (2.75)	4.36 (2.98)	5.13 (2.59)	4.58 (2.45)	4.83 (3.84)	0.473
MMSE, mean (SD)	28.91 (1.19)	28.74 (1.19)	27.63 (2.42)	27.02 (2.12)	21.22 (4.56)	<0.001
CDR-SB, mean (SD)	0.04 (0.17)	0.04 (0.14)	0.94 (0.57)	1.04 (0.74)	4.20 (1.40)	<0.001
Verbal Episodic Memory, mean (SD)	0.09 (0.96)	−0.09 (1.06)	−1.67 (1.01)	−2.55 (0.74)	−3.46 (0.72)	<0.001
Visual Episodic Memory, mean (SD)	0.00 (1.00)	−0.27 (1.08)	−1.06 (1.20)	−1.79 (1.20)	−3.12 (0.98)	<0.001
Executive Function, mean (SD)	−0.03 (1.02)	−0.08 (1.00)	−1.36 (0.86)	−0.85 (1.19)	−1.73 (2.28)	<0.001
Language, mean (SD)	0.11 (0.98)	0.11 (0.89)	−1.54 (1.85)	−1.16 (1.67)	−2.82 (2.09)	<0.001
Attention, mean (SD)	0.00 (1.00)	−0.22 (0.80)	−1.09 (1.57)	−0.86 (1.32)	−2.50 (1.61)	<0.001
Visuospatial, mean (SD)	0.21 (0.73)	0.10 (0.80)	−0.60 (1.39)	−0.70 (1.47)	−3.09 (3.54)	<0.001

MMSE = Mini-Mental State Examination; CDR-SB = Clinical Dementia Rating Scale, Sum of Boxes; HADS = Hospital Anxiety and Depression Scale.
Of the 320 healthy adults who underwent PET neuroimaging, 178 were scanned using ^{11}C-Pittsburgh compound B, 73 using ^{18}F florbetapir, and 69 using ^{18}F flutemetamol. Of the 57 adults with MCI who underwent PET neuroimaging, 49 were scanned using ^{11}C Pittsburgh compound B, four using ^{18}F florbetapir, and four using ^{18}F flutemetamol. Of the 36 adults with Alzheimer's disease who underwent PET neuroimaging, 35 were scanned using ^{11}C Pittsburgh compound B, and one using ^{18}F florbetapir. Participants who underwent PET neuroimaging using Pittsburgh compound B were scanned at baseline and at each 18 month follow-up time point. Participants who underwent PET neuroimaging using florbetapir or flutemetamol were scanned at the 36 month follow-up time point.

assessments were repeated 18 and 36 months after baseline. In this study, we report PET neuroimaging and *APOE* ε4 genotyping data obtained at baseline, and neuropsychological data obtained at baseline, 18 months and 36 months to examine the rate of cognitive change in relation to baseline levels of amyloid-β.

Data analysis

Individual outcome measures on individual tests were standardized against the baseline mean and standard deviation for the healthy older adult group, and then averaged to compute a cognitive composite score for verbal episodic memory [Logical Memory delayed recall, California Verbal Learning Test, Second Edition (CVLT-II) long delay recall, and CVLT-II d']; visual episodic memory [Rey Complex Figure Test 30 minute delayed recall, CogState One Card Learning task, and CogState One Back task); executive function [Stroop Colours/Dots, Letter Fluency, and Category Fluency Switching (Fruit/Furniture)]; language [Category Fluency (Animals/Boys' Names) and Boston Naming Test]; attention (Digit Symbol, CogState Detection task, and CogState Identification task); and visuospatial function (Rey Complex Figure Test Copy, and Clock Drawing). The process of selecting cognitive tasks for the formation of each composite score, and the validation of each cognitive composite score has been described in detail previously (Harrington *et al*., 2013).

A series of repeated measures linear mixed model analyses (using maximum likelihood estimation and an unstructured covariance matrix) were conducted to examine the relation between group [healthy older adult amyloid-β− (HA-Aβ−), healthy older adult amyloid-β+ (HA-Aβ+), MCI amyloid-β− (MCI-Aβ−), MCI amyloid-β+ (MCI-Aβ+) and Alzheimer's disease amyloid-β+ (AD-Aβ+)] and time (baseline, 18 month, and 36 month) on cognitive change. Linear mixed modelling was used because of its ability to model both fixed and random effects, which accounts for multiple sources of variability, and because it provides improved estimates of within-subject coefficients (i.e. random effects) in longitudinal studies. In these analyses, group, time, *APOE* status (ε4 carrier, ε4 non-carrier), and the group × time interaction were entered as fixed factors; participant as a random factor; age and premorbid intelligence as covariates; and cognitive composite score as the dependent variable. For each cognitive composite score, mean slope estimates were computed for each group. The magnitude of difference in the rates of change (i.e. slopes) of the HA-Aβ+, MCI-Aβ−, MCI-Aβ+, and AD-Aβ+ groups in relation to the HA-Aβ− group was expressed using Cohen's *d* and 95% confidence intervals (CIs) (Cohen, 1988).

