APOE and *BDNF* Val66Met polymorphisms combine to influence episodic memory function in older adults

Running title: *APOE* and *BDNF* Val66Met and episodic memory

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Abstract

Genetic polymorphisms of apolipoprotein E (*APOE*) and brain-derived neurotrophic factor (*BDNF*) have shown inconsistent associations with healthy adult cognitive functions. Recent investigations have suggested that *APOE* polymorphisms do not contribute to non-pathological cognitive function and that any effect is likely due to prodromal Alzheimer's disease (AD). Similarly, although *BDNF* Val66Met polymorphisms affect hippocampal morphology and function, associations with learning and/or memory have not always been found. This study sought to determine whether *APOE* and *BDNF* polymorphisms were associated, either independently or in combination, with adult cognition. Comprehensive neuropsychological assessments were conducted on 433 older adults, aged 50-79 years (M = 62.16, SD = 6.81), which yielded measures of episodic memory, working memory, executive function, and language processing. Participants underwent comprehensive neuropsychological assessment to ensure that only cognitively intact individuals comprised the sample. *APOE* and *BDNF* polymorphic data were used as predictors in general linear models that assessed composite cognitive domain variables, while covarying for education and age. Although no main effects for *APOE* or *BDNF* were found, the analysis identified a significant *APOE* x *BDNF* interaction that predicted episodic memory performance (p. = .02, η^2 = .02). Post-hoc analyses demonstrated that, in *BDNF* Val homozygotes, the cognitive consequences of *APOE* polymorphisms were minimal. However, in *BDNF* Met carriers, the hypothesized beneficial/detrimental effects of *APOE* polymorphisms were found. Our data show that concurrent consideration of both *APOE* and *BDNF* polymorphisms are required in order to witness a cognitive effect in healthy older adults.

Keywords: apolipoprotein E; APOE; brain-derived neurotrophic factor; BDNF; aging; episodic memory; polymorphisms; older adults

1. Introduction

Genetic variance has been postulated to account for individual differences in adult cognitive capacity [1]. Importantly, the heritability of cognitive function increases over the lifespan [2]. Although genome-wide investigations have supported the genetic basis for cognition [3], replicable single gene effects are rare. However, two candidate genes for adult cognitive function are apolipoprotein E (*APOE),* the largest known contributor to genetic risk for late onset Alzheimer's disease [4], and brain-derived neurotrophic factor (*BDNF*), a gene implicated in synaptic plasticity and neurogenesis [5]. While both genes have been associated with variance in healthy cognition [6], such associations have not been reliably replicated.

Inheritance of *APOE* ε4 is associated with an increased rate of accumulation of abnormal AD-like pathology and detrimental hippocampal morphology, among other negative effects [7-9]. Conversely, *APOE* ε2 is associated with neurological benefits [10], such as protection from the accumulation of AD-like pathology (Castellano *et al.*, 2011) and increased cortical thickness (Liu *et al.*, 2010). Some studies suggest no effect of *APOE* genotype on healthy cognition (Jorm *et al.*, 2007; Small *et al.*, 1998), while others report lowered cognitive functions associated with the *APOE* ε4 allele in aging populations (Deary *et al.*, 2004; Wilson *et al.*, 2002; Wisdom *et al.*, 2011). Recent data indicate that a specific *APOE* ε4-related cognitive phenotype does not exist independently from dementia or mild cognitive impairment (Foster *et al.*, 2013; Quintas *et al.*, 2013).

A second gene suggested to account for variance in healthy adult cognitive function is *BDNF*. The BDNF protein is a growth factor important to the maintenance, survival, and growth of neurons (Lu *et al*., 2013), as well as synaptic plasticity, neurogenesis, and cell survival (Bath

& Lee, 2006). The Met variant of the Val66Met human polymorphism has been linked to decreased activity-dependent secretion of BDNF at the synapse (Egan *et al.*, 2003), and reduced hippocampal volume and function (Bath & Lee, 2006). Multiple investigations have reported *BDNF* polymorphism-related memory effects (Egan *et al.*, 2003; Raz *et al.*, 2009). However, several other studies have reported negative results (Gong *et al.*, 2012; Houlihan *et al.*, 2009; Laing *et al.*, 2011; Stuart *et al*., 2014).

