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Serum Levels of Brain-Derived Neurotrophic Factor in Major Depressive Disorder: State - Trait Issues, Clinical Features, and Pharmacological Treatment

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Recent evidence supports 'the neurotrophin hypothesis of depression' in its prediction that Brain-Derived Neurotrophic Factor (BDNF) is involved in depression. However, some key questions remain unanswered, including whether abnormalities in BDNF persist beyond the clinical state of depression, whether BDNF levels are related to the clinical features of depression, and whether distinct antidepressants affect BDNF levels equally. We addressed these questions and investigated serum BDNF levels in 962 depressed patients, 700 fully remitted persons (≥ 6 months) and 382 healthy controls. We found serum BDNF levels to be low in antidepressant free depressed patients relative to controls (P=.007) and to depressed patients who were treated with an antidepressant (P=.001). BDNF levels of fully remitted persons (whether unmedicated or treated with an antidepressant) were comparable to those of controls. Analyzing the sample of antidepressant free depressed patients showed that BDNF levels were unrelated to the core clinical features of depression such as its severity or first versus a recurrent episode. The antidepressant associated up-regulation of serum BDNF in depressed patients was confined to SSRIs (P=.003) and St. John's wort (P=.03). Our results suggest that low serum levels of BDNF are a state abnormality that is evident during depression and normalizes during remission. Increases in serum levels of BDNF during antidepressant treatment appear to be confined to some antidepressants and do not parallel clinical characteristics, such as the severity of depressive symptoms.

Keywords: depression; brain-derived neurotrophic factor; antidepressants; BDNF

Introduction

Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin that has been linked to the viability of neurons in brain circuits that regulate emotion, memory, learning, sleep, and appetite.[1, 2] The neurotrophin hypothesis of depression is based on these functions of BDNF and postulates that depression results from stress induced decreases in BDNF expression and that antidepressants are efficacious because they increase BDNF expression.[3, 4] Consistent with this hypothesis are the findings that depression is accompanied by decreased central and peripheral levels of BDNF[5-7] and that antidepressants elicit an increase in BDNF levels in animal models for depression[8] and in depressed humans.[6, 7] Together with the latency of weeks before antidepressants become clinically effective,[9] these observations shaped the hypothesis that the efficacy of antidepressants depend on neuroadaptive changes that are brought about by changes in BDNF signaling.[3]

Taken together, there is reason to believe that BDNF is involved in depression and in antidepressant action. Results inconsistent with the neurotrophin hypothesis, however, also have been reported. There are, for example, studies that did not detect alternations in BDNF in depressed persons or in the course of treatment with an antidepressant.[10-12] Additionally, some questions remain unanswered so that the neurotrophin hypothesis is at best incomplete.[13] A major question that largely remains to be answered is whether low BDNF levels persist beyond the clinical state of depression.[14, 15] A second question is whether BDNF levels are related to the clinical features of depression, such as a first versus a recurrent episode.[16, 17] Yet a third outstanding question is whether all classes of antidepressants affect BDNF levels equally.[6, 7]

We studied, cross-sectionally, serum BDNF levels of depressed patients, remitted depressed persons, and never depressed persons. Our efforts had three concerns: (1) to compare serum BDNF levels of antidepressant free and antidepressant treated current and fully remitted depressed patients and never depressed persons, (2) to explore the associations between some of the core clinical features of depression and serum BDNF levels, and (3) to evaluate the association between the use of several distinct classes of antidepressants and serum BDNF levels.

