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ORIGINAL INVESTIGATION

High baseline BDNF serum levels and early psychopathological improvement are predictive of treatment outcome in major depression

Thorsten Mikoteit · Johannes Beck · Anne Eckert · Ulrich Hemmeter · Serge Brand · Roland Bischof · Edith Holsboer-Trachsler · Alexandra Delini-Stula

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Abstract
Rationale Major depressive disorder has been associated with low serum levels of brain-derived neurotrophic factor (sBDNF), which is functionally involved in neuroplasticity. Although sBDNF levels tend to normalize following psychopathological improvement with antidepressant treatment, it is unclear how closely sBDNF changes are associated with treatment outcome.
Objectives To examine whether baseline sBDNF or early changes in sBDNF are predictive of response to therapy.
Methods Twenty-five patients with major depressive disorder underwent standardized treatment with duloxetine. Severity of depression, measured by the Hamilton Depression Rating Scale, and sBDNF were assessed at baseline, and after 1, 2, and 6 weeks of treatment. Therapy outcome after 6 weeks was defined as response (≥50 % reduction in baseline Hamilton Depression Rating score) and remission (Hamilton Depression Rating score <8). The predictive values for treatment outcome of baseline sBDNF, and early (i.e., ≤2 weeks) changes in sBDNF and Hamilton Depression Rating score were also assessed.
Results At baseline, sBDNF correlated with Hamilton Depression Rating scores. Treatment response was associated with a higher baseline sBDNF concentration, and a greater Hamilton Depression Rating score reduction after 1 and 2 weeks. A greater early rise in sBDNF correlated with a decreased early Hamilton Depression Rating score reduction.
Conclusions Even though higher baseline sBDNF levels are associated with more severe depression, they may reflect an increased capacity to respond to treatment. In contrast, changes in sBDNF over the full course of treatment are not associated with psychopathological improvement.

Keywords Brain-derived neurotrophic factor (BDNF) · Serum · Depression · Treatment outcome · Early response · Response · Remission · Antidepressants · Serotonin norepinephrine reuptake inhibitor (SNRI) · Duloxetine

Thorsten Mikoteit and Johannes Beck contributed to this paper equally

T. Mikoteit (✉) · J. Beck · S. Brand · E. Holsboer-Trachsler
Center for Affective, Stress and Sleep Disorders (ZASS), Psychiatric Clinics of the University of Basel, Wilhelm Klein-Strasse 27, 4012 Basel, Switzerland
e-mail: thorsten.mikoteit@upkbs.ch

A. Eckert
Neurobiology Laboratory for Brain Aging and Mental Health, Psychiatric Clinics of the University of Basel, Basel, Switzerland

U. Hemmeter
Center of Education and Research (COEUR), Psychiatric Service Canton of St. Gallen, Wil, St. Gallen, Switzerland

R. Bischof · A. Delini-Stula
ADI International Institute for Advancement of Drug Development GmbH, Basel, Switzerland

Introduction

Brain-derived neurotrophic factor (BDNF) is one of a family of neurotrophins, located in the brain and peripheral tissues, playing an essential role in neuronal cell differentiation, growth, and survival (Hallbook 1999). Serum and plasma BDNF (s/pBDNF) levels are associated with functional and efficient neuronal functioning. Lower s/pBDNF levels have been observed in patients with major depressive disorders. Duman and Monteggia (2006) posited that a deficit in s/pBDNF in cases of major depressive disorders (MDD) is associated with increased stress, psychopathology, and impaired neuroplasticity.

Lower concentrations of sBDNF in depression, initially observed by Karege et al. (2005), have since been replicated

in several other studies (see reviews by Sen et al. 2008, and Bocchio-Chiavetto et al. 2010). Although the studies vary in design, sample size, and BDNF analysis, the association between MDD and lower BDNF levels is quite consistent. Despite the numerous replications of this link, the relationship between changes in BDNF levels and treatment outcome in patients with MDD are more inconsistent (Aydemir et al. (2006), Brunoni et al. (2008), Gervasoni et al. (2005), Kim et al. (2007), Shimizu et al. (2003), Yoshimura et al. (2007), and Huang et al. (2008)). All reported correlations between BDNF level increases and reduced depression, though methodological limitations (e.g., small sample sizes, pre-post-comparisons, use of a variety of antidepressants) preclude generalization and still leave questions about the link between MDD and BDNF change. Additionally, comparative studies investigating the differential effect of specific antidepressants on BDNF level changes during treatment indicate that the association between such changes and treatment outcome depends on the antidepressant employed. In a comparative study by Hellweg et al. (2008), amitriptyline treatment was associated with a significant increase in sBDNF concentrations, but with paroxetine treatment there was a slight decrease. Matrisciano et al. (2009) found a rise in sBDNF after 5-weeks treatment with sertraline, though only after 6-months treatment with venlafaxine. Finally, in a prospective study involving 4 weeks of antidepressant treatment with venlafaxine or mirtazapine, sBDNF levels declined with the former but increased with the latter (Deuschle et al. 2013).

To summarize, whereas the association between severe MDD and low s/pBDNF is well established, uncertainties remain about relations between changes in MDD and s/pBDNF during treatment. Given the inconsistent effects of different antidepressants on BDNF, the question arises whether an increase of BDNF levels are at all necessary for any therapeutic antidepressant effect. Another question is whether an increase of BDNF levels can predict treatment outcome. Three studies have examined this question. Haghighi et al. (2013) found an increase in pBDNF in patients treated with citalopram and with electroconvulsive therapy (ECT) but no significant advantage or disadvantage in treatment outcome. Tadić et al. (2011) reported that early non-increase in sBDNF concentrations was linked to non-response to antidepressant treatment. Further, they specifically tested how sensitive early change in pBDNF was as a predictor of treatment outcome (Dreimüller et al. 2012). Results indicated that a 100 % + increase in pBDNF concentration over baseline after 1 week, and a ≥20 % improvement in Hamilton Depression Rating Scale (HDRS) score at day seven both predicted the final response to antidepressant treatment with considerable sensitivity.

