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BDNF Val66Met, Aβ amyloid, and cognitive decline in preclinical Alzheimer's disease

Yen Ying Lim [a,b,*], Victor L. Villemagne [a,c,d], Simon M. Laws [e,f,g], David Ames [h,i], Robert H. Pietrzak [j], Kathryn A. Ellis [a,h,i], Karra D. Harrington [a], Pierrick Bourgeat [k], Olivier Salvado [k], David Darby [a], Peter J. Snyder [l], Ashley I. Bush [a], Ralph N. Martins [e,f], Colin L. Masters [a], Christopher C. Rowe [c,d], Pradeep J. Nathan [m,n,o], Paul Maruff [a,p], for the Australian Imaging, Biomarkers and Lifestyle (AIBL) Research Group

[a] *Mental Health Research Institute, The University of Melbourne, Parkville, Victoria, Australia*
[b] *Department of Psychiatry, The University of Melbourne, Parkville, Victoria, Australia*
[c] *Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Victoria, Australia*
[d] *Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia*
[e] *Centre of Excellence for Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, Joondalup, Western Australia, Australia*
[f] *Sir James McCusker Alzheimer's Disease Research Unit, Hollywood Private Hospital, Perth, Western Australia, Australia*
[g] *Co-operative Research Centre (CRC) for Mental Health, http://www.mentalhealthcrc.com, Australia*
[h] *Academic Unit for Psychiatry of Old Age, Department of Psychiatry, The University of Melbourne, Kew, Victoria, Australia*
[i] *National Ageing Research Institute, Parkville, Victoria, Australia*
[j] *Department of Psychiatry, Yale University School of Medicine, New Haven, Conn, USA*
[k] *Commonwealth Scientific Industrial Research Organization Preventative Health National Research Flagship, Australian e-Health Research Centre-BioMedIA, Brisbane, Queensland, Australia*
[l] *Lifespan Hospital System and Department of Neurology, Warren Alpert Medical School of Brown University, Providence, RI, USA*
[m] *Medicines Discovery and Development, GlaxoSmithKline, Clinical Unit, Cambridge, UK*
[n] *Brain Mapping Unit, Department of Psychiatry, University of Cambridge, Cambridge, UK*
[o] *School of Psychology and Psychiatry, Monash University, Clayton, Victoria, Australia*
[p] *CogState Ltd., Melbourne, Victoria, Australia*

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ABSTRACT

Brain-derived neurotrophic factor (*BDNF*) Val66Met polymorphism has previously been implicated in Alzheimer's disease (AD)–related cognitive impairment. We aimed to determine the relationship between *BDNF* Val66Met and beta-amyloid (Aβ) on cognitive decline, hippocampal atrophy, and Aβ accumulation over 36 months in 165 healthy adults enrolled in the Australian Imaging, Biomarkers and Lifestyle study. In healthy adults with high Aβ, Met carriers showed significant and moderate-to-large declines in episodic memory, executive function, and language, and greater hippocampal atrophy over 36 months, compared with Val/Val homozygotes. *BDNF* Val66Met was not found to be related to rates of change in cognition or hippocampal volume in healthy adults with low Aβ. *BDNF* Val66Met did not relate to the amount of Aβ or to the rate of Aβ accumulation in either group. High Aβ levels coupled with Met carriage may be useful prognostic markers of accelerated cognitive decline and hippocampal degeneration in individuals in the preclinical stage of AD.

1. Introduction

Current theories of Alzheimer's disease (AD) place beta-amyloid (Aβ) at the center of a series of events that result in synaptic loss and memory impairment (Masters and Selkoe, 2012). Although Aβ-related disruption to normal synaptic function is not well understood, growing evidence suggests that brain-derived neurotrophic factor (BDNF) is 1 downstream mediator of Aβ toxicity (Fahnestock, 2011; Garzon and Fahnestock, 2007; Peng et al., 2005). For example, BDNF and its main receptor, tropomyosin-related kinase B (TrkB), are necessary for the synaptic excitation and neuronal plasticity that subserve memory function (Hariri et al., 2003; Lee et al., 2012), impairment of which is the earliest and most frequent AD symptom (Sperling et al., 2011). Second, in AD and mild cognitive impairment,

* Corresponding author at: Mental Health Research Institute, 155 Oak Street, Parkville, VIC 3052, Australia. Tel.: +61 3 9389 2932; fax: +61 3 9035 8642.
E-mail address: y.lim@mhri.edu.au (Y.Y. Lim).