To investigate whether there was an effect of *APOE* ε4 on amyloid-β-related change in cognition, and to maximize the power to detect any subtle relationships, participants were classified into amyloid-β− (HA-Aβ−, MCI-Aβ−) and amyloid-β+ (HA-Aβ+, MCI-Aβ+) groups. The AD-Aβ+ group was excluded from this analysis, as there were no individuals with Alzheimer's disease that were amyloid-β−.

Linear mixed model analyses were then conducted to examine the relationship between group (amyloid-β−, amyloid-β+), *APOE* (ε4 carrier, ε4 non-carrier), and time (baseline, 18 months, and 36 months) on change in each cognitive composite score. In these analyses, only main effects or interactions involving *APOE* were interpreted.

To determine whether level of amyloid-β positivity (i.e. high amyloid-β+ or low amyloid-β+) was associated with increased rates of cognitive decline in non-demented individuals, we combined the HA-Aβ+ and MCI-Aβ+ groups. Receiver operating characteristic analysis of the AIBL Alzheimer's disease and healthy older adult cohorts were also performed (Rowe *et al*., 2013*a*). This indicated that for Pittsburgh compound B, an SUV ratio of 1.9 was the optimal cut-off point for distinction of individuals with Alzheimer's disease from age-matched healthy older adult. Thus, this higher SUV ratio cut-off point was used to define high amyloid-β+ and low amyloid-β+ (SUV ratio 1.5-1.9). Similarly, for flutemetamol, an SUV ratio threshold ⩾2.19 was used to discriminate between high amyloid-β+ and low amyloid-β+ (SUV ratio 1.5–2.19) non-demented individuals, and for florbetapir, the SUV ratio threshold used was ⩾1.29. Linear mixed model analyses were conducted to examine the relationship between amyloid-β positivity (low amyloid-β+ versus high amyloid-β+) and time (baseline, 18 months and 36 months) on change in each cognitive composite score.

Results

Demographic differences between amyloid-β− and amyloid-β+ subgroups in healthy older adults, mild cognitive impairment and Alzheimer's disease

There were statistically significant differences between the five groups in age and premorbid intelligence. In particular, the MCI-Aβ− and AD-Aβ+ groups had significantly lower premorbid intelligence when compared with the HA-Aβ−, HA-Aβ+ and MCI-Aβ+ groups, $P < 0.001$. The HA-Aβ− and HA-Aβ+ groups were also significantly younger than the MCI-Aβ− and MCI-Aβ+ groups, $P < 0.05$. Groups did not differ on symptoms of depression or anxiety (Table 1). There were significantly more *APOE* ε4 carriers in both the HA-Aβ+ and MCI-Aβ+ groups.

Comparison of rates of cognitive change in HA-Aβ+, MCI-Aβ−, MCI-Aβ+ and AD-Aβ+ groups relative to the HA-Aβ− group

Group × time interactions were statistically significant for all cognitive composite scores (Supplementary Table 1). The mean slope for each clinical group for each composite is given in Table 2. The magnitude of the difference in slopes for each group from that of the HA-Aβ− group is presented for each composite score in Fig. 2. In Fig. 2, the 95% CIs presented for each effect size also allows interpretation of significant differences (i.e. where 95% CIs do not overlap).

Post hoc comparison of group mean slopes over 36 months indicated that, relative to the HA-Aβ− group, the HA-Aβ+ group showed a significantly greater rate of decline over 36 months on the verbal episodic memory, and visual episodic memory composites, with the magnitude of these differences, by convention, moderate (Cohen, 1988) (Table 3 and Fig. 1A and B). No differences in group mean slopes were observed between the HA-Aβ− and HA-Aβ+ groups on any of the other cognitive composite scores. Similarly, relative to the HA-Aβ− group, the MCI-Aβ+ group showed a greater rate of decline over 36 months on the verbal episodic memory, and visual episodic memory composites, and also decline on the language, attention, and visuospatial function composites (Table 2 and Fig. 2). The difference in group

Table 2 Mean slopes and standard deviation of the slopes for each participant group, and the magnitude of difference in slopes of HA-Aβ+, MCI-Aβ−, MCI-Aβ+ and AD-Aβ+ groups from the HA-Aβ− group