Subjects and Methods

Subjects and sample collection

Subjects were from the Netherland Study of Depression and Anxiety (NESDA). Full details on the rationale, objectives, and protocol of NESDA are described in a previous paper by Penninx *et al.*[18] In brief, NESDA is a prospective cohort study (*N* = 2981) that recruited subjects in mental health care, primary care, and in the general population. Included were persons with a depressive and/or an anxiety disorder, persons with a depressive and/or an anxiety disorder in remission, and persons without a history or current depressive or anxiety disorders. Persons who were diagnosed with psychotic-, bipolar I or II -, obsessive-compulsive- or severe alcohol use disorder were not eligible. DSM-IV diagnoses[19] were assigned on the basis of responses to the Composite International Diagnostic Interview 2.1 (CIDI) lifetime version[20] that was administered by trained interviewers. At baseline, participants provided blood samples, underwent a medical examination, and gave written informed consent for the study that was approved by the Ethical Committees of the participating institutes.

Our study enrolled 2044 persons (68.6% of the NESDA sample). Based on diagnosis, antidepressant use and the availability of BDNF data we created 5 groups; antidepressant free depressed patients (*n*=541), antidepressant treated depressed patients (*n*=421), antidepressant free remitted depressed persons (*n*=539), antidepressant treated remitted depressed persons (*n*=161), and healthy persons who served as controls (*n*=382). Depressed patients met the criteria for a depressive episode within the last 6 months (n=541). The majority of these patients had a current diagnosis of depression (n=388), but some (n=153) had a diagnosis of depression 1-6 months prior to baseline and did not fulfill all criteria in the past month. Persons who were in full remission of depression were diagnosed with MDD somewhere in their lives, but had been free of depression and anxiety during at least 6 months. Persons were included in the control group when they had: (1) no lifetime mood or anxiety disorders, (2) no documented family history of depression or anxiety, and (3) a low score (≤ 14) on the Inventory of Depressive Symptoms (IDS).[21]

Antidepressants

Data on the use of antidepressants was acquired through drug container observation and self-report. Use of an antidepressant was defined as intake of minimally the daily dose as recommended by the World Health Organization[22] during the last month on at least 50% of the days. We coded for the use of Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs), and St. John's wort (Hypericum perforatum). The duration of use was expressed in months.

Clinical features of MDD

All subjects were characterized on the symptom severity of depression using the IDS.[21] Patient samples were further characterized on having a first or a recurrent depressive episode, the presence of comorbid anxiety, the age at onset of depression, the recency of depression, the chronicity of depression, and on the presenceof suicide ideation. The CIDI interview[20] served as source of information on the presence of a first or a recurrent depressive episode, the presence of a comorbid anxiety, age at onset of depression (ie., the age at which the first episode occurred), and the recency of depression (ie., fulfilling criteria in the past month versus fulfilling criteria in the past 6 months but not in the past month). Depression was considered chronic if symptoms had been present ≥ 24 months during the last 5 years, which was assessed using the Life Chart method.[23] The scale for suicide ideation[24] was used to examine the presence (yes vs. no) of suicide ideation during the past week.

BDNF protein measurements

Fifty millilitre of blood was withdrawn into vacuum tubes between 07:30 and 09:30 a.m. after an overnight fast. Following blood collection, serum was separated and stored at -85 Celsius until it was assayed. BDNF protein levels were measured using the Emax Immuno Assay system from Promega according to the manufacturer's protocol (Madison, WI, USA), in 1 laboratory (Maastricht University) by 1 technician who was blind to diagnoses. Undiluted serum was acid treated since this reliably increased the detectable BDNF in a dilution-dependent way. Greiner Bio-One high affinity 96-well plates were used. Serum samples were diluted 100 times and the absorbency was read in duplicate using a Biorad Benchmark microplate reader at 450 nm. The intra- and inter-assay coefficients of variation were found to be within 3%

and 9% respectively. Four persons had BDNF values that were below the reliable detection threshold of 1.56 ng/ml. These values were set at the lower detection limit. Positive outliers (mean + 3 STDs, n=6) were trimmed to the mean + 3 STDs value. There were no differences between persons with missing and non-missing BDNF with regard to gender (*P*=.71), age (*P*=.67), and diagnoses (*P*=.33).

