Neuropsychologia 49 (2011) 2384–2390

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Cognition and beta-amyloid in preclinical Alzheimer's disease: Data from the AIBL study

Kerryn E. Pike[a,b,c,d,*], Kathryn A. Ellis[e], Victor L. Villemagne[a,b,c], Norm Good[f], Gael Chételat[a,g], David Ames[e,h], Cassandra Szoeke[i], Simon M. Laws[j,k], Giuseppe Verdile[j,k], Ralph N. Martins[j,k], Colin L. Masters[b,c], Christopher C. Rowe[a,l]

[a] Department of Nuclear Medicine, Centre for PET, Austin Health, Heidelberg, VIC, Australia
[b] Mental Health Research Institute, Parkville, VIC, Australia
[c] Centre for Neurosciences, University of Melbourne, Parkville, VIC, Australia
[d] School of Psychological Science, La Trobe University, Bundoora, VIC, Australia
[e] Department of Psychiatry, University of Melbourne, Parkville, VIC, Australia
[f] CSIRO Mathematics, Informatics and Statistics, Australian E-Health Research Centre, Herston, QLD, Australia
[g] Inserm-EPHE-Université de Caen/Basse-Normandie, Unité U923, GIP Cyceron, CHU Côte de Nacre, Caen, France
[h] National Ageing Research Institute, Parkville, VIC, Australia
[i] CSIRO Neurodegenerative Disease, Mental Disorders & Brain Health, Preventative Health Flagship, CSIRO Molecular and Health Technologies, Parkville, VIC, Australia
[j] Centre of Excellence for Alzheimer's Disease Research & Care, School of Exercise Biomedical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia
[k] Sir James McCusker Alzheimer's Disease Research Unit (Hollywood Private Hospital), Perth, Western Australia, Australia
[l] Department of Medicine, University of Melbourne, Parkville, VIC, Australia

ARTICLE INFO

Article history:
Received 7 January 2011
Received in revised form 28 March 2011
Accepted 11 April 2011
Available online 16 April 2011

Keywords:
Memory
Ageing
PiB-PET
Amyloid imaging

ABSTRACT

The 'preclinical' phase of Alzheimer's disease is a future target for treatment, but additional research is essential to understand the relationship between β-amyloid burden and cognition during this time. We investigated this relationship using a large sample of apparently healthy older adults ($N = 177$), which also enabled examination of whether the relationship differed according to age, gender, years of education, apolipoprotein E status, and the presence of subjective memory complaints. In addition to episodic memory, a range of cognitive measures (global cognition, semantic memory, visuospatial performance, and executive function) were examined. Participants were aged over 60 years with no objective cognitive impairment and came from the imaging arm of the Australian Imaging, Biomarkers, and Lifestyle (AIBL) study of ageing. ^{11}C-PiB PET was used to measure β-amyloid burden and a PiB 'cut-off' level of 1.5 was used to separate participants with low PiB retention from those with high PiB retention. Thirty-three percent of participants had a PiB positive scan. PiB positive participants were 5 years older, twice as likely to carry an apolipoprotein E $\varepsilon 4$ allele, and their composite episodic memory was 0.26 SD worse than PiB negative volunteers. Linear regressions with β-amyloid burden as a dichotomous predictor, revealed an interaction between β-amyloid burden and gender, as well as age and education effects, in predicting episodic memory and visuospatial performance. In females, but not in males, increased β-amyloid was related to worse episodic memory and visuospatial performance. Furthermore, an interaction between β-amyloid burden and APOE status was found in predicting visuospatial performance, whereby there was a trend for increased β-amyloid to relate to worse visuospatial performance for those without an APOE $\varepsilon 4$ allele. There were no other main or interaction effects of β-amyloid on any of the other composite cognitive measures. These cross-sectional findings suggest that β-amyloid burden does not have a large effect on cognition in this subset of apparently healthy older people. The finding of gender differences deserves further research to answer definitively the important question of gender susceptibility to adverse cognitive effects from β-amyloid.