Composite	Mean slope (SD)					Cohen's *d* (95% CIs)			
	HA-Aβ− (*n* = 244)	HA-Aβ+ (*n* = 76)	MCI-Aβ− (*n* = 16)	MCI-Aβ+ (*n* = 41)	AD-Aβ+ (*n* = 36)	HA-Aβ− versus HA-Aβ+	HA-Aβ− versus MCI-Aβ−	HA-Aβ− versus MCI-Aβ+	HA-Aβ− versus AD-Aβ+
Verbal Episodic Memory	0.019 (0.415)	−0.185 (0.369)	0.274 (0.278)	−0.253 (0.323)	−0.278 (0.358)	**0.50 (0.24–0.76)**	**−0.62 (−1.13–−0.11)**	**0.67 (0.34–1.01)**	**0.73 (0.37–1.08)**
Visual Episodic Memory	0.077 (0.559)	−0.191 (0.494)	0.019 (0.374)	−0.259 (0.439)	−0.334 (0.539)	**0.49 (0.23–0.75)**	0.11 (−0.40–0.61)	**0.62 (0.28–0.95)**	**0.74 (0.38–1.09)**
Executive Function	−0.124 (0.627)	−0.011 (0.553)	0.141 (0.418)	−0.218 (0.482)	−0.768 (0.513)	−0.19 (−0.44–0.07)	−0.43 (−0.94–0.08)	0.15 (−0.18–0.49)	**1.05 (0.69–1.41)**
Language	−0.03 (0.490)	−0.150 (0.435)	−0.172 (0.332)	−0.568 (0.379)	−0.739 (0.408)	0.25 (−0.01–0.51)	0.29 (−0.21–0.80)	**1.13 (0.78–1.47)**	**1.48 (1.10–1.84)**
Attention	−0.123 (0.473)	−0.152 (0.420)	0.010 (0.318)	−0.341 (0.376)	−0.543 (0.461)	0.06 (−0.19–0.32)	−0.29 (−0.79–0.22)	**0.47 (0.14–0.81)**	**0.89 (0.53–1.25)**
Visuospatial	−0.311 (0.734)	−0.465 (0.654)	−0.372 (0.489)	−0.946 (0.566)	−2.022 (0.621)	0.22 (−0.04–0.47)	0.08 (−0.42–0.59)	**0.89 (0.55–1.23)**	**2.37 (1.97–2.77)**

Values in bold are significant at the $P < 0.05$ or $P < 0.001$ level.

Table 3 Effect of *APOE* on the relationship between amyloid-β and cognitive change over time across all participant groups

	Age	*P*-value	IQ	*P*-value	*APOE*	*P*-value	Amyloid-β	*P*-value	Time	*P*-value	Amyloid-β × APOE	*P*-value	Amyloid-β × Time	*P*-value	APOE × Time	*P*-value	Amyloid-β × APOE × Time	*P*-value
Verbal Episodic Memory	(1,376) 82.44	<0.001	(1,376) 24.58	<0.001	(1,378) 0.02	0.884	(1,407) 2.65	0.104	**(1,366) 9.22**	**0.003**	(1,376) 0.51	0.474	**(1,366) 16.94**	**<0.001**	**(1,366) 4.88**	**0.028**	(1,366) 3.19	0.075
Visual Episodic Memory	(1,377) 91.91	<0.001	(1,373) 19.94	<0.001	**(1,380) 4.40**	**0.037**	(1,415) 0.22	0.642	**(1,370) 3.92**	**0.048**	(1,379) 1.81	0.179	**(1,370) 18.19**	**<0.001**	(1,370) 0.00	0.968	(1,370) 0.20	0.656
Executive Function	(1,373) 44.65	<0.001	(1,371) 47.35	<0.001	(1,370) 1.97	0.161	(1,406) 0.37	0.541	**(1,354) 7.98**	**0.005**	(1,369) 0.37	0.544	(1,354) 0.04	0.848	(1,354) 0.00	0.954	(1,354) 0.77	0.381
Language	(1,377) 78.28	<0.001	(1,377) 64.62	<0.001	(1,374) 0.52	0.470	(1,393) 5.06	0.025	(1,357) 38.57	<0.001	(1,373) 0.07	0.790	**(1,357) 26.61**	**<0.001**	(1,357) 0.01	0.945	(1,357) 0.22	0.639
Attention	(1,378) 83.30	<0.001	(1,375) 46.43	<0.001	(1,377) 0.14	0.707	(1,412) 0.42	0.515	(1,353) 30.55	<0.001	(1,375) 0.87	0.351	(1,354) 4.04	0.045	(1,354) 0.41	0.520	(1,354) 0.00	0.974
Visuospatial	(1,373) 20.40	<0.001	(1,373) 22.17	<0.001	(1,336) 0.42	0.516	(1,371) 1.85	0.175	(1,360) 152.01	<0.001	(1,335) 0.16	0.690	**(1,360) 22.15**	**<0.001**	(1,360) 0.73	0.394	(1,360) 0.04	0.838

Values in bold are significant at the $P < 0.05$ or $P < 0.001$ level. The values in brackets are degrees of freedom, and the values NOT in brackets are F values, denoted as (df) F.

