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β-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease

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β-amyloid (Aβ) deposition is pathognomic for Alzheimer's disease (AD), but may occur in normal elderly people without apparent cognitive effect. Episodic memory impairment is an early and prominent sign of AD, but its relationship with Aβ burden in non-demented persons and in AD patients is unclear. We examined this relationship using ^{11}C-PIB-PET as a quantitative marker of Aβ burden *in vivo* in healthy ageing (HA), mild cognitive impairment (MCI) and AD. Thirty-one AD, 33 MCI and 32 HA participants completed neuropsychological assessment and a ^{11}C-PIB-PET brain scan. Multiple linear regression analyses were conducted relating episodic memory performance and other cognitive functions to Aβ burden. Ninety-seven percent of AD, 61% of MCI and 22% of HA cases had increased cortical PIB binding, indicating the presence of Aβ plaques. There was a strong relationship between impaired episodic memory performance and PIB binding, both in MCI and HA. This relationship was weaker in AD and less robust for non-memory cognitive domains. Aβ deposition in the asymptomatic elderly is associated with episodic memory impairment. This finding, together with the strong relationship between PIB binding and the severity of memory impairment in MCI, suggests that individuals with increased cortical PIB binding are on the path to Alzheimer's disease. The data also suggests that early intervention trials for AD targeted to non-demented individuals with cerebral Aβ deposition are warranted.

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

Abbreviations: AD = Alzheimer's disease; MCI = mild cognitive impairment; SUV = standardized uptake value

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Introduction

β-Amyloid (Aβ) deposition in the brain is implicated in the pathogenesis of Alzheimer's disease (AD) and is central to current aetiological theories (Masters and Beyreuther, 2006). While a strong relationship is evident between neurofibrillary tangles and cognition, consensus has not been reached on the relationship between Aβ burden and cognition (Cummings, *et al.*, 1996; Nagy *et al.*, 1996; Bartoo *et al.*, 1997; Kanne *et al.*, 1998; Mufson *et al.*, 1999; Bussière *et al.*, 2002; Giannakopoulos *et al.*, 2003; Guillozet, *et al.*, 2003; Thomas *et al.*, 2005; Markesbery *et al.*, 2006; Prohovnik *et al.*, 2006).

Most research into Aβ burden and cognition has focused on people with dementia, despite evidence for a long preclinical phase preceding the diagnosis of AD. Subtle cognitive deficits are present up to 9 years before dementia is diagnosed (Amieva *et al.*, 2005) and neuropathological studies in Down syndrome have demonstrated cortical Aβ plaques decades before the usual onset of dementia that almost invariably develops in these individuals (Beyreuther *et al.*, 1992). Neuropathological studies have also documented moderate numbers of Aβ plaques in the cerebral cortex of more than a quarter of nondemented persons aged over 75 years, equivalent to the prevalence of dementia

at age 85 years (Ferri *et al.*, 2005), suggesting that neuropathological changes precede the clinical expression of AD by many years (Price and Morris, 1999; Bennett *et al.*, 2006).

Mild cognitive impairment (MCI) is considered a transitional stage between healthy aging (HA) and AD (Petersen *et al.*, 2001), although up to 40% of people meeting the criteria for MCI do not develop overt clinical dementia (Busse *et al.*, 2006*a*). The degree of neuropathological change in MCI is variable, with many demonstrating AD-like pathological features (Markesbery *et al.*, 2006; Petersen *et al.*, 2006), but the relationship between Aβ burden and cognition in MCI is not well understood.

While post-mortem studies provide a comprehensive assessment of the neuropathologic changes at the time of death, conclusions from such studies can be limited by substantial delays between cognitive assessment and death in patients with AD, and the advanced age at death of non-demented cases (Bennett *et al.*, 2006). New Aβ-specific PET radiotracers allow quantitative analysis of Aβ burden *in vivo* and can therefore overcome such limitations. The best validated of these radiotracers is 'Pittsburgh Compound-B' (^{11}C-PIB; Klunk *et al.*, 2004), a carbon-11-labelled derivative of the thioflavin-T amyloid dye, that binds with high affinity and high specificity to neuritic Aβplaques (Klunk *et al.*, 2003). ^{11}C-PIB-PET studies in AD have shown robust cortical binding (Klunk *et al.*, 2004; Kemppainen *et al.*, 2006), and correlations with the rate of cerebral atrophy (Archer *et al.*, 2006), parietotemporal hypometabolism (Edison *et al.*, 2007), and decreased CSF $A\beta_{42}$ (Fagan *et al.*, 2006).