1. Introduction

The pathological processes underlying Alzheimer's disease (AD) begin years before the onset of symptoms (Amieva et al., 2005). When available, disease-modifying treatments targeting these processes are likely to be most efficacious at this 'preclinical' stage.

* Corresponding author at: School of Psychological Science, La Trobe University, Bundoora, VIC 3086, Australia. Tel.: +61 3 9479 5079; fax: +61 3 9479 1956.
E-mail address: k.pike@latrobe.edu.au (K.E. Pike).

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doi:10.1016/j.neuropsychologia.2011.04.012

This requires, however, a better understanding of the relationship between the pathophysiology and emergence of clinical symptoms. Much research has focused on identification of preclinical AD, culminating in a recent workgroup by the National Institute on Aging (NIA) and the Alzheimer's Association to define research criteria for preclinical AD (Sperling et al., 2011).

Integral to the proposed definition of preclinical AD is biomarker evidence of beta-amyloid (Aβ) accumulation, reflecting the growth in knowledge regarding biomarkers of AD. Deposition of Aβ is believed to be the initial step in the disease process (Villemagne et al., 2006). Cerebral Aβ deposition is found in up to 45% of apparently healthy older people (Bennett et al., 2006) and prevalence increases with age (Braak & Braak, 1997; Davies et al., 1988). Until recently, cerebral Aβ burden could only be measured at autopsy, with some, but not all, studies suggesting that increased AD pathology in apparently healthy older adults is related to decreased cognition. Furthermore, these studies are limited by the time lag between the last cognitive assessment and autopsy, whereas Aβ-neuroimaging techniques enable measurement of Aβ burden proximal to cognitive performance. Aβ-imaging studies to date, however, have demonstrated inconsistent results regarding the relationship between Aβ burden and cognition in apparently healthy older adults.

Previously, our group found that Aβ burden was related to decreased episodic memory performance in healthy older participants and that those participants with a PiB-positive scan performed 0.8 SD worse on memory tasks than those with a PiB-negative scan (Pike et al., 2007). We have also shown that apparently normal controls who decline on cognitive tasks over time are more likely to have a PiB positive scan than those with stable cognitive performance (Villemagne, Pike, et al., 2008). Mormino et al. (2009) found a relationship between PiB retention in hippocampal regions and episodic memory in apparently normal controls in one of their examined cohorts, although reported that this was mainly driven by 2/20 participants with high PiB retention. In addition, Braskie et al. (2008) found a relationship between a composite cognitive score and the retention of an alternative radiotracer that binds to Aβ as well as neurofibrillary tangles. In contrast, other studies (Aizenstein et al., 2008; Mintun et al., 2006) have not found a difference in cognitive performance between apparently healthy older participants with PiB-positive and PiB-negative scans. The small samples of these studies (from 10 to 43) may help explain the discrepant findings.

Recently, a large study ($N = 135$) was published examining cognition and Aβ burden as measured by PiB (Storandt, Mintun, Head, & Morris, 2009). No relationship was found between concurrent cognition and Aβ burden. Participants in their study had annual cognitive assessments in various longitudinal studies beginning in 1985, thus they were also able to examine decline over time and found relationships between Aβ burden and decline on the visuospatial and working memory measures, and one of their episodic memory tests (associate learning). They did not examine the effect of age, gender, years of education, apolipoprotein E (APOE) status, or memory complaints on the findings.

