Original Paper

Role of Serum Brain Derived Neurotrophic Factor and Central N-Acetylaspartate for Clinical Response under Antidepressive Pharmacotherapy

Sarah Nase[a] Stephan Köhler[a] Jacqueline Jennebach[a] Anne Eckert[b]
Nina Schweinfurth[b] Jürgen Gallinat[c] Undine E. Lang[b] Simone Kühn[c,d]

[a]Department of Psychiatry and Psychotherapy, Charité, University Medicine Berlin, Campus Mitte, Berlin, Germany, [b]Department of Psychiatry and Psychotherapy, Universitäre Psychiatrische Kliniken (UPK), Basel, Switzerland, [c]Department of Psychiatry, Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, [d]Max Planck Institute for Human Development Berlin, Germany

Key Words

Abstract

Background: The predictive therapeutic value of brain derived neurotrophic factor (BDNF) and its changes associated with the use of specific antidepressants are still unclear. In this study, we examined BDNF as a peripheral and NAA as a central biomarker over the time course of antidepressant treatment to specify both of their roles in the response to the medication and clinical outcome. *Methods:* We examined serum BDNF (ELISA kit) in a sample of 76 (47 female and 29 male) depressed patients in a naturalistic setting. BDNF was assessed before medication and subsequently after two, four and six weeks of antidepressant treatment. Additionally, in fifteen patients, N-acetylaspartate (NAA) was measured in the anterior cingulate cortex (ACC) with magnetic resonance spectroscopy (MRS). Over a time course of six weeks BDNF and NAA were also examined in a group of 41 healthy controls. *Results:* We found significant lower serum BDNF concentrations in depressed patients compared to the sample of healthy volunteers before and after medication. BDNF and clinical symptoms decreased significantly in the patients over the time course of antidepressant treatment. Serum BDNF levels at baseline predicted the symptom outcome after eight weeks. Specifically, responders and remitters had lower serum BDNF at baseline than the nonresponders and nonremitters. NAA was slightly decreased but not significantly lower in depressed patients when compared with healthy controls. During treatment period, NAA showed a tendency to increase. *Limitations:* A

Sarah Nase

Charite University Medicine Berlin, Chariteplatz 1, 10117 Berlin (Germany)
Tel +49 30 450 517 176, Fax +49 30 450 517 944, E-Mail sarah.nase@charite.de

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relative high drop-out rate and possibly, a suboptimal observation period for BDNF. **Conclusion:** Our data confirm serum BDNF as a biomarker of depression with a possible role in response prediction. However, our findings argue against serum BDNF increase being a prerequisite to depressive symptom reduction.

Introduction

There is an increasing number of preclinical and clinical studies that support the crucial role of neurotrophins, especially brain-derived neurotrophic factor (BDNF), in the development and treatment of depressive disorders [1, 2]. BDNF promotes neuronal survival, differentiation and synaptic stabilization, making it an important player in the maintenance of neuronal plasticity. The neurotrophin hypothesis of depression argues that a lack of BDNF leads to less neuronal plasticity, which in turn contributes to the pathophysiology of depression [3]. So, it is suggested that the changes in BDNF expression lead to the structural alterations and volume decrease in the limbic system and the prefrontal cortex (PFC), which are often found in depressed patients [4, 5]. Additionally, it is suggested that antidepressant drugs may help to restore the functional networks by inducing neurogenesis and facilitating synaptic connectivity [6]. In contrast to the immediate increase of monoamines in the synaptic cleft after taking antidepressants, the neuroptrophic effects take more time, which could be an explanation for the delay in the effects of antidepressant treatment.

In line with the neurotrophin hypothesis of depression, low BDNF blood levels in a depressive state were often found in humans, as well as an association of increasing BDNF concentrations with antidepressant treatment [7-16]. While peripheral BDNF reduction during depression has often been replicated, there are open questions about the exact role of BDNF in the pathophysiology and especially in the psychopharmacological treatment of depression. Thus the results, showing that especially the reduction of BDNF must be restored to achieve antidepressant response, are questioned by contrary findings in rather recent clinical and preclinical studies [17-21]. So, there is even evidence that there could be a clinical response in the absence of a BDNF increase [22-26]. BDNF predominantly acts in depression related brain regions like the hippocampus, the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC) [27]. The ACC is involved in several processes including reward anticipation, decision making, impulse control and emotional functions [28-30], which might reflect its crucial role for depression and its development. In animal and postmortem human studies, the influence of stress and depression show decreasing BDNF levels in these relevant brain regions [31]. Since direct brain analysis is not possible in living humans, serum or plasma BDNF is used as a neuroplasticity marker, which should reflect the BDNF brain concentration. To fill out this gap in research with humans, N-acetylaspartate (NAA) concentration as an *in-vivo* biomarker of neuroadaption and plasticity [32] can be measured by magnetic resonance spectroscopy (MRS). MRS is a noninvasive magnetic resonance imaging (MRI) method to measure brain metabolite concentrations. NAA is a central metabolite that is thought to reflect neuronal integrity, viability, and function [33]. It enhances mitochondrial energy production from glutamate [34] and is exclusively found in the brain [35]. Though only a few studies have examined this supposed connection so far, peripheral BDNF and NAA in the ACC seem to be positively associated [36-38].

Since in previous research there are heterogeneous findings, investigating the association of serum BDNF concentrations, antidepressive drug treatment and clinical response in longitudinal studies, we aim to assess the roles of serum BDNF and NAA during antidepressant treatment and their roles for treatment outcome.

Taking recent findings into consideration, we hypothesized that serum BDNF and NAA concentrations in the ACC are lower compared to healthy control subjects. Additionally,

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we also predicted that serum BDNF and NAA would increase in association with a positive treatment response and with remission of depression. Finally, we predicted that BDNF and NAA are both associated with each other and with symptom severity.