The current study utilizes ^{11}C-PIB-PET to investigate the relationship between Aβ burden and concurrent cognitive performance, and finds a strong relationship between PIB binding and episodic memory impairment in HA and MCI participants, but not in those with AD.

Methods

Participants

The study included 31 participants with mild to moderate AD, 33 people with MCI, and 32 asymptomatic volunteers from a healthy ageing study. Participants were excluded if they were not fluent in English, Mini-Mental State Examination (MMSE) was less than 12, or there was a history of acquired brain injury or alcoholism. Written informed consent was obtained prior to participation. The relevant committees at Austin Health and Monash University granted ethics approval. All AD participants met NINCDS-ADRDA criteria for probable AD (McKhann *et al.*, 1984). All MCI participants met the following recently published consensus criteria: (i) clinical opinion that they were neither normal nor demented, (ii) subjective report of decline over time with objective evidence of impairment, (iii) no significant functional loss (Winblad *et al.*, 2004). Participants were classified based on their clinical history, presentation and neuropsychological assessment where objective impairment was regarded as at least one neuropsychological test score falling 1.5 SD or more below relevant normative data. On neuropsychological assessment, 24 of the MCI participants had objective memory impairment (amnestic MCI), six had objective cognitive impairment without memory impairment (non-amnestic MCI) and three were classified as MCI based on self and reliable informant report of progressive decline (termed here 'subjective MCI'). The subjective MCI participants had evidence of premorbid superior cognitive abilities but current cognitive performance in the average or low average range. Most of the HA participants (91%) were recruited from the longitudinal healthy ageing study being conducted at the Mental Health Research Institute of Victoria (Weaver Cargin *et al.*, 2006). In all participants, apolipoprotein-E (ApoE) genotype was determined by PCR amplification of genomic DNA.

As shown in Table 1, groups were well matched for age, years of education and gender. HA were less likely to have an ApoE ε4 allele (Fisher's exact test = 0.004) and more likely to have a first-degree relative with AD (Fisher's exact test = 0.009) compared with MCI and AD participants. Characteristics of MCI participants are also shown in Table 1. Non-amnestic MCI cases were younger than those with amnestic MCI and all were male.

Neuropsychological assessment

Participants were administered the MMSE (Folstein *et al.*, 1975), 30-item Boston Naming Test (BNT; Saxton *et al.*, 2000), Digit Span forwards [DSp(f)] and backwards [DSp(b)] and Digit Symbol-Coding (DS-C) from the Wechsler Adult Intelligence Scale – Third edition (WAIS-III; Wechsler, 1997), California Verbal Learning Test – Second edition (CVLT-II; Delis *et al.*, 2000), Rey Complex Figure Test (RCFT; Meyers and Meyers, 1995), letter fluency (Benton, 1968) and category fluency tasks.

A composite episodic memory score was calculated by taking the average of the *z* scores (generated using the HA group as the reference) for RCFT (30 min) long delay and CVLT-II long delay. A composite non-memory cognition score was designed to examine participants' average performance on tasks not involving episodic memory. This was calculated by taking the average of the *z* scores for the BNT, letter fluency, category fluency, DSp(f), DSp(b), DS-C and RCFT copy.

Neuroimaging

All participants had a 3D spoiled gradient echo (SPGR) T1-weighted MRI for screening and co-registration with the PET images. Within 11 ± 22 days of the neuropsychological assessment, participants also had a ^{11}C-PIB-PET scan, as previously described (Rowe *et al.*, 2007). PET standardized uptake value (SUV) data acquired 40–70 min post-PIB injection were summed and normalized to the cerebellar cortex SUV, resulting in a region to cerebellar ratio termed the SUV ratio (SUVR). The cerebellar cortex was used as a reference region as it is relatively devoid of senile plaques and shows no PIB binding in controls or AD (Price *et al.*, 2005; Rowe *et al.*, 2007). Regions of interest (ROI) were drawn on the individual MRI and transferred to the co-registered PET images. Neocortical Aβ burden was expressed as the average SUVR of the area-weighted mean for the following cortical ROIs: frontal (consisting of dorsolateral prefrontal, ventrolateral prefrontal and orbitofrontal regions), superior parietal, lateral temporal, lateral occipital and anterior and posterior cingulate. No correction for partial volume was applied to the PET data.