We investigated whether common variations in *APOE* and *BDNF* Val66Met are associated, either independently or through gene-gene interaction, with healthy cognitive function. Three hypotheses were examined using baseline data from the prospective longitudinal Tasmanian Healthy Brain Project [11]: that *APOE* ε2 alleles are associated with better cognitive function and ε4 alleles are associated with worse cognitive function when compared to ε3 homozygotes; that *BDNF* Val homozygotes are associated with better cognitive function when compared to Met carriers; that a cumulative effect of the cognitive consequences associated with *APOE* and *BDNF* alleles results in the highest cognitive function in *APOE* ε2/*BDNF* Val carriers and the lowest cognitive function in *APOE* ε4/*BDNF* Met carriers.

2. MATERIALS AND METHODS

2.1 Participants

The sample consisted of community-residing adults, aged 50-79 years, who consented to comprehensive annual assessments of neuropsychological, health, and psychosocial function as part of the longitudinal Tasmanian Healthy Brain Project (THBP). The THBP is a prospective longitudinal study examining whether late-life education provides protection from dementia through enhancement of cognitive reserve [11]. Participants completed

screening before they were invited to participate and were excluded if they had a history of any condition independently associated with cognitive impairment (dementia; multiple sclerosis; previous significant head injury requiring hospitalization; epilepsy; history of cerebro-vascular complications; diabetes – poorly controlled; blood pressure complications – poorly controlled; other neurological disorders; chronic obstructive pulmonary disease; heart disease; blindness; deafness; psychiatric disorder). All participants were native-English speakers or spoke English as a primary language. Data from 433 participants enrolled in the THBP were available for analysis. The THBP was conducted with full approval from the Tasmanian Human Research Ethics Network and in accordance with the ethical guidelines of the National Health and Medical Research Council of Australia (NHMRC).

2.2 Materials

Participants completed a comprehensive test battery as described in detail elsewhere [11]. To ensure that the participants were free from symptoms of dementia and were in good physical and psychological health, the Mattis Dementia Rating Scale-2 [DRS-2; 12], Hospital Anxiety and Depression Scale [HADS; 13], and a Medical Health Status questionnaire [MHSq; 11] were used. The MHSq also screened general health, medical conditions, prescription medication use, drug and alcohol use for the preceding 12 months; as well as information on each participant's age, gender, handedness, height, weight, marital status, and educational and occupational history. Premorbid intellectual capacity was assessed using the Wechsler Test of Adult Reading [WTAR; 14]. An experienced clinical neuropsychologist reviewed the results of each participant to ensure compliance with the study protocol.

2.3 Neuropsychological assessment battery

Tests of cognitive function were selected to assess learning and memory, working memory, executive function, and language processing. In order to simplify data analysis and interpretation, a composite summary measure was derived for each assessed cognitive domain. The episodic memory variable comprised Rey Auditory Verbal Learning Test [RAVLT; 15], Logical Memory test [LM; 16], and Paired Associates Learning test [PAL; 17]. The working memory variable comprised WAIS-III Digit Span [DSP; 18], WAIS-III Letter-Number Sequencing [LNS; 18], Spatial Span [SSP; 17], and Spatial Working Memory [SWM; 17]. The executive function variable comprised Rapid Visual Processing [RVP; 17], 24-item Victoria version Stroop Test [19], and Trail Making Test [TMT; 19]. The language processing variable comprised WAIS-III Vocabulary [VOC; 18], WAIS-III Comprehension [COM; 18], and Boston Naming Test [BNT; 20].