These latter two studies suggest that early changes in s/pBDNF levels are associated with reduction in MDD symptoms, and in our view this merits further investigation. This we did in a prospective study with just one antidepressant (the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine), over 6 weeks and with regular and thorough assessment of sBDNF levels and depression.

The aims of the study were fourfold: (1) to assess changes in sBDNF levels over a 6-week course of treatment of patients with MDD; (2) to assess changes in severity of depression over this same period; (3) to correlate changes in sBDNF with changes in MDD, and lastly, (4) to predict treatment outcomes based on a combination of changes in sBDNF and MDD.

We believe the present study may shed more light on the association between sBDNF and MDD given that (a) only one antidepressant is used, (b) both BDNF and symptoms of MDD are assessed more frequently and more thoroughly, and (c) changes in BDNF and MDD symptoms are combined to predict treatment outcome.

Our four hypotheses were as follows: (1) following previous clinical studies of sBDNF concentrations in patients with MDD (Bocchio-Chiavetto et al. 2010; Sen et al. 2008), baseline sBDNF levels would be low and related to greater severity of depression; (2) sBDNF would normalize in parallel to reduction in depression; that is to say, patients with favorable treatment outcomes would have higher sBDNF levels at the end of the study than patients with unfavorable treatment outcomes; (3) following Tadić et al. (2011) and Dreimüller et al. (2012), sBDNF concentrations would increase early (i.e., in the first 2 weeks of treatment), and this early change would correlate with early HDRS regression; (4) either baseline sBDNF concentrations or early change of sBDNF or both would predict therapeutic outcome.

Method

Sample

An open prospective clinical study was conducted in three Swiss clinical centers between January 2010 and the end of 2011. Participants were female and male in- and outpatients suffering from an acute episode of MDD according to the International Classification of Diseases, 10th edition (ICD-10; World Health Organization 1994) and who fulfilled the clinical indication criteria for treatment with duloxetine. The study was carried out according to good clinical practice principles. The study protocol was approved by local and hospital ethical committees, and was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki. Local committees were regularly informed about the status and development of the study. All patients gave written informed consent prior to participation. Severity of depression was in excess of 17 points on HDRS-17 and more than 3 points on the Clinical Global Impression (CGI) scale. Patients had to be free of antidepressants for at least 3 days

(the elimination time for previous antidepressants). Patients were excluded from the study if previously treated with a selective serotonin reuptake inhibitor (SSRI) or venlafaxine, when there was an indication for another antidepressant than duloxetine, or when they were known non-responders to antidepressants. Those with clinically relevant psychiatric comorbidities or acute suicidality were excluded. Patients were also excluded if suffering from clinically relevant systemic diseases such as chronic liver or kidney insufficiency, malignant diseases, severe cardiovascular problems, and in the case of female patients, if pregnant or planning pregnancy or if they were breast feeding.

From 31 patients recruited between January 2010 and the end of 2011, six terminated the study prematurely. Of these, two declined the treatment and left the hospital following the baseline visit, one patient was withdrawn from the study due to non-compliance, and one because of transfer to another hospital. Two patients terminated the study because of adverse effects, e.g., moderate to severe insomnia. No serious adverse events were observed. Baseline characteristics, as well as blood samples, were collected from all patients included into the study. For the analyses of results, however, only patients completing the entire treatment period and with no missing assessments were considered. Of all those initially recruited, 25 patients fulfilled this requirement; 13 of these were treated as inpatients and 12 as outpatients. Demographic data for this sample are summarized in Table 1. Age did not differ between female (n=8; M=46.4, SD=15.5) and male participants (n=17; M=42.4, SD=11.2; $t(23)$=0.73, p=0.47). One patient suffered from various systemic concomitant diseases. During the study, 15 patients (60 %) were additionally treated with co-medication, i.e., most commonly with hypnotics (such as benzodiazepines or zolpidem) or analgesics such as non-steroid anti-inflammatory drugs (NSAID). Statistical analysis (i.e., a series of t tests for independent samples, and chi-square tests) revealed that co-medication did not systematically bias the results, especially neither BDNF values nor HDRS scores did differ between patients with co-medication or without. Furthermore, co-medication was not associated to HDRS≥ 50 % response or remission status at week 6.

Table 1 Patients' characteristics

n=25		Value
Gender	Males (%)	17 (68 %)
	Females (%)	8 (32 %)
Age	years, mean (SD)	43.7 (12.5)
Educational level	High school (%)	6 (24 %)
	Middle (%)	10 (40 %)
	Basic (%)	9 (36 %)
Depressive episode*	Mild (%)	1 (4 %)
	Moderate (%)	20 (80 %)
	Severe (%)	4 (16 %)
	Psychotic (%)	0 (0 %)
	Recurrant (%)	15 (60 %)
N of prior episodes	n (SD)	1.8 (2.0)
Duration of illness	years, mean (SD)	8.5 (9.5)
Duration of index episode	months, mean (SD)	10.1 (11.7)
Setting	inpatients (%)	13 (52 %)
	outpatients (%)	12 (48 %)
Pretreatment with AD	n (%)	18 (72 %)
Previous response to AD	n (%)	17 (68 %)
Mean dosage of duloxetine	Visit 1–3, mg (SD)	53.4 (11.5)
	Visit 1–5, mg (SD)	65.8 (16.1)
Baseline HDRS score	Mean (SD)	22.2 (4.9)
Baseline CGI score	Mean (SD)	5.1 (0.61)
Baseline sBDNF, ng/ml	Mean (SD)	5.0 (3.6)

AD antidepressant(s); *HDRS* Hamilton depression rating scale, *CGI* clinical global impression; *sBDNF* serum brain-derived neurotrophic factor; *SD* standard deviation

*Characterisation of depressive episode according to International Classification of diseases, 10th edition (ICD-10)

Procedure

Treatment schedule with duloxetine was uniform in all patients. The initial dose was 30–60 mg/day (mean=43.2 mg/day (SD±15.2 mg/day)) which was increased during the first week to an average dose of 63.6 mg/day (SD±13.2 mg/day) and by the second week to 69.6 mg/day (SD±18.8 mg/day). From the second week of treatment to the end of the study (week 3–6), there were no further dose adjustments. Depression severity was assessed with the HDRS-17 and CGI at baseline, and 1, 2, 4 and 6 weeks (±2 days) after the start of treatment.

