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Research report

Altered declarative memory in introverted middle-aged adults carrying the BDNF val66met allele

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HIGHLIGHTS

- Altered memory function in healthy middle-aged introverted BDNF val66met carriers.
- Gene-personality deleterious effects on declarative memory in healthy ageing.
- $BDNF_{Met}$-specific deleterious effects of introversion on declarative memory decline.

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ABSTRACT

Background: The val66met polymorphism of the brain-derived neurotrophic factor gene ($BDNF_{Met}$) is associated with impaired learning/memory function, affective dysregulation and maladaptive personality traits. Here, we examine the potential relationship between the $BDNF_{Met}$ allele, introversion and declarative memory in middle-age adults.
Methods: A total of 132 middle-aged healthy adults took part in this study that included taking a blood sample for genetic profiling, a short battery of neuropsychological tests and the NEO-Five Factor Inventory (NEO-FFI), widely used to assess the Big Five personality.
Results: Controlling for age, level of education and sex, a multiple analysis of covariance (MANCOVA) computing the effect of BDNF polymorphism on extraversion and declarative memory revealed a significant association ($D_{1,128} = 4.79$; $p = 0.03$; $\eta_p^2 = 0.053$). Using the Sobel Goodman Mediation Test, it was found that 25.61% of the relationship between genotype and declarative memory performance was mediated by introversion. Subsequent correlational analyses yielded a strong and significant correlation ($\beta = 0.53$; $p < 0.001$) between introversion and declarative memory specific to $BDNF_{Met}$ individuals.
Conclusion: this study highlights the pertinence of further investigating gene × personality × environment interactions to account for the significant variability that is observed in cognitive function in late life.

1. Introduction

Considerable research efforts are invested to shed light on the mechanisms underlying age-associated changes in cognitive function, particularly those pertaining to premature decline in learning and memory. The reduction of synaptic efficacy and the extensive loss of synapses, which are most pronounced in frontal lobe and hippocampal structures, are highly predictive of age-related cognitive decline [1,2]. Importantly, mechanisms of synaptic plasticity depend on neurotrophin availability; namely, neurotrophins secreted by the BDNF gene [3]. Accordingly, BDNF concentration depletion with age [4] is thought of as a major contributor to age-associated synaptic plasticity alterations [2]. Consistent with the integral role of BDNF on the ageing brain, animal research demonstrates that age-associated impairments in synaptic plasticity may be offset by the administration of exogenous BDNF or by stimulating BDNF receptor expression through lifestyle factors such as regular physical exercise [4] and nutrition [5].

Polymorphism in the BDNF gene, leading to a valine (Val) to methionine (Met) substitution at position 66 in the prodomain

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($BDNF_{Met}$), is significantly associated with reduced BDNF secretion in an activity-dependent manner [6]. Humans who are heterozygous for the $BDNF_{Met}$ variant exhibit increased susceptibility for reduced hippocampal volume [7], impaired learning and memory [8], executive function alterations [9] and affective dysregulation [10]. Furthermore, genetic association studies have found that lower levels of BDNF due to the presence of the $BDNF_{Met}$ polymorphism seem to confer higher risk for impaired memory performance at an earlier age compared with homozygous $BDNF_{Val}$ carriers [11]. Widespread interest in the $BDNF_{Met}$ variant stems from its frequent occurrence in the general population (about 35% of the Caucasian population carry at least one copy of the Met allele), making any functional consequence potentially significant to society [12].

Parallel to findings on genetic vulnerability, personality factors have been found to significantly modulate age-related cognitive performance. Research has shown that older adults who report high internal levels of control (i.e., the extent to which one believes they have control over events that affect them) perform as well as younger adults on tests of cognitive function compared with older adults who report low internal levels of control [13]. Similar findings have been reported for the modulating effect of self-esteem on cognitive function. Specifically, Pruessner and colleagues [14] reported that self-esteem moderates the relationship between age and cognition in that increased age and lower cognitive performance is restricted to older adults with low self-esteem [14]. Thus, individual differences in personality, such as self-esteem and sense of control, may determine cognitive integrity in later years.

The most common model used to assess personality traits is the five-factor model of personality (neuroticism, extraversion, openness, agreeableness, conscientiousness), which has been found to be relatively stable over years and possesses a strong biological basis [15,16]. High levels of neuroticism and low levels of extraversion (i.e. high introversion) have been found to associate with cognitive function. A 25-year follow-up study examining the relationship between personality and cognitive impairment in 4039 members of the Swedish Twin Registry showed that moderate extraversion was associated with lower risk of cognitive impairment in both case–control and co-twin designs, whereas cognitive effects of high neuroticism could only be verified with case–control analysis [17]. Of particular interest, a genome-wide association (GWA) study in a genetically isolated population within Sardinia of 3972 individuals showed a selective association of the trait extraversion/introversion with the BDNF gene [18]. A subsequent analysis of this association found that $BDNF_{Met}$ carriers are significantly more introverted (and thus score significantly lower on "extraversion") compared with controls [18]. Extraversion, one of the fundamental dimensions of personality [19], is an important trait to investigate as it has been found to explain the covariation of a wide variety of behaviours; extraversion predicts affective functioning and predicts well-being across a number of domains, including cognitive performance [20].