The data were further analysed using a receiver operating characteristic curve to establish the most accurate cut-off

Table 1 Selected participant characteristics and composite scores

	AD	MCI	HA	aMCI	nMCI	sMCI	MCI PIB+	MCI PIB−
N	31	33	32	24	6	3	20	13
Age	74.8 (10.2)	70.7 (9.6)	71.7 (6.6)	72.3 (8.0)	63.7 (11.6)	72.0 (14.8)	73.2 (7.4)	66.9 (11.4)
Education	12.1 (4.3)	12.4 (4.2)	12.2 (3.5)	12.1(4.0)	12.5 (4.4)	14.7 (5.8)	12.2 (3.9)	12.9 (4.7)
% Male	48	45	50	38	100	0	30	69
% ε4 ApoE	72[a]	58	31	63	50	33	80	23
% Family history	16	27	50	25	33	33	35	15
SUVR neocortex	2.42 (0.37)	1.85 (0.60)	1.40 (0.33)	2.04 (0.57)	1.24 (0.19)	1.59 (0.55)	2.27 (0.36)	1.21 (0.15)
MMSE	22.7 (3.6)	26.6 (2.2)*	29.2 (0.9)	26.1 (2.1)	27.8 (2.1)	28.0 (1.7)	26.0 (2.3)	27.5 (1.8)
Composite episodic memory[b]	−3.29 (0.68)	−2.04 (1.48)*	−0.02 (0.88)	−2.7 (1.0)	−0.1 (1.0)*	−0.6 (1.2)*	−2.7 (1.3)	−1.1 (1.3)*
Composite non-memory cognition[c]	−2.49 (1.34)	−0.92 (0.85)*	−0.01 (0.57)	−1.1 (0.7)	−0.8 (1.1)	0.2 (0.5)*	−0.9 (0.7)	−0.9 (1.0)

Note where Levene's test for homogeneity of variance was violated the appropriate *t* test was conducted. AD = Alzheimer's disease; MCI = mild cognitive impairment; HA = healthy aging; aMCI =amnestic MCI; nMCI = non-amnestic MCI; sMCI = subjective MCI; PIB+ = PIB positive (Standardized Uptake Value Ratio >1.6); PIB− = PIB negative (Standardized Uptake Value Ratio ≤1.6); MMSE = Mini Mental State Examination. Data are presented as mean (SD) unless otherwise indicated. [a] $n = 29$. [b]Calculated as the average of the z score for California Verbal Learning Test Second Edition long delayed recall and Rey Complex Figure Test 30 minute delayed recall. [c]Calculated as the average of the z scores for Rey Complex Figure Test copy, Digit Symbol – Coding, Boston Naming Test, Letter Fluency, Category Fluency, Digit Span (forwards), and Digit Span (backwards).
*$P < 0.01$. Significant differences are for MCI with both HA and AD, or for nMCI or sMCI compared to aMCI, or between the PIB+ and PIB− MCI groups.

value to distinguish AD from HA. This approach generated a cut-off value for ^{11}C-PIB SUVR of 1.6, which was used to categorize participants into those with 'AD-like' (PIB-positive, SUVR >1.6) images or those with 'HA-like' (PIB-negative, SUVR ≤1.6) images.

Statistical analysis

Data were analysed using SPSS software (version 11). Differences between groups for binomially distributed data were assessed using χ^2 tests. Independent sample *t*-tests were used to compare means of AD and HA to MCI, and to compare means within the MCI subgroups. Pearson's correlations were used to assess bivariate relationships. A series of multiple regression analyses were conducted to examine the possible mediating effect of diagnosis on the relationship between PIB binding and cognition. Moderated regression was also conducted to examine whether the relationship between PIB binding and memory differed across groups. Diagnosis was dummy coded using two variables: AD (participants with AD were coded 1, HA or MCI were coded 0) or HA (HA were coded 1, AD or MCI were coded 0). The interactions between PIB binding and group (AD × PIB; HA × PIB) were calculated by first centering the variables and then multiplying them together (Aiken and West, 1991). Age, gender and education were controlled in all analyses.