Laboratory analysis

For sBDNF sampling, blood (5 ml from antecubital vein) was collected at baseline, and after 1, 2, and 6 weeks, always at the same time in the morning. Two probes per sampling were collected from each patient into Vacutainer tubes (Becton Dickinson; Allschwil, Switzerland) and the tubes were appropriately labeled. After centrifuging (2,000×g, 10 min, 4 °C), serum was stored in at least two aliquots at −80 °C until assay. sBDNF was measured using a BDNF Emax Immunoassay Kit (Promega; Dübendorf, Switzerland) according to the manufacturer's instructions. Briefly, 96-well microplates (Nunc MaxiSorp™, Sigma-Aldrich; Buchs, Switzerland) were coated with anti-BDNF monoclonal antibody and incubated at 4 °C for 18 h. Then, the plates were incubated in a blocking buffer for 1 h at room temperature. The samples and BDNF standards were kept at room temperature (RT) under conditions of horizontal shaking during 2 h, followed by washing with the appropriate washing buffer. The plates were incubated with anti-human BDNF polyclonal antibody at RT for 2 h

followed by washing with washing buffer. The plates were further incubated with an anti-IgY antibody conjugated to horseradish peroxidase for 1 h at RT, and incubated in peroxidase substrate and tetramethylbenzidine solution to induce a color reaction. The reaction was stopped with 1 mol/L hydrochloric acid. The absorbance at 450 nm was measured with a microplate reader (Multiskan Ascent^{TM}, Thermo Electron Corp.). Measurements were performed at least in duplicates. Specificity of sBDNF analysis (i.e., cross-reactivity to related neurotrophins) was <3 %, sensitivity was at least 15 pg/ml.

Statistical analysis

Preliminary calculations: Pearson's correlations were computed between age, educational level, current and previous illness history and baseline sBDNF, HDRS, and CGI. Baseline values of sBDNF levels and HDRS and CGI scores did not correlate with age, education, duration of illness, duration of index episode or number of former depressive episodes (all p values>0.1). Therefore age, education and illness history were excluded as possible confounders.

Whether gender, setting of treatment, or pretreatment with another antidepressant had an effect on baseline conditions were tested using Student's t tests and Welch (w)-tests. Compared to outpatients, inpatients had higher baseline sBDNF concentrations (7.56±2.99 vs. 2.24±1.77 ng/ml; $w(19.7)=5.46$, $p=0.000$) and marginally higher HDRS and CGI scores (HDRS=23.9±5.8 vs. 20.4±2.7, $w(17.4)=2.0$, $p=0.07$; CGI=5.3±0.6 vs. 4.8±0.6; $t(23)=2.0$, $p=0.06$).[1] Baseline values of sBDNF, HDRS and CGI did not differ between females and males (sBDNF=5.11±3.49 vs. 4.96±3.82 ng/ml; $t(23)=0.09$, $p=0.92$; HDRS=22.4±5.2 vs. 22.2±4.8, $t(23)=0.09$, $p=0.93$; CGI=5.4±0.7 vs. 4.9±0.6; $t(23)=1.63$, $p=0.12$) or between those pre-treated with another antidepressant and those not pre-treated (sBDNF=5.51±3.55 vs. 3.95±3.85 ng/ml; $t(23)=1.00$, $p=0.33$; HDRS=22.2±4.9 vs. 22.3±5.1, $t(23)=0.01$, $p=1.00$; CGI=5.1±0.6 vs.5.0±0.8; $t(23)=0.42$, $p=0.68$).

A series of ANOVAs for repeated measures was performed to calculate changes in HDRS, CGI, and sBDNF values over four (sBDNF) and five (HDRS and CGI) time points. In case of deviations from sphericity, statistical tests were performed using Greenhouse–Geisser corrected degrees of freedom, though throughout the paper, the original degrees of freedom are reported with the relevant Greenhouse–Geisser epsilon value (ε). Single t tests were applied as between post hoc tests, with Bonferroni-Holm corrections for p values.

Pearson's correlations were computed for associations between HDRS, CGI, and sBDNF values.

Changes in HDRS score between different time points (weeks 1, 2, 4, 6) and baseline were reported as HDRS-W1delta (and, HDRS-W2delta, HDRS-W4delta, HDRS-W6delta, respectively).[2] Similarly, differences between sBDNF concentrations at week 1 (or weeks 2 or 6) and baseline were reported as sBDNF-W1delta (sBDNF-W2delta, sBDNF-W6delta). Differences from baseline values are reported as changes relative to baseline value.

To examine the extent to which response and remission were associated with sBDNF levels, cut-off variables were introduced; as described above, we introduced the factor responder at three different levels: (1) Early responder after 1 week of treatment, i.e., a decrease in HDRS score of 20 % or more after 1 week of treatment compared to baseline (HDRS≥20 % response at week 1). (2) Early responder after 2 weeks of treatment, i.e., a decrease in HDRS score of 20 % or more after 2 weeks compared to baseline (HDRS≥20 % response at week 2). (3) Responder after 6 weeks of treatment, i.e., a decrease in HDRS score of 50 % or more after 6 weeks of treatment compared to baseline (HDRS≥50 % response at week 6).

