

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.

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## 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 amyloid  $\beta$  ( $A\beta$ ) 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 apolipoprotein E (*APOE*)  $\epsilon$ 4 and high  $A\beta$  load [5] and is related to a faster rate of hippocampal atrophy in high  $A\beta$  individuals who already show symptoms of amnesic mild cognitive impairment [7]. These results point to a potential role of *BDNF*

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Val66Met in influencing the speed and severity with which neuropathology impedes normal cognitive functioning.

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*  $\epsilon$ 4 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 relating to course and study enrollment are available. Specifically, the mean annual equivalent full-time study load (EFTSL) completed across the follow-up period was 40.93% (SD = 35.01%), with an EFTSL of 100% representing an annual full-time study load, and an EFTSL of 12.5% representing the typical study load of a single undergraduate unit. Although some variance in course enrollments is likely to occur between time points, in the first year of participation, approximately half of experimental group participants were enrolled within the faculty of arts (55.8%), with health (12.2%) and science (11.2%) faculty enrollments also common. Greater detail on participant selection and recruitment is described elsewhere [29]. Demographic and clinical data for the final sample at baseline are presented in Table 1.

## 2.2. Procedure

Participants completed comprehensive assessments of neuropsychological, health, and psychosocial function at baseline, 12-, 24-, and 36-month follow-up ( $\pm$ one month). At baseline, symptoms of dementia, symptoms of depression and anxiety, general health, medical conditions, prescription medication use, drug and alcohol use, handedness, height, weight, and marital status were recorded. An experienced

neuropsychologist reviewed participant responses on screening tools to determine participant inclusion. Participants provided written consent before undertaking the assessments at each phase. This research was conducted in full compliance of NHMRC (Australia) Human Research Guidelines and was overseen by the Human Research Ethics Committee (Tasmania) Network. The research reported complies with the ethical rules for human experimentation as stated in the Declaration of Helsinki and complies with APA ethics standards.

## 2.3. Neuropsychological assessment battery

In the present analyses, standardized tests of episodic memory (Rey Auditory Verbal Learning Test 1–5 total recall, Logical Memory I immediate recall, Logical Memory II delayed recall, CANTAB Paired Associates Learning first trial memory score); working memory (WAIS Digit Span total recall, WAIS Letter-Number Sequencing total recall, CANTAB Spatial Working Memory between errors, CANTAB Spatial Span length); executive function (Stroop trial C, CANTAB Rapid Visual Processing A', Trail Making Test B); and language processing (WAIS Vocabulary, WAIS Comprehension, Boston Naming Test) were used (information relating to the reliability and validity of these tools is described in the study by Summers et al. [29]). Trained assessors performed the assessment of all participants at each study phase (baseline, 12, 24, 36 months).

## 2.4. Assessment of baseline cognitive reserve

A previously developed single-point estimate of prior CR was used [28]. Prior CR is a factor analysis-derived measure incorporating data from measures of lifetime education, occupational attainment, intelligence, and participation in cognitively stimulating leisure activities. This score represents an individual's estimated CR at their baseline THBP assessment. The Wechsler Test of Adult Reading was used to estimate premorbid intellectual capacity, the Lifetime of Experiences Questionnaire [30] to quantify history of complex cognitive engagement, and the Medical Health Screening questionnaire to record the number of years of prior formal education.

## 2.5. Genotyping

DNA was collected through the donation of saliva samples using Oragene DNA self-collection kits [31]. *APOE* and *BDNF* Val66Met polymorphisms were determined through one-step amplified refractory mutation system polymerase chain reaction and subsequent gel electrophoresis. For *APOE*, the method described by Donohoe et al. was followed [32]. For *BDNF* Val66Met, the method described by Sheikh and Hayden was followed [33]. In this study, carriers of *BDNF* Met included homozygotes and heterozygotes of the Met allele; *BDNF* Met homozygotes were not sufficiently prevalent to allow for specific subgenotype analysis.