Results

β-Amyloid burden

HA participants demonstrated significantly lower neocortical PIB binding than did MCI participants ($P < 0.001$), who in turn demonstrated significantly lower binding than AD participants ($P < 0.001$), as shown in Fig. 1. As Levene's test for homogeneity of variance was violated a corrected *t* value was computed to correct for heterogeneity of variance. Ninety-seven percent of AD cases were PIB-positive, compared with 61% of MCI and 22% of HA. The PIB scans with the median SUVR of the AD group, and the PIB-positive and negative divisions of the MCI and HA groups are shown in Fig. 2. All six of the non-amnestic MCI participants had a PIB-negative scan, whereas 18 (75%) of the amnestic subgroup and 2 (67%) of the subjective subgroup were PIB-positive. As shown in Table 1, 80% of MCI participants with a PIB-positive scan carried an ApoE ε4 allele, compared to only 23% of those with a PIB-negative scan ($P = 0.003$ by Fisher's exact test).

Cognition

As shown in Table 1, HA participants had higher composite scores for both memory and non-memory cognition than MCI participants, who in turn had significantly higher composite scores than AD participants. As expected by definition, the amnestic MCI subgroup demonstrated worse episodic memory than did the non-amnestic MCI subgroup, as shown in Table 1. The composite episodic memory score for PIB-positive MCI participants was 2.7 SD below HA, compared with 1.1 SD below in PIB-negative MCI participants. There were no differences between these MCI subgroups on the non-memory composite score.

Similarly, within the HA group, participants with a PIB-positive scan performed 0.8 SD worse on the composite episodic memory score than those with a PIB-negative scan ($P = 0.023$), but there were no differences on the composite non-memory score.

β-Amyloid burden and cognition

PIB binding had a strong negative relationship with composite episodic memory ($r = -0.73$, $P < 0.001$), and a moderate negative correlation with composite non-memory cognition ($r = -0.50$, $P < 0.001$). Figure 3 demonstrates that AD cases cluster in the region of high PIB binding with low episodic memory scores, conversely, HA cases cluster around the region of low PIB binding with high episodic memory scores, while participants with MCI are distributed across the spectrum.

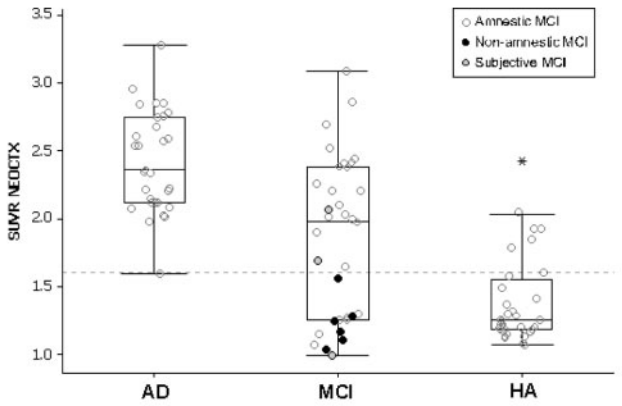

Fig. 1 Box plot showing the neocortical SUVR values (SUVR NEOCTX) for Alzheimer's disease (AD), mild cognitive impairment (MCI) and healthy aging (HA). Box indicates interquartile range. Circles indicate individual SUVR values, with outliers shown by *. Within the MCI group, the amnestic MCI cases are indicated by open circles, nonamnestic MCI by black circles, and subjective MCI by grey circles. Cases above the dotted line (at SUVR = 1.6) have PIB positive scans. Ninety-seven percent of AD, 61% of MCI and 22% of HA fall above this cut-off.

