Published in final edited form as:
Psychosom Med. 2011 October ; 73(8): 638–642. doi:10.1097/PSY.0b013e3182306a4f.

Neuroticism, depressive symptoms, and serum BDNF

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Abstract

Objective—Animal models and clinical studies suggest that brain-derived neurotrophic factor (BDNF) is involved in the pathophysiology of depression. We test whether serum and plasma levels of BDNF are associated with trait Neuroticism and its facets, and with state measure of depressive symptoms.

Method—In a community-based cohort (N = 2099) we measured serum and plasma BDNF concentration, administered the Revised NEO Personality Inventory (NEO-PI-R) and the Center for Epidemiologic Studies Depression Scale (CES-D). Covariates included age, sex, cigarette smoking, obesity, and antidepressant use.

Results—Serum BDNF concentrations were inversely related to Neuroticism ($r = -0.074$, $P < 0.001$), in particular the Depression facet ($r = -0.08$, $P < 0.001$). Lower BDNF concentrations were also associated with severe depressive symptoms (CES-D ≥ 28; OR = 0.906; 95%CI = 0.851–0.965). The association of serum BDNF with Neuroticism was independent of depressive symptoms, indicating that serum BDNF might represent a biological correlate of Neuroticism and not just of transient depressive states. Plasma BDNF was not associated with measures of depression.

Conclusions—Our study suggests that lower serum BDNF is associated with both a dispositional vulnerability to depression and acute depressive states in the general population.

Keywords

neuroticism; depression; brain-derived neurotrophic factor (BDNF); serum; plasma

Introduction

Brain-derived neurotrophic factor (BDNF) is a key protein in the survival, growth, and differentiation of neurons. A large body of evidence implicates BDNF in the pathophysiology of mood disorders and the therapeutic action of antidepressant treatment (1). In animal models, various stressors reduce BDNF levels, whereas chronic administration of antidepressant drugs up-regulates BDNF expression in the hippocampus (2), and infusion of BDNF in the hippocampus produces antidepressant effects (3). Peripheral BDNF administration increases adult hippocampal neurogenesis and produces

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Conflict of interest: The authors declare that they have no financial interest or other conflict of interest to disclose.

antidepressant-like behavioral responses (4). In humans, clinical studies have found increased peripheral levels of BDNF following a variety of antidepressant treatments, and compared to controls, untreated depressed patients have lower BDNF levels (5–9). Although this evidence supports the "neurotrophic hypothesis of depression," other findings are difficult to reconcile with this hypothesis (10, 11). In addition, a large clinical study (12) provides evidence for state, but not trait, effects of BDNF in depressive disorder.

This study tests the neurotrophic hypothesis in one of the largest community samples to date. We take a comprehensive approach by measuring BDNF concentration in both serum and plasma and by assessing a trait disposition to depression (Neuroticism), as well as state depressive symptoms. Neuroticism is a stable personality trait that reflects a chronic tendency to experience negative emotions; it is a strong predictor of depressive illness, in part because it shares genetic liability with major depression (13, 14). Neuroticism also correlates with blood-flow activity in the hippocampus (15) a key structure in the interplay of BDNF and depression. One study reported that BDNF concentration in serum is lower in individuals with higher Neuroticism scores, which suggests that low serum BDNF may reflect a vulnerability to mood disorders (16). A similar association was found with Harm Avoidance, a construct related to Neuroticism (17). However, two other studies found no association between Neuroticism and BDNF concentration in plasma (11, 18), so it is possible that there is an association of neuroticism with BDNF in serum but not plasma. To our knowledge, no study has examined whether depressive symptoms assessed with the Center for Epidemiologic Studies Depression Scale (CES-D) are associated with BDNF levels in serum or plasma.

Methods

Sample description

The SardiNIA project is an ongoing study supported by the National Institute on Aging and conducted in Sardinia, Italy. A detailed description of the study can be found elsewhere (19–22). We recruited over 62% of the population aged 14 to 102 years from four towns. In this study, we present data on 2099 subjects (62% women; Mean age = 51.7, SD = 15.2) that were assayed for serum levels of BDNF and a subsample of 482 subjects assayed for plasma levels of BDNF. After preliminary analyses on the first 482 subjects we stopped the assay on plasma to concentrate resources on the serum assay; thus, no specific criteria were used to select this subsample. Before blood collection (from July 2008 to June 2010), each subject signed a consent form approved by the institutional review boards (IRB) in Italy and the USA.