Table 1  
Baseline demographic, clinical, and cognitive statistics stratified by *BDNF* Val66Met genotype ( $N = 402$ )

Characteristic	<i>BDNF</i> Val/Val	<i>BDNF</i> Met+	<i>P</i>
<b>Demographic</b>			
<i>N</i> (%)	268 (67)	134 (33)	
Age (years)	60.47 (6.79)	59.90 (6.44)	.423
Female <i>N</i> (%)	181 (68)	88 (66)	.395
THBP experimental group	206 (77)	103 (77)	.547
<i>N</i> (%)			
WTAR premorbid IQ	112.84 (5.19)	112.83 (5.28)	.989
Previous education (years)	13.80 (2.69)	14.37 (2.73)	.049
Prior cognitive reserve (Z score)	-0.05 (1.01)	0.10 (0.99)	.154
<b>Clinical</b>			
DRS-2 AEMSS	12.15 (2.08)	11.93 (2.04)	.322
HADS anxiety (raw)	5.31 (3.20)	5.04 (2.66)	.416
HADS depression (raw)	2.36 (2.30)	2.40 (2.06)	.874
<b>Cognitive</b>			
Episodic memory (Z score)	-0.01 (1.02)	0.02 (0.96)	.736
Working memory (Z score)	0.01 (0.99)	-0.02 (1.02)	.766
Executive function (Z score)	-0.02 (1.01)	0.04 (0.98)	.588
Language processing (Z score)	0.00 (1.01)	-0.01 (0.98)	.922

Abbreviations: *BDNF*, brain-derived neurotrophic factor; THBP, Tasmanian Healthy Brain Project; WTAR, Wechsler Test of Adult Reading; DRS-2 AEMSS, age- and education-corrected Mayo Older American Normative Studies (MOANS) scaled score; HADS, Hospital Anxiety and Depression Scale.

NOTE. Data represented are mean values (SD) for continuous variables and proportions for categorical variables. The significance of differences in means and frequencies were determined through one-way analyses of variance and chi-square tests, respectively.

## 2.6. Statistical analysis

Scores representing baseline CR were first calculated for each participant using factor analysis–defined regression coefficients [28]. To achieve this, Z scores were imputed into the previously developed equation: CR = 0.370 (Wechsler Test of Adult Reading full-scale IQ) + 0.408 (prior education in years) + 0.567 (Lifetime of Experiences Questionnaire Young Adulthood Specific) + 0.565 (Lifetime of Experiences Questionnaire Young Adulthood Nonspecific) + 0.630 (Lifetime of Experiences Questionnaire Midlife Nonspecific) + 0.875 (Lifetime of Experiences Questionnaire Midlife Continuing Education Bonus) + 1.004 (Lifetime of Experiences Questionnaire Midlife Specific). As the present sample varied marginally from that which was included within the initial factor analysis sample, baseline CR scores were standardized after computation. To produce composite measures of episodic memory, working memory, executive function, and language processing, we first ensured that cognitive tests were suitable for domain-specific factor analyses (Kaiser-Meyer-Olkin measure of sampling adequacy statistic > 0.60; Bartlett's test of sphericity  $P < .05$ ; all diagonals of anti-image correlation matrices  $r > 0.5$ ). Factor analyses (principal components extraction method) were then conducted on raw baseline cognitive test scores (results available in Supplementary Table 1), with a single component retained to represent each cognitive domain. Baseline composite scores were generated from the analysis through the use of standardized regression coefficients; composite scores for subsequent time points (12-, 24-, 36-month follow-up) were calculated by multiplying baseline-referenced cognitive test Z scores by the component score coefficients determined through the factor analyses. Scores within the executive function domain were inverted so that higher scores represented better performance. Analyses of variance and chi-square tests were used to determine group differences in baseline characteristics and cognitive performance (Table 1). Missing data were handled through the use of maximum likelihood estimation methods.