We conducted a series of multiple linear regression analyses to examine whether diagnosis could explain the associations of PIB binding with episodic memory and with non-memory cognition, controlling for age, education and gender. The first set of analyses demonstrated that increased PIB binding was related to being diagnosed with AD ($\beta = 0.60$, $P < 0.001$) and not being diagnosed as a HA ($\beta = -0.59$, $P < 0.001$). Impaired memory performance was related to increased PIB binding ($\beta = -0.67$, $P < 0.001$), being diagnosed with AD ($\beta = -0.27$, $P < 0.001$), and not being diagnosed as a HA ($\beta = 0.58$, $P < 0.001$). In a model combining both PIB binding and diagnosis, the relationship between memory performance and PIB binding had diminished, but was still significant ($\beta = -0.30$, $P < 0.001$). Thus, diagnosis only partly explained the relationship between PIB binding and memory. The same method of analysis applied to non-memory cognition and PIB binding demonstrated a less robust negative correlation ($\beta = -0.50$, $P < 0.001$) that was eliminated when diagnosis was controlled ($\beta = -0.01$, $P = 0.91$).

Pearson correlations for each group showed a strong relationship between episodic memory and PIB binding in MCI ($r = -0.60$, $P < 0.001$) and HA ($r = -0.38$, $P = 0.034$), but not in AD ($r = 0.04$, $P = 0.85$), as shown in Fig. 4. The correlation in MCI persisted when only amnestic MCI were included ($r = -0.46$, $P = 0.023$). There was also a strong

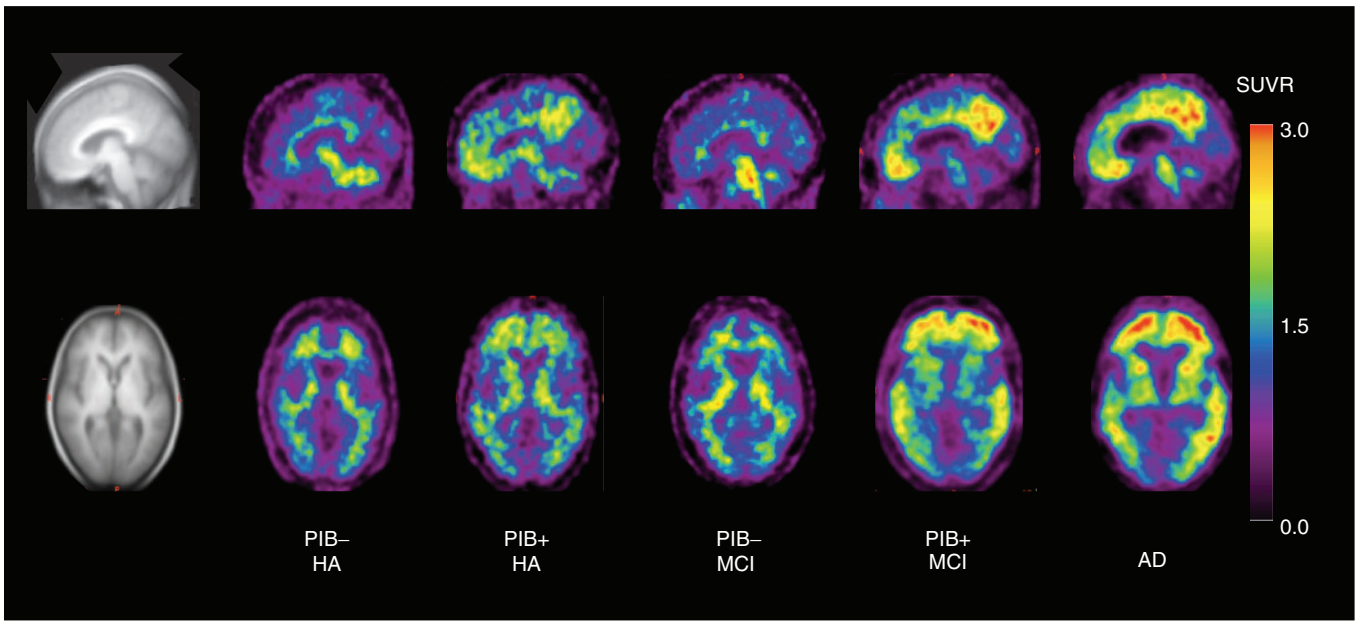

Fig. 2 Typical mid sagittal and transverse ^{11}C-PIB PET images. The scans shown are those of the participant with the median SUVR for the following subgroups: PIB negative HA (SUVR = 1.21), PIB positive HA (SUVR = 1.94), PIB negative MCI (SUVR = 1.25), PIB positive MCI (SUVR = 2.21) and AD (SUVR = 2.36). SUVR is the ratio of standardized uptake value in the neocortex to the cerebellar grey matter reference region and is a measure of neocortical Aβ burden. The scans have been registered to a standard average MRI (left).

correlation when all non-demented (MCI and HA) PIB-positive cases were included ($r=-0.51$, $P=0.006$).