Covariates

Potential variance due to gender, age, and educational level was controlled for in all analyses. Additionally, we controlled for Body Mass Index (BMI), physical activity, and smoking since these variables are associated with BDNF[25-27] and mood.[28-30] Data on weight and height was collected and BMI was calculated (weight/height^2). Information on physical activity was gathered using the International Physical Activity Questionnaire[31] and expressed as number of met-minutes (ie., the ratio of the amount of energy expenditure during activity to the energy expenditure at rest). Smoking status was dichotomized as current versus non-smoker. Time of the morning blood withdrawal and duration of serum storage were controlled for since BDNF levels vary according to variation on these variables.[32, 33]

Statistical analyses

All computations were performed in SPSS version 17.0 (SPSS, Chicago, Illinois). BDNF values were controlled for basic covariates in all analyses. Effect sizes on pair-wise comparisons were presented as Cohen's *d*.[34] A 2-tailed α level of .05 was used to determine statistical significance.

Analysis of Variance (ANOVA) was used to compare BDNF levels of antidepressant free depressed patients and antidepressant treated depressed patients,

antidepressant free patients and antidepressant treated persons who were in remission (≥ 6months), and controls. Post-hoc tests between the groups were performed following a significant *F*-statistic using Tukey tests.

A multivariable regression analysis was used to identify whether the clinical features of depression were associated with BDNF levels. Regression was performed in patient groups in which the mean BDNF level deviated significantly from the control group. Pearson correlation coefficients between predictors and BDNF levels were also calculated. Basic covariates were entered in the first step of regression. In the second step the clinical features of depression were entered. The regression model was fit using method enter. Tolerance of the predictors and normality of error variances was verified.

To establish whether the use of an antidepressant effected BDNF levels equally in current and remitted depression, a 2 (currently depressed vs. depression in (full) remission) × 2 (antidepressants; yes or no) ANOVA was performed. Potential antidepressant specific associations between the use of SSRI, TCA, SNRI, NaSSA, and St. John's wort and BDNF levels were evaluated by contrasting BDNF levels of persons who used 1 of these agents against the BDNF level of the antidepressant free persons. Analyses were repeated with the severity of depressive symptoms and the duration of antidepressant use as covariates.

Results

Demographics and clinical features

Demographical and clinical features among the 5 groups are given in **Table 1**. ANOVA and χ-square tests showed that, compared to controls, depressed and remitted persons were more likely to be female, to be older, to have received fewer

years of education, and to smoke. BMI was higher in current and remitted antidepressant treated depressed persons compared to controls and to antidepressant free depressed and remitted persons. The amount of physical activity was low in the antidepressant treated currently depressed group relative to the other groups. Post-hoc comparisons on demographical and clinical features between the current and remitted depressed groups are given in **Table 1**.

BDNF levels in persons with current or remitted depression and controls

An ANOVA model showed a main effect of diagnostic status on serum levels of BDNF ($F_{1,\ 1578}$=4.09, P=.01). Pair-wise comparisons (see **Figure 1**) indicated that serum BDNF levels were low in antidepressant free depressed patients compared to controls (d=0.19), to antidepressant free persons who were in full remission (d=0.15), and to antidepressant treated depressed patients (d=0.23). BDNF levels of antidepressant free persons who were in full remission and depressed patients who were treated with an antidepressant were comparable to those of controls.

BDNF and the clinical features of MDD

The exploration of the association between the clinical features of MDD and serum BDNF was restricted to the antidepressant free currently depressed group, since BDNF levels in this group were low relative to controls.

Pearson's correlation showed that female gender and being in the early remission phase of depression (1-6 months) versus having a current episode were negatively associated with serum BDNF. Age, BMI, age at onset of MDD, and the presence of comorbid anxiety were positively associated to serum BDNF (**Table 2**).