Materials and Methods

Subjects and procedure

Seventy-six in- and outpatients (47 females, 29 males) with the diagnosis of major depressive episode were recruited within the scope of the present study. They were treated in a naturalistic setting in the department of psychiatry and psychotherapy of the university hospital Charité Berlin. At the time point of study inclusion, patients were either unmedicated (n=64) or did not respond to current medication and were therefore willing to change the drug (n=12). Decision for the kind of antidepressant medication was made by the attending physician and was independent of the study. Before entering the study, patients provided written informed consent. Exclusion criteria were defined as drug use and alcohol dependence (AUDIT) [39] with use during the last year, psychotic symptoms, bipolar disorder, borderline personality disorder, neurological diseases, chronic medical disorders, and pregnancy. Demographic data (as seen in Table 1) and case history as well as body weight/body mass index (BMI) and smoking status (yes/no) where collected in an interview by an experienced psychologist. All patients were evaluated by a study coworker to confirm the diagnosis of a depressive episode with the 17 item version of the Hamilton Depression Rating Scale (HAMD) [40], and the Beck's Depression Inventory (BDI II) [41]. Inclusion criteria were defined as a minimum score of ≥16 points in the HAMD. The HAMD and BDI scores were used as baseline scores (T0), which indicated the time point of no medication or before medication change. At baseline, the T0 blood sample was collected. From this time point blood samples were collected weekly until week six. Due to organizational issues blood samples were collected every second week until T4 for all patients, and until T6 in 27 (35,5%) patients of the sample. In a subsample of 15 patients, we conducted magnetic resonance spectroscopy (MRS) to measure NAA concentrations in the anterior cingulate cortex (ACC).

The control group of healthy volunteers consisted of 41 mentally healthy subjects (25 females, 16 males), which were recruited via internet advertisements. In the healthy volunteers, we measured serum BDNF, NAA and BDI scores at baseline (T0) and again after six weeks (T6) to have comparable data to the group of depressed patients. All participants gave written informed consent in advance of inclusion into the study. Any psychiatric diagnosis was excluded on the basis of Mini International Neuropsychiatric Interview (M.I.N.I.) [42], which was conducted by a research psychologist. Demographic data, BMI and smoking status were collected and all exclusion criteria mentioned above were applied equally for the healthy subjects.

The study design was approved by the local ethics committee.

BDNF assessment

Blood samples of patients were taken in 8 ml BD vacutaner at T0 (before treatment or treatment change), T2 (after two weeks of medication), T4 (after four weeks of medication), and T6 (six weeks after medication). Blood samples were stored 20 minutes at room temperature (for clotting) and centrifuged 10 minutes with 2.500 rounds per minute at 4°C. Serum was isolated and stored at -80 °C until BDNF measuring occurred.

Serum BDNF levels were assessed with an enzyme linked immunoabsorbant assay (ELISA) kit (Promega BDNF Emax®, Madison, Wis., United States). Samples were appropriately diluted (between 1:100-1:150) and detection of total soluble BDNF was carried out in an antibody sandwich format like it is described in the manufacturer's protocol. The absorbance was measured within 30min in a microplate reader set at 450nm, and a correction wavelength set to 690nm, to determine BDNF concentrations according to the standard curve. All assays were carried out in duplicate and means were calculated.

NAA assessment

MRS data were collected at a 3 Tesla scanner (Siemens, Erlangen). Metabolites in the magnetic resonance spectrum were quantified immediately after acquisition of a high resolution T1 structural image using 3Tesla 1-H-MRS [point resolved spectroscopy (PRESS), 128/8 averages, 90° flip angle, TE = 80ms, TR = 3 sec., automatic shimming, 128/8 spectra with and without water suppression, respectively]. The Linear

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Combination of Model spectra commercial spectral fitting package (LCModel; Provencher, 1993; Göttingen, Germany) was utilized to analyze MRS data. For estimation of NAA concentration within the ACC voxel, we used a threshold of <=20% for CramérRao lower bounds.

A 20 x 30 x 25mm voxel was placed individually in the ACC (see Fig. 1). The voxel was positioned above the anterior portion of the corpus callosum with the anterior boundary of the box ending at the orthogonal of the genu of the corpus callosum and therefore cut across both hemispheres.

To correct for individual differences in GM, WM and CSF fractions within the MRS voxel, absolute NAA concentrations were transformed via the formula: NAA adjusted = (NAA absolute*(1/GM+WM)). Adjusted NAA concentrations are expressed in mmol/l, however only Z-standardized values were used for statistical analysis. For quantification of GM, WM and CSF, we used the unified segmentation approach of SPM8 and extracted voxelspecific fractions of GM, WM and CSF using python scripts (Python Software Foundation. Python Language Reference. Available at: "http://www.python.org/").

Fig. 1. Position of the anterior cingulate cortex (ACC) in human brain, where spectroscopy of N-acetylaspartate (NAA) was measured.
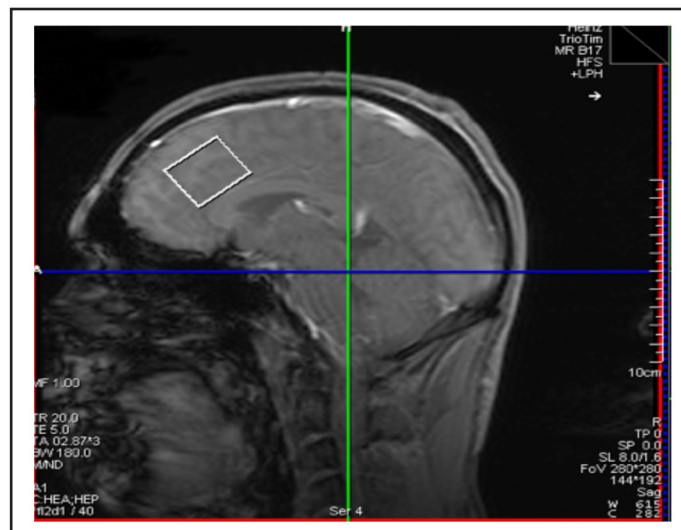
Statistical analysis

After testing for normality distribution (one-sample Kolmogorov-Smirnov-test), repeated measures general linear models were used to detect variations in BDNF and NAA as well as HAMD and BDI scores over the time course of six weeks of medication (with T0, T2, T4, and T6 as four time points) compared to healthy controls (between subject factors). Age and sex were entered as covariates of no interest.

Paired t-tests were computed to specify the observed effects over time points within groups. Independent t-tests were computed to detect differences between groups.