Personality assessment

Valid personality data were available for 2037 of the 2099 subjects of this study. Personality traits were assessed using the Italian version of the Revised NEO Personality Inventory (NEO-PI-R)(23, 24). The questionnaire consists of 240 items answered on a five-point Likert scale, from strongly disagree to strongly agree. In the SardiNIA sample, the NEO-PI-R showed good psychometric properties, with the factor structure closely resembling the American normative factor structure (congruence coefficients above 0.90), and internal consistency reliabilities for the five factors at or above 0.80. Available longitudinal data from other samples indicate that stability coefficients for the five factors are in the range of . 80 over intervals of 10 years (25).

The focus of this study was on Neuroticism, a stable trait that reflects a chronic tendency to experience a wide range of negative emotions. In addition to domain-level Neuroticism, we assessed six of its facets: Anxiety, Angry Hostility, Depression, Self-Consciousness,

Impulsiveness, and Vulnerability (23). Although these facets tend to covary, we tested whether BDNF is more strongly associated with depression than with the other facets of Neuroticism. The facets are heritable (26), highly stable in adulthood (25), and have been shown to provide greater specificity and power in the prediction of behaviors and health outcomes (20–22, 27, 28).

Depressive symptoms assessment

Symptoms of depression were assessed in 2037 subjects using the Italian version of the CES-D (29). The CES-D is a widely used scale composed of 20 items that assess the frequency of symptom occurrence on a 4-point scale from 0 (rarely) to 3 (most of the time) within the last week. In this sample the CES-D had good psychometric properties, with the internal consistency $\alpha = 0.86$. CES-D scores were significantly correlated with Neuroticism (r= 0.50) and each of the facets: Anxiety (r=0.43) Angry-Hostility (r=0.36), Depression (r=0.50), Self-Consciousness (r=0.37), Impulsiveness (r=0.09) and Vulnerability (r=0.40). To identify subjects with potential clinical depression, based on the distribution in our sample, we used CES-D scores ≥ 20 and ≥ 28 as cutoffs for moderate and severe symptoms of depression, respectively (30). Although a cut-off of 16 is generally considered to represent significant symptoms of depression, we selected more stringent cutoffs to reduce the risk of overestimation (31).

Measurement of serum and plasma BDNF concentration

Blood samples were drawn from subjects in the morning after an overnight fast. A total of 5.5ml of blood were collected in anticoagulant-free tubes for serum preparation, and 4.5ml of blood were collected in tubes with sodium citrate for plasma preparation. The blood samples were processed within 2 hours and serum and plasma samples were stored at −80°C until they were assayed, between 3 and 13 months (7 months average). BDNF concentration in serum and plasma were assayed with the commercially available BDNF E_{max}® ImmunoAssay System (Promega, Madison, WI), following the manufacturer's protocol. The microplate reader SpectraMax Plus^{384} (Molecular device) was used to record the absorbance at 450nm. All BDNF assays were performed in the same laboratory by the same biologists (ML and MGP), who were blind to the personality and depressive symptoms scores. This BDNF enzyme-linked immunosorbent assay (ELISA) has high specificity, with less than 3% cross-reactivity with other related neurotrophic factors (NGF, NT-3, and NT-4). This assay has a minimum sensitivity of 15.6pg/ml of BDNF. To measure concentrations within the range of the standard curve, the BDNF concentration was examined on serum samples diluted 1:70 and on plasma samples diluted 1:4, using the manufacturer recommended buffer. The concentration of each sample was determined in reference to standard curves from 7.8 to 500pg/ml BDNF ($R^2 \geq 0.94$), which were examined in duplicate in each plate (Coefficient of Variation <10%). As further control, we used the spike-and-recovery method to evaluate potential interference of our biological samples with the assay. For a subset of samples we measured the concentrations of the un-spiked aliquot and compared it with three aliquots spiked by adding 31.25, 62.5, and 125pg/ml of exogenous BDNF. The recovery rate of the spiked BDNF in the measured samples exceeded 95%.