For the main analyses, a series of linear mixed-effects models (LMMs) were used to assess whether variation in baseline CR and *BDNF* Val66Met, independently or through CR  $\times$  *BDNF* Val66Met interaction, was associated with cognitive change over a 36-month period. Baseline CR (continuous), *BDNF* (0, Val/Val; 1, Met carrier), and time (0, baseline; 1, 12 months; 2, 24 months; 3, 36 months) were the primary predictors of cognitive performance. To control for any potential influence of the THBP intervention, THBP group (0, control; 1 experimental) was also used as a predictor. Age at baseline (centered), gender, *APOE*, and symptoms of depression and anxiety were used as covariates. The LMMs were constructed with the following fixed effects:  $y = \text{age at baseline} + \text{gender} + \text{APOE} + \text{symptoms of depression} + \text{symptoms of anxiety} + \text{time} + \text{APOE} \times \text{time} + \text{BDNF} + \text{baseline CR} + \text{THBP group} + \text{BDNF} \times \text{baseline CR} + \text{BDNF} \times \text{THBP group} + \text{BDNF} \times \text{time} + \text{baseline CR} \times \text{THBP group} + \text{baseline CR} \times \text{time} + \text{THBP group} \times \text{time} + \text{BDNF} \times \text{baseline CR} \times$

$\text{THBP group} + \text{BDNF} \times \text{baseline CR} \times \text{time} + \text{BDNF} \times \text{THBP group} \times \text{time} + \text{baseline CR} \times \text{THBP group} \times \text{time}$ .

Participant intercept was included as a random effect. Models were fitted separately for each cognitive domain using maximum likelihood estimation and an autoregressive repeated covariance type. Cohen's *d* statistics were calculated to describe the magnitude of significant effects within the LMMs. To adjust for multiple comparisons, Bonferroni-adjusted *P* values were also calculated (number of separate LMMs = 4). All statistical analyses were conducted using IBM SPSS Statistics v21.

## 3. Results

### 3.1. Sample characteristics

Baseline characteristics stratified by *BDNF* Val66Met genotype group are displayed in Table 1. Within the demographic variables, a single significant difference was identified between groups in previous education (years). Here, *BDNF* Met carriers reported more years of education than *BDNF* Val homozygotes (Cohen's  $d = 0.208$ ). No significant differences existed between the groups in baseline function for any cognitive domain. Means and SDs for cognitive domain scores at each time point stratified by *BDNF* Val66Met genotype are presented in Table 2.

### 3.2. Predictors of cognitive function and cognitive change

The analyses examined the independent and interactive effects of baseline CR and *BDNF* Val66Met on 36-month change in cognitive performance relating to episodic memory, working memory, executive function, and language processing. Mean estimates and differences of predictors stratified by *BDNF* Val66Met group are presented in Table 3. In models

Table 2  
Sample neuropsychological performance stratified by *BDNF* Val66Met genotype

Domain	Time	<i>BDNF</i> Val/Val		<i>BDNF</i> Met+	
		N	Mean SD	N	Mean SD
Episodic memory (Z score)	Baseline	268	-0.01 1.02	134	0.02 0.96
	12 months	230	0.10 0.98	113	0.07 1.05
	24 months	226	0.30 0.99	112	0.33 0.98
	36 months	149	0.61 1.00	69	0.47 0.90
Working memory (Z score)	Baseline	268	0.01 0.99	134	-0.02 1.02
	12 months	230	0.06 1.02	113	-0.00 1.01
	24 months	226	0.09 0.99	112	0.12 0.93
	36 months	149	0.12 1.03	69	0.10 1.02
Executive function (Z score)	Baseline	268	-0.02 1.01	134	0.04 0.98
	12 months	230	0.08 1.04	113	0.07 1.13
	24 months	226	0.19 1.08	112	0.09 1.22
	36 months	149	0.13 1.08	69	0.17 1.12
Language processing (Z score)	Baseline	268	0.00 1.01	134	-0.01 0.98
	12 months	230	0.23 0.90	113	0.02 0.93
	24 months	226	0.15 0.95	112	0.15 0.81
	36 months	873	0.23 0.90	69	0.28 0.98

Abbreviations: *BDNF*, brain-derived neurotrophic factor; SD, standard deviation.

