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ORIGINAL ARTICLE

The brain-derived neurotrophic factor (*BDNF*) gene Val66Met polymorphism affects memory performance in older adults

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Objective: Memory impairment is an important contributor to the reduction in quality of life experienced by older adults, and genetic risk factors seem to contribute to variance in age-related cognitive decline. Brain-derived neurotrophic factor (BDNF) is an important nerve growth factor linked with development and neural plasticity. The Val66Met polymorphism in the *BDNF* gene has been associated with impaired episodic memory in adults, but whether this functional variant plays a role in cognitive aging remains unclear. The purpose of this study was to investigate the effects of the *BDNF* Val66Met polymorphism on memory performance in a sample of elderly adults.
Methods: Eighty-seven subjects aged $>$ 55 years were recruited using a community-based convenience sampling strategy in Porto Alegre, Brazil. The logical memory subset of the Wechsler Memory Scale-Revised was used to assess immediate verbal recall (IVR), delayed verbal recall (DVR), and memory retention rate.
Results: *BDNF* Met allele carriers had lower DVR scores ($p = 0.004$) and a decline in memory retention ($p = 0.017$) when compared to Val/Val homozygotes. However, we found no significant differences in IVR between the two groups ($p = 0.088$).
Conclusion: These results support the hypothesis of the *BDNF* Val66Met polymorphism as a risk factor associated with cognitive impairment, corroborating previous findings in young and older adults.

Keywords: Aging; brain-derived neurotrophic factor; cognition; memory; polymorphism

Introduction

Age-related cognitive decline is a natural process and has been considered an important contributor to loss of functional capacity and reduced quality of life in older adults.[1] Genetic risk factors account for $\sim$ 50% of variance in adult cognitive ability, and still account for the majority of age-related variability in the elderly.[2] The degree of cognitive decline in older adults is influenced by genetic predisposition to different cellular and molecular neurobiological factors that affect long-term cognitive ability.[2,3]

Brain-derived neurotrophic factor (BDNF) is a member of the nerve growth family that plays critical roles in regulating neuronal differentiation and synaptic plasticity - two complex neuronal processes implicated in learning and memory - throughout life.[4] Consistent with the view that regulation of BDNF levels has effects on memory processes, previous studies of potential neurobiological factors of cognitive impairment found that memory deficits are associated with changes in peripheral BDNF levels in patients with psychiatric disorders.[5,6] In addition, it has been suggested that BDNF synthesis declines throughout the life-span,[7] suggesting a specific neurobiological mechanism of age-related decline in human memory.

One viable candidate gene polymorphism for understanding declarative memory is the *BDNF* Val66Met (rs6265) single nucleotide polymorphism (SNP), which results in a valine (Val)-to-methionine (Met) substitution at codon residue 66 in the BDNF precursor peptide sequence.[8] The *BDNF* Val66Met polymorphism generates an alteration in BDNF trafficking to secretory granules and reduces its local secretion and distribution,[8] which exerts an important effect on episodic memory functioning.[9] However, recent meta-analyses investigating the relationship between the functional *BDNF* Val66Met polymorphism and performance on memory tasks have suggested heterogeneity in odds ratios among subjects.[3,10] For example, some genetic association studies found impaired episodic memory performance in *BDNF* Met allele carriers compared to Val/Val homozygotes,[11-13] whereas other reports found no effect of the *BDNF* Val66Met polymorphism on memory.[14-16] Specifically in terms of verbal memory, in a sample of elderly subjects, *BDNF* Met allele carriers had poorer delayed verbal recall (DVR) than Val/Val homozygotes.[9]

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On the other hand, other studies have shown no association of the Val66Met polymorphism and declarative memory in older[14,16] or young adults.[15,17]

Considering these heterogeneous findings and the lack of evidence linking the *BDNF* Val66Met polymorphism with cognitive performance in older adults without psychiatry disorders, the current study was designed to investigate the effect of *BDNF* Val66Met polymorphism on declarative memory performance in elders from community associations without global cognitive impairment. We hypothesized that the individuals with a genetic predisposition to expression of *BDNF* (Met allele carriers) would show lower declarative memory performance.