To relate response and remission with early serum BDNF levels, we used a univariate ANCOVA model (controlling for age and sex) with response and remission as separate factors and BDNF as dependent variable. Response was defined as a 50% improvement in the HAMD after eight weeks of treatment. Remission was defined as a Hamilton score of ≤ 8 after eight weeks of treatment.

Pearson correlations were calculated to detect associations between clinical indicators and biomarkers as well as associations in between HAMD and BDI and BDNF and NAA.

All calculations were conducted using Statistical Package of the Social Sciences (SPSS 17.0).

Results

Demographic data and clinical indicators

As shown in table 1, the groups of patients and healthy controls were comparable in demographic features. The proportions of male and female depressed patients corresponded to the reported incidence of major depression in the population [43]. Only the smoking status differed noticeable (17% smokers in healthy controls vs. 60% smokers in patients).

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Although, Pearson correlations between possible confound variables like smoking and body weight/BMI and BDNF/NAA-concentrations were not significant in either group ($p > .05$). The most frequently used antidepressants in our study were escitalopram and citalopram (50.0%) and 59.2% of the antidepressants were serotonine reuptake inhibitors.

Table 1. Demographic indicators of depressed patients and healthy controls

	Patients (n = 76)	Healthy controls (n = 41)
Gender		
male	29 (38.2%)	16 (39%)
female	47 (61.8%)	25 (61%)
Age		
years (SD/range)	39.05±11.127/39	36.56±15.2/45
BMI (SD)	27.16±9.39	24.54±5.097
Smoking status		
yes	60.6%	17.5%
no	39.4%	82.5%
Type of antidepressant		
escitalopram (SSRI)	42.1%	-
citalopram (SSRI)	7.9%	-
fluoxetine (SSRI)	2.6%	-
paroxetine (SSRI)	1.3%	-
sertraline (SSRI)	5.3%	-
trevilor/venlafaxin (SNRI)	14.5%	-
elontril (NDI)	11.8%	-
mirtazapine (NaSSA)	9.2%	-
lithium (augmented)	5.3%	-
School level		
secondary school	11.8%	4.9%
junior high school	30.9%	12.2%
high school	55.9%	82.9%
others	1.5%	-
Education		
no graduation	16.4%	22%
apprenticeship	53.7%	29.3%
university	26.9%	48.8%
PhD	3%	-
Employment situation		
employed	42.0%	39%
unemployed	29.0%	2.4%
students	15.9%	43.9%
housewife	1.4%	-
retired	1.4%	7.3%
other	7.2%	7.3%
Family status		
partnership	40.6%	66.7%
no partnership	59.4%	33.3%
Socio-economic level		
monthly income of more than 80%	1000–2000 € (87.9%)	1000–2000 € (80%)

In the self-report of depressive symptoms (BDI), scores declined significantly over the time course of antidepressant treatment of six and eight weeks (Fig. 2): $t(51)_{T0T6}$: 6.836 $p <$ .001; $t(43)_{T0T8}$=6.625, $p < .001$. In our sample we had 61.9% BDI responders with at least

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20% score decline at T4, 67.3% BDI responders with at least 20% score decline at T6, 44.2% BDI responders with at least 50% score decline at T6 and 51.2% BDI responders with at least 50% score decline at T8.

Whereas the BDI score declined in patients, there was no change in BDI scores in the healthy volunteers, which was stated by a significant interaction of *time and diagnose* of BDI scores in a repeated measures model (F(87) = 36.195, *p* = .000). Healthy controls showed no critical BDI score compared to patients and the scores of depressed and healthy subjects differed significantly at both time points (t$(108)_{T0}$ = 17.800 *p* < .001; t$(89)_{T6}$ = 6.844, *p* < .001).

Patients response to antidepressant medication is reflected by the HAMD scores as well with HAMD scores declining over the time course of therapy and study time (Fig. 2). In the depressed sample, there was a significant effect of *time* in HAMD score reduction after eight weeks of treatment (F(25) = 6.952, *p* <.001) and a significant difference in HAMD scores could be detected when comparing HAMD baseline with HAMD scores after six (t$(61)_{T0T6}$ = 14.047 *p* < .001) and eight weeks of antidepressant treatment (t$(52)_{T0T8}$ = 11.756 *p* < .001). Specifically, we had 47.9% responders (HAMD ≤ 50%) after four, 58.7% responders after six and 59.3% responders after eight weeks of treatment, of which 56.6% reached remission, which was defined as HAMD$_{T8}$ ≤ 8. There were no gender differences in HAMD and BDI scores over time (HAMD$_{T0T8}$ *p* = .773, BDI$_{T0T8}$ *p* = .409), nor at a single time point (HAM$_{T6}$ *p* = .364; HAM$_{T8}$ *p* = .115). Finally HAMD and BDI scores correlated significantly at any time point of the study ($r(67)_{T0}$ = .419**, $r(42)_{T8}$ = .841*).