Basic covariates were entered in the first step of the multivariable regression analysis, followed by the clinical features that were entered in step two. Tolerance of the predictors was high (all > 0.70) indicating that our individual predictors were not redundant with one another. Error variances were normally distributed. Results of the first step showed that gender and age were significant predictors of BDNF levels. Women had lower levels of BDNF compared to men (β=-0.10, *P*=.02) and older patients had higher levels of BDNF (β=0.11, *P*=.002) compared to younger patients. Results of the second step showed that none of the clinical features (listed in **Table 2**) was significantly associated with serum BDNF. Gender and age preserved its significance. BMI emerged as a significant (positive) predictor of serum BDNF. **Table 2** presents the results of the second step of the regression analysis.

BDNF and the use of antidepressants

A 2 (currently depressed vs. depression in (full) remission) × 2 (antidepressant use; yes vs. no) ANOVA showed that diagnostic status interacted with antidepressant use ($F_{1,\ 1578}$=4.19, *P*=.03) indicating that the use of an antidepressant during a depressive episode was associated with higher BDNF levels whereas in the remission phase the use of an antidepressant did not show such an association (see **Figure 2**). Main effects of diagnostic status and antidepressant use were not observed.

To uncover potential differences between various classes of antidepressants we compared BDNF levels of depressed patients who used SSRIs, SNRIs, TCAs, NaSSAs, or St. John's wort among each other and with BDNF level of antidepressant free depressed patients. This analysis was restricted to the currently depressed group since the effect of the use of an antidepressant on serum BDNF levels was confined to this group. In this group, 67% (n = 282) used and antidepressant for longer then 12

weeks. We observed a main effect of group ($F_{5,\ 941}$=4.29, P<.001). Post-hoc comparisons (see **Figure 2**) showed that, relative to not using an antidepressant, the use of SSRIs (d=0.39) and St. John's wort (d=0.63) was associated with high levels of BDNF. The use of a NaSSA was associated with low levels of BDNF relative to SSRI (d=0.54) and St. John's wort (d=0.85) use. Analyses were run with and without co-varying for the severity of depressive symptoms and for the duration of antidepressant use. These analyses revealed a similar pattern of results. Furthermore, serum BDNF levels were unrelated to treatment duration (r=-0.02, P=.65) which might suggests that our findings were not driven by duration of antidepressant use.

Discussion

Largely in accord with previous findings[6, 7] and with the neurotrophin hypothesis of depression[3, 4] our data showed that serum BDNF levels were low in antidepressant free depressed patients compared to healthy controls. Our data further showed that BDNF levels were low in depressed patients who were not on antidepressant medication compared to antidepressant free persons who were in full remission and that BDNF levels of this latter group were comparable to those of controls. Herewith we establish as one of the first[14] that low levels of BDNF in serum are a state characteristic for depression. In line with one study that reported low levels of BDNF in euthymic patients[15] we found that patients who were in early remission (1-6 months) had serum BDNF levels that were comparable to those of currently depressed patients. Thus serum BDNF levels remain low after clinical improvement has set in. This could indicate that low levels of BDNF are a consequence of depressive symptoms that persist into early remission. Alternatively, the low levels of BDNF during early remission might also represent a scar of a depressive episode. These

explanations could not be fully elucidated in the current study and longitudinal designs clearly are essential to understand this issue.

