

BDNF serum levels, but not BDNF Val66Met genotype, are correlated with personality traits in healthy subjects

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Abstract Consistent evidence in animal models has suggested that alterations in brain-derived neurotrophic factor (BDNF) brain expression and release are involved in the pathogenesis of mental illnesses, such as, mood, anxiety, and eating disorders. This hypothesis is supported by data emerging from biochemical studies on serum BDNF levels and genetic studies on the functional polymorphism Val66Met in the BDNF gene in patients and control subjects. Anxiety-related personality traits are associated with several mental disorders. However, they are also measurable in non-affected subjects and, so, may represent a useful “endophenotype” to study the biological correlation of the vulnerability factors in the general population. In this study, we analyzed putative correlations in subjects unaffected by mental disorders between personality traits, serum BDNF

levels ($N = 107$), and the BDNF Val66Met genotype ($N = 217$). Furthermore, we tested the possible interactions between these variables. A significant correlation has been observed between high scores of harm avoidance (HA) measured by the temperament and character inventory (TCI), and low BDNF serum concentration ($r = -0.253$, $P = 0.009$). In addition, an association has been evidenced between low BDNF levels in serum and the BDNF Val/Val genotype ($P = 0.021$). By analyzing putative concomitant effects of different variables on HA scores in a regression model, we observed a significant correlation only with BDNF serum concentrations ($P = 0.022$). The study results suggest that a decrease in serum BDNF concentrations may represent a biochemical marker associated with anxiety personality traits also retrievable in the general population.

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Introduction

Brain-derived neurotrophic factor (BDNF) is a neurotrophin widely expressed in the brain that plays a key role in the regulation of neurogenesis and in the differentiation of neural pathways during neurodevelopment as well as in the modulation of synaptic plasticity and dendritic growth in adulthood and during aging. Compelling evidence suggests that the pathophysiology of several mental illnesses, like mood and anxiety disorders, eating disorders (ED), and substance abuse, could be the result of an alteration in the synaptic plasticity caused by an altered expression and release of BDNF [6, 25, 36]. In particular, modifications in the regulation of the BDNF biological pathway may contribute to the enhanced response reactivity to stressful life

events associated with the aetiology and the onset of psychiatric illnesses [31, 41].

BDNF is also present at high levels in the blood, where it is mostly stored in platelets [13]. In recent years, the involvement of BDNF in the pathogenesis of mental illnesses and in their treatment has been corroborated by a series of biochemical studies in serum and plasma [36], suggesting that the neurotrophin peripheral levels might reflect alterations in the brain [22, 28].

Lower concentrations of BDNF in serum have been found in several psychiatric disorders, such as, bipolar disorder (BD) [10], major depression disorder (MDD) [2, 36], schizophrenia [32, 42], ED [33], and obsessive-compulsive disorder (OCD) [30]. Furthermore, literature has shown that different types of pharmacological and non-pharmacological treatments for mental disorders, such as antidepressant drugs (ADs) [15, 36], electroconvulsive therapy (ECT) [4], repetitive transcranial magnetic stimulation (rTMS) [46], and cognitive behavioral therapy [24], increase serum BDNF levels.

Further, the functional Val66Met polymorphism in the BDNF gene has been extensively studied in several psychiatric illnesses, reporting conflicting results for mood and anxiety disorders and more consistent associations for substance-related disorders, eating disorders, and schizophrenia [17]. In general, the genetic risk associated with the Val66Met variant does not seem to be disease-specific, although it may represent a common risk factor depending on the presence of additional genetic and environmental susceptibility factors.