Next, the cut-off variable remitter was introduced. At the end of the study, remission was reached if the HDRS score was 8 points or lower.

To compare HDRS, CGI, and BDNF values between HDRS≥20 % response at week 1 vs. HDRS≥20 % non-response at week 1, HDRS≥20 % response at week 2 vs. HDRS≥20 % non-response at week 2, HDRS≥50 % response at week 6 vs. HDRS≥50 % non-response at week 6, and remitters vs. non-remitters, a series of single t tests was performed.

Next, to combine patients with high or low sBDNF levels and further sBDNF change and MDD outcome, sBDNF levels at the beginning of the study were median-split into patients with high vs. low BDNF levels. Similarly, sBDNF-W2delta was median-split to produce groups with "low sBDNF rise" and "high sBDNF rise." Then, to calculate further distributions and odds ratios, a series of chi-square tests was performed.

Test results with an alpha level below 0.05 are reported as significant. Effect sizes for t and w tests were calculated following Cohen (1988), with 0.49≥d≥0.20 indicating small [S] (i.e., negligible practical importance), 0.79≥d≥0.50 indicating medium [M] (i.e., moderate practical importance), and d≥0.80 indicating large [L] (i.e., crucial practical importance) effect sizes. Effect sizes for ANOVAs were indicated with the partial eta squared (η^2), with $0.059\geq\eta^2\geq0.01$ indicating small

[1] Nevertheless, inpatients did not differ from outpatients concerning values of sBDNF levels and HDRS scores at later timepoints and changes of HDRS scores or sBDNF levels between any timepoint and baseline were not significantly different between setting groups.

[2] Accordingly, when HDRS score was declining over course of treatment, the value of HDRS-Wxdelta was negative.

[S], $0.139 \geq \eta^2 \geq 0.06$ indicating medium [M], and $\eta^2 \geq 0.14$ indicating large [L] effect sizes.

Analyses were conducted using SPSS 20.0 (IBM Company, NY, USA) for Windows.

Results

sBDNF concentrations and changes

Descriptive and statistical information for sBDNF concentrations are reported in Table 2. sBDNF concentrations differed significantly over time. Post hoc comparisons with Bonferroni-Holm corrections for p values showed that sBDNF levels increased significantly and continuously from baseline to week 2. Between week 2 and week 6, sBDNF levels decreased significantly again; sBDNF levels at baseline and week 6 did not differ significantly.

Change of depressive symptoms

Descriptive and statistical analyses of the HDRS and CGI values over time are summarized in Table 2. HDRS scores decreased significantly over time. Post hoc comparisons with Bonferroni-Holm corrections for p values revealed that decrease in HDRS score was significant after 1 week of treatment and continued to decrease significantly till week 4, while HDRS scores at weeks 4 and 6 did not differ statistically significantly. CGI scores decreased significantly over time (Table 2). Post hoc comparisons with Bonferroni-Holm corrections for p values revealed that CGI regression was also significant as early as week 1, decreased almost steadily thereafter, and was still decreasing between weeks 4 and 6.

Association between sBDNF levels and HDRS scores, early improvement, response, and remission

A higher baseline sBDNF level was associated with a higher baseline HDRS score (r=0.45, p=0.024).[3] There were no significant correlations between HDRS score and sBDNF values at weeks 1, 2, or the end of treatment (r's<0.1, p's>0.2). sBDNF levels did not differ between favorable and unfavorable treatment course at any time (i.e., sBDNF-W1/HDRS≥20 % response at week 1 vs. HDRS≥20 % non-response at week 1, sBDNF-W2/HDRS≥20 % response at week 2 vs. HDRS≥20 % non-response at week 2, sBDNF-W6/HDRS≥50 % response at week 6 vs. HDRS≥50 % non-response at week 6, and sBDNF-W6/remission vs. non- remission) (t tests: all p's>0.2).

[3] After including all initially recruited patients (n=31) into the analysis, correlation between baseline values of sBDNF and HDRS was similar (r=0.463; p=0.010).

Baseline sBDNF and sBDNF level changes after the first 2 weeks of treatment and treatment course

As Table 3 shows, baseline sBDNF concentrations were higher in patients with HDRS≥20 % response at week 2 than with HDRS≥20 % non-response at week 2 (descriptively, p=0.065, d=1.06 [L]), and baseline sBDNF levels were significantly higher in HDRS≥50 % response at week 6 than in HDRS≥50 % non-response at week 6 (p=0.024, d=1.15 [L]; Fig. 1). The "remission" and "non-remission" groups did not differ significantly in baseline sBDNF (p>0.1, d<0.22 [S]). As regards to change in sBDNF concentrations over time, sBDNF-W1delta and sBDNF-W2delta were descriptively higher in patients with HDRS≥50 % non-response at week 6 than patients with HDRS≥50 % response at week 6 (p=0.102, d=1.03[L] and p=0.146, d=0.81[L], resp., Fig. 1). Further, a higher sBDNF-W2delta, i.e., a significant rise in sBDNF levels over the first 2 weeks of treatment, was associated with a smaller HDRS-W2delta, i.e., a smaller decline in HDRS scores over 2 weeks (r=0.48; p=0.018). Finally, the more the absolute sBDNF-W1delta and the percentage of sBDNF-W1delta were higher, the lower the baseline sBDNF level (r=−0.42, p=0.036; r=−0.46, p=0.020, respectively).