Covariates

In the analyses we included covariates that have been associated with peripheral levels of BDNF in previous studies (11, 12, 32–34). These include sex, age, cigarette smoking (a dummy variable contrasting current smokers vs. non-current smokers and a dummy variable contrasting ever smokers vs. never smokers), obesity (Body Mass Index (BMI) $Kg/m^2 \geq 30$, derived from staff-assessed weight and height), and current use of selective serotonin reuptake inhibitors. Finally, we included a dummy variable that identified individuals who

required a trained psychologist to read and report their responses to the NEO-PI-R and CES-D (0=self-report, 1=administred).

Statistical analyses

We calculated descriptive statistics as means ±SD or percentages. We used the Kolmogorov-Smirnov test to evaluate whether the concentration of BDNF was normally distributed. To examine sex differences in BDNF levels, we conducted simple t-tests and multivariate analyses of variance to control for covariates. To examine whether age was associated with BDNF levels we computed Pearson correlations or partial correlations to control for covariates. The association between BDNF levels and personality traits were examined using partial correlations, using the above-listed covariates. Additional analyses examined potential interactions between BDNF and sex and age by adding the cross-product of the mean centered age and BDNF values in a third step of the hierarchical regression analyses. Logistic regression and multivariate analyses of variance were used to examine whether BDNF was predictive of CES-D scores ≥20 and ≥28, in models that included the covariates. All analyses were conducted using SPSS 13.0.

Results

Descriptive statistics for BDNF concentration in serum and plasma, the depression-related scales, and covariates are presented in Table 1. The BDNF concentration in serum for the 2099 subjects ranged from 1 to 27ng/ml (M = 14, SD = 3.0) and was normally distributed. In contrast, plasma concentration in the 482 subjects had a right-skewed distribution and showed a marked degree of variability (range from 26 to 844pg/ml, after 11 outliers +3SD above the mean value were trimmed; M = 247; SD = 191.6). This large variability for plasma is similar to what has been found in other samples (11, 35). To normalize the distribution we computed the natural log of the BDNF plasma concentration and used the transformed values in the parametric analyses. The correlation between the level of BDNF assayed in serum and plasma was modest (r = 0.21; P <0.001; n = 482), which suggests that these two measures are relatively independent. Moreover, we examined whether platelet count was related to the concentration of serum BDNF. Consistent with previous studies (36) and evidence that the BDNF measured in serum is stored in platelets (37), we found platelet count significantly correlated with serum BDNF (r = 0.41; P <0.001).

Age and sex differences in serum and plasma BDNF

Women had a slightly higher concentration of BDNF than men in serum (14.2 vs. 13.8ng/ml; d = 0.13; P = 0.01) and a trend for higher BDNF in plasma (258 vs. 226pg/ml; d = 0.17; P = 0.09), even after controlling for the covariates. This finding is surprising given that women tend to score higher on measures of depression, but the sex difference found in this sample is consistent with other non-clinical studies (11, 34, 35). In the full sample, controlling for the covariates, serum BDNF was not associated with age (r = 0.03; P = 0.20), but plasma BDNF levels were higher among older individuals (r = 0.10; P <0.05). There was an age by sex interaction for serum BDNF (P <0.001), such that age was positively associated with BDNF level for females (r = 0.09; P = 0.001), but there was a negative association for males (r = −0.07; P = 0.06). Supplementary analyses indicated that the association between serum BDNF and age among women became non-significant when controlling for menopause status (r = −0.01; P = 0.63), which suggest that hormonal factors might play a role.

Association of serum and plasma BDNF with Neuroticism

Table 2 presents partial correlations between serum and plasma concentrations and Neuroticism and its six facets. Individuals who scored higher on Neuroticism had lower

serum BDNF concentration (r = −0.074; $P < 0.001$). Analyses at the facet level indicated that the strongest association for serum BDNF was with the Depression facet (r = −0.08; $P < 0.001$). There was no significant association between Neuroticism or any of its facets and the level of BDNF in plasma (see Table 2). Furthermore, for both serum and plasma, the interactions between Neuroticism and age or sex were not significant, indicating that the above associations were similar for men and women and for younger and older adults. The associations of serum BDNF with the personality measures remained significant after controlling for the CES-D depressive symptoms scores: Including CES-D as a continuous variable in the model, serum BDNF was still correlated with Neuroticism (r = −0.069; $P = 0.002$) and the Depression facet (r = −0.073; $P = 0.001$), and the same was true when the CES-D was included as a dichotomous variable (CES-D ≥ 28) for both Neuroticism (r = −0.060; $P = 0.007$) and the Depression facet (r = −0.062; $P = 0.006$). These findings indicate that the association between serum BDNF and the trait measures are not due to acute depressive states.

