2010

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Plasma BDNF Concentration, Val66Met Genetic Variant, and Depression-Related Personality Traits

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Abstract

Brain derived neurotrophic factor (BDNF) regulates synaptic plasticity and neurogenesis, and BDNF plasma and serum levels have been associated with depression, Alzheimer's disease, and other psychiatric and neurodegenerative disorders. In a relatively large community sample, drawn from the Baltimore Longitudinal Study of Aging (BLSA), we examine whether BDNF plasma concentration is associated with the Val66Met functional polymorphism of the BDNF gene (n = 335) and with depression-related personality traits assessed with the NEO-PI-R (n = 391). Plasma concentration of BDNF was not associated with the Val66Met variant in either men or women. However, in men, but not in women, BDNF plasma level was associated with personality traits linked to depression. Contrary to the notion that low BDNF is associated with negative outcomes, we found lower plasma levels in men who score lower on depression and vulnerability to stress (two facets of Neuroticism) and higher on Conscientiousness and Extraversion. These findings challenge the prevailing hypothesis that lower peripheral levels of BDNF are a marker of depression.

Keywords

Brain derived neurotrophic factor; BDNF Val66Met; plasma; personality; depression; NEO-PI-R

Introduction

Several lines of research suggest that brain derived neurotrophic factor (BDNF) is linked to neurobiological and behavioral changes associated with depression (Brunoni et al., 2008, Duman & Monteggia, 2006, Pezawas et al., 2004, Schmidt & Duman, 2007). In animal models, adverse acute and chronic stressors decrease expression of BDNF, which can lead to neuronal atrophy in the hippocampus and other brain structures (Schmidt & Duman, 2007). Many, but not all (Taylor et al., 2005), neuroimaging studies find smaller hippocampus volume in depressed patients (Hickie et al., 2005, Koolschijn et al., 2009), and postmortem

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studies find reduced BDNF levels in the hippocampus of suicide subjects who did not receive antidepressant treatment (Karege et al., 2005b, Schmidt & Duman, 2007). Further, circulating levels of BDNF are reported to be lower in depressed patients compared to controls (Brunoni et al., 2008, Karege et al., 2005a, Kim et al., 2007, Lee et al., 2007, Piccinni et al., 2008a, Sen et al., 2008) and increase significantly with antidepressant treatment (Brunoni et al., 2008, Lee & Kim, 2008). These effects have been observed in both serum and plasma BDNF, and using different classes of antidepressant drugs or other treatments (Brunoni et al., 2008, Karege et al., 2005a, Piccinni et al., 2008a). These findings support the neurotrophin hypothesis of depression (Duman & Monteggia, 2006, Schmidt & Duman, 2007), and the view that peripheral BDNF concentration is a biomarker for depressive states and recovery (Brunoni et al., 2008, Lang et al., 2004, Lang et al., 2009, Lee & Kim, 2008, Piccinni et al., 2008a).

The first aim of this study is to examine whether BDNF concentration in plasma is associated with the personality trait of Neuroticism, a risk-factor for depression. Relatively little is known about how levels of BDNF are related to trait Neuroticism, a chronic susceptibility to experience negative emotions that shares large genetic variance with depression (Kendler et al., 2006). To date, only one study has examined the association between BDNF serum concentration and personality traits in a healthy European sample (n=118) (Lang et al., 2004). Consistent with the hypothesis that low levels of BDNF may be a marker of depression, BDNF serum concentration was negatively correlated with neuroticism. We aimed to replicate and extend this finding in a larger sample from the Baltimore Longitudinal Study of Aging (BLSA; n=391), in which we measured plasma instead of serum BDNF concentration. The concentration of BDNF assessed in serum reflects mainly the BDNF stored in platelets (Fujimura et al., 2002), whereas the much lower plasma level reflects the BDNF released from cells into circulating blood. Clinical evidence suggests that BDNF in plasma acts as a marker of depression (Brunoni et al., 2008, Lee & Kim, 2008, Piccinni et al., 2008a). In a non-clinical sample, we tested the hypothesis that BDNF released in plasma is associated with trait Neuroticism. In addition to factor-level Neuroticism, we considered the association with the facets of Neuroticism, as well as the other four factors of the Five-Factor Model of personality: Extraversion, Openness, Agreeableness, and Conscientiousness (Costa & McCrae, 1992).