Since joining forces with the Australian Imaging Biomarkers and Lifestyle (AIBL) study (Ellis et al., 2009), our sample has increased nearly 6-fold. We recently reported the amyloid imaging results from the cohort, but the relationship between cognition and PiB retention was only briefly examined; we found no difference between PiB-positive and PiB-negative apparently healthy older controls on the long delay free recall from the California Verbal Learning Test—second edition (CVLT-II; Rowe et al., 2010). The present paper aims to examine the relationship between concurrent cognitive performance and Aβ burden in greater depth in this large two-site sample. A number of composite cognitive measures were constructed to consider cognitive domains in addition to episodic memory. Furthermore, the large sample provides sufficient power to enable examination of some individual differences that may affect the relationship between Aβ burden and cognitive performance—including age, gender, years of education, APOE status, and the presence of any subjective memory complaints. The main goal of the present study was thus to investigate if, and under what circumstances, increased cerebral Aβ burden is associated with lowered cognition in apparently healthy older adults.

2. Methods

2.1. Participants

The participants for this study were the 177 (100 from Melbourne, 77 from Perth) apparently healthy older people (mean age = 72 ± 7, range 60–89) enrolled in the AIBL study, and reported in Rowe et al. (2010). All participants had no objective evidence of cognitive impairment, were fluent in English, and had no significant neurological history. Informed written consent was obtained prior to participation. Ethics approval was granted from the Human Research Ethics Committees at Austin Health, St Vincent's Health, Hollywood Private Hospital, and Edith Cowan University. APOE genotype was determined by direct sequencing, and 43% carried an APOE ε4 allele. Fifty percent of the volunteers were male, 54% had subjective complaints about their memory (established by the question: "do you have difficulties with your memory?"), and 54% had more than 12 years of education. Table 1 displays participant demographics according to PiB status.

2.2. Neuroimaging

All participants underwent a PiB-PET scan as previously described (Pike et al., 2007; Rowe et al., 2007) at Austin Health Centre for PET, Melbourne or WA PET and Cyclotron service, Sir Charles Gairdner Hospital, Perth. Each participant received ~370 MBq ^{11}C-PiB intravenously over 1 min. A 30-min acquisition in 3D mode starting 40 min after injection of PiB was performed with a Phillips Allegro™ PET camera. A transmission scan was performed for attenuation correction. PET images were reconstructed using a 3D RAMLA algorithm. Participants also received a 3D T1-weighed MRI acquisition with MP-RAGE, FLAIR, SWI, and DTI sequences, for screening and subsequent co-registration with the PET images. Co-registration 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). A region of interest template was placed on the MR and transferred to the co-registered PET images. Standardized uptake values (SUV) were calculated for all brain regions examined. SUV ratios (SUVR) were generated by normalising 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. In accordance with previous studies reporting marked PiB retention in cognitively unimpaired healthy controls (Aizenstein et al., 2008; Mintun et al., 2006; Pike et al., 2007; Rowe et al., 2007), most participants demonstrated low levels of PiB retention, but there was a subset of participants with higher PiB retention. Consequently, to identify a PiB 'cut-off' level to separate participants with low versus high PiB retention, a hierarchical cluster analysis was performed on all elderly apparently healthy participants yielding a mean cut-off for neocortical SUVR of 1.5.

Table 1
Participant demographics and composite cognitive scores split by PiB result.

	PiB negative ($N = 119$)	PiB positive ($N = 58$)
% female	50	50
% complainers	53	55
Age	69.8 (7.0)	75.2 (7.1)*
% Yrs ed < 13	46	47
% APOE ε4	33	64*
MMSE	28.9 (1.2)	28.5 (1.2)
Global	−0.21 (0.63)	−0.32 (0.76)
EM	0.07 (0.66)	−0.19 (0.88)*
EF	−0.13 (0.59)	−0.17 (0.57)
SM	−0.96 (2.49)	−0.89 (2.42)
VS	0.12 (0.85)	−0.09 (1.15)

Values are means (SD) unless otherwise noted. Differences between groups were determined using t-tests for continuous variables, or χ^2 test for independence for dichotomous variables: MMSE = Mini Mental State Examination; Global = Composite Global Cognition Score; EM = Composite Episodic Memory Score; EF = Composite Executive Function Score; SM = Composite Semantic Memory Score; VS = Visuospatial Composite Score.

* $p < .05$.