Association of serum and plasma BDNF with depressive symptoms (CES-D)

We tested whether BDNF levels predicted depressive symptoms above increasingly stringent thresholds. We performed logistic regressions to predict CES-D scores at and above 20 and 28, which correspond roughly to 1 SD and 2 SD above the mean in the current sample. After accounting for the covariates in the first step, plasma BDNF was not a significant predictor of depressive symptoms at either threshold (*Ps* >0.05). Although serum BDNF was not associated with the CES-D as a continuous score (r = −.032; p = 0.15), there was a significant association with very severe symptoms of depression, identified using the CES-D ≥ 28 threshold (OR = 0.908; 95% CI = 0.852 – 0.968; P = 0.003). This effect indicates that for each unit lower of serum BDNF, the risk of severe symptoms of depression was about 10% higher, and those at 1 SD below the mean on serum BDNF had about 30% greater risk of experiencing severe symptoms of depression. Controlling for covariates, a MANCOVA confirmed that subjects with severe depressive symptoms (CES-D ≥28) had lower serum BDNF (13.2 vs. 14.1; P = 0.002), an effect (d = 0.30) similar to the one reported in the largest clinical study to date (d = 0.19)(12). Finally, including trait neuroticism or trait depression in the model, the association between serum BDNF and severe depressive symptoms (CES-D ≥ 28) became weaker, but was still significant (Neuroticism: OR = 0.929; 95% CI = 0.865 – 0.996; P = 0.04; Depression: OR = 0.933; 95% CI = 0.872 – 0.999; P = 0.048).

Discussion

Our large population-based study complements previous clinical studies by examining the associations of peripheral BDNF levels with state and trait measures of depression. Consistent with the notion that a BDNF deficiency underlies mood disorders, low serum BDNF was associated with increased risk of severe depressive symptoms (CES-D), and Neuroticism, an enduring trait that reflects vulnerability to depression. Plasma BDNF was unrelated to these measures. These results are consistent with previous smaller studies that found an association between Neuroticism and BDNF in serum (16, 17) but not in plasma (11, 18). These findings and other evidence (7, 8) suggest that serum BDNF, in addition to its sensitivity to severe depressive states, might be a trait-like marker of disease susceptibility in the general population (16).

Furthermore, our findings support the hypothesis that lower serum BDNF reflects core emotional features of depression. Indeed, the detailed assessment of personality traits made it possible to examine whether the association between Neuroticism and BDNF was specific to certain aspects of Neuroticism: Serum BDNF was most strongly associated with the Depression facet of Neuroticism, and was unrelated to facets measuring trait anxiety and

impulsiveness. The NEO-PI-R Depression facet captures the core aspects of depressed mood, with items that assess the tendency to experience sadness, hopelessness, worthlessness, discouragement, guilt, and loneliness.

The correlations we observed in our large community-based sample seem modest compared to the effect sizes observed in smaller studies that compared clinical cases to controls (5). These differences might be real. Clinical cases are on the tail of the distribution on measures of depression, and comparing them to healthy controls might produce larger effect sizes. By contrast, correlations in cohort-based studies account for variations across the entire population. Indeed, we found stronger effects when we contrasted subjects with extreme CES-D values to the rest of the sample. In addition, it is also well known that smaller studies tend to provide less reliable estimates of effect size. Consistent with this interpretation, the largest clinical study to date (12) found differences between untreated depressed patients and controls that were smaller than what we reported here.

Of note, we found that BDNF levels in serum and plasma are not interchangeable ($r = 0.21$), as also reported in previous smaller studies (5, 33, 38). BDNF assessed in serum represents the portion of BDNF stored in platelets, which bind, store, and release BDNF upon activation by a number of factors, including physiological stress and injuries. But even with agonist stimulation, only about half of the BDNF in platelets is secreted (37), which suggests that platelets maintain a stable pool of BDNF, a “buffer system” (36). In contrast, the plasma assay measures BDNF released in the blood, which is quite unstable. Plasma BDNF, for example, has very low retest stability when measured twice within one year (11), and there are substantial changes even during one day (39). Such variability is one drawback to assessing BDNF in plasma and may help explain the lack of association with measures of depression. Previous studies have also reported a large degree of dispersion (11, 35), which suggests that it is a problematic feature of the plasma BDNF measurement. A recent study also raises methodological concerns regarding the assessment of BDNF in plasma and recommends measuring BDNF in serum (40). It is possible that our null finding is a false negative due to lack of power, but the present research is consistent with two other published studies (11, 18) that show there is no association of plasma BDNF with Neuroticism. Such evidence raises the question of whether plasma assessments are worthwhile in future studies.

