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Neurobiology of Aging 31 (2010) 1275–1283

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging

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Received 17 February 2010; received in revised form 1 April 2010; accepted 5 April 2010

Abstract

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, a participant of the worldwide Alzheimer's Disease Neuroimaging Initiative (ADNI), performed ^{11}C-Pittsburgh Compound B (PiB) scans in 177 healthy controls (HC), 57 mild cognitive impairment (MCI) subjects, and 53 mild Alzheimer's disease (AD) patients. High PiB binding was present in 33% of HC (49% in ApoE-ε4 carriers vs 21% in noncarriers) and increased with age, most strongly in ε4 carriers. 18% of HC aged 60-69 had high PiB binding rising to 65% in those over 80 years. Subjective memory complaint was only associated with elevated PiB binding in ε4 carriers. There was no correlation with cognition in HC or MCI. PiB binding in AD was unrelated to age, hippocampal volume or memory. Beta-amyloid (Aβ) deposition seems almost inevitable with advanced age, amyloid burden is similar at all ages in AD, and secondary factors or downstream events appear to play a more direct role than total beta amyloid burden in hippocampal atrophy and cognitive decline.

Keywords: Alzheimer's disease; Mild cognitive impairment; Amyloid imaging; Positron emission tomography; Magnetic resonance imaging

1. Introduction

Dementia is a leading cause of death, disability, and health expenditure in the elderly and Alzheimer's disease (AD) accounts for the majority of cases. The leading hypothesis on the cause of AD is that it results from excessive beta amyloid (Aβ) in the brain, either through increased production or impaired clearance of Aβ oligomers that then aggregate to form extracellular plaques and vascular wall deposits (Villemagne et al., 2006). However, there are many unanswered questions regarding this hypothesis including the timing and rate of Aβ deposition and its relationship to brain atrophy and cognitive decline.

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0197-4580/$ – see front matter
doi:10.1016/j.neurobiolaging.2010.04.007

Molecular neuroimaging techniques such as positron emission tomography (PET), in conjunction with related biomarkers in cerebrospinal fluid (CSF), are proving valuable in the early and differential diagnosis of AD (Fagan et al., 2006; Klunk et al., 2004; Rowe et al., 2007) and have the potential to increase our understanding of the neurobiology of AD through longitudinal observational studies of aging.

The Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship study of Aging (sometimes referred to as Australian Alzheimer's Disease Neuroimaging Initiative [ADNI]) was designed to improve the understanding of the pathogenesis of AD, focusing on its early diagnosis and the identification of factors that eventually may delay onset of AD, while also providing a cohort suitable for early intervention studies (Ellis et al., 2009). The objectives of the neuroimaging arm of AIBL were: (1) to evaluate the degree and pattern of ^{11}C-Pittsburgh Compound B (PiB) retention in a well-characterized cohort of healthy control (HC), mild cognitive impairment (MCI), and AD participants; (2) correlate Aβ burden with clinical and cognitive measures; (3) evaluate the relation between Aβ burden and ApoE genetic status; (4) establish the prevalence of Aβ deposition in asymptomatic HC and in HC with subjective memory complaints; (5) examine the relationship of gray and white matter atrophy to Aβ deposition; and (6) prospectively evaluate the rate and pattern of Aβ deposition and brain neurodegenerative changes over time. The latter will be the subject of future papers.

The imaging protocols and aspects of the clinical and neuropsychology assessment of AIBL were designed to permit comparison and pooling of data with the ADNI allowing AIBL to be a substantial contributor to the worldwide ADNI (WW-ADNI) research effort.

2. Methods

2.1. Participants

Written informed consent was obtained from all participants. Approval for the study was obtained from the St Vincent's Hospital, Melbourne, Austin Health, Edith Cowan University and Hollywood Private Hospital Human Research Ethics Committees. Healthy controls (HC) were recruited by advertisement in the community while the MCI and AD participants were recruited from tertiary memory disorders clinics or private geriatricians, psychiatrists, and neurologists who subspecialize in dementia. The study commenced in November 2006 and was designed as a prospective study to evaluate all participants every 18 months. The aim was to recruit 1000 participants, 60% HC, 20% MCI, and 20% mild AD with imaging of 25% of each group. Actual enrollment into the neuroimaging arm was 177 HC, 57 MCI, and 53 mild AD (26% of the cohort). Selection of MCI and AD for imaging was on a first come basis. HC selection was controlled to ensure a wide age spread from 60 years through to the very elderly and that approximately 50% had subjective memory complaint (SMC) and that approximately 50% were ApoE ε4 carriers.