In addition to stress, diet, mental and physical activity (Mattson et al., 2004), the circulating level of BDNF is hypothesized to be influenced by the Val66Met genetic variant. The Val66Met (or rs6265) is a functional single nucleotide polymorphism (SNP) in the 5′ pro-region of the BDNF gene that results in a valine to methionine substitution (G to A). In cell culture and animal models, the less frequent Met variant has a negative impact on the intracellular pathway and the activity-dependent secretion of BDNF, impairing memory and hippocampal function (Egan et al., 2003). Some studies have reported that Met carriers have smaller hippocampal volume (Montag et al., 2009, Pezawas et al., 2004), but others found no such association (Dutt et al., 2009). This SNP has been associated with mood and other neuropsychiatric disorders, but replication attempts have often provided inconclusive results (Green et al., 2006, Rybakowski, 2008, Schumacher et al., 2005, Tochigi et al., 2006). In previous studies, we found no association between the Val66Met polymorphism and Neuroticism (Terracciano et al., 2008c, in press). Although it has been hypothesized that the Val66Met variant influences circulating levels of BDNF (Lang et al., 2009), the role of this genetic factor remains elusive. Indeed, the Val66Met polymorphism was unrelated to the concentration of BDNF in whole blood in a healthy European sample (n=78) (Trjakovska et al., 2007) and was also unrelated to plasma concentration of BDNF in a healthy Asian sample (n=513) (Jiang et al., 2009). However, it was recently reported that in a healthy European sample (n=114) there was an association between the Val66Met genotype and serum BDNF concentration, such that individuals with the Met allele had higher BDNF.
levels (Lang et al., 2009). The direction of this effect was surprising given that the Met allele has a negative effect on intracellular trafficking and activity-dependent secretion of BDNF (Egan et al., 2003). Finally, a case-control study of major depression (n=122) found lower serum BDNF among the Met carriers (Ozan et al., 2009). The second aim of this study was to further explore the association between plasma concentration of BDNF and the Val66Met genotypes in an American, community-dwelling sample (n=335) drawn from the BLSA. In summary, we used a comprehensive approach to examine the links between BDNF plasma concentration with genetic and personality risk factors for depression.

Methods

Subjects

The sample was drawn from the BLSA, an ongoing multidisciplinary study of community-dwelling volunteers. BLSA participants volunteer for medical and psychological testing at regularly scheduled visits and are generally healthy. At enrollment, exclusionary criteria included a history of central nervous system disease (dementia, stroke, Parkinson's disease, epilepsy, and other neurological conditions), severe cardiac disease (including myocardial infarction, coronary bypass surgery, or angioplasty), and metastatic cancer. Psychiatric diagnosis of mood disorders was not performed, but current use of antidepressant medication was recorded and used as a covariate.

Blood samples were collected from 458 participants at regularly scheduled visits from January 2007 to June 2008. The sample includes 224 females and 234 males. Age ranged from 38 to 98 years (M = 70; SD = 11.8), and the education level was generally high (M = 17 years if education, SD = 2.5). About 67% (n = 303) of the sample was of European descent, 28% (n = 127) was of African descent, and 6% (n = 28) was of Asian or other ancestry. Genetic information was available for 335 subjects; 391 participants completed the personality questionnaire at the same visit as the BDNF assessment.

Subjects signed a consent form approved by the National Institute on Aging (Intramural Research Program) Institutional Review Board.

Personality, genetic, and covariates assessments

Personality traits were assessed using the Revised NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992). The questionnaire consists of 240 items answered on a five-point Likert scale, from strongly disagree to strongly agree. The NEO-PI-R assesses six facets for each of the five major dimensions of personality, Neuroticism, Extraversion, Openness to Experience, Agreeableness and Conscientiousness. The focus of this study is on Neuroticism and its six facets: Anxiety, Angry Hostility, Depression, Self-Consciousness, Impulsiveness, and Vulnerability (Costa & McCrae, 1992).

The NEO-PI-R has a robust factor structure that has been replicated in more than 50 cultures (De Fruyt et al., 2009, McCrae et al., 2005). In this sample, scores followed a normal distribution and were standardized (M = 50, SD = 10) using American combined gender norms (Costa & McCrae, 1992). The psychometric properties were good: the internal consistency reliabilities for the five factors were about 0.90. Longitudinal data indicate that stability coefficients for the five factors are in the range of 0.80 over intervals of 10 years (Terracciano et al., 2006).

The BDNF SNP rs6265 was genotyped with the 550k Illumina platform. Genotype data passed quality controls (genotyping completeness >99%, minor allele frequency > 1%), including Hardy-Weinberg equilibrium (p > 0.05)(Terracciano et al., in press).
As covariates we used age, sex, education, self-reported ethnicity, smoking status (4% current smokers vs. 96% others), Body Mass Index (BMI) derived from staff-assessed weight and height (M = 27.1; SD = 4.8), and current antidepressant use (5%).