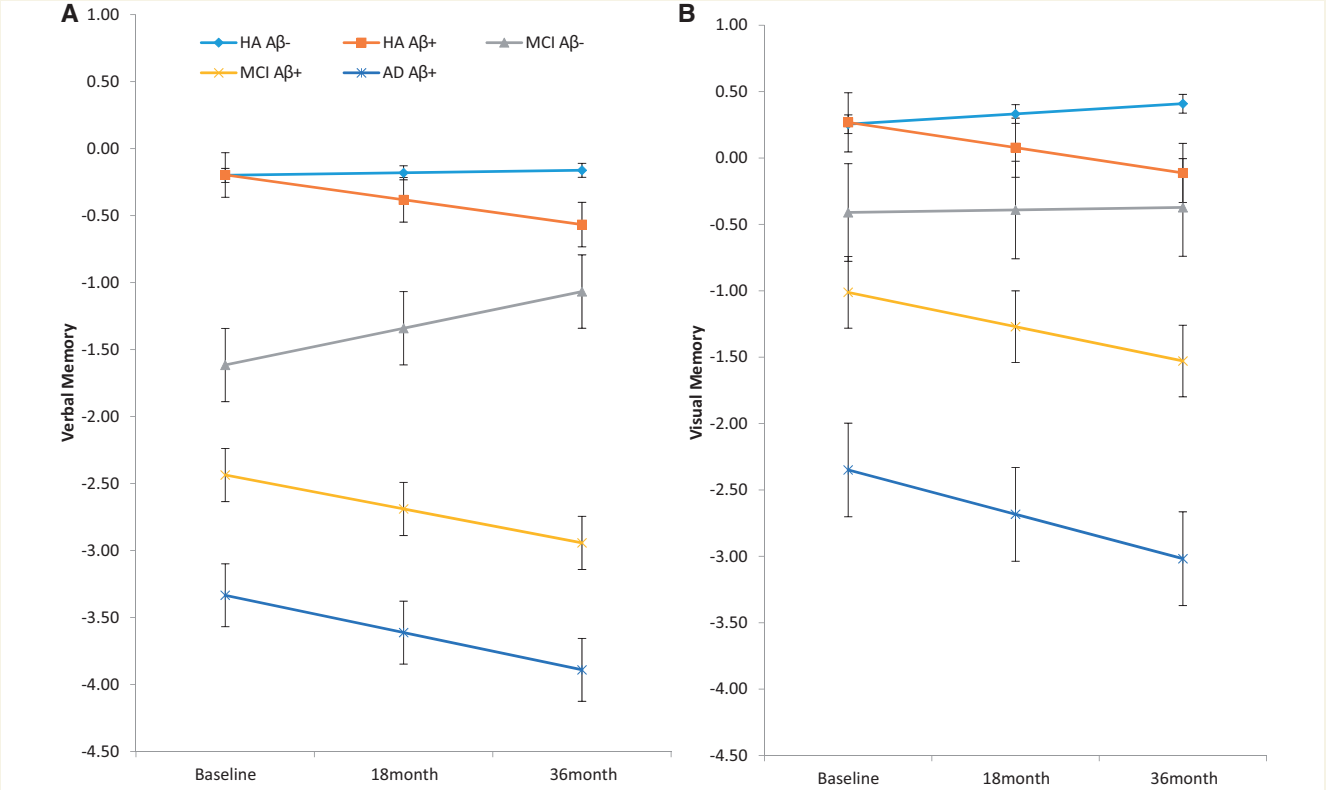

Figure 1 Linear trend of performance on the verbal memory composite (**A**) and the visual memory composite (**B**) for HA-Aβ−, HA-Aβ+, MCI-Aβ−, MCI-Aβ+, and AD-Aβ+ groups, from baseline to 36 months.