All participants were at least 60 years of age and in good general health with no history of stroke or other neurological disease. All AD patients met National Institute of Neurological and Communicative Disorders–Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria for probable AD (McKhann et al., 1984), and had a Clinical Dementia Rating (CDR) of 1 or more, while all participants in the MCI group met criteria of subjective and objective cognitive difficulties in the absence of significant functional loss and had a Clinical Dementia Rating of < 1 (Petersen et al., 1999; Winblad et al., 2004). Fifty-two MCI participants fulfilled criteria for "amnestic" MCI, and 5 were nonamnestic cases (4 were nonamnestic multidomain and 1 was nonamnestic single domain). HC were further separated in those who reported subjective memory complaints ($n = 95$) and those who did not ($n = 82$), according to their response to the question: "Do you have any difficulty with your memory?"

ApoE genotype was determined by direct sequencing.

2.2. Neuropsychological evaluation

The full battery comprised the Mini Mental State Examination (MMSE) of Folstein, California Verbal Learning Test – 2nd Ed. (CVLT-II, long delay), Logical Memory I and II (WMS; Story 1 only), Delis-Kaplan Executive Function System (D-KEFS) verbal fluency, 30-item Boston Naming Test (BNT), Wechsler Test of Adult Reading (WTAR), Digit Span and Digit Symbol-Coding subtests of the Wechsler Adult Intelligence Scale – 3rd Ed. (WAIS–III), the Stroop task (Victoria version), and the Rey Complex Figure Test (RCFT). For the purpose of assessing the association between memory impairment and neuroimaging findings, the results from the CVLT-II long delay were used.

2.3. Image acquisition

2.3.1. Magnetic resonance imaging

All subjects received magnetic resonance imaging (MRI) using the ADNI 3-dimensional (3D) Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence, with 1×1 mm in-plane resolution and 1.2 mm slice thickness, TR/TE/T1 = 2300/2.98/900, flip angle 9°, and field of view 240×256 and 160 slices. T2 fast spin echo (FSE) and fluid attenuation inversion recovery (FLAIR) sequences were also obtained.

2.3.2. Positron emission tomography

Each subject received ~370 MBq ^{11}C-PiB IV over 1 minute. A 30-minute acquisition in 3D mode consisting of 6 frames each of 5 minutes, starting 40 minutes after injection of PiB was performed using a Phillips Allegro (Phillips Medical Systems, Eindhoven, The Netherlands) PET cam-

era. A transmission scan was performed for attenuation correction. PET images were reconstructed using a 3D Ramla algorithm. PET data was corrected for partial volume effects using a 3-compartment model as previously described (Bourgeat et al., 2010).

2.4. Image analysis

2.4.1. MRI segmentation

As described elsewhere, T1- and T2-weighted magnetic resonance images for each subject were classified into gray matter (GM), white matter (WM). and CSF using an implementation of the expectation maximization segmentation algorithm (Ourselin et al., 2001). The algorithm computed probability maps for each tissue type and was used to assign each voxel to its most likely tissue type.

2.4.2. Region-based analysis

The Montreal Neurological Institute (MNI) single-subject MRI brain template (Collins et al., 1998) and corresponding Automated Anatomical Labeling (AAL) region of interest (ROI) template (Tzourio-Mazoyer et al., 2002) and tissues priors were spatially normalized to each participant to automatically obtain a parcellation for each selected atlas and provide spatial priors for GM, WM, and CSF to guide the segmentation. To improve the accuracy of analysis of the hippocampus, a separate, manually delineated template was drawn on the Montreal Neurological Institute single-subject every 1 mm on coronal slices, and was subsequently used for hippocampal volume.

ROI measurements were weighted averaged across both hemispheres. The measured volumes were normalized for head size using the total intracranial volume, defined as the sum of GM, WM, and CSF volumes. The volume results are presented as the proportion of the total intracranial volume.

Coregistration of each individual's MRI with the PET images was performed in PET native space with MilxView®, developed by the Australian e-Health Research Centre — BioMedIA (Brisbane, Australia). The MRI ROI template was then transferred to the coregistered PET images. Standardized uptake values (SUV) were calculated for all brain regions examined. SUV ratios (SUVR) were generated by normalizing the regional SUV to the cerebellar cortex SUV. Neocortical Aβ 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.

2.5. Determination of cutoff values

To establish the sensitivity, specificity, and accuracy of the neuroimaging techniques, a "cutoff" level was determined for each of the variables under study. For the MRI measures, the HC and AD data were analyzed with the "2-graph receiver operating characteristic" (TG-ROC) method (Greiner et al., 1995). This produced a cutoff for hippocampal volume of 0.004. In accord with previous studies reporting marked PiB retention in cognitively unimpaired HC (Aizenstein et al., 2008; Mintun et al., 2006; Pike et al., 2007; Rowe et al., 2007) a lack of normal distribution of PiB SUVR was observed in the 177 HC, and a PiB SUVR "cutoff" level was determined to separate those participants with low PiB retention from those with high PiB retention in the brain. Consequently, to identify a PiB "cutoff", analysis was performed on all elderly HC participants using a hierarchical cluster analysis, yielding a mean cutoff for neocortical SUVR of 1.5.