**Measurement of plasma BDNF concentration**

Blood samples were drawn from subjects in the morning after an overnight fast. Plasma BDNF levels were measured as described previously (Carlson et al., 2007, Martin et al., 2007) using a commercially available ELISA kit (Promega, Madison, WI) with the range of sensitivity from 7.8 to 500 pg/ml and inter-assay assay variation measured at 8.8% (low concentration), 2.9% (medium concentration), and 2.2% (high concentration).

**Data analysis**

We calculated descriptive statistics as means ± SD or percentages, as appropriate. We used Pearson correlation or t-tests to evaluate the association between plasma BDNF levels and the covariates. To further examine sex differences in BDNF levels, we conducted multivariate analyses of variance using sex as an independent variable, age, education, ethnicity, smoking status, BMI, and antidepressant use as covariates, and BDNF plasma concentration as the dependent variable. To evaluate the effect of the Val66Met variant on plasma BDNF we conducted a series of univariate and multivariate analyses of variance controlling for the covariates. We used zero-order and partial correlations to evaluate the association between plasma BDNF levels and personality traits, measured as continuous variables. All analyses were conducted using SPSS 13.0 (SPSS Inc., Chicago IL) and the significance level was set at p < 0.05. Rather than correct for multiple testing, which inflates type 2 errors (Perneger, 1998), we test specific hypotheses based on previous studies and examine the empirical p-values.

**Results**

**Plasma BDNF levels are greater in females compared to males**

BDNF plasma concentration in our sample ranged from 38 to 2475 pg/ml, with an average of 759 (s.d.=551) and a median of 587 pg/ml. Although the variability of the plasma BDNF was large, it is similar to the variability found in the largest previous study (Komulainen et al., 2008). Consistent with previous studies (Komulainen et al., 2008, Lommatzsch et al., 2005, Trajkovska et al., 2007), women had higher BDNF plasma concentrations than men (M=878, s.d.=542 vs. M=646, s.d.=536; t = −4.6, p < 0.001), even after controlling for age, education, ethnicity, smoking status, BMI, and antidepressant use as covariates, and BDNF plasma concentration as the dependent variable. To evaluate the effect of the Val66Met variant on plasma BDNF we conducted a series of univariate and multivariate analyses of variance controlling for the covariates. We used zero-order and partial correlations to evaluate the association between plasma BDNF levels and personality traits, measured as continuous variables. All analyses were conducted using SPSS 13.0 (SPSS Inc., Chicago IL) and the significance level was set at p < 0.05. Rather than correct for multiple testing, which inflates type 2 errors (Perneger, 1998), we test specific hypotheses based on previous studies and examine the empirical p-values.

**Val66Met and Plasma BDNF**

Of the 335 participants with both genotype and plasma BDNF concentration, 224 had Val/Val, 98 had Val/Met, and 13 had the Met/Met genotype. The major allele frequency was 77% among European-Americans and 96% among African-Americans. Consistent with previous studies (Montag et al., 2009, Pezawas et al., 2004), given the low number of Met/Met genotype, we repeated the analyses combining them with the heterozygous group (Val/Val + Met/Met).
BDNF plasma levels by genotypes are presented in Figure 1. There were no significant differences in BDNF plasma concentration among the Val66Met genotype groups (Val/Val $M=776$, s.d.$=531$; Val/Met $M=700$, s.d.$=583$; Met/Met $M=684$, s.d.$=597$; $P > 0.05$), even after controlling for age, sex, education, ethnicity, BMI, smoking status, and antidepressant use ($P > 0.05$). To avoid a confound due to population stratification, an analysis within the two larger ethnic groups was performed. There were no significant associations observed in the stratified analysis. We also examined whether there was significant interaction by sex, however, the relationship between BDNF genotype with plasma BDNF concentration was not modified by sex.

**Plasma BDNF and personality**

In the full sample of 391 participants who had both the personality questionnaire and the BDNF assessment at the same visit, we found no association between plasma BDNF concentration and Neuroticism ($r = 0.07$; $P = 0.18$), even after controlling for covariates ($r = 0.04$; $P = 0.49$)(see Table 1). Contrary to the negative association between serum BDNF and Neuroticism previously reported (Lang et al., 2004), we found evidence that plasma BDNF correlated positively, rather than negatively, with two facets of Neuroticism. Specifically, controlling for covariates we found a trend for Depression ($r = 0.08$; $P = 0.10$) and a significant positive correlation with Vulnerability ($r = 0.13$; $P = 0.01$). Similarly unexpected, lower Conscientiousness was associated with higher BDNF ($r = -0.11$; $P = 0.03$).