We were unable to replicate the earlier findings that a higher depression severity[17, 35], having a recurrent compared to a first episode of MDD[16], and the occurrence of suicide ideation[36, 37] are accompanied by lower levels of BDNF. In fact, we even found that the early remission phase, which was accompanied by a lower symptom severity of depression (mean IDS scores were 22.4 ± 11.4 vs. 32.4 ± 12.1 in early remitted and currently depressed patients respectively), was associated with somewhat lower BDNF levels compared to the current depressive state. The other clinical features (i.e., age at onset of depression, the presence of comorbid anxiety, and the chronicity of depression) also were unrelated to serum BDNF in multivariable analyses. These findings, given the size of the current cohort, give us confidence in excluding the clinical features of depression as potential correlates of serum BDNF levels. This might be an important conclusion, since it hints that other (than specifically depression related) factors may be at play in the relative fall of BDNF levels during a depressive episode. Interestingly, being male and having a higher BMI were found to be positively associated with BDNF among antidepressant free depressed patients. Although these findings were unsought, they parallel the results of some previous studies[17, 38, 39] and they give ground to interesting hypotheses. For example, since weight loss is a prime behavioral abnormality of depression[19] and often a residual symptom in early remission[40, 41] it could be that, alternations in BDNF levels are mediated by (transient) changes in eating behavior during, or in the aftermath of, a depressive episode. Likewise, weight gain is a documented side effect of antidepressant treatment[42, 43] and thus the absence of weight loss could potentially

explain the absence of a relative fall of BDNF in depressed patients during treatment with an antidepressant.

Alternative factors that have been proposed to underlie the low levels of BDNF during depression are exposure to stressful life events. Two studies, for example, found that adverse life events are associated with lower peripheral BDNF levels within a depressed and bipolar patient samples.[44, 45] Therefore, it seems worthwhile to integrate a wider range of variables, notably (early) adverse life events, but also genetic variants and their interactions with environmental variables[46] in models that study the link between BDNF and depression.

Additionally, we found that serum BDNF levels were higher in antidepressant treated patients compared to patients who were antidepressant free. This finding largely is in accord with previous findings.[6, 7] We were able to expand previous findings by showing that the use of an antidepressant is associated with increased serum BDNF during a depressive episode but not during remission. This suggests that antidepressant induced increases in BDNF occur in a disease state when BDNF functioning might be defective and not in remission when BDNF functioning is normalized. Additionally, we found the increase in serum BDNF levels to be a specific associate of the use of SSRIs and St. John's wort and not of the use of SNRIs, TCAs, or NaSSAs. Although not directly confirmed, this finding might be explained by increased availability of extra-synaptic levels of serotonin. It is known that serotonin stimulates the expression of BDNF. [47, 48] In line with this we found the highest BDNF levels in patients who were treated with an agent that generally leads to an increase in the availability of serotonin (ie., SSRIs and St John's wort).[49, 50] Furthermore, we found the lowest levels of BDNF in patients who were treated with agents that have little or no impact on the availability of serotonin (ie., NaSSAs).[43, 51]

Nevertheless, this antidepressant specific finding seems at odds with the specific prediction of the neurotrophin hypothesis, stating that increases in BDNF levels are a key mediator for an antidepressant response to occur.[3] According to this prediction, one might expect that antidepressants that are known to be about equally efficacious in the treatment of the symptoms of depression[50-52] would have similar effects on serum BDNF levels. Yet another finding that seems hard to reconcile with the neurotrophin hypothesis is that the group of depressed persons who used antidepressants (prolonged and frequently) had the highest BDNF levels, but also the highest symptom severity of depression. This suggests, to our belief that increases in peripheral BDNF levels do not parallel clinical effectiveness, or at least have no *direct* effects on the depression characteristics such as its severity. Such a conclusion on the absence of direct effects could also be drawn on the findings that the severity of a depressive episode was unrelated to serum BDNF levels and that persons who were in early remission had similar levels of BDNF yet marked lower levels of depression severity compared to depressed patients.

Caution, however, is warranted when interpreting our findings on the associations between the use of an antidepressant and serum levels of BDNF because our subjects were not randomly assigned to the various drugs (or no drug) conditions. Thus our findings might be confounded by indication. An additional limitation of our study is that we relied on data that were collected in a single wave, precluding any form of causality. Furthermore, we measured serum levels of BDNF and assume that these measurements mirror the amount of BDNF in the brain. This assumption is validated on preclinical work that showed that cortical and peripheral levels of BDNF are correlated[53-55] but remains complicated, because in addition to neurons, several other tissues serve as sources of BDNF in serum.[54] However, various strengths of our study

seem evident and these include the use of multivariable techniques and the large sample size (that relates positive to all previous studies and to two previous meta-analyses [6, 7] as well).