2.6. Statistical evaluation

Normality of distribution was tested using the Shapiro-Wilk test and visual inspection of variable histograms. Statistical evaluations between group means were performed using a Tukey-Kramer HSD test followed by a Dunnet's test to compare each group with controls, Categorical differences were evaluated using Fisher's exact test. Age-corrected Pearson's product-moment correlation analyses were conducted between PiB SUVR and other variables. Statistical significance was defined as $p < 0.05$. Corrections for multiple comparisons were performed using false discovery rate (FDR). Data are presented as mean ± SD unless otherwise stated.

3. Results

Demographic characteristics of the cohort are shown on Table 1. The MCI group was slightly, but significantly,

Table 1
Demographic characteristics of the 287 participants enrolled in AIBL, who underwent neuroimaging evaluation

	HC	MCI	AD	HC nMC	HC SMC
n	177	57	53	81	96
Age	71.6 ± 7.4	75.5 ± 7.5[a]	72.6 ± 8.9	72.0 ± 7.5	71.2 ± 7.4
Gender (M/F)	89/88	29/28	23/30	42/39	47/49
MMSE	28.8 ± 1.2	27.0 ± 2.3[a]	20.5 ± 4.9[a]	28.9 ± 1.1	28.6 ± 1.3
%ApoE ε4	43%	55%	69%[a]	49%	38%
CVLT-II l.d.	0.90 ± 0.95	−1.40 ± 1.04[a]	−2.47 ± 0.83[a]	1.04 ± 0.85	0.78 ± 1.01

Key: AD, Alzheimer's disease; AIBL, Australian Imaging, Biomarkers and Lifestyle; CVLT-II l.d., California Verbal Test II long delay (z scores); HC, healthy controls; HC nMC, healthy controls with no memory complaints; HC SMC, healthy controls with subjective memory complaints; MCI, mild cognitive impairment.

[a] Significantly different from controls ($p < 0.05$).

older than the HC and AD groups. Forty-three percent of the HC group were ε4 carriers (69 heterozygous, 7 homozygous), compared with 55% of MCI (26 heterozygous, 5 homozygous), and 69% of AD (23 heterozygous, 11 homozygous). HC, MCI, and AD groups differed significantly in average MMSE scores ($p < 0.05$). The HC-SMC and HC-non-memory complaint (nMC) did not differ significantly in terms of demographic characteristics (age, gender balance, APOE 4 carrier proportions; all $p > 0.05$) nor cognitive measures (MMSE and CVLT-II long delay z score; both $p > 0.05$).

Neocortical PiB binding was higher in AD than in the MCI group, which, in turn was higher than in HC (Fig. 1). In the HC and MCI groups neocortical PiB binding did not follow a normal distribution. Using the cutoff for neocortical PiB SUVR of 1.5 derived from hierarchical cluster analysis to separate high from low PiB binding, high binding was found in 33% of HC affecting 49% of ApoE-ε4 allele carriers versus 21% of noncarriers. High PiB binding was found in 68% of MCI and 98% of AD patients. Interestingly, 31% of the 52 MCI subjects who fulfilled criteria for "amnestic" MCI had low PiB binding. Among subjects with high PiB binding, neocortical SUVR was lower in HC (2.00 ± 0.38) than in MCI (2.30 ± 0.47) that, in turn, was less than in AD (2.48 ± 0.47). In AD, on visual inspection of the images, PiB binding was greatest in the orbitofrontal, posterior cingulate, precuneus, and lateral temporal cortex and in the striatum, with relative sparing of medial temporal, occipital, and sensorimotor areas. When present in HC, the distribution was similar to AD though uptake was generally less intense and there was less involvement of the posterior cingulate/precuneus region.