Fig. 2. Scores of Hamilton Depression Rating Scale (HAMD) and Beck´s Depression Inventory (BDI) during time course of the study for depressed patients and healthy controls.
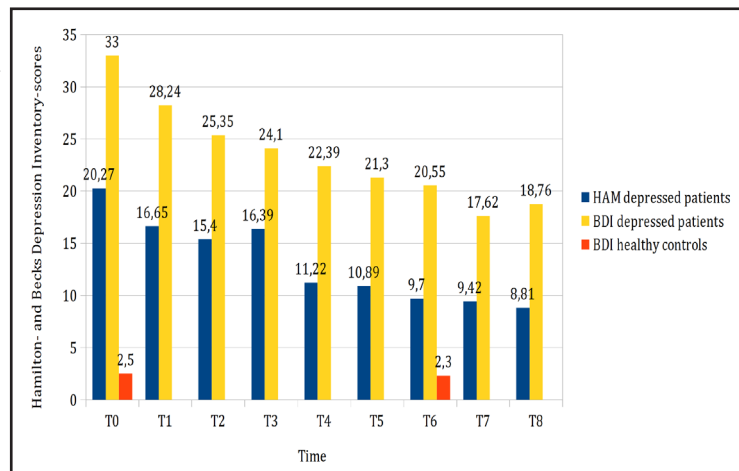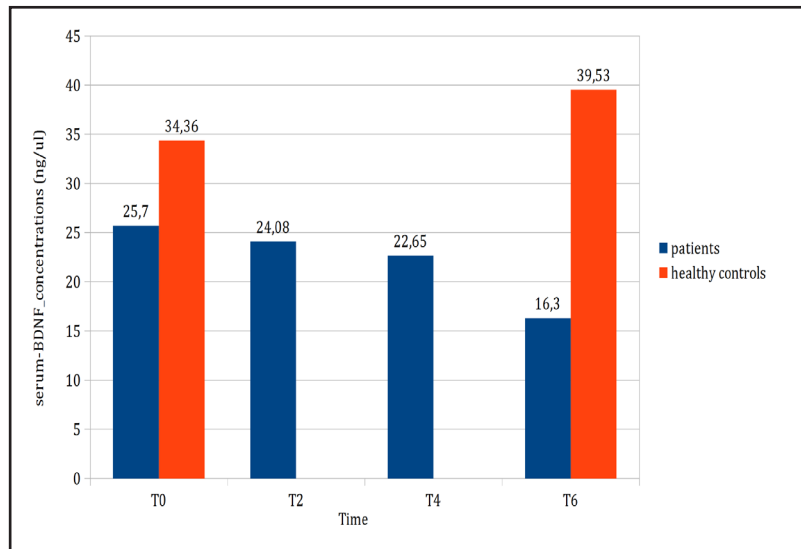

BDNF

In a repeated measures general linear model investigating serum BDNF variations before and after six weeks as dependent variable (T0-T6) and controlling for age and sex, *time* was a significant factor (F(59) = 7,441, *p* = .008), as well as the interaction of *time and diagnose* (BDNF$_{patients}$ < BDNF$_{controls}$: F(59) = 6.179, *p* = .016); moreover we found a significant interaction of *time and age* (F(59) = 4.816 *p* = .032). Pearson correlations revealed that a single significant positive association between age and serum BDNF ($r(38)$ = .390*) in the healthy controls at baseline (T0) accounted for this result, whereas there was no more association at T6 in this group and no association between age and serum BDNF in the depressed patients to either time point.

Descriptive statistics showed decreasing serum BDNF concentrations in the depressed sample, whereas in the control sample there was a slight (*p* < .05) increase (Fig. 3). In depressed patients paired t-Tests showed no statistical significant deviations in serum BDNF between baseline and week four of medication (p_{T0T4} > .05), but a significant decrease in serum BDNF concentrations between baseline and week six (t$(26)_{T0T6}$ = 2.435, *p* = .022). Serum BDNF in

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Fig. 3. Brain derived neurotrophic factor-concentrations (ng/ul) of patients and healthy controls in time course of the study.


healthy controls did not differ between the two time points ($p_{T0T6} > .05$). Independent t-tests revealed statistically significant differences between patients and controls serum BDNF at both time points (t(108)$_{T0}$ = 3.333, p = .001; t(62)$_{T6}$ = 7.926, p = .000).

BDNF and clinical symptoms

Pearson correlations did not show a consistent association between BDNF and clinical symptoms on HAMD and BDI ($p > .05$).

We split the depressed sample into "responder" (≤ 50%) and "remitter", the group of patients who had a reduction of 50% in HAMD rating between T0 and T8 ("responders" (T8 ≤ 50%), respectively, who had a HAMD-score of 8 or less ("remitters" = HAMD ≤ 8). Depressed patients who did not achieve this reduction in HAMD ratings were in the non-responder/non-remitter group. When we computed a univariate ANCOVA comparing these responder/remitter groups to non-responders/remitters, controlling for age and sex, we found a significant difference between these two groups at baseline (T0). As shown in Figure 4, the remitter/responder had significant lower serum BDNF concentrations at baseline (T0) than non-responder and non-remitter (F(44)$_{remisson}$ = 7.619, p = .008; F(45)$_{respond}$ = 6.403, p = .015). These findings remained significant after applying Bonferroni correction for multiple testing (p < .025).

In making the same calculation with BDI responders (BDI ≤ 50% at T8), we found the same but non-significant pattern of lower serum BDNF at baseline in the BDI-responder group compared to the non-responder group.
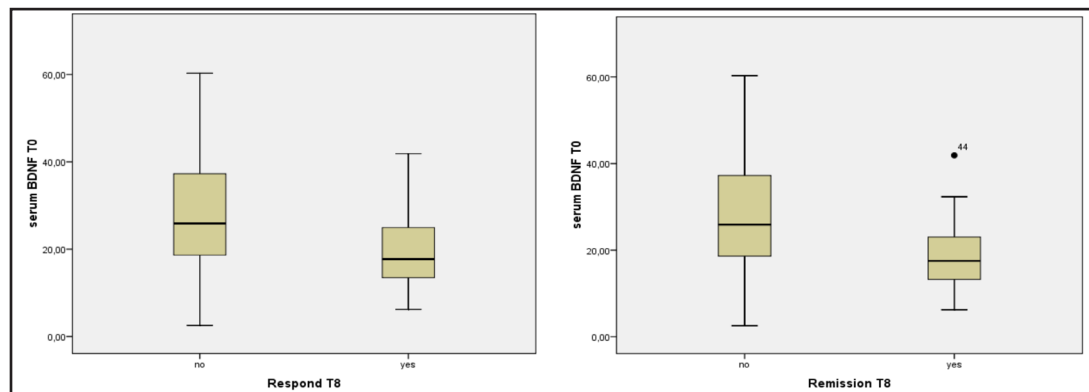
Fig. 4. Responder and remitter have lower serum Brain derived neurotrophic factor-concentrations at baseline (T0) than non-responder/remitter.

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NAA

Although descriptive statistics showed lower NAA concentrations in depressed patients compared to controls at baseline (Fig. 5), independent t-tests only show a statistical trend ($t(52)_{T0} = 1.855$, $p = .069$). While NAA increases in the depressed group, it decreases in the control group, but paired t-test display no significant differences between the two time points in either group (patients, NAA_{T0T6}: $p > .05$; control NAA_{T0_T6}: $p > .05$) and independent t-tests show no difference at T6 of NAA between the two groups.