Personality traits are supposed to identify stable dimensional characteristics that can be quantitatively assessed in the general population and also in patients affected by mental disorders. In particular, anxiety-related traits—such as neuroticism, measured by the NEO-personality inventory (NEO), and harm avoidance (HA), measured by the temperament and character inventory (TCI)—are associated with the risk of developing different psychiatric disorders [1, 5, 9] and might represent a useful “endophenotype” to study in the general population the biological correlates of mental illnesses and to identify common vulnerability factors. “Endophenotypes” in psychiatry have been defined as internal phenotypes measurable by a neurophysiological, biochemical, endocrinological, neuroanatomical, neuroimaging, cognitive, and neuropsychological techniques that should be heritable, co-segregate with a psychiatric illness, yet be present even when the disease is not (i.e. state independent), and be found in non-affected family members at a higher rate than in the population [16]. A previous study [25] has reported a correlation between low BDNF serum concentrations and high scores of neuroticism in healthy volunteers, suggesting that BDNF serum levels could be a

risk marker for mood disorders. A recent meta-analysis [12] summarized the data obtained in nine studies about the involvement of BDNF Val66Met polymorphism in anxiety-related personality traits. The results of this meta-analysis showed a statistically significant decrease in neuroticism scores for both Met/Met and Val/Met subjects compared to Val/Val, in contrast to the results obtained for HA scores.

In light of the above rational, we hypothesize that reduced BDNF serum levels and the Val66Met polymorphism in the neurotrophin gene may be associated with the psychiatric endophenotype, measurable as personality anxiety traits in the general population. In order to examine our hypothesis, the aims of our study were the following: (1) to replicate the correlation reported between anxiety-related personality traits and serum BDNF or BDNF Val66Met polymorphism in an Italian DSM-IV axis I disorder-free subject sample and (2) to test possible interactions between these variables.

Materials and methods

Participants

A total of 330 unrelated volunteers (aged 18–90) were recruited through different sources (hospital visitors, cultural and elderly associations, trade unions, word of mouth, and newspaper advertising). All subjects gave written informed consent to the study participation according to the institutional guidelines of the local Ethic Committee (Fatenebenefratelli Hospital “San Giovanni di Dio”—Brescia, Italy). All participants were screened for DSM-IV Axis I disorders through the Mini-International Neuropsychiatric Interview (M.I.N.I. [38]). Additionally, the familial history (first-degree relatives) of Axis I disorders was assessed. The M.I.N.I. was performed by experienced raters, after training and assessment of valid inter-rater reliability. Moreover, an anamnestic schedule was compiled to assess the presence of any medical condition or pharmacological treatment. The Mini Mental State Examination (M.M.S.E. [11]) was administered in subjects older than 40 to exclude people with cognitive impairment (MMSE score $\geq 27/30$). After this screening, 111 subjects were excluded and 219 were considered “non-affected subjects” and consequently included in the analysis of polymorphism and personality traits. For two individuals, the genotyping results were not obtained. To avoid possible confounding effects, 112 people were excluded from the “non-affected subjects” for the analysis of BDNF serum concentrations and personality traits because they took drugs for medical conditions like hypertension, heart problems, diabetes, etc. The seven Cloninger’s dimensions of personality were assessed by the

Italian version of TCI, a 240-item, true–false, self-report questionnaire that measures seven dimensions of personality: the four temperament factors—novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P); and the three character factors—self-directedness (SD), cooperativeness (C), self-transcendence (ST).

BDNF serum determination

Venous blood samples were collected in the morning (between 8:00 and 9:00 a.m.) after an overnight fast in anticoagulant-free tubes. Tubes were kept at room temperature for 2 h, followed by 1 h at 4°C before serum separation by centrifugation at 3,000 rpm for 15 min at 4°C. Serum samples were stored at –80°C until the time of assay. BDNF levels were measured by the ELISA method using the human BDNF Quantikine kit (R&D system, Minneapolis, USA) according to the manufacturer's instructions. All BDNF measurements were performed in duplicate. The intra-assay coefficient of variation was <8%. BDNF concentration was expressed as equivalent to human recombinant proteins. The detection limit of the assay was 20 pg/ml.