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BDNF mRNA is reduced substantially in the hippocampus and temporal lobe (Garzon and Fahnestock, 2007; Lee et al., 2012; Peng et al., 2005), with the extent of BDNF loss associated with the magnitude of cognitive impairment (Garzon and Fahnestock, 2007; Peng et al., 2005). Third, in AD murine models, pharmacologically increasing BDNF can ameliorate synaptic dysfunction and improve memory (Caccamo et al., 2010; Lee et al., 2012). Likewise, changes in BDNF secretion occur with improved memory and cognition induced by aerobic exercise in humans at risk for AD (Baker et al., 2010; Intlekofer and Cotman, in press), and in AD murine models (Cotman et al., 2007; Intlekofer and Cotman, in press). However, there is currently no direct evidence that BDNF moderates any Aβ-related changes in cognition or neurodegeneration in AD.

A polymorphism (rs6265, Val66Met) that affects secretion of mature BDNF has been implicated in learning and memory in healthy humans, whereby carriage of the Met allele is associated with poor memory, reduced hippocampal volume, and lower hippocampal activation on functional imaging (Egan et al., 2003; Hariri et al., 2003; Peng et al., 2005; Sambataro et al., 2010). In AD, cross-sectional genetic association studies show that Met carriers have greater impairment in memory and executive function (Ventriglia et al., 2002), reduced regional cerebral blood flow in hippocampal and medial temporal lobe regions (Xu et al., 2010), and reduced hippocampal and prefrontal cortical volumes (Connor et al., 1997). In contrast, other studies have observed greater cognitive impairment (Harris et al., 2006; Nagata et al., 2012; Voineskos et al., 2011), reduced brain structure volumes (Dennis et al., 2011, Voineskos et al., 2011), and increased risk of AD (Voineskos et al., 2011) in Val/Val homozygotes. The absence of a clear relationship between *BDNF* Val66Met and AD could be due to the small samples, or to cross-sectional study designs, or could indicate that other factors (e.g., age, gender) may moderate relations between *BDNF* Val66Met and AD (Fahnestock, 2011). As yet, no *BDNF* Val66Met association study has taken into account levels of Aβ.

Because AD has a long preclinical stage in which the rate of cognitive decline over periods of 3 years or less is agreed to be linear (Albert et al., 2007; Bateman et al., 2012; Villemagne et al., 2011), genetic influences may become clearer from prospective study of the preclinical stage. Furthermore, as the complexity of AD pathological changes increase with disease severity, associations between *BDNF* Val66Met and AD may be more obvious in preclinical stages in which the disease presents almost exclusively as subtle abnormalities in memory (Fahnestock, 2011; Lim et al., 2012). Thus, the aim of this study was to determine the extent to which *BDNF* Val66Met influences Aβ-related memory decline (Lim et al., 2012; Villemagne et al., 2011) and reduction in hippocampal volume (HV) (Chételat et al., 2012) in healthy older adults. We hypothesized that Aβ-related memory decline, and reduction in HV in healthy adults, would be greater in carriers of the Met allele. As BDNF may be a downstream mediator of Aβ toxicity (Fahnestock, 2011), we also hypothesized that *BDNF* Val66Met would not affect the rate of Aβ accumulation. Finally, we explored whether changes in other areas of cognition were associated with *BDNF* Val66Met and Aβ.