Prediction of treatment outcome as a function of baseline sBDNF, early sBDNF changes, and HDRS≥20 % response at weeks 1 or 2

To investigate the predictive value of baseline sBDNF levels, early sBDNF rise, and a combination of both, for treatment outcome, χ^2 tests were performed, as presented in Table 4. Patients with "high baseline sBDNF" or with "high baseline sBDNF" and "low sBDNF-W2delta" were more likely to be final responders (HDRS≥50 % response at week 6) than patients with "low baseline sBDNF" or with "low baseline sBDNF" and "high sBDNF-W2delta". 60 % of patients with "low baseline sBDNF" and "high sBDNF-W2delta"had a HDRS≥50 % non-response at week 6, while 90 % of patients of fulfilling the criteria had a HDRS≥50 % response at week 6. To evaluate the predictive value of sBDNF variables, we also analyzed the association of HDRS≥20 % response at weeks 1 and 2 with treatment outcome. HDRS≥20 % response at week 2 marginally predicted HDRS≥50 % response at week 6 (χ^2(n=25, df=1)=3.18, p=0.08; Table 4). HDRS≥20 % response at week 2 rather than baseline HDRS scores (Table 3) were associated with treatment outcome.

To summarize, a high baseline sBDNF and a low sBDNF rise at the beginning of treatment were associated with favorable treatment outcome, even if the baseline HDRS score was high.

Table 2 Hamilton depression rating scores (HDRS) and clinical global impression scores (CGI) and brain-derived neurotrophic factor serum concentrations (sBDNF) at baseline and over 6 weeks of treatment

	Mean (±SD)	ANOVA	Post hoc comparisons (p)			
			Baseline vs.	Week 1 vs.	Week 2 vs.	Week 4 vs.
HDRS, score	Baseline: 22.2 (±4.9) Week 1: 16.9 (±7.6) Week 2: 13.8 (±7.5) Week 4: 9.0 (±6.6) Week 6: 7.5 (±5.6)	F(4, 92)=45.37 p=0.000 η^2=0.664 [L] ε=0.67	Week 1: 0.001 Week 2: <0.0001 Week 4: <0.0001 Week 6: <0.0001	week 2: 0.047 Week 4: <0.0001 Week 6: <0.0001	Week 4: 0.005 Week 6: 0.001	Week 6: n.s.
CGI, score	Baseline: 5.1 (±0.61) Week 1: 4.5 (±0.83) Week 2: 4.0 (±1.00) Week 4: 3.5 (±1.14) Week 6: 2.8 (±1.25)	F(4, 92)=39.28 p=0.000 η^2=0.631 [L] ε=0.67	Week 1: 0.001 Week 2: <0.0001 Week 4: <0.0001 Week 6: <0.0001	Week 2: 0.049 Week 4: <0.0001 Week 6: <0.0001	Week 4: n.s. Week 6: <0.0001	Week 6: 0.009
sBDNF, ng/ml	Baseline: 5.01 (±3.64) Week 1: 8.66 (±5.93) Week 2: 11.03 (±8.00) Week 4: — Week 6: 5.99 (±3.66)	F(3, 72)=7.97 p=0.001 η^2=0.249 [L] ε=0.76	Week 1: 0.056 Week 2: 0.009 Week 6: n.s.	Week 2: n.s. Week 6: n.s.	Week 6: 0.016	–

n.s. p>0.05; *[L]* large effect size

Table 3 Baseline values and early changes in HDRS scores and sBDNF concentrations in patients with (non-)response after 2 or 6 weeks, or with (non-) remission after 6 weeks

	HDRS≥20 % response at week 2 (n=20) vs. HDRS≥20 % non-response at week 2 (n=5)		HDRS≥50 % response at week 6 (n=18) vs. HDRS≥50 % non-response at week 6 (n=7)		Remission (n=16) vs. non-remission (n=9)	
Baseline sBDNF ng/ml	5.68±3.59	t(23)=1.94, p=0.065	6.00±3.57	t(23)=2.41, p=0.024	5.33±3.09	t(23)=0.58, p=0.567
	2.33±2.67	d=1.06 [L]	2.44±2.51	d=1.15 [L]	4.43±4.62	d=0.22 [S]
sBDNF-W1delta ng/ml	3.26±6.96	t(23)=0.60, p=0.553	1.77±3.37	t(6.55)=1.77, p=0.123	1.83±3.57	t(23)=1.99, p=0.058
	5.23±4.04	d=0.35 [S]	8.49±9.83	d=0.91 [L]	6.88±9.10	d=0.73 [M]
sBDNF-W1delta (%)	134±310	t(4.12)=1.34, p=0.250	63±103	t(6.04)=1.93, p=0.102	70±108	t(8.10)=1.77, p=0.114
	894±1263	d=0.83 [L]	859±1091	d=1.03 [L]	671±1016	d=0.83 [L]
sBDNF-W2delta ng/ml	6.57±9.00	t(23)=0.37, p=0.718	5.15±7.91	t(23)=1.11, p=0.279	5.13±8.32	t(23)=.93, p=0.362
	5.06±3.12	d=0.22 [S]	9.15±8.61	d=0.48 [S]	8.29±7.84	d=0.39 [S]
sBDNF-W2delta (%)	265±517	t(23)=1.47, p=0.156	193±479	t(7.26)=1.63, p=0.146	212±506	t(23)=1.52, p=0.142
	749±1111	d=0.56 [M]	797±934	d=0.81 [L]	629±874	d=0.58 [M]
Baseline HDRS score	22.3±5.1	t(23)=0.12, p=0.905	23.2±4.9	t(23)=1.69, p=0.106	22.4±4.2	t(23)=0.18, p=0.857
	22.0±4.1	d=0.06	19.7±4.0	d=0.78 [M]	22.0±6.1	d=0.08
HDRS-W1delta score	−6.6±5.6	t(23)=2.01, p=0.056	−6.2±1.5	t(23.00)=2.26, p=0.034	−6.3±5.8	t(23)=0.98, p=0.336
	−1.2±3.3	d=1.17 [L]	−2.3±0.9	d=3.15 [L]	−4.0±5.3	d=0.41 [S]
HDRS-W1delta (%)	−30.6±26.6	t(23)=1.98, p=0.060	−29.7±29.5	t(23)=1.23, p=0.228	−29.4±29.0	t(23)=0.92, p=0.366
	−5.7±17.2	d=1.11 [L]	−15.2±14.4	d=0.62 [M]	−19.1±21.9	d=0.40 [S]
HDRS-W2delta score	−10.7±5.3	t(15.17)=6.86, p=0.000	−10.4±6.6	t(22)=2.55, p=0.018	−10.4±6.9	t(22)=2.01, p=0.057
	0.4±2.4	d=2.70 [L]	−3.6±3.9	d=1.25 [L]	−5.1±4.9	d=0.89 [L]
HDRS-W2delta (%)	−49.4±23.8	t(22)=4.70, p=0.000	−46.1±30.8	t(22)=2.01, p=0.057	−47.3±32.1	t(22)=1.91, p=0.070
	2.8±11.9	d=2.77 [L]	−20.2±22.8	d=0.96 [L]	−24.0±22.7	d=0.84 [L]