BDNF Val66Met polymorphism genotyping

Genomic DNA was isolated from peripheral white blood cell samples with a commercially available kit (GENTRA). The single base polymorphism Val66Met (G196A) in the BDNF gene was screened by polymerase chain reaction (PCR). The primers used for the PCR were as follows: forward 5' AGGTGAGAAGAGTGATGACC 3' and reverse 5' CTGGACGTGTACAAGTCTGC 3'. PCR conditions were as follows: denaturation at 95°C for 5 min, followed by 32 cycles at 95°C for 30 s, 58°C for 30 s, 72°C for 30 s, with a final elongation step at 72°C for 5 min. The PCR products were analyzed using SNaPshot genotyping following the current manufacturer's protocol. Briefly, the PCR extension reactions were carried out for 30 cycles at 96°C for 10 s, 50°C for 5 s, and 60°C for 30 s in a PCR 9700 instrument (Applied Biosystems, Foster City, USA), and the products were digested with Shrimp alkaline phosphatase to dephosphorylate unincorporated fluorescent ddNTPs. The extension primer sequence was 5' TCATT GGCTGACACTTTTCGAACAC 3'. The SNaPshot reaction products were analyzed in 3130xl DNA Analyzer (Applied Biosystems, Foster City, USA) by mixing 1 µl of SNaPshot product with 0.5 µl of GS120 Liz Size Standard and 9.5 µl of Hi-Di Formamide (Applied Biosystems, Foster City, USA) for each sample and denaturing the injection mix at 95°C for 5 min prior to the analysis using POP7 polymer (Applied Biosystems, Foster City, USA) in E5 dyeset. Subsequent automated genotype analysis of the data was

performed with GeneMapper 4.0 (Applied Biosystems, Foster City, USA).

Statistical analysis

The Pearson test was performed to evaluate the correlations between TCI scores and BDNF serum concentrations. Regression analysis was used to calculate the effects of covariates, correlated significantly with BDNF and/or with personality traits (gender and BMI—body mass index), on putative correlations between BDNF peripheral levels and TCI scores. The associations between Val66Met polymorphism and personality traits or BDNF serum concentrations were examined with analysis of variance (ANOVA).

All analyses were conducted using SPSS statistical software version 12.0 (SPSS Inc. Chicago, IL).

Results

BDNF serum concentration and personality traits

We selected 107 participants according to the inclusion/exclusion criteria (no personal or familiar history of Axis I diagnosis, MMSE ≥ 27 , no medical illnesses, no pharmacological treatments). This group was sex balanced (49% men), normally distributed for age (45.36 ± 14.74 years (mean $\pm$ standard deviation); range of ages 22–87), BMI (23.93 ± 3.27 ; range 17–33), and education level (13 ± 5 years; range 5–24). Mean level of serum BDNF in the samples was 39.99 ± 8.96 ng/ml. No significant gender and age effects on BDNF serum were found (gender: $P = 0.388$; age: $P = 0.844$), whereas a correlation was observed between serum concentration and BMI ($r = 0.200$, $P = 0.039$). Harm avoidance was correlated with gender, but not with age (gender: $P = 0.031$; age: $P = 0.311$).

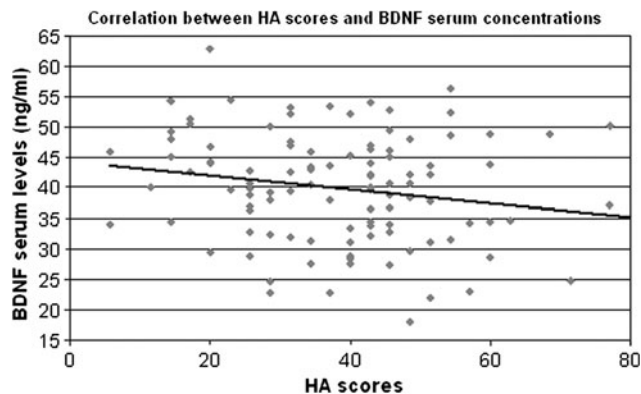
The results of correlation analyses between BDNF serum levels and TCI scores in healthy subjects are shown in Table 1.