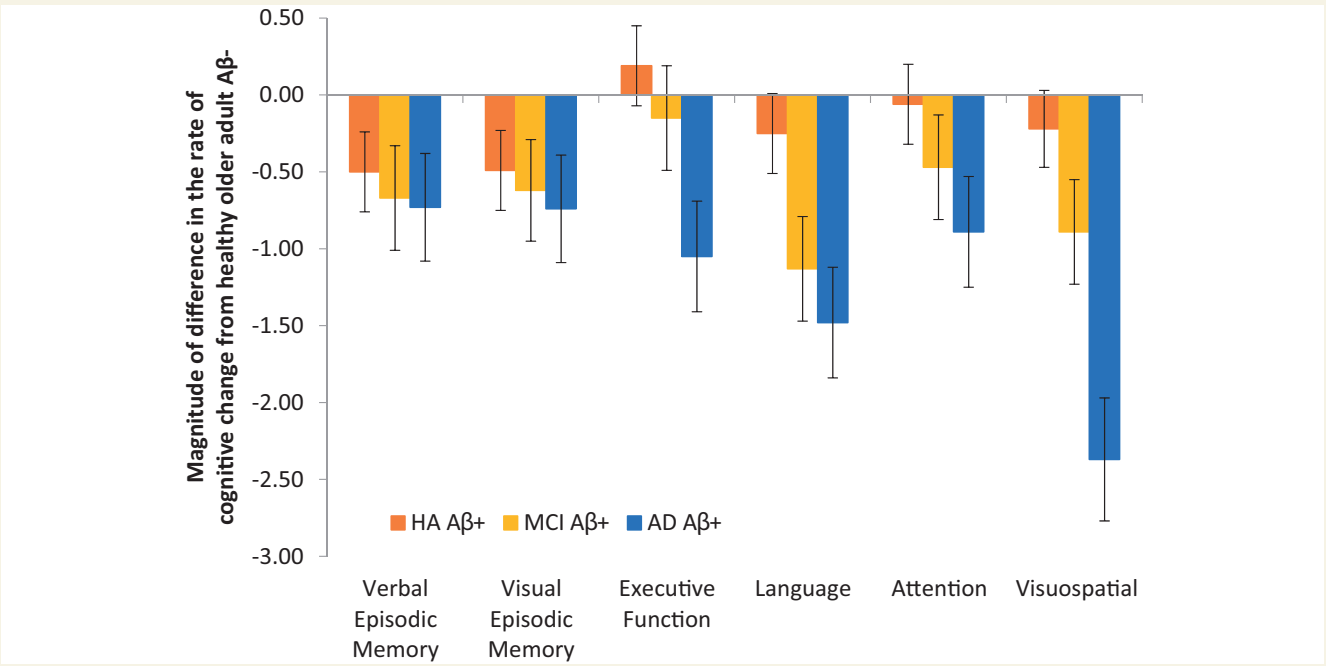

Figure 2 Magnitude of difference (Cohen's *d*) in the rate of change in each cognitive composite score between the HA-Aβ+, MCI-Aβ+, and AD-Aβ+ groups relative to the HA-Aβ− group (represented by '0' line). Error bars represent the 95% CIs of the difference in the rate of cognitive change.

mean slopes was by convention, moderate-to-large in magnitude. Relative to the =HA-Aβ− group, the AD-Aβ+ group showed greater rates of decline over 36 months on all cognitive composite measures, and the magnitude of difference in group mean slopes was large (Table 2 and Fig. 2). Of note, the MCI-Aβ− group showed no decline on any of the cognitive composite scores relative to the HA-Aβ− group, rather, they showed improvement on the verbal episodic memory composite with this improvement, relative to the HA-Aβ− group, moderate-to-large in magnitude (Table 2).

The effect of *APOE* ε4 on the relationship between amyloid-β and cognitive change

Analysis of the effect of *APOE* ε4 carriage on the relationship between amyloid-β and cognitive change over 36 months showed no significant interactions for any cognitive composite score (Table 3). The only statistically significant effect identified from this analysis was the main effect of *APOE* on cognitive change over 36 months for the verbal memory composite score (Table 3).

The effect of low or high amyloid-β positivity on cognitive change in non-demented individuals

Amyloid-β positivity × time interactions were statistically significant for verbal and visual episodic memory and language composites (Table 4). Relative to low amyloid-β+ non-demented individuals, high amyloid-β+ non-demented individuals showed a significantly greater rate of decline over 36 months that was moderate in magnitude, for the verbal episodic memory, visual episodic memory, and language composites only (Table 4). This analysis was then repeated in only the HA-Aβ+ group. When compared with the low amyloid-β+ healthy older adult group, the high amyloid-β+ healthy older adult showed significantly greater rate of decline over 36 months that was moderate in magnitude for the verbal episodic memory [*d* (95% CI) = 0.44 (0.00–0.89)] and visual episodic memory [*d* (95% CI) = 0.73 (0.27–1.18)] composites.

Discussion

The first hypothesis that all aspects of cognitive function would remain stable in healthy older adults and individuals with MCI who were amyloid-β− was supported partially. Specifically, amyloid-β− healthy older adults showed no change in verbal or visual episodic memory (Fig. 1) or any other aspect of cognitive function over 36 months (Table 2). However, amyloid-β− individuals with MCI showed improvement in verbal memory over 36 months that was, by convention (Cohen, 1988), moderate-to-large in magnitude (Table 2 and Fig. 1A). The absence of decline in memory or any other cognitive function over 36 months in amyloid-β− healthy older adults replicates and extends previous observations of cognitive stability over 6, 18 and 36 months in negative

Table 4 Results of linear mixed model analyses examining change in cognitive performance over 36 months in high and low amyloid-β+ non-demented individuals, mean slopes and standard deviation of the slopes for high and low amyloid-β+ groups, and Cohen's *d* of the difference between slopes

Composite	Covariates				Fixed factors						Low amyloid-β+ (*n* = 46) Mean (SD)	High amyloid-β+ (*n* = 73) Mean (SD)	Cohen's *d* (95% CI)
	Age	*P*-value	IQ	*P*-value	Amyloid-β positivity	*P*-value	Time	*P*-value	Amyloid-β positivity × Time	*P*-value			
Verbal Episodic Memory	**(1,117) 43.92**	**<0.001**	**(1,117) 6.38**	**0.013**	(1,114) 0.71	0.401	**(1,102) 16.51**	**<0.001**	**(1,102) 6.82**	**0.010**	−0.062 (0.458)	−0.287 (0.656)	**0.38 (0.01–0.75)**
Visual Episodic Memory	**(1,114) 29.09**	**<0.001**	**(1,116) 4.88**	**0.029**	(1,114) 0.06	0.803	**(1,100) 9.37**	**0.003**	**(1,100) 7.94**	**0.006**	−0.015 (0.651)	−0.360 (0.932)	**0.41 (0.04–0.78)**
Executive Function	**(1,116) 12.66**	**0.001**	**(1,117) 14.34**	**<0.001**	(1,102) 0.39	0.533	(1,100) 1.71	0.194	(1,100) 0.00	0.967	−0.075 (0.634)	−0.080 (0.907)	0.01 (−0.36–0.38)
Language	**(1,115) 30.84**	**<0.001**	**(1,116) 11.32**	**0.001**	(1,115) 2.51	0.116	**(1,101) 25.00**	**<0.001**	**(1,101) 5.47**	**0.021**	−0.143 (0.573)	−0.394 (0.819)	**0.34 (0.00–0.68)**
Attention	**(1,116) 42.51**	**<0.001**	**(1,116) 26.37**	**<0.001**	(1,105) 0.01	0.934	**(1,88) 20.38**	**<0.001**	(1,88) 0.16	0.691	−0.193 (0.499)	−0.231 (0.715)	0.06 (−0.31–0.43)
Visuospatial	**(1,113) 10.33**	**0.002**	**(1,114) 5.24**	**0.024**	(1,95) 1.26	0.264	**(1,107) 49.09**	**<0.001**	(1,107) 2.63	0.108	−0.476 (0.947)	−0.762 (1.351)	0.24 (−0.14–0.60)