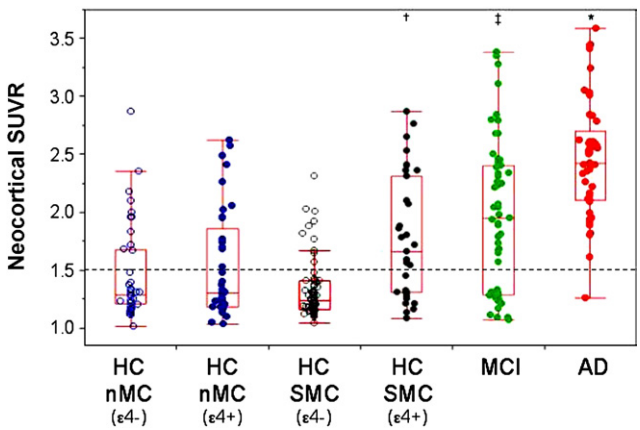

Fig. 1. Box and whiskers plot of beta amyloid (Aβ) burden by clinical classification in the Australian Imaging, Biomarkers and Lifestyle (AIBL) cohort. Aβ burden in the Alzheimer's disease (AD) group was significantly higher (*) compared with the mild cognitive impairment (MCI) and healthy control (HC) group. Aβ burden in the MCI group was significantly higher (‡) than in HC. HC with subjective memory complaints (SMC) with at least 1 ApoE ε4 allele had significantly higher (†) Aβ burden than non-ε4 SMC and HC with no memory complaints (nMC). Dotted line denotes threshold between high and low Pittsburgh Coumpound B (PiB) binding.

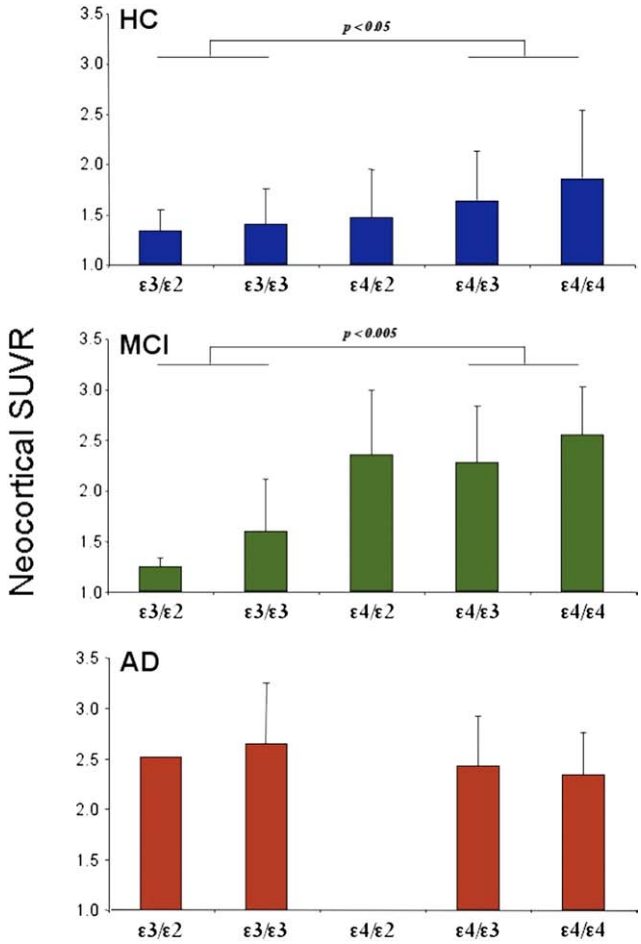

Fig. 2. Relation between beta amyloid (Aβ) burden as measured by Pittsburgh Coumpound B (PiB) and ApoE genetic status. In the healthy control (HC) and mild cognitive impairment (MCI) groups, carriers of at least 1 ApoE-ε4 allele had significantly higher Aβ burden. No differences were observed in the Alzheimer's disease (AD) group.

PiB SUVR was significantly greater in ε4 carriers in the HC ($p = 0.0002$) and MCI groups ($p < 0.0001$) but there was no difference in the AD group (Fig. 2). In the MCI group, carriers of a least 1 ε4 allele had significantly greater hippocampal atrophy than noncarriers (0.0043 ± 0.0004 vs. 0.0036 ± 0.0004, $p = 0.008$). No differences were observed in hippocampal volumes between ε4 carriers and noncarriers in the HC or AD groups.

HC with high PiB binding were significantly older than those with low PiB binding (75.3 ± 7.03 vs. 69.7 ± 6.91, respectively; $p < 0.0001$). In the HC group, PiB binding increased steadily with age (Fig. 3) and the prevalence of subjects with high PiB binding increased from 18% of those aged 60–69 years, to 37% on those aged 70–79 years, to 65% of those aged > 80 years. Five of 6 HC aged > 85 had high PiB binding. The correlation of neocortical SUVR with age was significantly stronger in ε4 carriers with both greater and more frequent PiB binding at an earlier age than