Methods

Sample

The sample comprised 126 older adults recruited from Porto Alegre, state of Rio Grande do Sul, Brazil, using a community-based convenience sampling strategy. In brief, volunteers were recruited by the research team at community associations from 2013 to 2014. All subjects provided written informed consent for participation in accordance with the study protocol, as approved by the Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS) Ethics Committee (protocol no. 241.863; CAAE 01764012.0.0000.5336). The inclusion criteria were as follows: age $>$ 55 years and no diagnosis of dementia or neurological disorders (e.g., neurodegenerative disorders, stroke, epilepsy). We included volunteers with diagnoses of mild depression and who were well controlled on treatment for chronic medical conditions, including diabetes, hypertension, hypothyroidism, osteoporosis, and rheumatoid arthritis, due to the high prevalence of these clinical conditions in aging individuals.[18] After enrollment, all participants were assessed for the following exclusion criteria: (A) fewer than 4 years of formal education (n=29); (B) history of traumatic brain injury (n=0); (C) Mini Mental State Examination (MMSE) below of the cutoff point of 21/22 (n=10); and (D) treatment with benzodiazepines (n=0). After application of these criteria, 87 older adults were retained for analysis. The final sample was divided by *BDNF* Val66Met genotype (Val/Val homozygotes and Met allele carriers).

Clinical assessment

Demographic characteristics were assessed by two well-trained psychologists through self-report during a clinical interview. Information on sociodemographic status and health history was also obtained. The MMSE[19] was used as a dementia screening tool based on the cutoff point suggested by Almeida[20] for Brazilian elderly individuals with some formal education.

The Mini International Neuropsychiatric Interview Plus (MINI-Plus)[21,22] was used to investigate psychiatric disorders according to the DSM-IV criteria. The Geriatric Depression Scale-Short Form (GDS-15),[23] a 15-item self-report assessment that measures depression symptoms in the elderly, was also applied. In addition, the Brazilian version of the Childhood Trauma Questionnaire (CTQ)[24,25] was administered to investigate experiences of childhood abuse and neglect during early ages, as it has been suggested that such events could have a significant impact on neurodevelopment and, consequently, lead to long-lasting cognitive disabilities.[26]

Memory assessment

The logical memory (LM) subtest of the Wechsler Memory Scale-Revised (WMS-R),[27] a verbal declarative memory task, was used to evaluate short-term and long-term verbal memory performance. Subjects were told two short stories and asked to freely recall their content immediately and 30 min after listening. The sum of the number of correctly recalled sentences was used to generate an immediate verbal recall (IVR) score and a DVR score. Percent memory retention (retention rate) was then calculated as DVR/IVR $\times$ 100.

BDNF genotyping

DNA was isolated from peripheral blood by the salting-out procedure.[28] Prior to genotyping, DNA was assessed using a Qubit 2.0® fluorometer (Life Technologies, USA) in accordance with manufacturer instructions (dsDNA HS assay Kit; Life Technologies, USA). The *BDNF* Val66Met polymorphism (rs6265 SNP) was genotyped using the TaqMan® SNP assay (ID: C 11592758 10; Life Technologies, USA) in a StepOne™ real-time polymerase chain reaction (PCR) system (Applied Biosystems, USA), following manufacturer instructions. Standard PCR was carried out using TaqMan® Real-Time PCR Master Mix (Life Technologies, USA) as indicated by the manufacturer. Data acquisition was performed using the allelic discrimination analysis module of StepOne™ version 2.0 software (Applied Biosystems, USA). The *BDNF* Val66Met polymorphism was also tested for Hardy-Weinberg equilibrium.