Values in bold are significant at the $P < 0.05$ or $P < 0.001$ level; amyloid-β positivity indicates main effect of membership in the low amyloid-β+ (i.e. SUV ratio 1.5–1.9) or high amyloid-β+ (SUV ratio >1.9) groups. The values in brackets are degrees of freedom, and the values NOT in brackets are F values, denoted as (df) F.

amyloid-β healthy older adults from AIBL (Villemagne *et al*., 2011; Lim *et al*., 2012, 2013*b*; Ellis *et al*., 2013) and other cohorts (Doraiswamy *et al*., 2012; Small *et al*., 2012; Snitz *et al*., 2013). In individuals with amyloid-β− MCI, the finding of no cognitive decline is also consistent with the results of previous 18 and 36 month studies (Doraiswamy *et al*., 2012; Lim *et al*., 2013*a*, *b*), which converge to suggest that even when characterized clinically within a highly specialized Alzheimer's disease memory clinic, MCI without a positive amyloid-β biomarker most likely reflects neurological or psychiatric conditions other than Alzheimer's disease (Dubois and Albert, 2004). The moderate-to-large improvements in verbal episodic memory over 36 months observed in the amyloid-β− MCI group suggests that the abnormality in memory observed at the baseline assessment may have reflected, at least in part, the effects of situationally-raised levels of depression or anxiety that can occur when individuals with memory difficulties are confronted with formal cognitive tests (Beaudreau and O'Hara, 2008), the effects of subclinical mental health, sleep, or physical health. These factors may have then resolved with experience in the AIBL study, and consequently the magnitude of memory impairment was reduced. However by themselves, these factors cannot account fully for the baseline memory impairment in the amyloid-β− MCI group as all individuals in this group were still classified as meeting clinical criteria for MCI by a consensus panel after 36 months in the study.

The second hypothesis that in healthy older adults, individuals with MCI and individuals with Alzheimer's disease, amyloid-β positivity would be associated with decline in memory over 36 months was supported. For amyloid-β+ healthy older adults, the rate of decline in verbal and visual episodic memory over 36 months was moderate in magnitude when compared with memory changes in amyloid-β− healthy older adults (Fig. 1). No difference between amyloid-β− or positive healthy older adults was observed in the rate of change for any cognitive function other than memory. These data confirm previous examinations of the current sample conducted over shorter time intervals or with other measures of memory (Lim *et al*., 2012, 2013*a*, *b*). They are also consistent with observations made in other prospective studies of older individuals who have elevated amyloid-β on PET neuroimaging to suggest that specific memory decline is the hallmark of preclinical Alzheimer's disease (Darby *et al*., 2011; Villemagne *et al*., 2011; Doraiswamy *et al*., 2012; Small *et al*., 2012; Snitz *et al*., 2013). When compared with amyloid-β− healthy older adults, individuals with amyloid-β+ MCI also showed greater rates of decline in verbal and visual episodic memory, with the magnitude of the decline moderate to large by convention (Fig. 2). However, in amyloid-β+ MCI, decline was also observed for language, attention and visuospatial function, with the magnitude of decline in these other domains of cognition equivalent to that observed for the decline in episodic memory (Fig. 2). Finally, when compared with amyloid-β− healthy older adults, amyloid-β+ patients with Alzheimer's disease showed large decline across all areas of cognitive function (Fig. 2) with the largest decline observed for language and visuospatial function.

The observation that there was substantial overlap between the confidence intervals for the magnitude of decline for amyloid-β+ healthy older adult, MCI and Alzheimer's disease groups (Fig. 2) suggest that the rate of decline in verbal and visual episodic memory was equivalent between these groups over 36 months. Among amyloid-β+ individuals who met clinical criteria for MCI, decline in cognition extended from memory to language, attention and visuospatial functions, with the magnitude of this decline large but equivalent across these cognitive domains. In some of our own previous studies of non-demented individuals with elevated amyloid-β (Villemagne *et al*., 2011, 2013), we have categorized cognitive functions as either memory or non-memory and observed that in general, amyloid-β-related cognitive change in non-demented older individuals was specific to episodic memory. However, results of the current study indicate that when examined more carefully, clinically significant decline occurs in cognitive domains other than memory, most notably in language and visuospatial function, among individuals with amyloid-β+ MCI. One interesting aspect of these data is that no decline was observed for executive function in individuals with amyloid-β+ MCI. This result contrasts with prior suggestions that impairment in executive function is an important characteristic of early Alzheimer's disease (Baudic *et al*., 2006; Traykov *et al*., 2007). One reason for this may be that we classified individuals with early Alzheimer's disease based on the clinical classification of MCI with additional biomarker confirmation (i.e. amyloid-β positivity), whereas previous studies that have found impairment in executive function were conducted only in clinically classified MCI. Further, several authors have suggested that the presence of impairment in executive function in individuals with MCI may be indicative of a non-Alzheimer's disease aetiology (Dubois and Albert, 2004; Petersen, 2004).