2.4 Genotyping

DNA samples were collected with Oragene DNA self-collection kits [21]. *APOE* and *BDNF* genotypes were determined through one-step amplified refractory mutation system polymerase chain reaction (ARMS-PCR) and subsequent gel electrophoresis. For *APOE*, rs429358 and rs7412 were determined by following the method described by Donohoe, Salomaki [22]. For *BDNF*, Val66Met was determined by following the method described by Sheikha, Hayden [23]. PCR amplifications were undertaken in a 12 µl reaction volume that contained approximately 50 ng of genomic DNA. PCR amplicons were resolved on 2% agarose gel. Genotyping was repeated on samples to ensure accuracy, with the proportion of

concordance >99% for both polymorphisms. If a discrepancy in results was obtained, the samples were run a third time to establish genotype.

2.5 Procedure

Trained assessors performed the assessment of all participants at baseline THBP assessment [11]. The assessment process took approximately four hours to complete and was undertaken in a quiet well-lit room. Subjects were encouraged to take 10-minute breaks when required to reduce fatigue.

2.6 Data analysis

In order to investigate whether *APOE* and *BDNF* genotypes were associated with healthy cognitive function, we first computed the cognitive domain variables through factor analysis (principal components extraction method). Factor coefficients for each of the test scores were combined into a single factor score using a regression method for the episodic memory, working memory, executive function, and language processing domains. The extracted factor that explained the highest proportion of variance was retained to represent each domain (Table 1). We then fitted general linear models to each cognitive domain, using *APOE* and *BDNF* genotype data as predictors, while covarying for age and education. The independent *APOE* variable had three levels: ε2 carriers (genotypes: ε2/ε2 & ε2/ε3); ε3 homozygotes; and ε4 carriers (genotypes: ε3/ε4 & ε4/ε4). To assist in interpretation, participants with the ε2/ε4 genotype were excluded from the analysis. The independent *BDNF* variable had two levels:

Val homozygotes and Met carriers. An alpha value of .05 was used for all statistical tests. All data were analyzed in SPSS v21.

[INSERT TABLE 1 HERE]

3. RESULTS

3.1 Subjects

Genotype data were available for 433 participants that had completed THBP baseline assessment. Eleven participants were excluded due to *APOE* ε2/ε4 genotype. The characteristics of the remaining 422 THBP participants are presented in Table 2. Participants were 62.16 (*SD* = 6.81) years old and had an above average IQ (*M* = 112.47, *SD* = 5.52), overall. The majority were female (66.7%) and had completed a mean of 13.97 (*SD* = 2.73) years of education. The *APOE* genotype distribution in our study was 11.11% ε2 carrier, 56.4% ε3 homozygote, and 32.5% ε4 carrier, and did not differ significantly from Hardy-Weinberg equilibrium ($\chi^2_{(1,\, N = 433)} = 0.02$, *p.* = 0.90). The *BDNF* Val66Met genotype allele distribution was 67% Val homozygote and 33% Met carrier, and also did not differ significantly from Hardy-Weinberg equilibrium ($\chi^2_{(1,\, N = 433)} = 0.37$, *p.* = 0.54). Univariate ANOVAs were conducted on demographic and screening variables, with a single significant gene-related effect identified in education (years) measure ($F_{(1,431)} = 6.48$, *p.* = .01, *d* = .26, power = .726). Here, more years of education were reported in *BDNF* Met carriers (*M* = 14.45, *SD* = 2.74) than in *BDNF* Val homozygotes (*M* = 13.74, *SD* = 2.70), overall.

[INSERT TABLE 2 HERE]

3.2 Genotype and cognitive function

General linear models, using *APOE* and *BDNF* as predictors, were fitted to the composite cognitive variables while covarying for education and age. The education covariate showed a significant association with every cognitive domain ($p. < .05$), while the age covariate was significantly associated with each cognitive domain ($p. < .01$), excluding language processing ($p. = .06$). When each gene was considered independently, the univariate ANCOVA did not detect any simple main effects within cognitive domains, after controlling for age and education (Table 3).