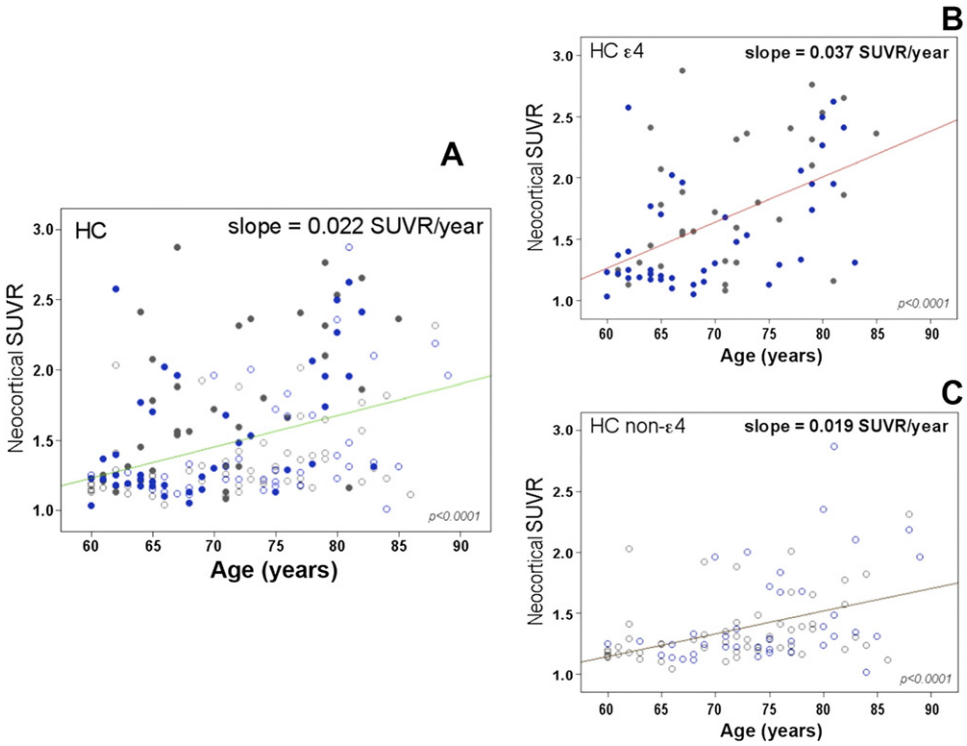

Fig. 3. Correlation between beta amyloid (Aβ) burden and age in healthy control (HC) subjects. There was a significant correlation between Aβ burden and age (A), and correlation that was stronger in ApoE ε4 carriers (B) than in non-ε4 carriers (C).

in noncarriers (slope 0.037 SUVR/year vs. 0.019 SUVR/year, respectively; $p = 0.03$) (Fig. 3).

No differences were observed in PiB binding between males and females in the HC or MCI groups while in AD, males had significantly higher PiB binding than females (2.33 ± 0.47 vs. 2.63 ± 0.47; $p = 0.02$).

Subjective memory complaint was not associated with elevated PiB binding except in ε4 carriers (Fig. 1). There were no significant differences in memory scores between HC with or without memory complaints nor between HC with high versus low PiB binding. While memory impairment was significantly greater in MCI with high PiB binding compared with those with low PiB binding (CVLT-II long delay -1.59 ± 0.84 vs. -0.98 ± 1.32; $p = 0.04$), no correlation was found between PiB binding and MMSE or memory scores, although there was a trend between CVLT-II long delay and Aβ burden ($r = -0.24$; $p = 0.07$).

Global and hippocampal gray matter values, as well as white matter and ventricular volumes are presented in Table 2. The AD group had significantly lower hippocampal gray matter volume than MCI and HC, while the MCI group in turn, had significantly lower hippocampal gray matter volume than HC (Fig. 4). The AD group had significantly lower global gray and white matter volumes and larger ventricles than HC (Fig. 4). Hippocampal volume, global gray and white matter volumes, as well as ventricular volumes were associated with age in the HC group (correlation coefficients of −0.28; −0.41; −0.41; and +0.29, respec-

Table 2
Neuroimaging profile of the AIBL cohort

	HC	MCI	AD	HC nMC	HC SMC
n	177	57	53	81	96
Neocortical SUVR	1.49 ± 0.44	1.96 ± 0.64[a,b]	2.46 ± 0.49[a]	1.49 ± 0.43	1.50 ± 0.44
Hippocampus	0.0041 ± 0.0003	0.0038 ± 0.0005[a,b]	0.0036 ± 0.0004[a]	0.0042 ± 0.0002	0.0041 ± 0.0004
Global gray matter	0.44 ± 0.02	0.42 ± 0.02[a]	0.42 ± 0.02[a]	0.44 ± 0.01	0.43 ± 0.02
White matter	0.29 ± 0.03	0.29 ± 0.02	0.28 ± 0.03	0.29 ± 0.03	0.29 ± 0.03
Ventricles	0.016 ± 0.008	0.021 ± 0.01[a,b]	0.026 ± 0.01[a]	0.017 ± 0.007	0.016 ± 0.009

Key: AD, Alzheimer's disease; AIBL, Australian Imaging, Biomarkers and Lifestyle; HC, healthy controls; HC nMC, healthy controls with no memory complaints; HC SMC, healthy controls with subjective memory complaints; MCI, mild cognitive impairment; SUVR, standardized uptake value ratio.