In conclusion, we believe that our data indicate that low levels of BDNF in blood serum are a state characteristic of depression and thus an abnormality that is evident during the clinical state and the early remission phase of depression but not when the symptoms of depression are in full remission. Our findings further suggest that some of the core clinical features of depression are unrelated to serum levels of BDNF. Finally, increases in serum levels of BDNF appear to be a specific pharmacological effect of a subset of antidepressants that does not parallel depression characteristics such as the severity of depression.

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TABLE AND FIGURE LEGENDS

Table 1 Demographic and clinical characteristics (percentages (%) or mean ± standard deviation) of participants by depression diagnosis (never, current, and remitted) and antidepressant use (yes versus no).

Abbreviations: IDS, Inventory of Depressive Symptoms; MDD, Major Depressive Disorder; NaSSA, Noradrenergic and Specific Serotonergic Antidepressant; SNRI, Serotonin and Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressant.

[1] Mean met-minutes (ie., ratio of energy expenditure during activity to energy expenditure at rest) divided by 1000.

[2] Symptoms were considered chronic if they were present for at least 24 months during the last 5 years.

[3] Included social phobia, panic disorder with and without agoraphobia, agoraphobia, and generalized anxiety disorder.

[A] Indicates a statistical significant difference (at $P < .05$) between the antidepressant treated and antidepressant free current MDD groups.

[B] Indicates a statistical significant difference (at $P < .05$) between the antidepressant treated and antidepressant free remitted MDD groups.

Table 2 Results of correlation and multiple regression analyses of demographical and clinical characteristics with serum levels of BDNF in antidepressant free patients with MDD.

Abbreviations: 95% CI, 95 Percent Confidence Interval; IDS, Inventory of Depressive Symptoms; IPAQ, International Physical Activity Questionnaire; MDD, Major Depressive Disorder.

[a] Univariate correlation with serum levels of BDNF; Pearson's *r* for continuous variables and Spearman's *rho* for dichotomous variables.

[b] In minutes from 06:00 AM.

[c] The presence of a current (1 month) versus an early remission (1 to 6 months of remission) diagnosis.

* Denotes statistical significance of the univariate correlation at $P < .05$. ** Denotes statistical significance of the univariate correlation at $P < .01$.

Figure 1. Plotted are mean serum BDNF levels by diagnoses and antidepressant use. Error bars reflect the standard error of the mean.

* Denotes statistical significance at P < .05. ** Denotes statistical significance at P <.01.

Figure 2. Plotted are mean serum BDNF levels by specific class of antidepressant (St John's wort, SSRIs, SNRIs, TCAs, and NaSSAs). The dashed line indicates the mean BDNF level of the antidepressant free depressed group. Error bars reflect the standard error of the mean.

* Denotes statistical significance at P < .05. ** Denotes statistical significance at P < .01.

Table 1 Demographic and clinical characteristics (percentages (%) or mean ± standard deviation) of participants by depression diagnosis (never, current, and remitted) and antidepressant use (yes versus no)