Absolute values and relative changes of HDRS and sBDNF concentrations are reported by mean and range of standard deviation (±SD). Group differences are tested by t tests for statistical significance. Effect sizes d are reported. *[L]* large effect size, i.e., d≥0.80; *[M]* medium effect size, i.e., 0.79≥ d≥0.50; *[S]* small effect size, i.e., 0.49≥d≥0.20;*remission* HDRS score ≤7 after 6 weeks; *HDRS-W1delta* HDRS change between week 1 and baseline; *HDRS-W2delta* HDRS change between week 2 and baseline; *sBDNF-W1delta* sBDNF level change between week 1 and baseline; *sBDNF-W2delta* sBDNF level change between week 2 and baseline

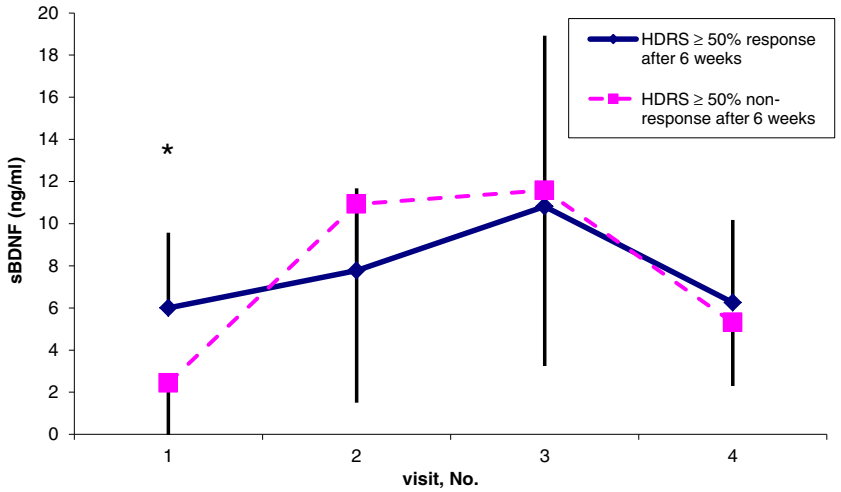

Fig. 1 Courses of sBDNF concentrations in the group of patients with HDRS≥50 % response at week 6 vs. the group of patients with HDRS≥50 % non-response at week 6; (*$p<0.05$)

Discussion

The key findings of the present study are that in a sample of patients suffering from major depressive disorders, a higher baseline level of sBDNF concentration, along with an early improvement to treatment predicted successful treatment outcome after 6 weeks. However, an initial increase in sBDNF concentrations during treatment was not associated with successful treatment outcome. Further, treatment remission was not associated with sBDNF levels.

We now consider in turn our four hypotheses. First, on the basis of previous clinical studies (cf. Bocchio-Chiavetto et al. 2010; Brunoni et al. 2008; Sen et al. 2008), we expected that low baseline sBDNF concentrations would be associated with more severe depression. This hypothesis was not supported. Instead, patients with initially high sBDNF levels were also

Table 4 Prediction of therapy outcome (i.e., HDRS≥50 % response or remission after 6 weeks) as a function of high baseline sBDNF concentrations, low sBDNF level rises by 2 weeks, early HDRS≥20 % response after 1 week and after 2 weeks, respectively, or by a combination of these conditions

	HDRS≥50 % response at week 6 (n=18/25, 72.0 %)		Remission (n=16/25, 64.0 %)	
	ppv	χ^2 Test OR (CI)	ppv	χ^2 Test OR (CI)
High baseline sBDNF (n=13/25, 52.0 %)	12/13 92.3 %	χ^2 (n=25, df=1)=5.54, p=0.02 12.0 (1.2–123.7)	10/13 76.9 %	χ^2 (n=25, df=1)=1.96, p=0.16 3.3 (0.6–18.5)
Low sBDNF W2delta (n=12/25, 48.0 %)	11/12 91.7 %	χ^2 (n=25, df=1)=4.43, p=.04 9.4 (0.9–95.9)	9/12 75.0 %	χ^2 (n=25, df=1)=1.21, p=.27 2.6 (0.5–14.1)
High baseline sBDNF and low sBDNF W2delta (n=10/25, 40.0 %)	9/10 90.0 %	χ^2 (n=20, df=1)=5.50, p=0.02 13.5 (1.2–152.2)	7/10 70.0 %	χ^2 (n=20, df=1)=1.82, p=0.18 3.5 (0.5–22.3)
HDRS≥20 % response at week 1 (n=13/25, 52.0 %)	11/13 84.6 %	χ^2 (n=25, Df=1)=2.13, p=0.14 3.9 (0.6–26.1)	10/13 76.9 %	χ^2 (n=25, Df=1)=1.96, p=0.16 3.3 (0.6–18.5)
HDRS≥20 % response at week 2 (n=20/25, 80.0 %)	16/20 80.0 %	χ^2 (n=25, df=1)=3.18, p=0.08 6.0 (0.7–48.9)	14/20 70.0 %	χ^2 (n=25, df=1)=1.56, p=0.21 3.5 (0.5–26.6)
High baseline sBDNF and HDRS≥20 % response at week 2 (n=12/25, 48.0 %)	11/12 91.7 %	χ^2 (n=16, df=1)=7.11, p=0.01 33.0 (1.6–698.0)	9/12 75.0 %	χ^2 (n=16, df=1)=3.20, p=0.07 9.0 (0.7–122.8)
High baseline sBDNF and low sBDNF W2delta and HDRS≥20 % response at week 2 (n=9/25, 36.0 %)	8/9 88.9 %	χ^2 (n=13, df=1)=5.31, p=0.02 24.0 (1.1–518.6)	6/9 66.7 %	χ^2 (n=13, df=1)=1.94, p=0.16 6.0 (0.4–85.2)