Table 3  
Mean estimates and estimate differences for 36-month cognitive performance stratified by *BDNF* Val66Met polymorphism ( $N = 402$ )

Domain	Predictor	Mean unadjusted estimate (95% CI)		Mean adjusted estimate (95% CI)		Difference of adjusted estimates		
		<i>BDNF</i> Val/Val	<i>BDNF</i> Met+	<i>BDNF</i> Val/Val	<i>BDNF</i> Met+	<i>P</i>	Adjusted <i>P</i>	Cohen's <i>d</i>
Episodic memory	CR	0.083 (-0.311, 0.476)	0.082 (-0.231, 0.395)	0.117 (-0.240, 0.473)	0.159 (-0.125, 0.444)	.816	>.999	-0.023
	Group	0.111 (-0.363, 0.586)	0.405 (0.020, 0.790)	-0.017 (-0.452, 0.418)	0.158 (-0.197, 0.514)	.429	>.999	-0.070
	Time	0.179 (0.068, 0.290)	0.142 (0.051, 0.233)	0.157 (0.046, 0.267)	0.110 (0.017, 0.203)	.404	>.999	0.084
	CR × group	-0.067 (-0.512, 0.379)	-0.171 (-0.533, 0.190)	0.004 (-0.400, 0.407)	-0.210 (-0.538, 0.117)	.297	>.999	0.104
	CR × time	0.017 (-0.043, 0.078)	0.058 (-0.011, 0.126)	0.020 (-0.039, 0.080)	0.063 (-0.005, 0.130)	.165	.660	-0.132
	Group × time	0.013 (-0.116, 0.143)	0.006 (-0.100, 0.112)	0.017 (-0.112, 0.145)	0.016 (-0.089, 0.122)	.996	>.999	0.000
Working memory	CR	0.049 (-0.348, 0.447)	0.150 (-0.164, 0.464)	0.044 (-0.322, 0.410)	0.192 (-0.099, 0.482)	.428	>.999	-0.078
	Group	0.123 (-0.350, 0.595)	0.407 (0.023, 0.791)	-0.022 (-0.461, 0.417)	0.241 (-0.118, 0.600)	.240	.960	-0.108
	Time	0.043 (-0.050, 0.135)	0.025 (-0.051, 0.101)	0.035 (-0.057, 0.127)	0.015 (-0.062, 0.093)	.672	>.999	0.041
	CR × group	0.026 (-0.426, 0.478)	0.099 (-0.265, 0.463)	0.120 (-0.297, 0.536)	0.082 (-0.254, 0.418)	.860	>.999	0.018
	CR × time	0.076 (0.026, 0.126)	0.033 (-0.024, 0.090)	0.077 (0.026, 0.127)	0.037 (-0.020, 0.094)	.117	.468	0.145
	Group × time	-0.005 (-0.113, 0.103)	0.028 (-0.060, 0.116)	-0.003 (-0.110, 0.105)	0.032 (-0.056, 0.120)	.528	>.999	-0.060
Executive function	CR	0.075 (-0.341, 0.491)	-0.011 (-0.341, 0.320)	0.086 (-0.277, 0.449)	0.063 (-0.227, 0.354)	.904	>.999	0.012
	Group	0.169 (-0.333, 0.672)	0.394 (-0.014, 0.803)	-0.017 (-0.462, 0.428)	0.131 (-0.234, 0.495)	.516	>.999	-0.056
	Time	0.046 (-0.074, 0.166)	0.013 (-0.085, 0.111)	0.027 (-0.092, 0.146)	-0.016 (-0.117, 0.084)	.476	>.999	0.070
	CR × group	0.169 (-0.301, 0.640)	0.059 (-0.323, 0.441)	0.289 (-0.121, 0.698)	0.027 (-0.307, 0.361)	.210	.840	0.126
	CR × time	-0.059 (-0.123, 0.006)	0.052 (-0.022, 0.125)	-0.059 (-0.123, 0.006)	0.058 (-0.015, 0.131)	<.001	.002	-0.330
	Group × time	0.021 (-0.118, 0.160)	0.030 (-0.084, 0.144)	0.025 (-0.114, 0.163)	0.040 (-0.074, 0.153)	.832	>.999	-0.021
Language processing	CR	0.261 (-0.087, 0.610)	0.354 (0.076, 0.631)	0.256 (-0.091, 0.603)	0.354 (0.077, 0.631)	.580	>.999	-0.054
	Group	0.083 (-0.339, 0.505)	0.345 (0.001, 0.688)	0.056 (-0.366, 0.479)	0.317 (-0.028, 0.663)	.226	.904	-0.108
	Time	0.018 (-0.086, 0.123)	0.039 (-0.047, 0.124)	0.014 (-0.090, 0.118)	0.036 (-0.052, 0.124)	.674	>.999	-0.041
	CR × group	0.143 (-0.251, 0.537)	-0.061 (-0.381, 0.260)	0.154 (-0.240, 0.547)	-0.054 (-0.373, 0.266)	.300	>.999	0.104
	CR × time	-0.011 (-0.068, 0.046)	0.009 (-0.055, 0.074)	-0.009 (-0.066, 0.047)	0.012 (-0.052, 0.076)	.464	>.999	-0.067
	Group × time	0.039 (-0.083, 0.161)	0.033 (-0.067, 0.133)	0.043 (-0.079, 0.164)	0.038 (-0.062, 0.137)	.937	>.999	0.008