[INSERT TABLE 3 HERE]

[INSERT FIGURE 1 HERE]

3.3 Gene-gene cognitive interactions

When gene-gene interactions were examined, a significant *APOE* x *BDNF* effect was detected by ANCOVA only for episodic memory, with age and education entered as covariates (Table 3). Subsequent follow-up univariate ANCOVAs were conducted to test for *APOE*-related differences for *BDNF* Val homozygotes and Met carriers separately, after controlling for age and education. The results showed that, for *BDNF* Val homozygotes, no differences in episodic memory were identified as a result of variation in *APOE* genotype

($F_{(2, 265)} = 0.63$, $p. = .54$, $\eta^2 < 0.01$, power = .228). However, for *BDNF* Met carriers, *APOE* genotype was associated with significant variation in age- and education-adjusted episodic memory scores ($F_{(2, 132)} = 5.12$, $p. < .01$, $\eta^2 = 0.06$, power = 1.00). Post-hoc analysis by least squares difference (LSD) revealed that for *BDNF* Met carriers, those who were also *APOE* ε2 carriers had significantly higher ($p. < .05$) episodic memory scores than those who were *APOE* ε3 homozygotes or *APOE* ε4 carriers. Although *APOE* ε3 carriers had higher episodic memory scores than *APOE* ε4 carriers, the difference did not reach significance (Figure 1).

4. DISCUSSION

The present investigation sought to determine whether common genetic variations in the *APOE* and *BDNF* genes were associated with normal non-pathological cognitive function in older adults. Data from the Tasmanian Healthy Brain Project (THBP) were used to generate composite variables of episodic memory, executive function, working memory, and language processing, with general linear models subsequently fitted. Our first and second hypotheses, that variation in *APOE* or *BDNF* genotype is independently associated with cognitive function, were not supported. The third hypothesis, that a cumulative effect of the alleles' cognitive consequences resulted in the highest cognitive function in *APOE* ε2/*BDNF* Val carriers and the lowest cognitive function in *APOE* ε4/*BDNF* Met carriers, was partially supported. Although the lowest mean episodic memory performance was found in *APOE* ε4/*BDNF* Met alleles carriers, unexpectedly high episodic memory performance was observed in *APOE* ε2/*BDNF* Met carriers. The main finding of this study is that the predicted effect of variation in *APOE* was identified in our dataset, but only in carriers of the *BDNF* Met allele.

The hypothesis that *APOE* is independently associated with a distinct cognitive phenotype in healthy adults has not received consistent support. Earlier studies described an *APOE* ε4-related impairment in episodic memory [24, 25] that was not seen in our investigation. Methodological differences may account for this. The sample in the present study is comprised of older adults with extensive cognitive assessment confirming that they were all cognitively intact and medical screening to ensure that they were physically healthy. The extensive screening of the present sample to ensure all were healthy may have reduced the likelihood that we would detect cognitive effects attributable to *APOE* ε4's effect on risk for dementia. Furthermore, if *APOE* ε4 is associated with accelerated cognitive ageing rather than simply conferring reduced cognitive processing [6, 26], then it is possible that our sample may be younger than the age at which ageing-related differences can be identified by cross-sectional analysis. Our sample was, on average, 10 years younger than those cohorts in studies reporting *APOE*-related differences [24, 25]. However, our findings add to an increasing body of evidence from recent investigations that report no cognitive differences in healthy individuals due to *APOE* genotype, even in subjects aged above 70 years [27, 28]. Our data provide further evidence that an association between *APOE* genotype and cognition in cognitively intact subjects may instead reflect emerging prodromal AD in these samples [29].