A general linear model (repeated measures) with NAA variations as the dependent variable and sex and age as covariates displayed no effect of time nor of group and time interaction ($p > .05$), i.e. NAA does not significantly change in the time course of six weeks of medical treatment.

We did not find associations between NAA and serum BDNF, neither between NAA and clinical symptom measures (HAMD/BDI) at the same time points.

Referring to figure 4, though not significant, when controlling for age and sex, univariate ANCOVAs showed the same tendency of lower NAA at baseline in the HAMD responder/ remitter compared to the non-responder/remitter. The same tendency was shown for baseline NAA being decreased in BDI responders (BDI ≤ 50%), with tendency to significance at T6 ($F(7) = 4.634$; $p = .068$).

Fig. 5. N-acetylaspartate-concentrations at baseline and after six weeks for patients and healthy controls.
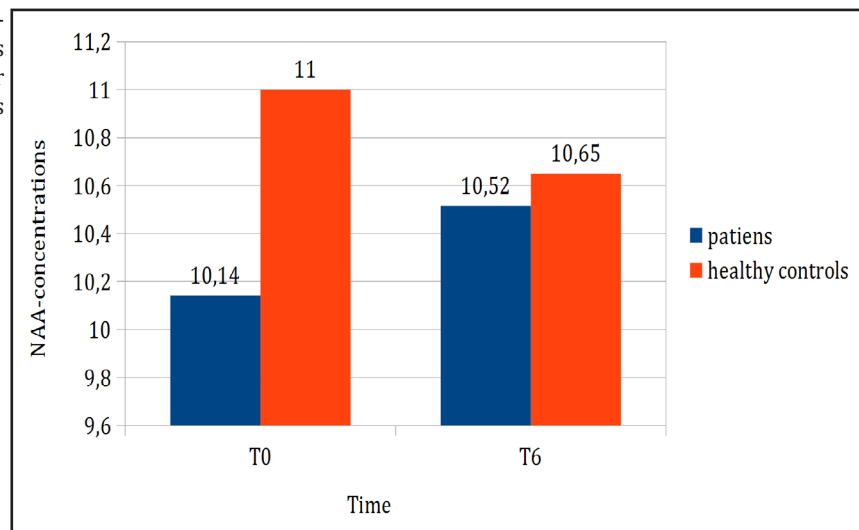
Discussion

In the present study, we examined prospectively the role of serum BDNF and central NAA during initial antidepressant medication, respectively change of antidepressant, in patients with a major depression over a time course of six weeks.

Our results confirm our first hypothesis that BDNF is significantly lower in depressed patients compared with healthy controls. This finding has been demonstrated in previous research and thus we can suppose that low peripheral BDNF is a biomarker of depressive disorders [44].

We found no variations in serum BDNF after four and a decrease in serum BDNF after six weeks of antidepressant treatment. A significant decrease of psychopathological symptoms in the HAMD and the BDI scores at the end of the study was detected. This findings did not support our second hypothesis since we did not find an increase of serum BDNF in association with a positive treatment response or remission of depression. However, we found that a low BDNF level at baseline (T0) predicts response to treatment, which confirms

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the suggestion that low serum BDNF is a precondition for clinical amelioration in response to antidepressant treatment. Additionally, in our study, baseline BDNF in BDI responders compared to non-responders was consistently lower, but did not reach significance. This was also the case for baseline NAA, which was lower in HAMD/BDI responders/remitters. Thus, in our sample, there is a pattern of lower biological markers at baseline being associated with subsequent clinical response. Similarly, Ricken et al. [45] found that low BDNF levels predicted a lithium response. Other studies did not show any difference in baseline BDNF between responders or remitters but instead an early serum BDNF rise, which predicted response or remission [16, 21, 46].

However, in our sample, BDNF values did not change and even decreased after six weeks of antidepressant treatment. Although contrary to the neurotrophin hypothesis, this is in line with several recent studies that do not show a BDNF increase over the course of antidepressant treatment and other studies that also reported a clinical response to treatment without BDNF increase [18, 22] or BDNF variations, independent of continuous application of antidepressants [47-49]. Our results were found while controlling for age and sex. Furthermore, we neither found significant associations between serum BDNF concentrations/NAA concentrations and body weight/BMI or smoking (Pearson correlations $p > .05$), which have been previously reported to affect peripheral BDNF levels [50-52]. Taken together, our results suggest that reduced BDNF might be a precondition to response to antidepressive medication rather than its consecutive change directly parallels clinical symptoms.

In contrast to most studies that assess BDNF in an acute state or for a few weeks under medication, there are some studies that argue that low peripheral BDNF might be associated with a chronic rather than an initial depressive state [24, 47]. Bus et al. [47] showed that over two years, serum BDNF persistently decreased in a group of depressed patients independently of remission and antidepressant treatment. Furthermore, in this depressed group, they found a steeper serum BDNF decrease compared to healthy controls and initially depressed subjects. Hence it has been suggested that BDNF may not only be crucial in the development of depression but that depression may contribute to low BDNF even in a remitted state. Furthermore, in neuroimaging studies, neuronal atrophies are rather found in episodic and chronic than in first episode depression [53, 54] which is supposed to be due to the toxic impact of glucocorticoid hyperactivation caused by chronic stress [55]. This evidence suggests that, mediated by the toxic impact of cortisol/glucocorticoides on depression-related brain regions, only chronic stress might lead to a downregulation of BDNF and finally contributes to depression development and its maintenance. This guided us to two speculations: First, BDNF increase may occur over longer periods of time and more likely as a consequence of symptom amelioration and may not be necessary for primary response and remission, even if some antidepressants do affect BDNF concentrations [56, 57]. According to Duman [58], the observed serum BDNF decrease could reflect a latency in the synthesis process of BDNF. Secondly, the initial antidepressant effect on neuroplasticity may be reduced with long term administration [47]. Since in our sample most of the patients had a history of antidepressive treatment (77%), this may have affected their BDNF response to medication, which could reflect a potential tolerance to the neuroplasticity effect of antidepressants like Bus et al. [47] speculate.