Comparison of Pearson correlations can be misleading, however, when the variance of the independent variable—episodic memory in this case—differs between groups (Baron and Kenny, 1986). To address this issue, we conducted a moderated regression with episodic memory as the criterion variable and the following predictors: age, gender, education, PIB binding, diagnostic variables and the interaction between each of the diagnostic variables and PIB binding. Moderation is indicated by a significant interaction (Aiken and West, 1991). There was no significant effect of the HA × PIB product term ($\beta=0.06$, $P=0.41$). There was, however, a strong trend ($\beta=0.14$, $P=0.056$) for an effect of the AD × PIB product term. This trend supports the results of the Pearson correlations and tentatively suggests that there is a different relationship between PIB binding and memory in AD compared with nondemented participants (MCI and HA), when age, gender and education are controlled. We explored the nature of this trend further by deriving equations from the standardized β values in regression analysis to represent the relationship between PIB binding and memory in AD compared with MCI and HA. These equations demonstrated a stronger negative relationship between PIB binding and episodic memory in the nondemented groups ($\beta=-0.25$), compared with AD ($\beta=-0.12$).

Discussion

Aβ burden, assessed *in vivo* by ^{11}C-PIB PET, was related strongly and inversely to episodic memory performance, but this differed between groups. A much stronger relationship was evident in the HA and MCI participants than in those with AD. Other cognitive functions had a weaker relationship to Aβ burden, which disappeared when diagnosis was controlled. The stronger relationship of AD-related pathological changes to episodic memory compared with other cognitive domains is consistent with previous post-mortem research (Nagy *et al.*, 1996; Thomas *et al.*, 2005; Bennett *et al.*, 2006). All the non-amnestic MCI participants had a PIB-negative scan, compared to only 25% of the amnestic MCI cases.

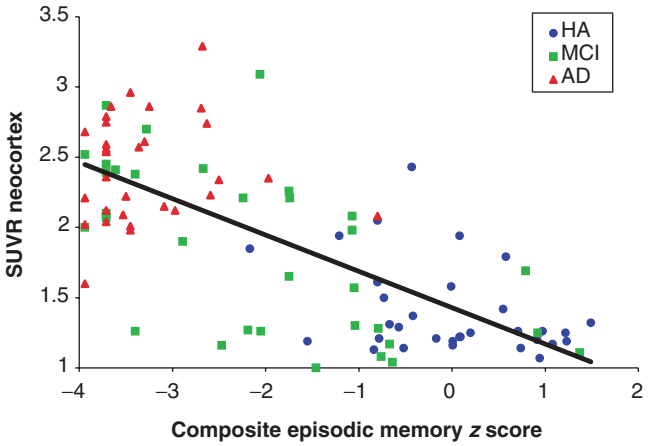

Fig. 3 Relationship between Aβ burden (SUVR neocortex) and composite episodic memory score ($r=-0.73$, $P<0.001$).

β-Amyloid distribution and episodic memory networks

Although a central role for the medial temporal lobe (MTL) in episodic memory function is well established (Cohen and Eichenbaum, 1993; Squire and Zola, 1996), Aβ deposition does not occur there early or in abundance (Braak and Braak, 1991; Edison *et al.*, 2007). This poses questions about the basis of the association between Aβ distribution and episodic memory impairment. The MTL may be particularly sensitive to the neurotoxic effect of Aβ (Roder