The data obtained demonstrated significant correlations between low BDNF serum levels and higher scores in the HA dimension ($P = 0.009$; Fig. 1) and its respective subscales as anticipatory worry HA1 ($P = 0.023$) and Fatigability/asthenia HA4 ($P = 0.023$), whereas a trend of correlation was found with the Fear of uncertainty HA2 ($P = 0.057$) subscale. A correlation was also detected between serum BDNF and lower scores in resourcefulness SD3 ($P = 0.008$) and Exploratory excitability NS1 subscales, the latter showing only a trend ($P = 0.06$). No further correlations were found with the other personality traits (Table 1).

Table 1 Correlation between BDNF serum concentration and TCI scores, corrected for gender and BMI, in 107 healthy subjects

Temperament dimensions			Character dimensions		
TCI scales	<i>r</i>	<i>p</i> *	TCI scales	<i>r</i>	<i>p</i> *
NS: Novelty seeking	0.080	0.418	SD: Self-directedness	0.082	0.406
NS1: Exploratory excitability	0.184	0.060	SD1: Responsibility	0.075	0.445
NS2: Impulsiveness	0.018	0.852	SD2: Purposeful	0.003	0.975
NS3: Extravagance	−0.061	0.537	SD3: Resourcefulness	0.256	0.008
NS4: Disorderliness	0.021	0.832	SD4: Self-acceptance	−0.014	0.885
HA: Harm avoidance	−0.253	0.009	SD5: Congruent	0.064	0.518
HA1: Anticipatory worry	−0.222	0.023	C: Cooperativeness	0.023	0.818
HA2: Fear of uncertainty	−0.186	0.057	C1: Social acceptance	0.116	0.240
HA3: Shyness	−0.129	0.190	C2: Empathy	−0.075	0.448
HA4: Fatigability/asthenia	−0.221	0.023	C3: Helpfulness	0.105	0.285
RD: Reward dependence	0.126	0.200	C4: Compassion	0.039	0.691
RD1: Sentimentality	0.121	0.218	C5: Pure-hearted	−0.155	0.114
RD3: Attachment	0.010	0.919	ST: Self-transcendence	−0.040	0.683
RD4: Dependence	0.133	0.176	ST1: Self-forgetful	0.001	0.992
P/RD2: Persistence	−0.068	0.489	ST2: Transpersonal	−0.024	0.810
			ST3: Spiritual acceptance	−0.061	0.537

*Data marked in bold indicate significant result ($P < 0.05$)

**Fig. 1** Correlation between BDNF serum concentration and HA scores

Val66Met BDNF polymorphism and personality traits

We selected 217 subjects according to the inclusion/exclusion criteria (no personal or familiar history of Axis I diagnosis, MMSE ≥ 27). The genotype distributions were in the Hardy–Weinberg equilibrium ($\chi^2 = 2.75$; $P = 0.1$) (HWE program John Ott version 1.10). The genotype frequencies of Val/Val, Val/Met, and Met/Met were 0.59 (127/217), 0.33 (72/217), and 0.08 (18/217), respectively.

Subjects for the three genotypes were homogeneous for the demographic characteristics of gender (94 men, 123 women; $\chi^2 = 1.21$; $P = 0.55$) and age (49.65 ± 15.89 years; average $\pm$ SD; $F = 1.71$; $P = 0.18$). We did not find any significant association between BDNF

Val66Met polymorphism and TCI personality traits (data not shown).

Interaction between BDNF Val66Met polymorphism and BDNF serum concentration on harm avoidance

Subjects in the BDNF serum concentration sample ($n = 105$) were also genotyped for the BDNF polymorphism. The genotype frequencies on this subgroup were of 0.62 Val/Val, 0.27 Val/Met, and 0.11 Met/Met.