Recent pathophysiological models of Alzheimer's disease suggest that the rate of amyloid-β accumulation usually slows after individuals meet clinical criteria for Alzheimer's disease (Jack *et al*., 2010, 2013; Villemagne *et al*., 2013). Thus, when the low amyloid-β levels of younger adults are considered, the temporal relationship between amyloid-β accumulation and age across the lifespan tends to become sigmoidal in nature (Jack *et al*., 2010; Bateman *et al*., 2012; Villemagne *et al*., 2013). These same models suggest that like amyloid-β accumulation, the rate of cognitive decline may also reach a plateau once individuals meet clinical criteria for Alzheimer's disease, especially given that once individuals meet clinical criteria for Alzheimer's disease, while the association between amyloid-β burden and cognitive performance is weak or non-existent, there is a high association between the rates of amyloid-β accumulation and the rates of cognitive decline, probably reflecting the simultaneous or parallel slowing of both processes (Jack *et al*., 2013; Villemagne *et al*., 2013). Results of the current study show that despite meeting clinical criteria for Alzheimer's disease, decline in memory continues at the same rate as that observed for non-demented amyloid-β+ older individuals. However, in these same individuals who are amyloid-β+ and have Alzheimer's disease, rates of decline in all non-memory domains are substantially increased when compared to those observed for amyloid-β+ healthy older adults. Taken together, as decline in memory is characteristic of Alzheimer's disease even in the earliest preclinical stage (Braak and Braak, 1991; Sperling *et al*., 2011), memory decline in Alzheimer's disease

also persists at the same rate. However, as the disease progresses, other cognitive domains become affected and therefore, the rate of decline in the non-memory domains is more pronounced when compared to that observed in the earlier stages of the illness (i.e. preclinical stage) where there is little or no decline in these same non-memory functions. This suggests that the assessment of cognitive domains in addition to memory may provide greater insight into the disease progression of individuals once they meet clinical criteria for Alzheimer's disease.

The *APOE* ε4 allele did not moderate the relationship between amyloid-β and decline for any cognitive domain in individuals who are amyloid-β− (amyloid-β− healthy older adults and individuals with MCI) or individuals who are amyloid-β+ (amyloid-β+ healthy older adults and individuals with MCI) (Table 4). We have reported previously that the *APOE* ε4 allele did not moderate amyloid-β-related decline in memory in studies conducted over shorter time intervals (i.e. 6 and 18 months) (Lim *et al*., 2012, 2013*c*; Ellis *et al*., 2013). In these previous studies, inclusion of *APOE* ε4 status (ε4 carrier or non-carrier) and amyloid-β status (negative or positive) in our statistical models has resulted in decline being observed for both *APOE* ε4 and amyloid-β status (Lim *et al*., 2012; Ellis *et al*., 2013); however, the strength of *APOE* ε4-related cognitive decline has always been substantially less than that observed for amyloid-β. In the current study, we observed this effect again in the combined sample of healthy older adults and individuals with MCI, assessed over a longer period of time than has been done previously. The only effect of *APOE* ε4 status observed was that for decline in verbal episodic memory. Taken together, these data support the hypothesis that while *APOE* ε4 carriage is a risk factor for amyloid-β positivity, once this occurs, *APOE* ε4 does not moderate disease progression, at least at a level which can be detected by cognitive assessments.

In healthy older adults, SUV ratio has been consistently shown to have a skewed distribution, as opposed to the normal distribution typically observed in clinical and cognitive variables (Jack *et al*., 2008; Rowe *et al*., 2010). As such, in order to parametrically determine associations between amyloid-β levels and cognitive markers, we and others have separated amyloid-β into two categories (positive and negative). However, as sample sizes of individuals who had undergone neuroimaging have grown, there is now some evidence to suggest that additional prognostic information can be derived from the degree of amyloid-β positivity. Recently, we showed that when a receiver operating characteristic analysis of healthy older adult and Alzheimer's disease groups was conducted, an SUV ratio of $\geqslant$1.90 was the optimal cut-off for a diagnosis of Alzheimer's disease (Rowe *et al*., 2013*a*). Further, a high amyloid-β+ scan (e.g. SUV ratio $>$1.90) in non-demented individuals (i.e. healthy older adult and individuals with MCI) was associated with significantly higher positive predictive rates of progression to the next disease stage than a low amyloid-β+ scan (e.g. SUV ratio 1.50–1.90) in non-demented individuals (Rowe *et al*., 2013*a*). These data suggest that there is some dose-dependent effect of the level of amyloid-β positivity on memory decline in non-demented individuals. For example, non-demented individuals with higher levels of amyloid-β positivity may be closer in time to a clinical diagnosis of Alzheimer's disease (Rowe *et al*., 2013*a*; Villemagne *et al*., 2013). In accord with this previous observation, the results of this study show that high amyloid-β+ non-demented individuals show greater rates of decline in episodic memory and language when compared to low amyloid-β+ individuals. Taken together, these results suggest that grouping data into at least two categories of abnormality may be useful in determining the disease risk level in non-demented individuals.