As mentioned above, it has also been suggested that BDNF may not only be crucial in the development of depression but that depression may contribute to low BDNF even in a remitted state. Since more than half of the patients (53.9%) in our sample had a history of episodic or chronic depression, this could account for our finding of a further decreasing serum BDNF in the time course of antidepressant medication independently of response or remission. In regard to trait depression, Lang et al. [59] as well as Terracciano et al. [60] found that mentally healthy subjects with depressive personality traits have lower serum BDNF concentrations than subjects without these personality traits. Moreover, female patients were over-represented in our sample (61.8%), which might account for our finding that

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disease duration is associated with decreased BDNF levels as shown before by de Azevedo Cardoso et al. [61].

The heterogeneity of prescribed antidepressants in our sample could be another explanation of our results. The most frequently used antidepressants in our study were escitalopram/citalopram (50.0%). Escitalopram and citalopram (SSRIs) have been shown not to increase BDNF specifically [23]. With 14.5%, venlafaxine (SNRI) was the secondly most often given antidepressant in our sample. Deuschle et al. [48] found a serum BDNF decrease in venlafaxine treated patients, but a serum BDNF increase in mirtazapine (NaSSA) treated responders. Miro et al. [62] and Dias et al. [63] also found a BDNF downregulation after two weeks of fluoxetine (SSRI) treatment. Therefore, one might argue that the observed BDNF non-increase/decrease might be a specific phenomenon of SSRIs and SNRIs in contrast to other antidepressants. Indeed, other studies found that other antidepressant treatment strategies as serotonergic modulators increase BDNF concentrations, i.e. lithium [45] and antipsychotic medications [64]. Another hypothesis has been published recently by Vasquez et al. [65] who argue that chronic stress induces NMDA receptor stimulation, leading to changed calcium signaling and BDNF downregulation. According to this model, NMDA receptor antagonists should increase BDNF more effectively than conventional antidepressants.

There was no association of NAA with clinical symptoms and response. NAA quantitatively increased over the time course of six weeks of antidepressant treatment, which is in line with our second hypothesis. Though NAA is regarded as a biomarker of neuroplasticity and is assumed to be associated with depressive symptoms, we failed to show a significant difference in NAA concentrations between depressed patients and healthy controls (p = .069). We suppose that this might be due to the small sample size of depressed patients (n = 15). Additionally, we measured NAA in the ACC, whereas the literature suggests that hippocampal NAA action might be more important for depression than NAA variations in the ACC [66, 67].

There are several limitations to the present study. First of all, we had a high drop-out rate during the study, which is due to the fact that the time period of eight weeks of data assessment was quite long for the patients. Therefore, the sizes of subgroups were different. Patients and healthy control sample sizes were due to time limitations (3 years). Moreover, the observation period was possibly too short to show BDNF serum recovery. Finally, NAA changes might be rather expected in the hippocampus than in the ACC.

In future studies, a longer evaluation period might highlight if the studied biomarkers actually change with depression remission or are more likely associated with stable characteristics of depressed patients. Moreover, since there is evidence that the Val/Met-polymorphism in healthy subjects influence the BDNF-concentrations [37, 68], it might also be useful to take genetic variations in account, when exploring human BDNF.

In conclusion, our results support the assumption that changes of biological markers like BDNF and NAA are not necessary preconditions for recovery and symptom reduction. In turn, our results suggest that reduced BDNF might be a precondition to response to antidepressive medication rather than its consecutive change directly parallels clinical symptoms. BDNF serum concentration may also selectively react to specific antidepressant treatments and not to the clinical treatment per se. However, if our result can be reproduced over longer time periods and in larger samples, BDNF might be considered a reliable predictor of antidepressant response independent of the class of antidepressant used.

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Disclosure Statement

References

1   Brunoni AR, Lopes M, Fregni F: A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int J Neuropsychopharmacol 2008;11:1169-1180.

2   Hashimoto K: Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. Psychiatry Clin Neurosci 2010;64:341-357.

3   Stein DJ, Daniels WM, Savitz J, Harvey BH: Brain-derived neurotrophic factor: the neurotrophin hypothesis of psychopathology. CNS Spectr 2008;13:945-949.

4   Drevets W, Price JL & Furey ML: Brain structural and functional abnormalities in mood disorders: Implications for neurocircuitry models of depression. Brain Struct Funct 2008;213:93-118.

5   Macqueen G, Yucel K, Taylor VH, Macdonald K, Joffe R: Posterior hippocampal volumes are associated with remission rates in patients with major depressive disorder. Biol Psychiatry 2008;64:880–883.

6   Belmaker RH, Agam G: Major depressive disorder. N Engl J Med 2008;358:55-68.

7   Aydemir C, Yalcin ES, Aksaray S, Kisa C, Yildirim SG, Uzbay T, Goka E: Brain-derived neurotrophic factor (BDNF) changes in the serum of depressed women. Prog Neuropsychopharmacol Biol Psychiatry 2006;30;1256-1260.

8   Aydemir O, Deveci A, Taskin OE, Taneli F, Esen-Danaci A: Serum brain-derived neurotrophic factor level in dysthymia: a comparative study with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1023-1026.

9   Gervasoni N, Aubry JM, Bondolfi G, Osiek C, Schwald M, Bertschy G, Karege F: Partial normalization of serum brain-derived neurotrophic factor in remitted patients after a major depressive episode. Neuropsychobiology 2005;51:234-238.

10   Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S: 2005. Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci 255, 381-386.

11   Groves JO, 2007. Is it time to reassess the BDNF hypothesis of depression? Mol Psychiatry 2007;12:1079-1088.

12   Huang TL, Lee CT, Liu L: Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. J Psychiatr Res 2008;42:521-525.

13   Martocchia A, Curto M, Scaccianoce S, Comite F, Xenos D, Nasca C, Falaschi GM, Ferracuti S, Girardi P, Nicoletti F, Falaschi P: Effects of escitalopram on serum BDNF levels in elderly patients with depression: a preliminary report. Aging Clin Exp Res 2014;26:461-464.

14   Neto FL, Borges G, Torres-Sanchez S, Mico JA, Berrocoso E: Neurotrophins role in depression neurobiology: a review of basic and clinical evidence. Curr Neuropharmacol 2011;9:530-552.