After Bonferroni's correction, we found an association trend between BDNF Val66Met genotypes and BDNF serum concentration ($F = 2.772$; $P = 0.067$) on HA. We grouped Met allele carriers together (Val/Met and Met/Met) for analyses because the low frequency of the Met/Met homozygotes prevents enough observations for meaningful analysis. Furthermore, pairwise comparisons showed that the BDNF serum level of the Val/Met genotype (42.81 ± 9.37) differed significantly from the levels associated with Val/Val subjects (38.38 ± 8.45 , $P = 0.03$), whereas no differences were found with Met/Met genotype (41.95 ± 9.96). Thus, we carried out an ANCOVA analysis considering the Met allele as dominant and we observed higher BDNF serum levels in Met carriers, compared to the Val/Val homozygotes ($F = 5.514$; $P = 0.021$; Fig. 2). Because BDNF serum levels showed a correlation with BMI, we also carried out the ANCOVA with BMI as a covariate and the result remained significant ($P = 0.028$).

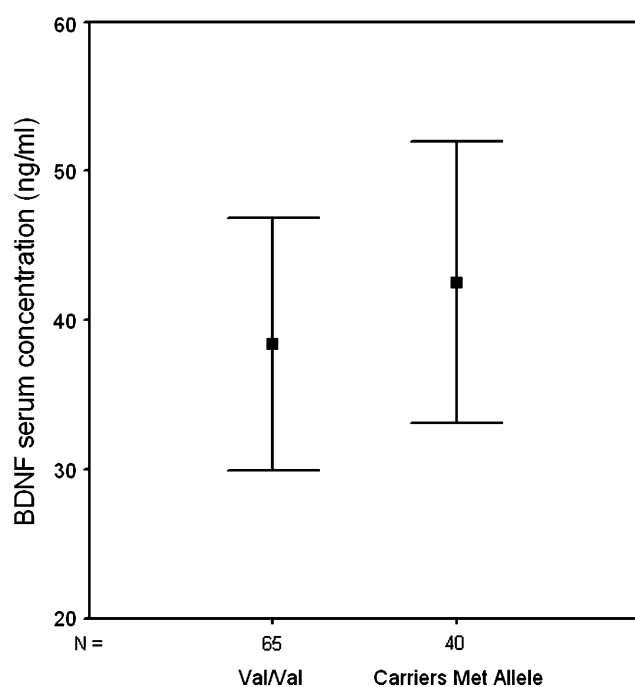


Fig. 2 Brain-derived neurotrophic factor (BDNF) serum concentrations (means $\pm$ SD) for Val/Val and carriers of the Met allele

On the basis of these results, we wanted to analyze putative interactions between BDNF serum concentration and Val66Met polymorphism on personality traits. Thus, we carried out a regression analysis with HA as the dependent variable, BDNF genotypes (Val/Val vs. Met carriers) and Gender as independent variables, and BDNF serum concentration and BMI as covariates. Factors such as BMI ($P = 0.382$), Gender ($P = 0.112$), and BDNF Val66Met polymorphism ($P = 0.822$) had no effect on HA, whereas a significant correlation was confirmed between BDNF serum concentrations and HA ($F = 5.39$; $P = 0.022$).

Discussion

Our results indicate that higher scores in anxiety-related TCI scales are correlated with low BDNF serum concentrations in healthy subjects. These data are in line with the findings of Lang et al. [25], supporting the hypothesis that a decrease in BDNF serum levels might be associated with a risk endophenotype for the development of anxiety and mood disorders. We did not find any correlation between BDNF serum concentrations and gender, confirming the results of a recent meta-analysis [3]. No correlations were observed with age; this is in line with previous studies in comparable samples [29, 40].