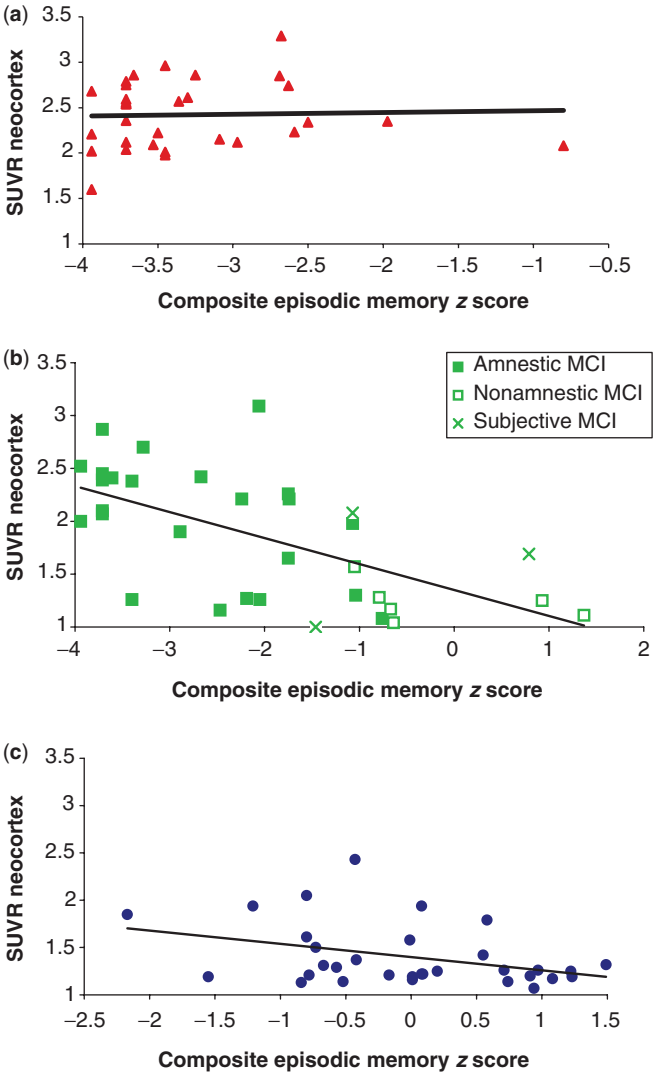

Fig. 4 Relationship between Aβ burden (SUVR neocortex) and composite episodic memory score in (**a**) AD ($r=0.04$, $P=0.85$), (**b**) MCI ($r=-0.60$, $P<0.001$) and (**c**) HA ($r=-0.38$, $P<0.034$).

et al., 2003; Resende *et al.*, 2007), either directly or through Aβ-induced neurofibrillary tangles, which are known to correlate with memory impairment in established AD (Nagy *et al.*, 1996; Guillozet *et al.*, 2003; Bennett *et al.*, 2004). Alternatively, memory impairment may be related to the presence of soluble Aβ oligomers in the MTL (Klein, 2006), which ^{11}C-PIB-PET is not thought to detect. It is also plausible to postulate that Aβ is related to memory performance through its effect on other parts of the memory network. Specifically, the posterior cingulate demonstrates hypometabolism (Minoshima *et al.*, 1997; Buckner *et al.*, 2005), atrophy (Buckner *et al.*, 2005) and Aβ deposition early in AD (Buckner *et al.*, 2005; Mintun *et al.*, 2006), and has been implicated in memory processes by virtue of its anatomical (Nestor *et al.*, 2004; Buckner *et al.*, 2005) and functional MTL connections (Buckner *et al.*, 2005; Johnson *et al.*, 2006).

β-Amyloid burden and memory in HA and MCI

Despite documentation of Aβ in non-demented cases, only one previous study (Guillozet *et al.*, 2003) examined the relationship between Aβ burden, memory and non-memory cognition in non-demented participants. They reported no relationship between any of the cognitive tasks and Aβ plaque density, but the sample was small (5 HA, 3 MCI). In contrast, with a much larger sample, we found a strong relationship between Aβ (as measured by PIB binding) and concurrent episodic memory performance in both HA and MCI. This is consistent with a recent report from a large post mortem study of reduced memory performance in HA participants who had AD neuropathologic changes at autopsy (Bennett *et al.*, 2006). Together with the findings of a preferential relationship with memory, the earliest and most predictive cognitive change detectable in AD, these results suggest that Aβ deposition is an early event in the pathological process of AD.