In this study, we have reported estimates of the mean and standard deviation of the slope for the relationship between amyloid-β and each cognitive composite score over 36 months for all stages of the disease. The finding that amyloid-β positivity is associated with cognitive decline across all stages of Alzheimer's disease accords with drug development strategies that have aimed at reducing the effect of amyloid-β on the brain. Therefore, the slope estimates presented here may serve as a guide to inform the rate of amyloid-β-related decline in cognitive function that would be expected to occur in placebo groups at each stage of the illness. Further, they could be used to estimate effect sizes and sample sizes that would be required to provide sufficient statistical power to detect the extent to which amyloid-β- modifying drugs can halt or delay amyloid-β-related cognitive decline.

An important caveat when interpreting the results of this study is that the AIBL study is not an epidemiological but a convenience sample. The selection of MCI groups was biased towards the inclusion of individuals with amnestic MCI. Further, in the recruitment of healthy older adults, participants in AIBL were highly educated, and few had existing or untreated medical, neurological, or psychiatric illnesses. As such, it would be important for these findings to be replicated in amyloid-β+ individuals in population-based samples, such as the Mayo Clinic Study of Aging (Roberts *et al*., 2008), where it is possible that amyloid-β-related decline in cognition may be greater than that observed here. A second caveat is that participants who underwent ^{18}F-florbetapir or ^{18}F-flutemetamol PET imaging were scanned only at their 36-month follow-up assessment, and the number of individuals who underwent neuroimaging using the three different compounds was uneven (Table 1). Importantly though, ^{11}C-PiB, ^{18}F-florbetapir and ^{18}F-flutemetamol are commonly used to measure use Aβ levels (Clark *et al*., 2011; Rowe *et al*., 2013*b*; Vandenberghe *et al*., 2010), and we have shown previously that accumulation of Aβ in HA and MCI groups occur at a rate of less than 0.05 per year (Villemagne *et al*., 2013). Finally, we did not consider whether healthy older adult and MCI amyloid-β+ groups progressed to the next disease classification at a faster rate than amyloid-β− individuals. This was because the primary aim of this study was to consider the disease as a continuous process, and to determine the rate of cognitive decline associated with amyloid-β positivity in each clinical group. Further, previous studies of the same group have shown that after even after removal of individuals for whom the disease had progressed to the next stage (i.e. from healthy to MCI, or from MCI to Alzheimer's disease), decline in memory remained of equivalent magnitude (Lim *et al*., 2012, 2013b; Ellis *et al*., 2013), suggesting that this memory decline is a characteristic of individuals with amyloid-β+ groups, and not merely a consequence of amyloid-β+ groups containing more individuals for whom the disease had progressed.

These limitations notwithstanding, results of this study suggest that the combined detection of a positive biomarker for Alzheimer's disease and objectively-defined decline in memory are reliable indicators of the earliest stages of Alzheimer's disease, and that amyloid-β positivity in individuals with MCI provides additional confirmation that the underlying aetiology is due to Alzheimer's disease. Importantly, these findings suggest that amyloid-β+ healthy older adults may be promising candidates for clinical trials aiming to modify or halt the progression of Alzheimer's disease in its very early stages.

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Conflict of interest

YYL, KE, KH, and CLM report no conflicts of interests. PM is a full-time employee of CogState Ltd., the company that provided the CogState tests used in this study. RHP is a scientific consultant to CogState Ltd. DA has served on scientific advisory boards for Novartis, Eli Lilly, Janssen, Prana and Pfizer Inc.; has received funding for travel from Janssen and Pfizer Inc., has served as Editor-in-Chief for *International Psychogeriatrics*; 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. NTL is the current Editor-in-Chief for *International Psychogeriatrics,* receives research support from NHMRC, has served on scientific advisory boards for Lundbeck and Novartis, has served as a consultant for Schwabe and has received speaker honoraria and travel support from Pfizer, Novartis and Lundbeck. RM is a consultant to a small biotech company, Alzhyme, although currently receives no financial benefits or fees; also holds stock for Alzhyme which is not listed. VV serves as a consultant for Bayer Schering Pharma; and receives research support from NHMRC and NEDO, Japan. CR previously served on scientific advisory boards for Bayer Schering Pharma, Elan Corporation, and AstraZeneca; has received speaker honoraria from GE Healthcare and Bayer Schering Pharma; and receives research support from GE Healthcare, Bayer, Piramal, Avid Radiopharmaceuticals, SIEF, NHMRC, DCRC, an anonymous Foundation and the Alzheimer's Association.

Supplementary material

Supplementary material is available at *Brain* online.

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