Statistical analysis

Variables were tested for normality of distribution by the Kolmogorov-Smirnov test. Descriptive statistics for demographic variables, *BDNF* Val66Met polymorphism status, and memory measures were calculated, and results were presented as mean and standard deviation (SD), percentage, or both as appropriate. The specific statistical tests used for the demographic and clinical characteristics of the sample are given in the Results section.

Multivariate general linear models were used to test the influence of the *BDNF* Val66Met polymorphism on IVR, DVR, and retention memory scores. Gender, age, years of education, and MMSE, CTQ, and GDS scores were included as covariates of interest. A p-value $<$ 0.05 was considered statistically significant. All analyses were performed using SPSS version 20 and graphs plotted in GraphPad Prism version 6.

Results

Table 1 summarizes the sociodemographic and clinical variables of the sample, stratified by *BDNF* Val66Met

genotype. The chi-square (χ^2) test was used to estimate the allelic frequency of the *BDNF* Val66Met polymorphism on the basis of Hardy-Weinberg equilibrium. The frequencies of the 87 subjects analyzed in our study were 29.9% Met allele carriers and 70.1% Val/Val homozygotes, which is consistent with Hardy-Weinberg equilibrium (p = 0.840) and similar to the frequencies previously reported for another elderly sample.[16]

Multivariate general linear models using *BDNF* Val66Met genotype as predictor were fitted to the composite cognitive variables while covarying for age, gender, years of education, and MMSE, CTQ, and GDS scores. We found further evidence for the association between the *BDNF* Val66Met polymorphism and cognitive impairment in this sample of older adults without psychiatric disorders. Regarding LM assessment, Met allele carriers had lower DVR scores compared to participants homozygous for Val/Val (p = 0.004) (Figure 1A). In addition, Met allele carriers had a lower retention rate when compared to Val/Val homozygotes (p = 0.017) (Figure 1B). However, no significant between-group differences were found for IVR (p = 0.088) (Figure 1A).

Discussion

In this study, we addressed the relationship between the *BDNF* Val66Met polymorphism and verbal memory processes related to IVR and DVR, as well as memory

Table 1 Demographic and clinical characteristics of the sample

	Val/Val (n=61)	Met allele (n=26)	Statistics	p-value
Age (years)	68.61 (7.60)	71.62 (8.51)	t = -1.629	0.107
Education (years)	8.90 (3.96)	9.08 (4.03)	t = -0.188	0.851
GDS score	3.97 (3.34)	3.65 (2.68)	t = 0.423	0.674
MMSE	27.98 (2.17)	27.69 (2.16)	t = 0.573	0.568
Gender				
Male	13 (21.3)	8 (30.8)	χ^2 = 0.891	0.414
Female	48 (78.7)	18 (69.2)		
Clinical variables				
Diabetes	9 (90.0)	1 (10.0)	χ^2 = 2.132	0.135
Hypertension	35 (66.0)	18 (34.0)	χ^2 = 1.076	0.214
Hypothyroidism	13 (76.5)	4 (23.5)	χ^2 = 0.407	0.768
Osteoporosis	10 (66.7)	5 (33.3)	χ^2 = 0.371	0.745
Rheumatoid arthritis	8 (66.7)	4 (33.3)	χ^2 = 0.268	0.735
Depression	20 (64.5)	11 (35.5)	χ^2 = 0.720	0.466
Cigarette use	18 (85.7)	3 (14.3)	χ^2 = 0.940	0.462
Alcohol use	12 (85.7)	2 (14.3)	χ^2 = 0.480	0.695
CTQ	38 (73.1)	14 (26.9)	χ^2 = 0.541	0.483

Age, years of education, and GDS and MMSE scores data presented as mean (SD). Gender and clinical variables presented as n (%).
CTQ = Childhood Trauma Questionnaire; GDS = Geriatric Depression Scale; MMSE = Mini Mental State Examination; SD = standard deviation.
Demographic and clinical profiles were compared between groups with the t test (quantitative variables) and χ^2 test (categorical variables).