Characteristic		Controls *(n = 382)*	Current MDD no antidepressants *(n = 541)*	Current MDD antidepressants *(n = 421)*	Remitted MDD no antidepressants *(n = 539)*	Remitted MDD antidepressants *(n = 161)*	*P value*
Female	%	61.0	66.7	67.0	71.1	70.8	<.05
Age		45.7 ± 12.3	39.8 ± 12.6	42.6 ± 11.0	43.1 ± 12.9	45.4 ± 10.8	<.001 [A, B]
Education (years)		13.4 ± 3.3	11.9 ± 3.2	11.7 ± 3.3	12.6 ± 3.1	12.1 ± 3.3	<.001
BMI		25.4 ± 4.6	25.5 ± 5.4	26.3 ± 5.6	25.3 ± 4.6	26.6 ± 5.6	<.01 [A, B]
Mean met-minutes (week) [1]		3.7 ± 3.0	3.5 ± 3.3	3.2 ± 3.3	3.8 ± 3.1	3.1 ± 2.8	<.01 [B]
Smoker	%	16.5	38.7	46.0	35.5	34.3	<.001 [A]
Alcohol dependent	%	5.4	23.3	20.0	17.0	13.7	<.001
Depression severity, IDS		5.3 ± 3.5	29.6 ± 12.7	34.5 ± 13.1	16.8 ± 10.3	20.3 ± 10.6	<.001 [A, B]
Age of onset of MDD		NA	26.1 ± 12.3	27.4 ± 12.6	27.6 ± 12.2	28.2 ± 11.7	=.35
Chronic MDD [2]	%	NA	27.5	38.3	11.1	18.7	<.001 [A, B]
> 1 episode of MDD	%	NA	63.6	58.2	54.6	61.5	<.05 [A]
Comorbid anxiety [3]	%	NA	42.2	47.7	NA	NA	<.05
Suicide ideation [4]	%	NA	22.4	29.3	5.2	6.2	<.001 [A]
Antidepressant medication							
SSRI	%	NA	NA	62.7	NA	65.8	=.27
SNRI	%	NA	NA	16.4	NA	13.0	=.06
TCA	%	NA	NA	8.1	NA	13.0	=.19
NaSSA	%	NA	NA	8.6	NA	2.5	<.05
St. John's wort	%	NA	NA	4.3	NA	5.6	=.32
Duration of use (months)		NA	NA	7.5 ± 4.9	NA	10.9 ± 3.5	<.001

Abbreviations: IDS, Inventory of Depressive Symptoms; MDD, Major Depressive Disorder; NaSSA, Noradrenergic and Specific Serotonergic Antidepressant; SNRI, Serotonin and Norepinephrine Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor; TCA, Tricyclic Antidepressant.

[1] Mean met-minutes (ie., ratio of energy expenditure during activity to energy expenditure at rest) divided by 1000.

[2] Symptoms were considered chronic if they were present for at least 24 months during the last 5 years.

[3] Included social phobia, panic disorder with and without agoraphobia, agoraphobia, and generalized anxiety disorder.

[A] Indicates a statistical significant difference (at $P < .05$) between the antidepressant treated and antidepressant free current MDD groups

[B] Indicates a statistical significant difference (at $P < .05$) between the antidepressant treated and antidepressant free remitted MDD groups

Table 2 Results of correlation and multivariable regression analyses of demographical and clinical characteristics with serum levels of BDNF in antidepressant free patients with MDD

	r [a]	*B*	*95% CI B*	β	*t*	*P value*
Gender (1 = male, 2 = female)	-0.13**	-0.65	-1.24 to -0.06	-0.10	-2.15	.03
Age (continuous , years)	0.17**	0.03	0.01 to 0.06	0.11	1.98	.04
Education (continuous , years)	-0.04	-0.01	-0.09 to 0.08	-0.005	-0.11	.91
BMI (continuous)	0.13**	0.06	0.01 to 0.10	0.09	1.97	.04
Met-minutes (continuous, IPAQ)	-0.02	-0.001	-0.01 to 0.01	-0.009	-0.21	.83
Smoker (1 = no, 2 = yes)	-0.02	-0.07	-0.04 to 0.02	-0.02	-0.44	.66
Time of Blood withdrawal (continuous) [b]	-0.04	-0.004	-0.12 to 0.02	-0.04	-1.11	.23
Duration of serum storage (continuous, days)	0.02	0.14	-0.40 to 0.68	0.02	0.49	.62
MDD status (1 = current, 2 = early remitted) [c]	-0.11*	-0.15	-0.50 to 0.25	-0.04	-0.64	.52
MDD severity (continuous, IDS)	0.03	-0.007	-0.04 to 0.02	-0.06	-1.12	.24
MDD type (1= single episode, 2 = recurrent)	0.01	0.05	-0.56 to 0.66	0.007	0.15	.88
Comorbid anxiety disorder (1 = no, 2 = yes)	0.08*	0.31	-0.36 to 0.97	0.05	0.91	.36
Age at onset MDD (continuous)	0.14**	0.08	-0.04 to 0.18	0.07	1.25	.21
Chronic MDD (1 = no, 2 = yes)	0.07	0.19	-0.49 to 0.87	0.03	0.55	.58
Suicide ideation (1 = no, 2 = yes)	0.06	0.59	-0.13 to 1.33	0.07	1.51	.12