[a] Significantly different than controls ($p < 0.05$).

[b] Significantly different than AD ($p < 0.05$).

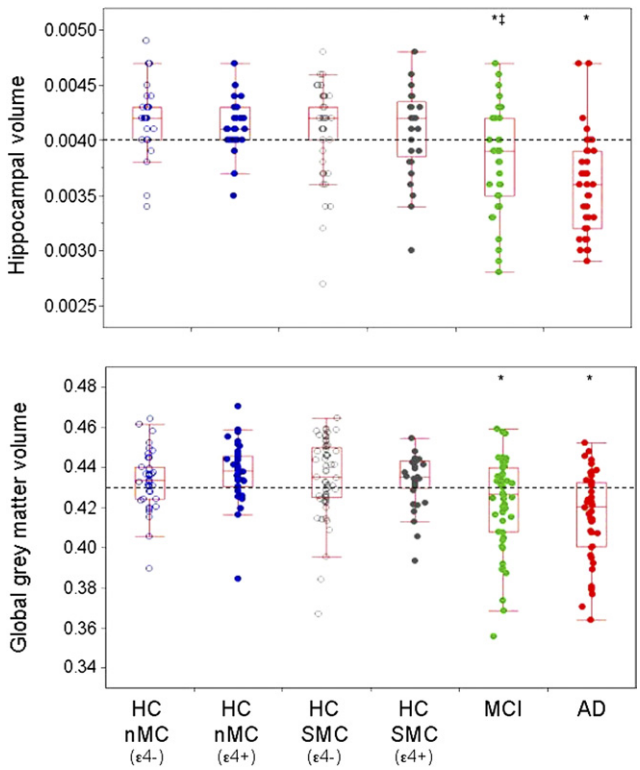

Fig. 4. Box and whiskers plot of global and hippocampal gray matter volumes by clinical classification in the Australian Imaging, Biomarkers and Lifestyle (AIBL) cohort. Global gray matter (GM) volume in the Alzheimer's disease (AD) and mild cognitive impairment (MCI) groups were significantly lower (*) compared with healthy control (HC) group. Hippocampal volume was significantly lower (*) in the AD group compared with MCI and HC. Hippocampal volume in the MCI group was significantly lower (‡) than in HC. No differences were observed between subjective memory complaint (SMC) subjects and noncomplainers, nor between HC ε4 carriers and non-ε4 carriers. Dotted line denotes threshold between atrophy/nonatrophy.

tively; all $p < 0.0003$). A stronger association between MRI volumetrics and age was observed in the MCI group (−0.46; −0.44; and −0.39 for hippocampal volume, global gray matter volume, and ventricular volume, respectively), while in the AD group only hippocampal volume ($r = -0.29$, $p = 0.05$) and white matter volume ($r = -0.31$, $p = 0.04$) were associated with age. Subjective memory complaint was not associated with lower hippocampal volumes. While hippocampal volume correlated with memory impairment in the MCI group (CVLT-II long delay: $r = 0.29$, $p = 0.04$) and MMSE in HC ($r = 0.19$, $p = 0.01$), no correlations were found in AD. Global gray matter volume correlated with MMSE only in the AD group ($r = 0.39$, $p = 0.008$). Neocortical PiB binding correlated inversely with hippocampal volume in MCI ($r = -0.38$, $p = 0.006$) and weakly in HC ($r = -0.20$, $p = 0.01$), but no correlation was found in AD patients. Importantly, significant correlations between neocortical PiB binding and hippocampal volume in HC and MCI were still present if nonpartial volume-corrected PET data were utilized in the analysis ($r = -0.20$, $p = 0.01$ and $r = -0.37$, $p = 0.006$, respectively). No correlation between hippocampal PiB binding and hippocampal volume was observed in any of the groups. There was also an inverse correlation between neocortical PiB binding and global gray matter volume in the HC group using either partial volume corrected or noncorrected data ($r = -0.30$, $p < 0.0001$ and $r = -0.25$, $p < 0.001$, respectively) but not in the MCI group. In the AD group an association between neocortical PiB binding and global gray matter volume was only present when partial volume corrected data were used.

Using a neocortical SUVR threshold of 1.5 to separate individuals with high PiB binding from those with low or no PiB binding, PiB scans had 73% accuracy for distinguishing AD from HC (Fisher's test, $p < 0.0001$) with sensitivity of 98% and specificity of 66% (Table 3). Hippocampal volume also had an accuracy of 73% (Fisher's test, $p < 0.0001$) but lower sensitivity (78%) and higher specificity (80%). Global gray matter volume had test accuracy of 64% (Fisher's test, $p < 0.0001$) (Table 3).