2. Methods

2.1. Participants

Participants were recruited from the group of healthy controls (hereafter termed healthy adults [HA]) enrolled in the Australian Imaging, Biomarkers and Lifestyle (AIBL) Flagship Study of Ageing (Ellis et al., 2009; Rowe et al., 2010). The process of recruitment of HAs in AIBL has been described in detail (Ellis et al., 2009). Exclusion criteria included the following: schizophrenia; depression (15-item Geriatric Depression Score [GDS] of 6 or greater); Parkinson's disease; cancer (except basal cell skin carcinoma) within the last 2 years; symptomatic stroke; uncontrolled diabetes; or current regular alcohol use exceeding 2 standard drinks per day for women or 4 per day for men. A clinical review panel considered all available medical, psychiatric, and neuropsychological information to confirm the cognitive health of each participant. Only HAs who had undergone Pittsburgh compound B (PiB)—positron emission tomography (PET) and neuroimaging with structural magnetic resonance imaging (MRI), *BDNF* genotyping, and cognitive testing at baseline, 18 months, and 36 months were included in this study (demographic and clinical characteristics are shown in Table 1). The study was approved by and complied with the regulations of 3 institutional research and ethics committees (Ellis et al., 2009). All participants provided written informed consent before study participation. Selection of healthy participants to undergo PiB-PET neuroimaging in the AIBL study was biased to ensure that approximately 50% were *APOE* ε4 carriers (Rowe et al., 2010).

2.2. Measures

2.2.1. Neuroimaging

PiB-PET imaging methodology has been described in detail elsewhere (Rowe et al., 2010; Villemagne et al., 2011). PET standardized

Table 1
Baseline demographic, clinical, and lifestyle characteristics of the overall group, and for each SUVR and BDNF Val66Met group

	Overall (n = 165)	PiB− (n = 116)	PiB+ (n = 49)	Val/Val (n = 107)	Met carrier (n = 58)
Female, n (%)	82 (49.70%)	58 (50.00%)	24 (48.98%)	54 (50.47%)	28 (48.28%)
APOE ε4, n (%)	70 (42.42%)	38 (32.76%)	32 (65.31%)	43 (40.19%)	27 (46.55%)
Met carrier, n (%)	58 (35.15%)	44 (37.93%)	14 (28.57%)	—	—
Age (y)	71.36 (7.15)	70.03 (6.90)	74.51 (6.81)	72.21 (6.96)	69.79 (7.30)
SUVR Neocortex	1.40 (0.40)	1.17 (0.09)	1.97 (0.27)	1.42 (0.40)	1.37 (0.41)
MMSE	28.75 (1.20)	28.80 (1.20)	28.61 (1.22)	28.81 (1.15)	28.71 (1.24)
CDR-SB	0.04 (0.19)	0.05 (0.21)	0.02 (0.10)	0.04 (0.20)	0.04 (0.17)
Premorbid IQ	108.81 (7.31)	108.14 (7.86)	110.39 (5.57)	109.39 (6.90)	107.72 (7.96)
HADS-D	2.78 (2.29)	2.73 (2.10)	2.90 (2.70)	2.83 (2.31)	2.68 (2.26)
HADS-A	4.17 (2.88)	4.11 (2.68)	4.31 (3.32)	4.31 (2.98)	3.91 (2.69)
Body mass index	26.52 (3.99)	26.46 (3.72)	26.65 (4.35)	26.50 (3.58)	26.55 (4.47)
MAC-Q (at 36 mo)	25.08 (4.41)	25.10 (4.31)	25.03 (4.74)	25.06 (4.25)	25.13 (4.74)
IPAQ (at 36 mo)	4056.49 (3537.80)	3910.72 (3271.87)	4489.11 (4262.37)	4039.07 (3319.71)	4092.63 (3997.44)

Note: One-way analysis of variance indicated that age was significantly different between PiB− and PiB+ groups, and premorbid IQ was significantly different between Val/Val and Met carriers, $p < 0.05$. The χ^2 test also indicated that number of *APOE* ε4 carriers were higher in the PiB+ group compared with the PiB− group, $p < 0.001$. No other variables shown in the table differed by PiB status or *BDNF* Val66Met polymorphism, all p's > 0.05.

Key: BDNF, brain-derived neurotrophic factor; CDR-SB, Clinical Dementia Rating Scale, sum of boxes score; HADS-A, Hospital Anxiety and Depression Scale, Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression Subscale; IPAQ, International Physical Activity Questionnaire; MAC-Q, Memory Complaint Questionnaire; MMSE, Mini-Mental State Examination; PiB, Pittsburgh compound B; SUVR, standardized uptake value ratio.