Similarly, support for the hypothesized cognitive effect associated with variation in *BDNF* Val66Met was not found in our dataset. Although the *BDNF* Met variant is associated with deficits to hippocampal morphology and function [5, 30], we found no significant differences between Val homozygotes and Met carriers on any cognitive domain. This supports previous investigations reporting no differences in cognitive processing and memory due to *BDNF*

polymorphic variation [31-33]. However, the notion that *BDNF* is associated with memory function is not likely to be spurious, with a number of studies finding that a deficit in memory function is associated with the *BDNF* Met variant [34-36]. Disparities in results may be due to the profound differences in effects that variation in *BDNF* exerts across the lifespan [37]. Such gene by environment interactions indicate that the neurological effects conferred by the *BDNF* polymorphism are complex, and ensure that differences in sample demographics, particularly age, diminish the idea of a simple risk allele for cognitive function.

Our investigation identified a significant *APOE* x *BDNF* gene-gene interaction that was associated with episodic memory function. The basis for this interaction was the *BDNF* genotype-dependent effects that variation in *APOE* exerted. Here, the hypothesized beneficial and detrimental effects on episodic memory function associated with the *APOE* ε2 and *APOE* ε4 polymorphisms, respectively, were found only in *BDNF* Met carriers, with no cognitive implication associated with variation in *APOE* in *BDNF* Val homozygotes. Two possible explanations for this effect are given. First, there is a biological interaction related to the systems or ageing-related roles of the encoded proteins. Second, the additive effects of the polymorphisms caused the analyses to reach statistical significance. The 'additive' explanation does not, however, account for our finding that *APOE* ε2/*BDNF* Met carriers had the highest episodic memory function, as *BDNF* Met polymorphisms were hypothesized to be associated with decreased cognitive function.

Interactions between *APOE* and *BDNF* have been previously investigated with mixed results. One study demonstrated a negative association between *BDNF* Met polymorphisms and working memory capacity, but found no influence of *APOE* on cognition, either independently or in combination with *BDNF* [38]. Another investigation showed an additive

effect of *APOE* and *BDNF* on hippocampal activity during a memory encoding task: although reduced medial temporal lobe activation showed a dose-dependent relationship with *APOE* ε4 and *BDNF* Met polymorphisms, the combined effect of both genes explained more variance than when they were considered individually [39]. The researchers concluded that both genes exert converging, but independent, effects on memory function. Finally, a recent study identified an interaction between *APOE* and *BDNF* in the putative preclinical phase of AD associated with β-amyloid deposition in the brain [40]. In cognitively normal older adults, *BDNF* Met carriers showed a significantly higher amyloid load than *BDNF* Met non-carriers, but only if they were *APOE* ε4 carriers. Notably, variation in *BDNF* polymorphisms did not have an effect on amyloid load in *APOE* ε4 non-carriers. These investigators also found an inverse relationship between episodic memory and amyloid burden that was only present in *APOE* ε4/*BDNF* Met carriers. Moreover, *APOE* and *BDNF* have been suggested to combine to affect the progression of pathological morphological AD-related changes in the preclinical phase [41]. Taken together, these findings suggest that our data may reflect a combination of an interaction of APOE and BDNF effects on medial temporal lobe activation, amyloid load, and atrophy, which culminate in cognitive outcomes.

With interactions between *APOE* and *BDNF* reliably identified in previous research, knowledge of accurate population-based genotype frequencies is important for predicting the efficacy of possible future interventions. In our sample, the *BDNF* Val66Met polymorphism influenced whether variation in *APOE* exerted cognitive effects. Consequently, as *BDNF* Met carriers comprised 33% of our sample, a third of our participants were exposed to the cognitive implications of polymorphic variation in *APOE*. A meta-analysis of 643 subjects of varying ethnicities reported that 37% of their sample were *BDNF* Met carriers [42]. Similarly, a meta-analysis of 3322 subjects of majorly European descent reported that 36% of

their sample were *BDNF* Met carriers [43]. Our data show that, in *BDNF* Met carriers, 6% of the variance in episodic memory performance was accounted for by variation in *APOE* genotype. Although initially a small effect, if an individual's genetic makeup accounts for 50% of overall adult cognitive function [2], 12% of the genetically-derived episodic memory function in *BDNF* Met carriers is accounted for by the interaction identified in our study. Overall, our genotype frequencies are consistent with those previously identified in the literature and, as a result, our findings indicate that a large proportion of individuals in the greater population may show affected episodic memory due to variation in *BDNF* Val66Met and *APOE*.