4. Discussion

This is the first report on AIBL neuroimaging studies, where 287 participants (26% of the whole AIBL cohort) underwent MRI and PiB PET scans. Out of the 287 participants, 177 (62%) were classified as HC, 57 (20%) fulfilled

Table 3
Diagnostic Performance of PiB and MRI Measures

	Neocortical PiB	Hippocampal volume	Global gray matter volume
Threshold[a]	1.5	0.004	0.43
Sensitivity	98% (95% CI, 88–100%)	78% (95% CI, 63%–89%)	67% (95% CI, 52%–80%)
Specificity	66% (95% CI, 59–73%)	80% (95% CI, 73%–86%)	71% (95% CI, 63%–78%)
PPV	47% (95% CI, 38–57%)	52% (95% CI, 40%–64%)	39% (95% CI, 29%–51%)
NPP	99% (95% CI, 95–100%)	93% (95% CI, 87%–96%)	89% (95% CI, 82%–93%)
Test accuracy	73%	73%	64%

Key: CI, confidence interval; MRI, magnetic resonance imaging; NPV, negative predictive value; PiB, Pittsburgh Coumpound B; PPV, positive predictive value; ROC, Receiver-Operating Characteristic; SUVR, standardized uptake value ratio.

[a] For PiB a threshold of 1.5 for the neocortical SUVR was determined by hierarchical cluster analysis of the healthy controls (HC). For hippocampal volume and global gray matter volume the threshold was determined by double ROC analysis of the Alzheimer's disease (AD) and HC.

criteria for MCI (90% amnestic type), and 53 (18%) fulfilled criteria for AD. The AIBL study was designed to improve understanding of the pathogenesis of AD, focusing on early AD diagnosis, while also providing a cohort suitable for early intervention studies (Ellis et al., 2009). The objective of the present report was to establish a profile of neuroimaging findings for each group in order to be able to longitudinally evaluate changes in beta-Aβ deposition, brain volume, and cognition.

The AD group showed higher Aβ burden, as defined by PiB, than MCI and HC groups, in accord with previous reports (Rowe et al., 2007). One of the 53 participants classified as AD had low PiB binding. This may be due to incorrect clinical diagnosis as, even in highly specialized centers, the accuracy of clinical diagnosis compared with postmortem histopathological diagnosis is around 85%–90% (Gearing et al., 1995; Lim et al., 1999; Rasmusson et al., 1996). Alternatively, PiB might have failed to bind Aβ deposits in this individual. There have been 2 reports of low PiB binding in patients with a moderate number of plaques on histopathological examination (Cairns et al., 2009; Leinonen et al., 2008). It is possible that different conformations of aggregated Aβ might have different binding profiles to PiB (Levine and Walker, 2010; Lockhart et al., 2007) that on occasion will lead to a false negative scan. Our data suggest that this is a rare occurrence. Our findings in the MCI and HC groups are also in accord with previous reports, with 2 thirds of the MCI and 1 third of the HC participants presenting with high PiB retention (Aizenstein et al., 2008; Pike et al., 2007; Rowe et al., 2007). It should be noted that the HC in the imaging arm of AIBL are not representative of the general population due to preferential inclusion of ApoE-ε4 allele carriers. These make up 43% of the HC in this study, about twice the prevalence of ApoE-ε4 in the general population. In this study we found that ApoE-ε4 allele carriers are twice as likely to have high PiB binding than healthy elderly ε4 non-carriers.

As previously reported (Reiman et al., 2009; Rowe et al., 2007) ApoE ε4 status is associated with higher Aβ burden. In the HC and MCI groups, Aβ burden was associated with ApoE genetic status, with ε4 allele carriers presenting with significantly higher Aβ burden than noncarriers. In contrast, no association between ApoE genetic status and Aβ burden was found in the AD group. The finding that HC carriers of an ApoE-ε4 allele have earlier Aβ deposition than HC noncarriers is well in agreement with the ApoE literature (Petersen et al., 1996). In this study, subjective memory complaint did not indicate greater likelihood of prodromal AD with no increase in PiB binding, no reduction of hippocampal volume, and no reduction in memory test scores compared with noncomplainers, except when an ApoE-ε4 allele was also present as this combination was associated with elevated PiB binding.

Remarkably, the prevalence of AD in the general population (Tobias et al., 2008) follows the same behavior over time as the prevalence of Aβ deposition in asymptomatic HC but lags by over a decade, whether the Aβ deposition is measured in vivo by PET as in this study or in postmortem studies (Braak et al., 1996; Davies et al., 1988; Sugihara et al., 1995) (Fig. 5). Our study shows that amyloid deposition is almost inevitable with advanced age with 5 of the 6 HC aged over 85 demonstrating high PiB binding.