During the last decade, several evidences showed that BDNF is critically connected with neural plasticity

regulation, considering its key role in neural responsiveness, synaptic morphology, neurotransmitter release, and balance of excitation and inhibition [35]. In particular, BDNF has a direct impact on neuronal growth and plasticity in the frontal cortex, hippocampal, and amygdale networks. Alterations in BDNF-TrkB signaling are related to deficits in brain functions, such as, learning, memory, and overall cognition. Reduced serum concentration of BDNF was consistently observed in several psychiatric illnesses, such as, BD [10], MDD [2, 36], schizophrenia [32, 42], OCD [30], and ED [33], suggesting that it could represent a common trait marker in psychiatric disorders. Different pieces of evidence suggest that serum BDNF concentrations might reflect the neuronal integrity of cortical and hippocampal regions [7, 28], whereas a recent study [34] using an animal model of electroconvulsive therapy has demonstrated a correlation between content of BDNF in the brain and serum.

We did not observe any association between BDNF Val66Met polymorphism and HA. This lack of association is consistent with recent meta-analysis [12] that did not report any significant effect on personality traits of the BDNF Val66Met genotype. Nonetheless, when including only studies using NEO inventory rather than TCI, the meta-analysis has shown that individuals carrying at least one Met allele of the BDNF genotype have decreased neuroticism scores. Unfortunately, this meta-analysis was conducted on five studies: three on Caucasians [19, 26, 37] and two on Asians [20, 39]. The genotype frequency could represent an important bias on results obtained because the frequency of control subjects homozygous for the Met allele is about six times more in Asians than in Caucasians [12].

We found decreased BDNF concentrations in Val/Val subjects when compared to the Met carriers. In a recent study, Lang et al. [27] detected an association between serum BDNF protein concentration and Val66Met genotype in healthy Caucasian subjects. These authors sustained the hypothesis that people who carry the Val/Val genotype and have low BDNF serum concentrations might be more vulnerable to develop anxiety symptoms. Our data are in line with Lang's study [27], supporting the hypothesis that individuals with low BDNF serum levels and, consequently, high scores in anxiety-related personality traits might be more vulnerable to develop depression or anxiety disorders. On the contrary, we did not observe any effect of the BDNF Val66Met polymorphism on personality traits, while an association was observed between Met carriers and higher neurotrophin serum levels. In line with our data, a recent study [8] showed that Met carriers had higher BDNF levels; however, they showed reduced serum BDNF levels when exposed to childhood abuse, and they consequently developed depression. These data suggest that Met

carriers are particularly sensitive to the stress-induced downregulation of BDNF. Stress plays an important role in the development and progression of mental disorders [23, 43]. Data from animal studies show that life event stressors greatly impact BDNF in the brain [5, 44]; many different types of stress experimental paradigms decreased BDNF expression in the hippocampus [6], one of the limbic structures that have been implicated in different psychiatric disorders [21, 41, 45].

The exposure to environmental risk factors is an important variable to evaluate the role of the Val66Met genotype in the susceptibility to psychiatric disorders, particularly considering controversial data about a possible association with depression or anxiety. In the Gratacos meta-analysis [17], the Met allele increased the risk for ED and schizophrenia, but it conferred a protective effect in substance-related disorders, and no association was found with mood disorders. Furthermore, Gatt et al. [14] identified an involvement of the Met allele in depression with anxiety, while the BDNF Val/Val genotype contributed specifically to elevated levels of anxiety in the absence of significant depression. This suggested that the Val/Val genotype might have a specific role in the disposition for anxiety.

Beyond BDNF, other biochemical parameters have been associated with anxiety personality traits. A recent study reported an association of HA dimension scores with increased serum levels of C-reactive protein, another biochemical marker that showed alterations in mood disorders [18].

In conclusion, our study supports the hypothesis that the decrease in serum BDNF levels could represent a common endophenotype associated with anxiety and mood disorders, also retrievable in the non-affected population. Further studies in larger samples, integrating the role of BDNF Val66Met polymorphism, BDNF levels, and the putative effects of the exposure to life stress events, might help to clarify whether low BDNF serum levels could represent a vulnerability marker for the development of mental disorders.

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