High baseline sBDNF sBDNF≥3.5 ng/ml; *low sBDNF W2delta* sBDNF W2delta≤70 %; *ppv* positive predictive value, i.e., the probability rate of a positive treatment outcome (HDRS≥50 % response at week 6 or remission) in patients fulfilling a precondition as listed in column 1; e.g., 92.3 % of patients with high baseline sBDNF reached the condition of HDRS≥50 % response at week 6

those with highest remission and response rates. These results are at odds with the negative association between severity of untreated depression and sBDNF levels reported by others (Gervasoni et al. 2005; Gonul et al. 2005; Karege et al. 2002; Shimizu et al. 2003; Yoshimura et al. 2007). We found the opposite correlation between baseline values of HDRS and sBDNF; i.e., more severe depression was linked with higher baseline sBDNF levels. In the absence of any clues in the current literature as to why our pattern of results does not match previous findings, we offer the following speculations. First, though the patient sample was heterogenous concerning age, gender, educational level, and variables of illness history, appropriate statistical procedures rigorously excluded possible confounding effects. Second, in a previous study (Giese et al. 2013), we found that quality of sleep as well as tobacco consumption alter sBDNF levels, and perhaps these confounders should have been more thoroughly controlled before the beginning of treatment. Next, further possible BDNF confounders, which we did not control for, are body weight, platelet count, health-related life style, daily exercise level, drinking habits, and hormonal status in fertile women (Berchtold et al. 2001; Bus et al. 2011; Chan et al. 2008; Lommatzsch et al. 2005; Pluchino et al. 2013; Schmidt-Kassow et al. 2012; Tang et al. 2008; Vanevski and Xu 2013; Ziegenhorn et al. 2007). Finally, in animal studies, Larsen et al. (2010) showed that chronic unpredictable stress also induced a rise in sBDNF. Therefore, though highly speculative, we consider, that higher sBDNF levels in patients with more severe depression before treatment may reflect more pronounced unspecific stress responses, which could reflect a compensatory mechanism.

Our second hypothesis was that there would be a gradual increase in sBDNF levels towards normal in parallel to amelioration of depression, resulting in higher sBDNF levels in patients with response or remission than in patients with unfavorable treatment outcome. The hypothesis was not supported. Although HDRS scores (and CGI scores) decreased steadily towards normality, an initial sBDNF increase between baseline and week 2 was not stable but fell back to baseline levels. This seems to be in line with some previous studies. Though some clinical studies on sBDNF in MDD show a trend to normalization (Aydemir et al. 2006; Gonul et al. 2005), others do not (Deuschle et al. 2013; Matrisciano et al. 2009). While in previous studies, patient samples were treated with a variety of different antidepressant agents (Gervasoni et al. 2005; Gonul et al. 2005; Tadić et al. 2011), and therefore differential effects might have been missed, this study was restricted to the effect of duloxetine. In animal studies (Larsen et al. 2007, 2008) as well as in clinical comparative studies (Başterzi et al. 2009; Deuschle et al. 2013; Hellweg et al. 2008; Matrisciano et al. 2009), it has been shown that the degree and temporal course of BDNF changes depend on the antidepressant used, and sBDNF level increases under antidepressant treatment are less likely with serotonin norepinephrine reuptake inhibitor (SNRI) than with SSRI (Başterzi et al. 2009; Matrisciano et al. 2009). Therefore, as our data indicate, and in line with other studies on SNRI, HDRS response or remission under duloxetine treatment seems not to be causally linked to normalization of a low baseline sBDNF. Results from a study using one antidepressant do not necessarily extend to treatment schedules with other agents.

Our third hypothesis, following Tadić et al. (2011), was that there would be changes in sBDNF levels during the early course of treatment and that an early increase in sBDNF concentrations would co-occur with a simultaneous decrease in HDRS score. We found, as did Tadić et al. (2011), an increase in BDNF serum levels in the first 2 weeks of treatment, accompanied by a regression in HDRS score. However, contrary to expectation, degree of early sBDNF increase (sBDNF-deltaW2) correlated negatively with degree of HDRS score regression; i.e., the more HDRS decreased over the first 2 weeks of treatment, the less sBDNF concentrations increased. Therefore, it seems that the acute early rise in sBDNF is associated with more acute or severe pathology rather than with favorable early treatment outcomes. This would be in line with the observation that stress induces rise of sBDNF (Larsen et al. 2010). Remarkably, Gervasoni et al. (2005) also found that increases in sBDNF levels were linked to more severe depression. Therefore, our results are partly in line with existing literature, supporting the idea that a pronounced sBDNF increase is associated with more severe pathology.