Fig. 5. Comparison of the age prevalence of beta amyloid (Aβ) deposition as detected at postmortem in cognitively unimpaired subjects (green triangles), the age prevalence of Alzheimer's disease (AD) in the general population (red diamonds), and the prevalence of high PiB binding in healthy controls (HC) from the Australian Imaging, Biomarkers and Lifestyle (AIBL) cohort (blue dots). The postmortem and epidemiological data behave in a similar exponential fashion. The Pittsburgh Coumpound B (PiB) positron emission tomography (PET) results are closely related to the postmortem data, both suggesting that Aβ deposition precedes the diagnosis of AD by ~15 years.

In AD patients the age-corrected Aβ burden was significantly higher in males than in females. This suggests that for similar cognitive impairment, females may be more susceptible to the effects of Aβ, requiring a lower Aβ burden to manifest dementia.

A correlation between PiB binding and degree of memory impairment in nondemented individuals has been previously reported (Pike et al., 2007) but we were not able to replicate this finding in the AIBL cohort. In our MCI group there was a trend relating PiB binding to memory impairment after age correction (CVLT-II long delay: $r = -0.24$, $p = 0.07$). The most likely explanation for this discrepancy is the lower proportion of nonamnestic MCI in the AIBL cohort. Only 5 out of 57 MCI were nonamnestic. Nonamnestic MCI are more likely to have low PiB binding and therefore drive a correlation between memory scores and PiB binding within an MCI group. The finding in our cohort that 31% of amnestic MCI did not have elevated PiB binding suggests that subject selection for therapeu-

tic trials in MCI by current criteria will include a large proportion of subjects that are unlikely to have prodromal AD, even if the criteria are tightened to include only amnestic MCI subjects.

The clinical diagnosis of AD is typically based on progressive cognitive impairments while excluding other diseases. This precludes early intervention with disease-modifying medications during the presymptomatic period, which by arresting neuronal loss would presumably achieve the maximum benefits of such therapies. Therefore diagnosis should move away from the identification of signs and symptoms of neuronal failure — indicating that central compensatory mechanisms have been exhausted and extensive synaptic and neuronal damage is present — to the noninvasive detection of specific biomarkers for particular traits underlying the pathological process (Clark et al., 2008). The AIBL study has demonstrated that amyloid imaging may be a useful tool in this regard, detecting a high proportion of nondemented individuals with significant Aβ deposition in the brain. At this stage of disease development even a modest effect on amyloid deposition could substantially delay the clinical onset of the disease. However, our study has also shown a lack of direct correlation between PiB binding and cognitive impairment indicating that other factors, perhaps downstream mechanisms triggered by amyloid formation, may also need to be addressed to successfully prevent the development of dementia.

The role of imaging and quantifying Aβ burden in vivo is becoming increasingly important. When antiamyloid therapies become available, amyloid imaging would not only allow assessment of eligibility of adequate candidates but also monitoring such therapies, while also permitting its evaluation as a potential predictor of treatment response. In the meantime, the ability of amyloid imaging in detecting Aβ deposition seems to be well suited for subject selection and monitoring efficacy in antiamyloid therapy trials, thus aiding in reducing sample size, and minimizing cost while maximizing outcomes.

Follow-up clinical and cognitive assessment and imaging 18 months from enrollment in the AIBL study is underway. This will provide information on the rate of amyloid deposition, further clarify the relationship between amyloid accumulation and cognitive decline, and assess the predictive value of neuroimaging modalities for cognitive decline and progression to clinical Alzheimer's disease.

Disclosure statement

All authors declare no conflicts.

Written informed consent was obtained from all participants. Approval for the study was obtained from the St Vincent's Hospital, Melbourne, Austin Health, Edith Cowan University and Hollywood Private Hospital Human Research Ethics Committees.

Acknowledgements

We thank the AIBL Study Group (www.aibl.csiro.au) and Prof. Michael Woodward, Dr. John Merory, Dr. Peter Drysdale, Ms. Tanya Betts, Dr. Rachel Mulligan, Dr. Uwe Ackermann, Dr. Gordon Chan, Dr. Kenneth Young, Dr. Sylvia Gong, Dr. Alex Bahar-Fuchs, Mr. Neil Kileen, Mr. Tim Saunder, Ms. Jessica Sagona, and Mr. Jason Bradley and for their assistance with this study.

The study was supported by the Commonwealth Scientific Industrial Research Organization (CSIRO) P-Health Flagship Collaboration Fund through the Australian Imaging, Biomarkers and Lifestyle Flagship study of Ageing (Australian Imaging, Biomarkers and Lifestyle [AIBL]), the Austin Hospital Medical Research Foundation, Neurosciences, Victoria, and the University of Melbourne.

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