Given the sex differences in personality (Costa et al., 2001) and BDNF plasma concentration observed in this and other samples (Komulainen et al., 2008, Lommatzsch et al., 2005, Trajkovska et al., 2007), we examined whether the association between plasma BDNF and personality traits differed for women and men. As reported in Table 1, although no association was found for women, men with higher BDNF scored higher on Neuroticism, and particularly the Depression (Figure 2) and Vulnerability facets, and lower on Extraversion (especially the facets of Assertiveness: $r = -0.25$, and Activity: $r = -0.22$) and Conscientiousness (especially the Self-Discipline facet: $r = -0.23$). Therefore the association observed in the combined sample was driven by the depression-prone personality profile of men with higher plasma BDNF.

**Discussion**

In this study we tested the hypotheses that plasma concentration of BDNF is associated with the functional Val66Met variant and that low plasma BDNF is associated with stable personality traits related to depression. Both hypotheses were rejected. First, we found no evidence that the Val66Met variant was associated with circulating BDNF levels in plasma. Second, low plasma BDNF was not associated with high Neuroticism. On the contrary, we found that men with higher plasma BDNF concentration tend to score higher on Neuroticism, specifically the facets of Depression and Vulnerability, and lower on Extraversion and Conscientiousness. These unexpected associations were specific to the male sample; there were no significant associations in the female sample. The direction of this finding is surprising, given that low, not high, BDNF has been considered a marker of depression (Brunoni et al., 2008, Lang et al., 2004, Lang et al., 2009, Piccinni et al., 2008a, Sen et al., 2008) and neurological disorder such as Alzheimer’s disease (Komulainen et al., 2008).

The detailed personality assessment revealed the strongest association between BDNF and the Vulnerability facet. Individuals who score high on Vulnerability feel that they are unable to cope with stress, feel helpless, and panic in difficult situations (Costa & McCrae, 1992). These individuals have poor coping strategies and are at higher risk of depression (Canuto et al., 2009, Frokjaer et al., 2008). In addition, patients with Alzheimer’s disease (Siegler et al.,
1994, Siegler et al., 1991) were rated higher on this facet of Neuroticism. At the factor level, lower Extraversion and Conscientiousness were associated with higher BDNF, both unexpected findings that might be due to chance. It is interesting to note, however, that introverts are more likely to experience anhedonia and dysthymic/depressed mood (Bienvenu et al., 2004, Clark et al., 1994, Jylha et al., 2009, Watson et al., 2005), and report lower life satisfaction (Costa & McCrae, 1980, Watson & Clark, 1992). Recent research suggest that low Conscientiousness is also a risk factor for depression (Kendler & Myers, 2009, Weiss et al., 2009), and it is linked to health-risk behaviors (Rush et al., 2009, Terracciano et al., 2008a,2009) and negative health outcomes, such as inflammation and dyslipidemia (Sutin et al., in press-a,b), Alzheimer's disease (Siegler et al., 1994, 1991, Wilson et al., 2007), and mortality (Terracciano et al., 2008b, Wilson et al., 2004).

As shown in supplementary Table 1, average BDNF plasma values vary widely across studies. Surprisingly, the average BDNF plasma concentration in our and other non-clinical samples (Komulainen et al., 2008, Lommatzsch et al., 2005) is similar to the average value reported in a recent meta-analysis of depressed groups (Brunoni et al., 2008). Although methodological differences make comparisons across studies difficult, the observation that most depressed groups have BDNF concentrations similar to those found in non-clinical cohorts does not support the hypothesis that depressed patients have lower BDNF values.

The discrepancy between the current and previous studies that examined the genetic (Lang et al., 2009) and personality (Lang et al., 2004) correlates of peripheral BDNF concentration might be partially explained by the measurement of BDNF in plasma vs. serum. This would be consistent with the notion that the concentration of BDNF in plasma is state-dependent, whereas the concentration in serum is more stable, trait-like (Brunoni et al., 2008, Lee & Kim, 2008, Piccinni et al., 2008a). BDNF assessed in plasma might be particularly sensitive to temporary changes in physical and mental activity, diet, and stress. In support of this hypothesis, we found low retest stability in a small group retested after one year (test-retest correlation: r = 0.33; P = 0.14; n=22), and other evidence suggests substantial variation throughout the day (Piccinni et al., 2008b). Still, it remains unclear why BDNF levels in plasma would be associated with depression-related traits (in men), whereas serum BDNF would be inversely associated with depression-related traits. Future studies should address these questions by assessing both serum and plasma BDNF in the same sample, and ideally test for associations with both stable (trait) and time-dependent (state) measures of depression.