15   Piccinni A, Marazziti D, Catena M, Domenici L, Del Debbio A, Bianchi C, Mannari C, Martini C, Da Pozzo E, Schiavi E, Mariotti A, Roncaglia I, Palla A, Consoli G, Giovannini L, Massimetti G, Dell'Osso L: Plasma and serum brain-derived neurotrophic factor (BDNF) in depressed patients during 1 year of antidepressant treatments. J Affect Disord 2008;105:279-283.

16   Yoshimura R, Mitoma M, Sugita A, Hori H, Okamoto T, Umene W, Ueda N, Nakamura J: Effects of paroxetine or milnacipran on serum brain-derived neurotrophic factor in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1034-1037.

17   Birkenhager TK, Geldermans S, Van den Broek WW, van Beveren N, Fekkes D: Serum brain-derived neurotrophic factor level in relation to illness severity and episode duration in patients with major depression. J Psychiatr Res 2012;46:285-289.

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www.karger.com/nsg

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Nase et al.: BDNF and NAA in Treatment of Depression

18   Brunoni AR, Machado-Vieira R, Zarate CA Jr, Vieira EL, Vanderhasselt MA, Nitsche MA, Valiengo L, Bensenor IM, Lotufo PA, Gattaz WF, Teixeira AL: BDNF plasma levels after antidepressant treatment with sertraline and transcranial direct current stimulation: results from a factorial, randomized, sham-controlled trial. Eur Neuropsychopharmacol 2014;24:1144-1151.

19   Jevtovic S, Karlovic D, Mihaljevic-Peles A, Seric V, Vrkic N, Jaksic N: Serum Brain-derived neurotrophic factor (BDNF): the severity and symptomatic dimensions of depression. Psychiatr Danub 2011;23:363-369.

20   Ladea M, Bran M: Brain derived neurotrophic factor (BDNF) levels in depressed women treated with open-label escitalopram. Psychiatr Danub 2013;25:128-132.

21   Yoshimura R, Kishi T, Hori H, Katsuki A, Sugita-Ikenouchi A, Umene-Nakano W, Atake K, Iwata N, Nakamura J: Serum Levels of Brain-Derived Neurotrophic Factor at 4 Weeks and Response to Treatment with SSRIs. Psychiatry Investig 2014;11:84-88.

22   Basterzi AD, Yazici K, Aslan E, Delialioglu N, Tasdelen B, Tot Acar S, Yazici A: Effects of fluoxetine and venlafaxine on serum brain derived neurotrophic factor levels in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 32009;3:281-285.

23   Matrisciano F, Bonaccorso S, Ricciardi A, Scaccianoce S, Panaccione I, Wang L, Ruberto A, Tatarelli R, Nicoletti F, Girardi P, Shelton RC: Changes in BDNF serum levels in patients with major depression disorder (MDD) after 6 months treatment with sertraline, escitalopram, or venlafaxine. J Psychiatr Res 2009;43:247-254.

24   Molendijk ML, Spinhoven P, Polak M, Bus BA, Penninx BW, Elzinga BM: Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N=9484). Mol Psychiatry 2014;19:791-800.

25   Pallavi P, Sagar R, Mehta M, Sharma S, Subramanium A, Shamshi F, Sengupta U, Qadri R, Pandey RM, Mukhopadhyay AK: Serum neurotrophic factors in adolescent depression: gender difference and correlation with clinical severity. J Affect Disord 2013;150:415-423.

26   van der Meij A, Comijs HC, Dols A, Janzing JG, Oude Voshaar RC: BDNF in late-life depression: effect of SSRI usage and interaction with childhood abuse. Psychoneuroendocrinology 2014;43:81-89.

27   Campbell S, Macqueen G: The role of the hippocampus in the pathophysiology of major depression. J Psychiatry Neurosci 2004;29:417-426.

28   Bush G, Luu P, Posner MI: Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 2000;4:215-222.

29   Decety J, Jackson PL: The functional architecture of human empathy. Behav Cogn Neurosci Rev 2004;3:71-100.

30   Jackson PL, Brunet E, Meltzoff AN, Decety J: Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 2006;44:752-761.

31   Duman RS, Monteggia LM: A neurotrophic model for stress-related mood disorders. Biol Psychiatry 2006;59:1116-1127.

32   Aydin K, Ciftci K, Terzibasioglu E, Ozkan M, Demirtas A, Sencer S, Minareci O: Quantitative proton MR spectroscopic findings of cortical reorganization in the auditory cortex of musicians. AJNR Am J Neuroradiol 2005;26:128-136.

33   Yildiz-Yeşiloğlu A, Ankerst DP: Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: a systematic review of the *in vivo* proton magnetic resonance spectroscopy findings. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:969–995.

34   Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM: N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. Prog Neurobiol 2007;81:89-131.

35   Kraguljac NV, Reid M, White D, Jones R, den Hollander J, Lowman D, Lahti AC: Neurometabolites in schizophrenia and bipolar disorder – a systematic review and meta-analysis. Psychiatry Res 2013;203:111-125.

36   Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR: The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;112:257-269.

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Neurosignals 2016;24:1-14

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www.karger.com/nsg

13

Nase et al.: BDNF and NAA in Treatment of Depression

37 Gallinat J, Schubert F, Bruhl R, Hellweg R, Klar AA, Kehrer C, Wirth C, Sander T, Lang UE: Met carriers of BDNF Val66Met genotype show increased N-acetylaspartate concentration in the anterior cingulate cortex. Neuroimage 2010;49:767-771.

38 Lang, UE, Hellweg R, Seifert F, Schubert F, Gallinat J: Correlation between serum brain-derived neurotrophic factor level and an in vivo marker of cortical integrity. Biol Psychiatry 2007;62:530-535.

39 Rist F, Scheuren B, Demmel R, Hagen J, Aulhorn I: Der Münsterer alcohol use disorders identification test (AUDIT-G-M); in Glöckner-Rist A, Rist F, Küfner H (eds): Elektronisches Handbuch zu Erhebungsinstrumenten im Suchtbereich (EHES) 2003, 3.00. Mannheim: Zentrum für Umfragen, Methoden und Analysen.

40 Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.