Increased understanding of complex gene-environment [37] and epigenetic [44] interactions weakens the notion that simple risk alleles cause deterioration in cognitive function. In investigations that do find significant main effects for gene polymorphisms on cognitive function, the effect size is often very small. For example, a meta-analysis [26] of 77 studies comprising 40,942 cognitively normal adults identified an association of *APOE* ε4 with reduced episodic memory (d = -0.14), reduced global cognitive ability (d = -0.05), reduced executive function (d = -0.06), and slowed perceptual speed (d = -0.07). Similarly, Deary and colleagues [24] found that the *APOE* ε4 polymorphism accounted for just 2% of the variance in verbal episodic memory performance. Investigations that examine single gene cognitive effects, and ignore environmental or gene product interactions, are unlikely to produce significant or translatable results. However, such studies can be useful in identifying potential targets for more complex investigations. In our study, no cognitive effect was identified due to genetic variation unless genes were considered in combination. Large-scale investigations that utilize whole-genome sequencing may be best suited to answer questions relating to the genetics of human cognition [45], provided interpretations of any association identified take

account of the magnitude of the effect size of the association rather than just statistical significance of an effect.

A limitation of the present research is that physical activity and diet were not measured or controlled for. Specifically, our general linear models did not covary for such variables while detecting the cognitive effects of polymorphic variation. This is particularly important when investigating *BDNF*, as evidence from animal studies reliably describes elevated BDNF secretion in hippocampal regions of mice after exercise [46]. BDNF signaling may also mediate the protective effects of diet and exercise on neurodegeneration [47]. Moreover, the inhibition of BDNF action has been demonstrated to negate the cognitive and synaptic benefits of exercise [48]. A recent study demonstrated that exercise provided protection against diet induced cognitive decline, an effect likely due to the increased presence of BDNF in hippocampal CA3 region [49]. Future *BDNF* investigations should consider measures of physical activity in the design of their statistical analyses.

In conclusion, our study did not support the hypotheses that variation in *APOE* or *BDNF* is associated with cognitive function in healthy older adults. However, we did identify a significant *APOE* x *BDNF* interaction that was associated with episodic memory capacity. This effect demonstrated that, in *BDNF* Val homozygotes, the cognitive implications of *APOE* genotype were minimal, whereas, in *BDNF* Met carriers, the hypothesized beneficial/detrimental association with *APOE* polymorphisms was found. Our data show the effects of single genes on cognition are neither simple nor reliable, and that consideration of multiple genes and interactions is necessary.

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Conflicts of interest

Dr. M. Summers reports personal fees from Eli Lily (Australia) Pty Ltd, grants from Novotech Pty Ltd, outside the submitted work; Prof. Vickers reports grants from Bupa Foundation (Australia) Limited, grants from J.O. & J.R. Wicking Trust, outside the submitted work. All other authors have nothing to disclose.

Table 1. Factor analysis results for composite cognitive domain variables

Cognitive domain	Initial eigenvalue	Variable	*N*	Mean	SD	Loading
Episodic memory	2.50 (62.39%)	RAVLT 1-5 total	418	52.95	8.86	.76
		LM I immediate recall total	418	48.45	8.02	.89
		LM II delayed recall total	418	30.30	6.24	.86
		PAL first trial memory score	418	18.33	3.48	.63
Working memory	2.06 (51.53%)	Digit span	418	18.66	3.93	.77
		Letter-number sequencing	418	11.61	2.40	.80
		SWM between errors	418	25.45	18.99	-.64
		SSP length	418	5.75	1.20	.65
Executive function	1.79 (59.50%)	Stroop trial C	414	26.30	7.65	.75
		RVP A’	414	0.91	0.05	-.81
		TMT trial B	414	59.16	19.09	.75
Language processing	1.89 (62.88%)	WAIS Vocabulary	432	56.59	6.28	.88
		WAIS Comprehension	432	26.20	3.33	.78
		Boston Naming Test	432	57.50	3.39	.71

Note: Data in parentheses represent the proportion of variance (%) explained by the resulting factor.

