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Featured Article

The *BDNF* Val66Met polymorphism moderates the effect of cognitive reserve on 36-month cognitive change in healthy older adults

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Abstract

Introduction: Cognitive reserve (CR) and *BDNF* Val66Met are independently associated with the rate of cognitive decline in preclinical Alzheimer's disease. This study was designed to investigate the interactive effects of these variables on 36-month cognitive change in cognitively intact older adults.

Methods: Data for this investigation were obtained from 445 community-residing participants of the Tasmanian Healthy Brain Project, who underwent genetic screening and annual assessment of neuropsychological, health, and psychosocial function.

Results: Our main result was that *BDNF* Val66Met moderated the relationship between baseline CR and change in executive function performance, in that CR-related differences in function decreased across the follow-up period in *BDNF* Val homozygotes, but became more pronounced in *BDNF* Met carriers. Similar effects were not observed within the other memory- and language-related cognitive domains.

Discussion: Inheritance of *BDNF* Met may be associated with a detrimental influence on the relationship between CR and cognitive change in cognitively intact older adults, but this effect may be restricted to the executive function domain.

Keywords: Cognitive reserve; Brain reserve; Brain-derived neurotrophic factor; BDNF; Aging; Cognitive function; Cognitive change

1. Introduction

Current evidence indicates that Alzheimer's disease (AD) may develop over the course of multiple decades before symptoms of dementia emerge [1,2], highlighting the need for presymptomatic interventions aimed at reducing risk of disease [3]. This has led to an increased importance in investigating dementia risk factors in cognitively normal adults. One recent development in this field has been the identification of a role for the *BDNF* Val66Met polymorphism in preclinical AD [4,5]; preclinical AD is a proposed disease state whereby normal cognitive functioning persists in the presence of AD biomarkers [6]. In healthy individuals with high brain β-amyloid (Aβ) load, recent work has found that *BDNF* Met is associated with larger declines in multiple cognitive domains compared with *BDNF* Val homozygotes [4]. Carriage of *BDNF* Met has also been shown to hasten the onset of clinically significant cognitive impairment associated with the presence of both *APOE* ε4 and high Aβ load [5] and is related to a faster rate of hippocampal atrophy in high Aβ individuals who already show symptoms of amnestic mild cognitive impairment [7]. These results point to a potential role of *BDNF* Val66Met in influencing the speed and severity with which neuropathology impedes normal cognitive functioning.

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One of the other major influences on the association between neuropathology and level of cognitive function is cognitive reserve (CR; [8]). Although estimates of cognitive resilience that incorporate measures of brain integrity, cognitive integrity, and AD biomarkers may more accurately predict risk of cognitive decline than CR alone [9], CR has been implicated in modulating susceptibility to AD pathology–related cognitive deficits in preclinical stages [10] and is thought to exert a substantial effect on later life dementia risk [11]. The CR hypothesis suggests that individuals who have engaged in more frequent cognitive stimulation across the lifespan develop a cognitive and neural reserve that delays the onset of cognitive impairment from underlying pathology [12]. CR is typically estimated using proxy measures of lifetime engagement in cognitive activities, such as years of education [13], occupational attainment [14], frequency of participation in cognitively stimulating leisure activities [15], as well as other nonlifestyle factors, such as crystallized intelligence [16]. Despite similarities between the effects of CR and *BDNF* Val66Met on resilience and susceptibility to pathology, little is known about the potential association of CR and variation in the *BDNF* Val66Met polymorphism and how these factors may interact to influence cognitive function.

CR may relate to *BDNF* Val66Met through a simple cumulative process of independent effects on the expression of preclinical cognitive deficits, but CR may also interact with *BDNF* Val66Met through the impact of this polymorphism on cortical plasticity. For engagement in cognitively stimulating activities to result in increased neural reserve, alterations to the structure and/or function of the brain must occur [17]. An individual who inherits a genetic variant that is associated with impaired cortical plasticity may then, hypothetically, experience different cognitive outcomes in response to the same level of cognitive stimulation as another individual who did not inherit that variant. *BDNF* Val66Met is a polymorphism that may be used to investigate such hypotheses, as the *BDNF* Met variant has been associated with lowered activity-dependent secretion of BDNF protein [18], in addition to impaired synaptic plasticity and transmission [19,20]. In support, our recent cross-sectional study reported that *BDNF* Val66Met moderates the relationship between CR and older adult executive function [21], with the predicted positive relationship between CR and cognitive performance observed within *BDNF* Val homozygotes but not within *BDNF* Met carriers.

Although the *BDNF* Val66Met polymorphism is not consistently and reliably associated with the cognitive performance of older adults [22,23], some evidence does indicate that inheritance of *BDNF* Met is associated with a greater detrimental effect of age on memory function [24]. In addition, older carriers of *BDNF* Met have been reported to experience both lowered [25], and a faster rate of aging-related decline in, perceptual speed [26]. Finally, a recent investigation reported that, although carriage of *APOE* ε4 was associated with reduced executive function performance in older cognitively intact individuals, the presence of *BDNF* Met was observed to intensify this deficit [27].

The present study was designed to investigate the independent and interactive effects of variation in *BDNF* Val66Met and CR on 36-month cognitive change in a sample of healthy older adults. We used a comprehensive multivariate estimate of CR that was calculated through a previously developed factor analysis–derived equation of the construct [28]. Three hypotheses were tested: (1) lower baseline CR is associated with a detrimental effect on rate of cognitive change compared with higher baseline CR; (2) *BDNF* Met is associated with a detrimental effect on rate of cognitive change compared with *BDNF* Val/Val; (3) the *BDNF* Val66Met polymorphism moderates the extent to which baseline CR affects rate of cognitive change.

2. Methods

2.1. Participants

Data for this investigation were obtained from 445 participants of the Tasmanian Healthy Brain Project (THBP), which is an ongoing interventional cohort study into whether later life tertiary education protects from aging-related cognitive decline and dementia. The THBP sample comprised community-residing individuals who were aged between 50 and 79 years at study entry (recruitment phase: 2011–2014) and who were excluded from participation if they had a history of any medical, psychiatric, or psychological condition independently associated with impairments to cognitive function (e.g., dementia, -multiple sclerosis, previous significant head injury requiring hospitalization, clinical diagnosis of depression or anxiety). Of these 445 participants, 29 were excluded because of having withdrawn from the study before completing any follow-up testing, and 14 were excluded because of not being native English speakers. Complete neuropsychological, genetic, and covariate data were available for 402 participants at baseline, 343 participants at 12-month follow-up, 338 participants at 24-month follow-up, and 218 participants at 36-month follow-up. The present study included 964 person-years of follow-up, which equated to an average follow-up time of 2.4 years.

Participants from both the THBP experimental group and the control group were included in this study, with any potential effect of the intervention statistically adjusted for. THBP experimental group participants completed at least 12 months of study at the University of Tasmania, Australia, with a minimum study load of two units of study, at an undergraduate or postgraduate level, completed in a single year; control group participants did not complete any university-level study. Although future THBP research will aim to provide greater clarification with regard to the cognitive outcomes of the intervention and, in particular, level of engagement with the education intervention (e.g., number of units of university study completed), some preliminary data