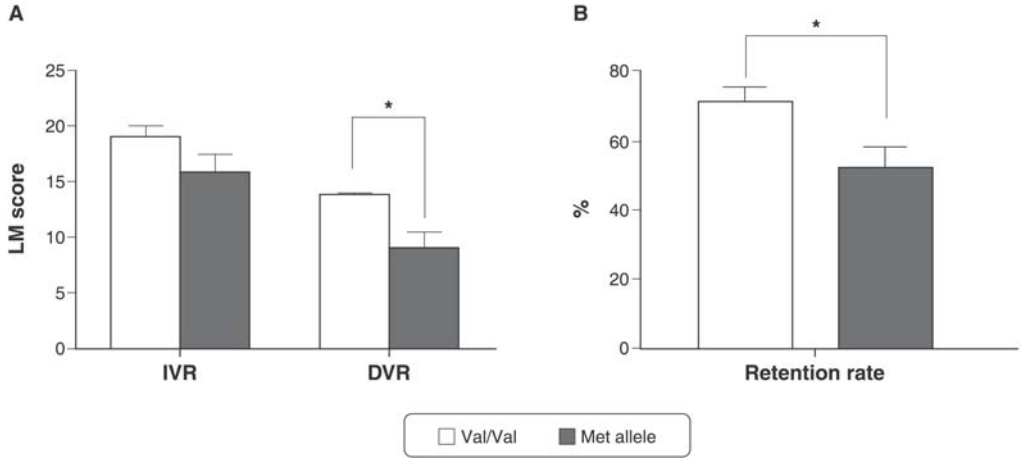

Figure 1 Effect of *BDNF* Val66Met polymorphism on memory performance. Data presented as mean (standard deviation). A) IVR: Val/Val, 19.00 (7.38); Met, 15.85 (8.02); DVR: Val/Val, 13.87 (7.46); Met, 8.26 (7.25). B) Retention rate: Val/Val, 71.53 (31.20); Met: 52.06 (26.84). MANCOVA among groups adjusted for age, gender, years of education, CTQ score, GDS score, and MMSE score: A) IVR: $F_{1,85}$ = 2.980, p = 0.088; DVR: $F_{1,85}$ = 8.710, * p = 0.004 (Met allele carriers < Val/Val homozygotes). B) Retention rate: $F_{1,85}$ = 5.934, * p = 0.017 (Met allele carriers < Val/Val homozygotes). CTQ = Childhood Trauma Questionnaire; DVR = delayed verbal recall; GDS = Geriatric Depression Scale-Short Form; IVR = immediate verbal recall; LM = logical memory; MANCOVA = multivariate analysis of covariance; MMSE = Mini Mental State Examination.

retention, through a declarative memory task in a sample of older adults. *BDNF* Val66Met genotype variation affected DVR and memory retention processes, but did not influence IVR performance. Our results were in line with those of some previous studies that demonstrated impairments in verbal memory in *BDNF* Met allele carriers when compared to Val/Val homozygotes.[8,11,13,29]

Taken together, these findings provide further evidence of the relationship between the *BDNF* Val66Met polymorphism and performance in both recall and retention processes. Since LM requires that information retention for the immediate and delayed tasks beyond that which would be possible based on models of working memory,[30] it has been suggested that, to perform successfully on distinct memory phases, a wide-ranging set of processes such as encoding, storage, and retrieval would be required. Moreover, the hippocampus is considered to play major roles in DVR and retention,[31] suggesting that altered BDNF function in this brain region might lead to impairment in verbal memory tasks.