Abbreviations: CR, cognitive reserve; *BDNF*, brain-derived neurotrophic factor; LMM, linear mixed-effects model.

NOTE. Adjusted estimates included covariates of age, gender, apolipoprotein E genotype, apolipoprotein E genotype × time, and symptoms of depression and anxiety; adjusted *P* values represent Bonferroni-corrected values (number of separate LMMs = 4).



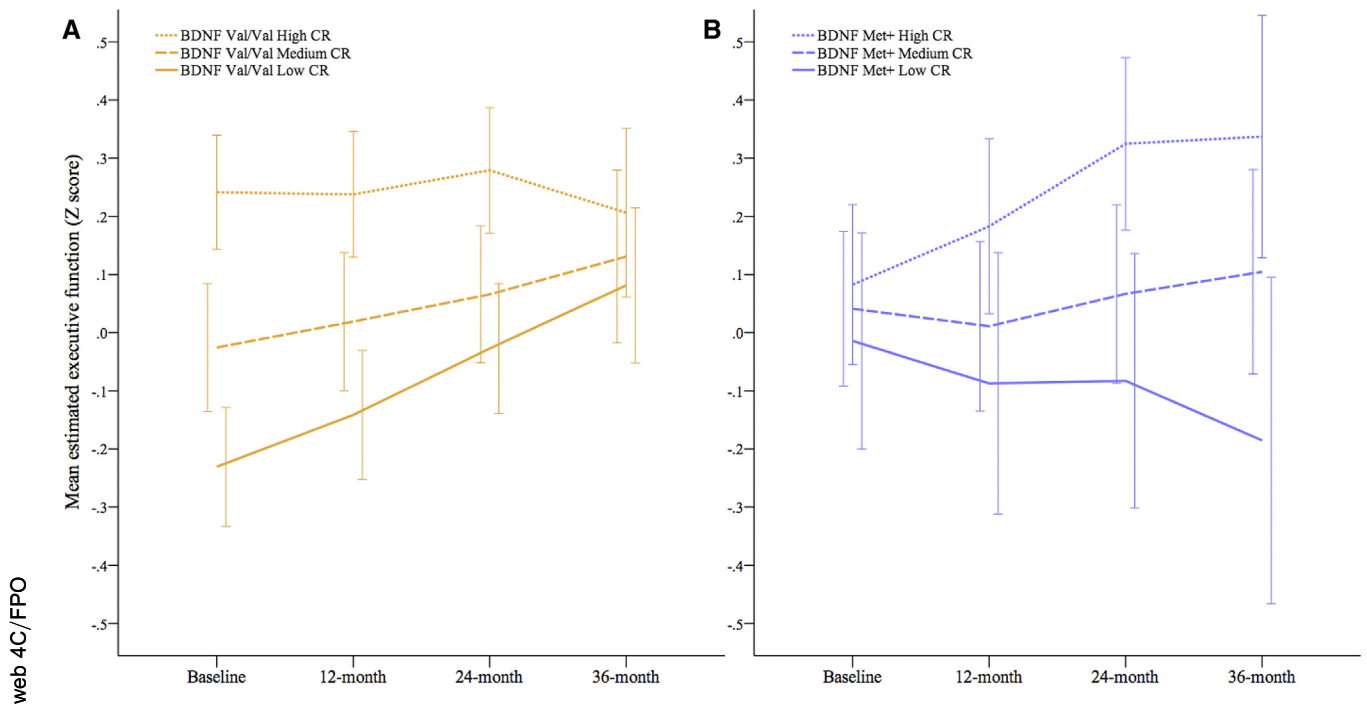


Fig. 1. CR and *BDNF* Val66Met interact to influence change in executive function. Figure shows mean estimated executive function score, stratified by CR tertile group, for (A) *BDNF* Val homozygotes and (B) *BDNF* Met carriers. Performance was estimated by a linear mixed-effects model that included covariates of Tasmanian Healthy Brain Project group, age, gender, apolipoprotein E genotype, apolipoprotein E genotype  $\times$  time, and symptoms of depression and anxiety. Error bars represent 95% confidence intervals. Abbreviations: *BDNF*, brain-derived neurotrophic factor; CR, cognitive reserve.

adjusted for age, gender, *APOE*, *APOE*  $\times$  time, and symptoms of depression and anxiety, multiple significant effects of the predictor variables were identified. Time was positively associated with episodic memory (adjusted  $P < .001$ ), and baseline CR was positively associated with language processing (adjusted  $P = .004$ ). A baseline CR  $\times$  time interaction was significantly associated with working memory initially ( $P = .016$ ), but not following Bonferroni correction (adjusted  $P = .064$ ). However, this effect was subsumed within a significant baseline CR  $\times$  group  $\times$  time interaction for working memory (adjusted  $P = .038$ , Cohen's  $d = 0.247$ ), whereby the association of CR on change in performance was different between the experimental group (estimate = 0.008, 95% CI =  $-0.022$ , 0.038) and the control group (estimate = 0.077, 95% CI = 0.025, 0.129). Finally, a single significant *BDNF*  $\times$  baseline CR  $\times$  time interaction was identified for executive function (Fig. 1), which indicated that the association of CR on change in performance was significantly different between *BDNF* Val homozygotes and *BDNF* Met carriers (Table 3; difference of estimate =  $-0.117$ , 95% CI =  $-0.181$ ,  $-0.052$ ).