Table 2. Descriptive statistics for study population stratified by *APOE* and *BDNF*

		APOE ε2+		*APOE* ε3/ε3		*APOE* ε4+	
	N	Val/Val	Met+	Val/Val	Met+	Val/Val	Met+
Demographics							
N		34	13	158	80	90	47
Age (years)	422	61.09 (6.56)	64.85 (7.26)	62.49 (6.96)	62.05 (6.61)	61.98 (6.78)	61.09 (6.54)
Gender (male/female)	422	10/24	5/8	50/108	26/54	29/61	20/27
Education (years)	422	13.38 (2.82)	15.46 (2.57)	13.86 (2.79)	14.76 (2.75)	13.62 (2.56)	13.60 (2.65)
WTAR IQ	421	112.09 (4.80)	113.31 (3.73)	112.49 (5.87)	112.81 (4.91)	112.37 (5.08)	111.76 (7.39)
Screening							
DRS-2 AEMSS	422	11.94 (2.12)	12.31 (1.49)	11.97 (2.17)	11.76 (2.14)	12.19 (1.99)	12.11 (2.12)
HADS anxiety	421	5.03 (2.83)	5.15 (2.64)	5.28 (3.27)	5.16 (3.05)	5.59 (3.20)	4.89 (2.44)
HADS depression	421	2.79 (2.26)	2.46 (1.27)	2.30 (2.22)	2.30 (2.03)	2.51 (2.33)	2.70 (2.39)
Cognitive performance							
Episodic memory	407	-0.15 (0.92)	0.49 (0.67)	0.01 (1.04)	0.03 (0.92)	0.05 (1.01)	-0.22 (1.13)
Working memory	407	-0.07 (0.72)	0.18 (0.86)	-0.01 (1.06)	-0.09 (0.96)	0.09 (1.00)	-0.02 (1.01)
Executive function	403	-0.25 (1.06)	0.15 (0.83)	-0.03 (1.04)	-0.02 (0.96)	0.11 (0.90)	0.07 (1.10)
Language processing	421	-0.14 (1.08)	0.52 (0.57)	-0.02 (1.03)	-0.01 (1.00)	0.11 (0.85)	-0.14 (1.14)

Note: Data represent mean values (SD) for continuous variables and proportions for categorical variables.

Table 3. Summary statistics for the general linear models that assessed the cognitive implications of variation in *APOE* and *BDNF* genotypes, independently and in combination

Cognitive domain	Predictor	*N*	df	F	*P*.	η^2	Obtained power
Episodic memory	*APOE*	407	2, 399	1.28	.28	.01	.268
	BDNF	407	1, 399	0.76	.38	.00	.147
	APOE x *BDNF*	407	2, 399	3.87	**.02**	.02	.707
Working memory	*APOE*	407	2, 399	0.51	.60	.00	.152
	BDNF	407	1, 399	0.01	.93	.00	.064
	APOE x *BDNF*	407	2, 399	1.08	.34	.00	.228
Executive function	*APOE*	403	2, 395	0.71	.49	.00	.188
	BDNF	403	1, 395	0.46	.50	.00	.097
	APOE x *BDNF*	403	2, 395	1.39	.25	.01	.304
Language processing	*APOE*	421	2, 413	0.83	.44	.00	.195
	BDNF	421	1, 413	0.01	.92	.00	.065
	APOE x *BDNF*	421	2, 413	1.47	.23	.01	.316

Note: Results were derived from analysis of covariance (ANCOVA) models after adjusting for age and education.

Figure 1. The significant *APOE* x *BDNF* Val66Met interaction in age- and education-adjusted episodic memory scores (*N* = 407). * = *significant post-hoc group difference (p. < .05).*

Figure 1

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