Another important consideration for future studies is the accumulating evidence that women have higher level of BDNF plasma compared to men (Komulainen et al., 2008, Lommatzsch et al., 2005, Trajkovska et al., 2007), which highlights the need to consider sex-specific effects. The source of the sex difference in BDNF concentration is unclear, but it could be related to several factors, such as genetics, sex hormones, physical activity, diet, or other lifestyle and psychological differences. Investigating these sex differences is another area of considerable interest for future studies. Finally, our study was based on adults older than those sampled in previous studies, which might have contributed to the different results. Interestingly, in this sample plasma BDNF concentrations and Neuroticism scores were lower in older individuals. Future studies should include samples that span a broad age range.

In conclusion, our findings are not aligned with the current understanding of the relationship between depression and peripheral levels of BDNF (Brunoni et al., 2008). Current theories of depression suggest that decreased expression of BDNF may contribute to the atrophy of brain regions observed in depressed patients, and increases in BDNF contribute to antidepressant therapeutic action (Brunoni et al., 2008, Duman & Monteggia, 2006, Schmidt
It is possible that our association between higher plasma BDNF and higher scores on depression-related traits is limited to circulating BDNF in plasma, rather than BDNF expression in brain structures. In rodents, however, it has been reported that BDNF crosses the blood-brain barrier (Pan et al., 1998), and one study suggests that cortical levels strongly correlate with platelet BDNF concentration (Karege et al., 2002) but another reports that BDNF concentration in plasma is unrelated to levels found in the cortex and hippocampus (Martin et al., 2007). Although more research is needed to elucidate the relation between peripheral and brain levels of BDNF, the provocative hypothesis that lower circulating BDNF levels are associated with depression might be too simplistic. In animal models, infusion of BDNF in the hippocampus has antidepressant-like effects, but in the ventral tegmental area-nucleus accumbens (VTA-NAc) it produces depressive-like effects (Berton et al., 2006, Eisch et al., 2003, Schmidt & Duman, 2007). When taken together with previous findings, our data from the BLSA cohort contribute to the understanding of the links between plasma BDNF concentration, personality traits and depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Paul T. Costa receives royalties from the Revised NEO Personality Inventory.

Reference


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Genes Brain Behav. Author manuscript; available in PMC 2011 July 1.


Figure 1.
Brain derived neurotrophic factor (BDNF) concentration in plasma by BDNF Val66Met genotypes. Analyses of variance indicate no significant differences between groups, even after controlling for covariates. There were 224 Val/Val genotype, 98 Val/Met, and 13 Met/Met genotype.
Figure 2.
Association between trait Depression (assessed with the NEO-PI-R) and plasma BDNF concentration in male (N=196) and female (N=196). The partial correlations (r) controlling for age, education, BMI, ancestry, and smoking status are displayed.
Table 1

Association between personality traits and BDNF plasma concentration.

<table>
<thead>
<tr>
<th>NEO-PI-R scales</th>
<th>Total r</th>
<th>Female r</th>
<th>Male r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroticism</td>
<td>0.04</td>
<td>−0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>N1: Anxiety</td>
<td>0.05</td>
<td>−0.01</td>
<td>0.12</td>
</tr>
<tr>
<td>N2: Angry Hostility</td>
<td>0.02</td>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>N3: Depression</td>
<td>0.08</td>
<td>−0.04</td>
<td>0.23 **</td>
</tr>
<tr>
<td>N4: Self-consciousness</td>
<td>0.01</td>
<td>−0.07</td>
<td>0.13</td>
</tr>
<tr>
<td>N5: Impulsiveness</td>
<td>0.08</td>
<td>0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>N6: Vulnerability</td>
<td>0.13 *</td>
<td>0.01</td>
<td>0.25 **</td>
</tr>
<tr>
<td>Extraversion</td>
<td>−0.05</td>
<td>0.08</td>
<td>−0.16 *</td>
</tr>
<tr>
<td>Openness</td>
<td>0.06</td>
<td>0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>−0.03</td>
<td>−0.12</td>
<td>0.05</td>
</tr>
<tr>
<td>Conscientiousness</td>
<td>−0.11 *</td>
<td>−0.05</td>
<td>−0.20 **</td>
</tr>
</tbody>
</table>

Note: Total sample N = 391. Male sample N = 196. Female sample N = 195. Partial correlations controlling for sex, age, education, BMI, ancestry, smoking status, and current antidepressant use.

* P < 0.05;
** P < 0.01.