#### 4. Discussion

In this investigation, we examined whether variation in CR or *BDNF* Val66Met, either independently or through CR-gene interaction, affected 36-month cognitive change

in healthy older participants of the Tasmanian Healthy Brain Project. Although no longitudinal differences were identified in any cognitive domain between *BDNF* Val homozygotes and Met carriers, we found that baseline CR had a positive association with change in working memory performance that was stronger in the THBP control group. We also found that the *BDNF* Val66Met polymorphism interacted with baseline CR to affect 36-month 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. This suggests that CR may affect the higher order cognitive processing of aging individuals differently based on variation in *BDNF* Val66Met, which is noteworthy given that associations of CR and cognitive change are typically only observed in conjunction with the presence of significant neuropathology [34].

Higher CR is reliably associated with higher cognitive function in middle and older age, independent of any potential protective effect on age-related decline or dementia risk [35]. The results of our previous cross-sectional analysis support this, where we found positive relationships between CR and function in multiple cognitive domains [21]. In the present study, we found that CR exerted an effect on the rate of change in working memory performance, with higher CR associated with a greater improvement in performance across the

36-month follow-up period. However, this modulation of working memory performance by CR was identified solely in the subgroup of control participants of the THBP ( $N = 93$ ), and may simply be a result of differences in demographic and cognitive variables. Should this effect represent more than a sampling bias, it may reflect a buffering of negative aging-related memory changes by CR, although reports are mixed regarding a role of CR in cognitive aging [36]. This result may also be due to the use of better cognitive strategies to achieve greater improvements in functioning over time in individuals with higher CR, as improved cognitive strategy selection is hypothesized to underpin part of the cognitive benefits of CR [37].