The dynamics of sBDNF changes under antidepressant treatment are complex. The early sBDNF rise seems to reflect rapid posttranscriptional mechanisms (Jacobsen and Mørk 2004; Musazzi et al. 2009), while the increase in BDNF-RNA-expression occurs later and depends on the antidepressant employed (De Foubert et al. 2004; Khundakar and Zetterström 2006; Larsen et al. 2008). Further, the early sBDNF increase could also be associated with an agonist-stimulated release of BDNF from platelets, the main BDNF pool in blood, the extent of which varies according to the antidepressant administered (Watanabe et al. 2010). Finally, the discrepancy between sBDNF increase and psychopathological improvement may also be explained by a rapid and saturable mechanism of blood–brain-barrier transfer, which may be subject to as yet unknown regulating factors (Pan et al. 1998).

To summarize, the temporal changes in sBDNF under antidepressant treatment for MDD are subject to numerous kinetic influences and vary with the particular antidepressant employed.

While this study using duloxetine demonstrated an early though transient sBDNF rise, studies with other antidepressants have not reported sBDNF levels during the first 2 weeks,

and may have missed an early but transient sBDNF change (e.g., Başterzi et al. 2009; Deuschle et al. 2013; Hellweg et al. 2008; Matrisciano et al. 2009).

Again, as with sBDNF level changes following 6 weeks of treatment, changes early in treatment did not correspond to changes in HDRS scores. Though the early rise in sBDNF during treatment seems to be a robust phenomenon in our study, it is not necessarily linked in any causal fashion to the early antidepressant effect of duloxetine. Instead, it seems that this early increase in sBDNF reflects an early reaction to the start of therapy with a drug, independent to its subsequent efficacy.

Our fourth hypothesis was that baseline sBDNF and early change in sBDNF, along with early HDRS≥20 % response, would predict therapeutic outcome, i.e., therapy response or remission. Results support the hypothesis in that we found significantly higher baseline sBDNF concentrations in response patients than in non-response patients, with large effect sizes. Additionally, high baseline sBDNF levels were predictive to response, while low baseline sBDNF were predictive to non-response. We conclude, therefore, that baseline sBDNF is an indicator of individual resources for recovery from depression rather than an indicator of actual baseline severity.

Concerning BDNF changes, we found a pattern in which a greater rise in sBDNF levels during the first 2 weeks was associated with an unfavorably low baseline sBDNF, and with later non-response. This pattern supports the impression that the early sBDNF rise at the beginning of duloxetine treatment maybe a stress-associated phenomenon which is linked to more severe pathology and proneness to depression rather than to a favorable course of illness. Indeed, and contrary to expectations, a greater early rise in sBDNF is a negative prognostic indicator for response to duloxetine treatment.

In line with Stassen et al. (1996) and Tadić et al. (2011), we replicated the finding that HDRS≥20 % response in the first 2 weeks of treatment was a positive predictive marker for HDRS≥50 % response after 6 weeks of treatment. This result, in such a small sample, further supports the robustness of the results and conclusions of Stassen et al.'s studies (Stassen et al. 1993, 1996, 1997).

In addition, we were able to show that baseline sBDNF concentrations have a similar and indeed better predictive power with respect to treatment effects than "HDRS≥20 % response at week 2." While it is obvious that a serum marker, which is derived before treatment commences, is of more value to clinical practice than observation of the course of treatment over 2 weeks, our results show a combination of both variables ("baseline sBDNF" and "HDRS≥20 % response at week 2") improves prediction.

Various limitations of this study require mention. First, due to the open design of the study, none of the possible study biases can be excluded. The statistical analysis indicates some highly significant changes, and is based on multiple analyses of a small sample; therefore, the pattern of results should be interpreted with caution. Nevertheless, though this pilot study sample was small and lacked sufficient power to examine detailed associations between HDRS score and BDNF level changes, it is remarkable that effect sizes for differences between responders and non-responders were so large (Cohen 1988). We also note that effect size calculations are independent from sample sizes. Additionally, these results justify further well-designed studies with larger sample sizes. We also acknowledge that the small sample size and lack of control group might be an issue from the point of view of statistics. Accordingly, again, caution is warranted in interpreting the present pattern of results.

Further, though epidemiologically major depression is more common in women than in men, in the present sample, men were overrepresented. Therefore, this naturalistic sample is not representative for other clinical samples.

Another limitation of this study is that the influence of unassessed factors like body weight or smoking cannot be excluded. Additionally, we could not take into account status of functionally relevant BDNF-gene-polymorphisms like the val66met polymorphism: meta-analyses show that heterozygotes are more likely to respond to antidepressant treatment than homozygotes (Kocabas et al. 2011; Zou et al. 2010).

The antidepressant selected for the treatment was duloxetine, a dual-acting drug, characterized by a balanced increase of both noradrenaline and serotonin concentrations in the brain (Bymaster et al. 2001). While the strength of this study is that patients received a uniform antidepressant treatment, our results cannot be generalized to treatments with other antidepressants. Further, in lack of a control group, we could not proof the specificity of sBDNF-level changes under duloxetine treatment in comparison to treatment with other antidepressants.

Finally, although sBDNF levels after 6 weeks did not differ from baseline sBDNF levels, it remains possible that sBDNF would have normalized with longer treatment; in a small study of various antidepressants, Matrisciano et al. (2009) found that BDNF did not increase after 5 weeks of treatment with venlafaxine but did after 6 months.

In conclusion, this open, prospective multi-center study of 25 patients with moderate major depression revealed low sBDNF is not necessarily associated with more severe depression. Early sBDNF rise is not linked to a positive treatment outcome. The combination of high baseline sBDNF, low early sBDNF rise, and early HDRS response predicted overall treatment response. Further, larger and controlled studies are necessary to confirm these clinically relevant results.

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