In addition, we found that our PIB-positive MCI subgroup were more likely to carry an ApoE ε4 allele and demonstrate worse memory impairment (resembling AD) compared with the PIB-negative MCI subgroup. These characteristics are indicative of early AD and suggest the PIB-positive MCI group represent preclinical AD. Our rate of PIB positive scans in MCI is also in accord with the expected proportion that will develop AD (Busse *et al.*, 2006*a*). Although our longitudinal follow-up assessments are not complete, 18-month follow-up data has been obtained on 5 of the 33 MCI participants. These consist of three PIB-positive amnestic MCI participants who have all converted to AD, a PIB-negative amnestic MCI participant who has shown stable cognitive functioning and a PIB-positive subjective MCI participant who has developed objective cognitive impairment and now meets criteria for amnestic MCI. Forsberg *et al.* (in press, Neurobiology of Aging) also report conversion of PIB-positive but not PIB-negative MCI cases to AD over an 8-month follow-up period. As none of our non-amnestic MCI participants had PIB-positive scans, we hypothesize that the aetiology of their cognitive problems may include depression (Aggarwal *et al.*, 2005), dementia where Aβ deposition is not a feature (e.g. frontotemporal dementia; Rowe *et al.*, 2007), or they may prove to be part of the 5–10% who have stable MCI, or the 20% who revert to apparent normality (Busse *et al.*, 2006b).

One of the limitations of our study is the high proportion (50%) of HA participants with a family history of dementia. This represents a selection bias, with many of our HA participants volunteering because they had a family member with dementia, and is somewhat concerning given that family history is one of the primary risk factors for AD (Blacker and Tanzi, 1998; Zekanowski *et al.*, 2004). It could mean that our HA group have an increased risk of developing dementia compared to healthy elderly individuals randomly recruited from the population, and that they may be more likely to have a PIB-positive ('AD-like') scan.

β-Amyloid burden and memory in AD

In contrast to the strong relationship between PIB binding and memory in MCI and HA, a much weaker relationship was found in AD. Some studies have reported a relationship between Aβ and memory in AD (Nagy *et al.*, 1996; Kanne *et al.*, 1998; Thomas *et al.*, 2005; Edison *et al.*, 2007), but the relationships are inconsistent and disappear when different pathological criteria are used (Nagy *et al.*, 1996; Edison *et al.*, 2007), or are only present after particular corrections (Kanne *et al.*, 1998). Our data suggest that by the time dementia has developed and AD can be diagnosed, Aβ deposition is well advanced and the relationship between Aβ and memory has reached a plateau. This finding raises several possibilities. It may be that the continued presence of a given level of amyloid progressively destroys cell function, with accelerating cognitive decline as all reserve function is exhausted. Alternatively, factors such as ischaemic neuronal damage, perhaps due to micro-vascular amyloid angiopathy, may contribute to acceleration of cognitive decline in people with AD.

Methodological explanations for the observed lack of correlation between PIB binding and memory impairment in AD include the restricted range of dementia severity in our study (MMSE 22.7 ± 3.6) and 'floor' effects with cognitive testing. Almost all our AD participants had very low scores on the episodic memory tasks, limiting the range of results and therefore possibly obscuring a correlation. With less demanding tasks, however, we also found no correlation between performance and Aβ burden in the AD group (e.g. for MMSE, $r = -0.08$, $P = 0.68$). Our findings accord with a recent report that PIB binding does not change significantly in AD over a 2-year period, even in participants with significant cognitive decline between scans

(Engler *et al.*, 2006). Of interest, Nagy *et al.* (1996) found that the relationship between Aβ and memory in AD was best represented by a square root function, lending support to our idea of a relationship that plateaus.

In conclusion, our study shows that Aβ deposition is associated with impaired episodic memory in non-demented individuals, providing support for the proposal that Aβ imaging can detect the preclinical phase of AD. Further longitudinal study is required to confirm this interpretation. These findings have implications for the timing of potential anti-amyloid therapeutics, suggesting that such therapy should be evaluated in mildly symptomatic or asymptomatic individuals with increased brain Aβ burden to assess the potential for the prevention of dementia.

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