41 Hautzinger M, Keller F, Kühner C: Beck Depression-Inventar (BDI II). Revision. Harcourt Test Services 2006, Frankfurt/Main.

42 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC: 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:S22-33;quiz 34-57.

43 Robert Koch-Institut (Hrsg): Depression. Faktenblatt zu GEDA 2012: Ergebnisse der Studie »Gesundheit in Deutschland aktuell 2012«. RKI, Berlin 2014. www.rki.de/geda.

44 Hashimoto K: Brain-derived neurotrophic factor (BDNF) and its precursor proBDNF as diagnostic biomarkers for major depressive disorder and bipolar disorder. Eur Arch Psychiatry Clin Neurosci 2015;265:83-84.

45 Ricken R, Adli M, Lange C, Krusche E, Stamm TJ, Gaus S, Koehler S, Nase S, Bschor T, Richter C, Steinacher B, Heinz A, Rapp MA, Borgwardt S, Hellweg R, Lang UE: Brain-derived neurotrophic factor serum concentrations in acute depressive patients increase during lithium augmentation of antidepressants. J Clin Psychopharmacol 2913;33:806-809.

46 Tadic A, Wagner S, Schlicht KF, Peetz D, Borysenko L, Dreimuller N, Hiemke C, Lieb K: The early non-increase of serum BDNF predicts failure of antidepressant treatment in patients with major depression: a pilot study. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:415-420.

47 Bus BA, Molendijk ML, Tendolkar I, Penninx BW, Prickaerts J, Elzinga BM, Voshaar RC: Chronic depression is associated with a pronounced decrease in serum brain-derived neurotrophic factor over time. Mol Psychiatry 2015;20:602-608.

48 Deuschle M, Gilles M, Scharnholz B, Lederbogen F, Lang UE, Hellweg R: Changes of serum concentrations of brain-derived neurotrophic factor (BDNF) during treatment with venlafaxine and mirtazapine: role of medication and response to treatment. Pharmacopsychiatry 2013;46:54-58.

49 Mikoteit T, Beck J, Eckert A, Hemmeter U, Brand S, Bischof R, Holsboer-Trachsler E, Delini-Stula A: High baseline BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression. Psychopharmacology (Berl) 2014;231:2955-2965.

50 Bhang SY, Choi SW, Ahn JH: Changes in plasma brain-derived neurotrophic factor levels in smokers after smoking cessation. Neurosci Lett 2010;468:7-11.

51 Lommatzsch M, Zingler D, Schuhbaeck K, Schloetcke K, Zingler C, Schuff-Werner P, Virchow JC:The impact of age, weight and gender on BDNF levels in human platelets and plasma. Neurobiol Aging 2005;26:115-123.

52 Míguez-Burbano MJ, Luis Espinoza L, Vargas M, LaForest D: Mood Disorders and BDNF Relationship with Alcohol Drinking Trajectories among PLWH Receiving Care. J Alcohol Drug Depend 2014;2:148.

53 MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, Nahmias C, Young LT: Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci U S A 2003;100:1387-1392.

54 McKinnon MC, Yucel K, Nazarov A, MacQueen GM: A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. J Psychiatry Neurosci 2009;34:41-54.

55 Aan het Rot M, Mathew SJ, Charney DS: Neurobiological mechanisms in major depressive disorder. CMAJ 2009;180:305-313.

56 Calabrese F, Molteni R, Racagni G, Riva MA: Neuronal plasticity: a link between stress and mood disorders. Psychoneuroendocrinology 2009;1:S208-216.

KARGER

Neurosignals 2016;24:1-14

DOI: 10.1159/000442607
Published online: February 01, 2016

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www.karger.com/nsg

14

Nase et al.: BDNF and NAA in Treatment of Depression

57 Yulug B, Ozan E, Gonul AS, Kilic E: Brain-derived neurotrophic factor, stress and depression: a minireview. Brain Res Bull 2009;78:267-269.

58 Duman RS: Role of neurotrophic factors in the etiology and treatment of mood disorders. Neuromolecular Med 2004;5:11-25.

59 Lang UE, Hellweg R, Gallinat J: BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits. Neuropsychopharmacology 2004;29:795-798.

60 Terracciano A, Lobina M, Piras MG, Mulas A, Cannas A, Meirelles O, Sutin AR, Zonderman AB, Uda M, Crisponi L, Schlessinger D: Neuroticism, depressive symptoms, and serum BDNF. Psychosom Med 2011;73:638-642.

61 de Azevedo Cardoso T, Mondin TC, Wiener CD, Marques MB, Fucolo Bde A, Pinheiro RT, de Souza LD, da Silva RA, Jansen K, Oses JP: Neurotrophic factors, clinical features and gender differences in depression. Neurochem Res 2014;39:1571-1578.

62 Miro X, Perez-Torres S, Artigas F, Puigdomenech P, Palacios JM, Mengod G: Regulation of cAMP phosphodiesterase mRNAs expression in rat brain by acute and chronic fluoxetine treatment. An in situ hybridization study. Neuropharmacology 2002;43:1148-1157.

63 Dias BG, Banerjee SB, Duman RS, Vaidya VA: Differential regulation of brain derived neurotrophic factor transcripts by antidepressant treatments in the adult rat brain. Neuropharmacology 2003;45:553-563.

64 Lee AH, Lange C, Ricken R, Hellweg R, Lang UE: Reduced brain-derived neurotrophic factor serum concentrations in acute schizophrenic patients increase during antipsychotic treatment. J Clin Psychopharmacol 2011;31:334-336.

65 Vasquez CE, Riener R, Reynolds E, Britton GB: NMDA receptor dysregulation in chronic state: a possible mechanism underlying depression with BDNF downregulation. Neurochem Int 2014;79:88-97.

66 Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R: Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003;301:805-809.

67 Surget A, Saxe M, Leman S, Ibarguen-Vargas Y, Chalon S, Griebel G, Hen R, Belzung C: Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. Biol Psychiatry 2008;64:293-301.

68 Lang UE, Hellweg R, Kalus P, Bajbouj M, Lenzen KP, Sander T, Kunz D, Gallinat J: Association of a functional BDNF polymorphism and anxiety-related personality traits. Psychopharmacology (Berl) 2005;180:95-99.

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