Abbreviations: 95% CI, 95 Percent Confidence Interval; IDS, Inventory of Depressive Symptoms; IPAQ, International Physical Activity Questionnaire; MDD, Major Depressive Disorder.

[a] Univariate correlation with serum levels of BDNF; Pearson's *r* for continuous variables and Spearman's *rho* for variables.

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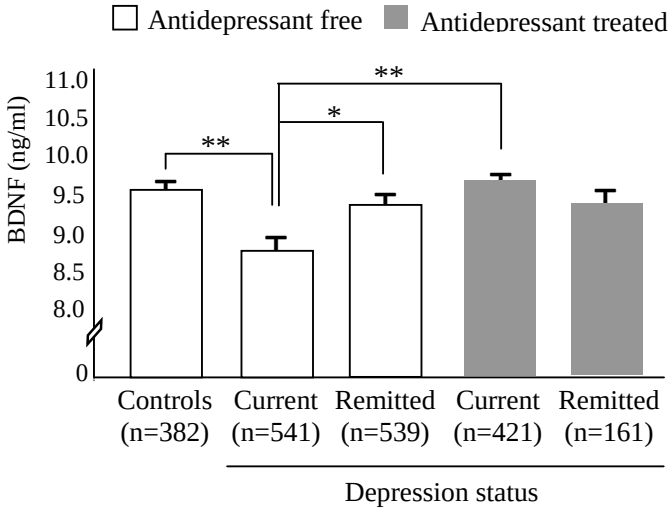

Figure 1. Plotted are mean serum BDNF levels by diagnoses and antidepressant use. Error bars reflect the standard error of the mean.

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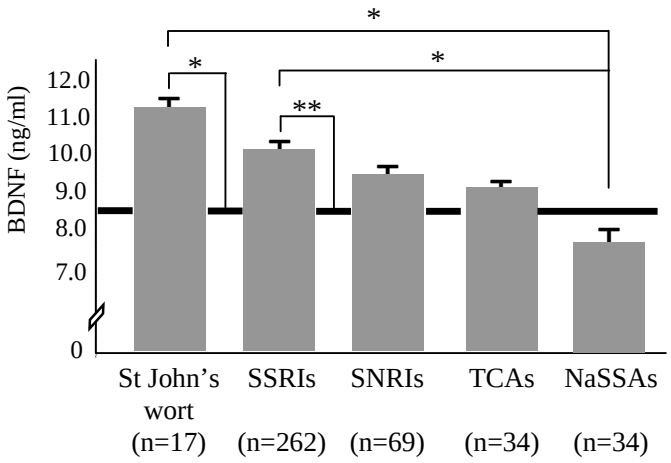

Figure 2. Plotted are mean serum BDNF levels by specific class of antidepressant (St John's wort, SSRIs, SNRIs, TCAs, and NaSSAs). The dashed line indicates the mean BDNF level of the antidepressant free depressed group (n=541). Error bars reflect the standard error of the mean.

* Denotes statistical significance at P < .05. ** Denotes statistical significance at P < .01.