Over recent years, the association between genetic polymorphism and personality traits has been studied to explain age-associated variance in cognitive performance [21,22]. However, the relationship between BDNF, personality and cognitive performance during human ageing remains unclear. Here, we examine the potential relationship between polymorphism in the BDNF gene, the personality trait extraversion and declarative memory in middle-age adults, an age range during which the $BDNF_{Met}$ allele exerts known deleterious neurobehavioral consequences [23]. Based on previous research by Terracciano and colleagues, it was hypothesized that performance on a declarative memory task would be most impaired in carriers of the $BDNF_{Met}$ allele who display a more introverted personality type (i.e. score low on extraversion).

2. Materials and methods

2.1. Participants

Participants in this study consisted of 132 adults, aged between 50 and 65 years, with an average age of 58.09 (SD = 3.93). They were recruited through advertisements placed in various media (newspapers, internet and flyers). Participants who responded to the ad were screened for conditions that are known to influence cognitive performance, including presence of an Axis I psychiatric disorder (e.g. major depression), diabetes, uncontrolled thyroid conditions, uncontrolled hypertension, chemotherapy/radiation exposure, stroke/TRI, and having undergone cognitive testing in the last year. The Met allele is rarely found in a homozygous state; in this case there were 3 homozygous carriers of this allele, compared to 49 heterozygous carriers and 80 homozygous Val allele carriers. Participants were therefore subdivided into two groups, the first consisting of homozygous Val allele carriers (henceforth referred to as $BDNF_{Val}$; $n = 80$) and the second consisting of both heterozygous and homozygous carriers of the Met allele (henceforth referred to as $BDNF_{Met}$; $n = 52$).

BDNF groups did not significantly differ on age ($F_{1,129} = 0.804$; $p = 37$) or education ($\chi^2 = 5.436$; $p = 0.214$), and both genotype groups had an equal proportion of men and women ($\chi^2 = 0.036$; $p = 0.85$) with slightly more women than men in both groups (61% were female). See Table 1 for demographic information.

2.2. Procedure

Eligible participants were tested at the Douglas Mental Health University Institute. All participants provided informed consent before undergoing the study procedure. Blood samples were taken for genotyping and for analyses of biological markers (e.g. cholesterol, thyroid, insulin). Participants further underwent a medical exam and an electrocardiogram to ensure that all individuals were in relatively good health. Following blood draw and medical examination, and after eating a light breakfast, participants were administered a series of neurocognitive tasks and psychological questionnaires. The protocol for this study was approved by the Ethics Board of the Douglas Mental Health University Institute (#03/40).

2.2.1. Neurocognitive and psychological testing

The neuropsychological test battery included the *Digit Span* test from the WAIS-III [24], which assesses short term/working memory function; a verbal fluency test including measures of phonemic and categorical fluency, which assesses general frontal lobe function/executive functions [24]. More importantly, for the purpose of the current study both immediate and delayed Story Recall of the Wechsler Memory Scale (WMS-II) Logical Memory [24] test was administered as a primary measure of declarative memory. Briefly, participants were read a short story after which they had to recall as much information as they could (i.e. from retelling the story to providing story details) both immediately after the story was read to them (i.e. immediate recall) and after a 25-min delay (i.e. delay recall). Total score for immediate and delayed recall was calculated by summing the number of correct story items recalled by the participant. This task has proved to be highly sensitive to early age-associated memory dysfunctions [25]. Notably, these three neurocognitive measures were also chosen for their excellent test-retest reliability in middle-aged healthy adults (ranging from 0.74 to 0.88) [26,27]. Psychological questionnaires consisted of the NEO-Five Factor Inventory (NEO-FFI), widely used to assess the Big Five personality traits (i.e. neuroticism, extraversion, openness, conscientiousness and agreeableness), which are reported to remain relatively stable during adult life [28]. NEO-FFI test-retest reliability coefficients in adults range from 0.72 to 0.83 across the Big Five personality traits (neuroticism = 0.79, extraversion = 0.79, openness = 0.80, agreeableness = 0.75, conscientiousness = 0.83) [19].

2.2.2. Genotyping

Genomic DNA extraction from buffy coat was performed using Qiagen EZ1 DNA kit (Hilden, Germany). Genotype profiling of BDNF rs6265 (val66met) polymorphism was performed with PCR followed by pyrosequencing. Amplification was performed using a PCR approach, with the following primer pairs: forward biotin 5′-GGACTCTGGAGAGCGTGAAT-3′ and reverse 5′-CCGAACTTTCTGGTCCTCATC-3′. Genomic DNA (250–500 ng) was amplified with 10 pM/of each primer, 1 × PCR buffer (Quiagen kit), 0.4 mM dNTP, 1.0 mM $MgCl_2$, and 0.01 U of Quiagen Taq polymerase. Amplification was carried out on a Biometra Tprofessional Basic thermocycler (Biometra, Göttingen, Germany) with the following conditions for 35 cycles: 30 s at 95 °C, 30 s at 61.2 °C and 1 min at 72 °C. These 35 amplification cycles were preceded by a 2-min hot start at 95 °C and followed by a final 4-min extension to the last cycle at 72 °C. PCR products were visualized on a 1.2% agarose gel. The val66met polymorphism was subsequently determined via an established pyrosequencing protocol [29] with oligo sequencing 5′-GCTGACACTTTCGAACA-3′. The sequence to analyze was: CA/GTGATAGAAGAG.