Despite a growing body of evidence to support the evaluation of specific memory processes through defined memory tasks, as well as several neuroimaging studies pointing to the involvement of specific brain regions in the integrity of memory functioning, the neurobiological mechanisms underlying memory remain poorly understood. Some authors[4,11] argue that learning and memory consolidation processes could be dependent of BDNF-induced activation of long-term potentiation (LTP) in the central nervous system, which would lead to a long-lasting enhancement of signal transmission between hippocampal synapses. In addition, BDNF is considered necessary for the activation of other signaling cascades involved in LTP activation, such as extracellular signal-regulated kinase, that also participate in consolidation and retrieval of encoded memories.[4] Considering the evidence for the effect of the *BDNF* Val66Met variant in activity-dependent BDNF response in the hippocampus, it is interesting to note that *BDNF* Met allele carriers have been shown to have smaller hippocampal volumes,[32] altered hippocampal patterns,[33] and reduced hippocampal neuronal integrity[8] when compared to Val/Val homozygotes. These findings are generally explained by irregular intracellular trafficking and impaired secretion of BDNF, leading to long-lasting changes in cell development and hippocampal plasticity,[9,34] suggesting a possible mechanism for genetic effects on memory performance.

One previous report using data from older adults suggested that the *BDNF* Met allele is associated with higher memory performance,[35] whereas other studies found no effect of *BDNF* Val66Met variant on memory in older[14,16,36] or young adults.[15,17] Differences in socioeconomic status as well as in age range between the samples analyzed in these studies might explain these contradictory findings. Our sample was composed of older adults with a younger mean age and from a lower-income setting when compared with the two cohorts of the elderly Scottish population published in 2006.[16] Although our sample size is small, our data do not reflect a sample-specific effect, as they corroborate previous findings associating the *BDNF* Met allele and memory impairments in older adults.[9,29]

Given the complexity of neuronal processes underlying the *BDNF* Val66Met polymorphism and memory performance in elderly, we believe that our findings are in accordance with the modulation hypothesis proposed by a previous study.[37] According to the authors, this nonlinear hypothesis assumes that the magnitude of the genetic predisposition for poorer cognition performance conditioned by the *BDNF* Met allele could be increased in the elderly, especially when chemical and structural brain resources are declining with the life-span. Therefore, they suggested that age-related loss of neurochemical factors could modulate the effect of the *BDNF* Val66Met polymorphism on memory performance. In this context, given that hippocampal-dependent functions decline during aging, we believe neuronal plasticity could be a possible mechanism for involvement of genetic risk factors in declarative memory performance.

Our results should be interpreted within the context of the limitations of our study. Although we controlled for covariates, sample size was certainly an issue, considering categorical and dimensional measures, and will have limited the reliability of our statistical analyses. In addition, the design of our study precluded assessment of individual memory impairment over time, although we could estimate the effects of the aging process. We also used a single task to assess declarative memory performance; further studies should consider using a battery of tasks to evaluate multiple types of memory. Moreover, although our sample was formally non-psychiatric, we did not exclude subjects with mild to moderate depressive symptoms, and could not exclude common clinical diseases related to the aging process (Table 1). Unfortunately, studies with healthy elderly subjects represent a challenge in this field. Finally, it is already known that the *BDNF* Val66Met polymorphism has effects on other cognitive domains besides memory, including distinct components of executive functions,[35,38] reasoning,[16] attention,[39] and visual-auditory working memory.[40] Therefore, we were not able to restrict the effects of this SNP to memory.

In summary, this study verified the influence of the *BDNF* Val66Met polymorphism in specific memory processes, as identified by modifications in DVR and retention scores. This suggests that Met allele carriers have impairments in storage and retrieval processes, supporting the modulation hypothesis of genetic effects on cognition. The present data should be relevant for future meta-analyses evaluating the relationship between *BDNF* Met allele carrier status and cognitive decline in older adults. Future longitudinal studies coupled with neuroimaging approaches could bring us closer to getting a clear picture of the role of *BDNF* variations in memory performance across the life-span, especially in older age.

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Disclosure

The authors report no conflicts of interest.

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