There are some limitations to consider when evaluating the results of this study. First, although the analyses included many covariates thought to influence BDNF levels, it is possible that we missed some important confounding factors, such as life events, social adversity, or other environmental stressors. The SardiNIA sample, however, is part of an isolated population characterized by a relative homogeneous genetic and cultural background. These features reduce the risk of false association due to population admixture. Another potential limitation was the use of the CES-D. Although a valid and widely-used measure of depressive symptoms, it does not provide a diagnosis of major depression.

In conclusion, this study suggests that serum BDNF is linked to depression vulnerability and severe depressive symptoms in the general population. These findings increase our understanding of the role of BDNF in depression vulnerability, and support the value of further research on the interplay of BDNF and antidepressant treatment. Given the large economic cost of Neuroticism, estimated to exceed those of common mental disorders (41), these associations can have large public health implications.

Acknowledgments

We thank the individuals who participated in this study.

Support: This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

Acronyms

BDNF	brain-derived neurotrophic factor
NEO-PI-R	Revised NEO Personality Inventory
CES-D	Center for Epidemiologic Studies Depression Scale
ELISA	enzyme-linked immunosorbent assay
BMI	body mass index
NGF	nerve growth factor
NT	Neurotrophin

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Table 1

Descriptive statistics for BDNF concentration, depression measures, and covariates in the total sample and separately for women and men

	Total (N[1] = 2099)	Women (N = 1297)	Men (N = 802)
BDNF concentrations			
Serum BDNF, ng/ml	14 (3.0)	14.2 (3.0)	13.8 (3.1)
Plasma BDNF, pg/ml	247.4 (191.6)	258.2 (194.8)	226.5 (183.9)
Depression measures			
CES-D	12.3 (7.9)	13.7 (8.5)	10.0 (6.1)
CES-D ≥ 20	324 (15.9%)	267 (21.1%)	57 (7.4%)
CES-D ≥ 28	114 (5.6%)	101 (8%)	13 (1.7%)
Neuroticism	56.0 (9.5)	58.1 (9.7)	52.5 (8.0)
Anxiety	56.7 (9.2)	58.6 (9.3)	53.4 (8.1)
Angry Hostility	53.2 (9.3)	53.5 (9.6)	52.7 (8.8)
Depression	53.4 (9.6)	54.9 (10.1)	51.0 (8.0)
Self-Consciousness	51.8 (10.0)	53.1 (10.3)	49.7 (9.1)
Impulsiveness	46.9 (9.2)	47.1 (9.2)	46.6 (9.2)
Vulnerability	56.1 (10.7)	58.2 (10.9)	52.6 (9.3)
Covariates			
Age	51.4 (15.3)	50.8 (15.2)	52.5 (15.4)
BMI	26.1 (4.6)	25.4 (5.0)	27.4 (3.8)
BMI ≥ 30	382 (18.2%)	207 (16%)	175 (21.8%)
Current smoker	15%	12%	20%
Ever smoker	38%	25%	61%
SSRI use	2%	2%	1%

[1] N = 482 for plasma; N = 2037 for CES-D and for NEO-PI-R. The reported data are means with SD in parenthesis, or counts with percentages if followed by the % sign.

Abbreviations: BDNF, Brain-derived neurotrophic factor; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CES-D, Center for Epidemiological Studies Depression Scale; SSRI = Selective Serotonin Reuptake Inhibitor.

Table 2

Partial correlation of serum and plasma BDNF concentrations with Neuroticism and its facets.

	Serum (N = 2037)	Plasma (N = 469)
Neuroticism	−.07**	−.01
Anxiety	−.04	.04
Angry Hostility	−.06**	−.07
Depression	−.08**	.00
Self-Consciousness	−.06**	.01
Impulsiveness	−.01	.02
Vulnerability	−.02	.03

Covariates: Age, Sex, administration method, cigarette smoking, obesity (BMI ≥ 30), and Selective Serotonin Reuptake Inhibitor use.

* $P < .05$;

** $P < .01$