Our most significant finding was an interaction between *BDNF* Val66Met and CR in predicting change in executive function performance. Here, results indicated that *BDNF* Val66Met status determined whether CR-related differences in performance decreased or increased across the 36-month follow-up period. This effect has been identified in a previous baseline analysis of this data set [21], which identified a stronger association of CR and executive function in *BDNF* Val homozygotes than in *BDNF* Met carriers. Overall, this set of results suggests that the expected positive association of lifetime exposure to cognitively stimulating activities and cognitive performance is weaker in *BDNF* Met carriers and that this may culminate in the amplification of CR-related differences in aging-related cognitive trajectories. Despite this, the present results also indicated that the influence of any of the included predictors on 36-month cognitive change did not vary by the *BDNF* Val66Met polymorphism in the other assessed cognitive domains (i.e., episodic memory, working memory, language processing), with negligible or very small effect sizes identified. Similarities between CR and executive function may explain why this CR effect was observed solely in the executive function domain [38], and both constructs share commonalities in relation to cognitive flexibility [8,39] and a reliance on frontal lobe activity [40,41].

Interpretation of the present results should be undertaken with consideration of the following limitations: (1) at baseline, our sample consisted of high-functioning older adults who were well educated and likely had higher CR than average (mean IQ = 112.86, mean years of education completed = 13.98). Therefore, our results may not be applicable to wider populations; (2) *APOE* has been shown to interact with *BDNF* Val66Met in healthy, preclinical, and AD individuals [5,42,43] but we were not able to include an *APOE* × *BDNF* Val66Met interaction term due to the small number of cases in the *APOE*  $\epsilon$ 4/*BDNF* Met group; (3) patterns of aging-related cognitive decline were not observable in the sample, overall. This may be partly accounted for by practice effects [44], and similar

patterns of cognitive change in healthy older adults have been reported in other cohorts, even in the absence of intervention [45]; (4) the THBP intervention may have had an influence on the cognitive trajectories described in our study. However, our analyses included THBP group interaction terms to adjust for any potential effect of the intervention, and experimental/control group membership was evenly distributed across *BDNF* groups at baseline.

Independent detrimental effects of *BDNF* Met on age-related change in episodic memory [24] and perceptual speed [26], which is a cognitive process closely related to executive function [46], have been reported previously. In addition, a recent investigation reported that inheritance of *BDNF* Met is associated with a steeper aging-related decline in executive function performance [27], although the authors only identified this effect in conjunction with the presence of *APOE*  $\epsilon$ 4. Although we did not find support for the notion that *BDNF* Met directly affects cognitive trajectories in older adults, our results have identified an indirect pathway through which *BDNF* Met may exert a negative influence on aging-related change in the executive function domain. This indirect effect may provide one explanation as to why the *BDNF* Val66Met polymorphism does not always show significant associations with older adult cognitive performance (e.g., [22,23]).

In conclusion, our results indicate that CR is associated with performance in multiple cognitive domains in healthy older adults and interacts with *BDNF* Val66Met to influence change in executive function performance. If future research confirms that *BDNF* Met confers a susceptibility to cognitive decline due to low CR, the *BDNF* Met carrier group represents a well-defined population that could be targeted for cognitive stimulation-based interventions aimed at reducing the negative effects of advancing age on cognitive function and, potentially, the prevalence of dementia.

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## Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.trci.2017.04.006>.

## RESEARCH IN CONTEXT

1. Systematic review: Using both PubMed and Google Scholar, the authors reviewed literature related to independent and interactive cognitive associations of cognitive reserve (CR) and the *BDNF* Val66Met polymorphism in both aging and dementia.
2. Interpretation: We found that baseline CR interacted with the *BDNF* Val66Met polymorphism to influence patterns of 36-month cognitive change. This suggests that low CR may be a risk factor for cognitive decline in *BDNF* Met carriers. However, this effect was present solely within the executive function domain and was absent within the episodic memory, working memory, and language-processing domains.
3. Future directions: Research should investigate whether cognitive stimulation-based interventions aimed at reducing cognitive decline and dementia risk are differentially effective in *BDNF* Val66Met polymorphism groups. Furthermore, it is essential that interactive effects of CR and *BDNF* Val66Met are investigated in preclinical and clinical cohorts.

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