



Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Serum brain-derived neurotrophic factor in bipolar and unipolar depression: A potential adjunctive tool for differential diagnosis

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ARTICLE INFO

Article history:

Received 22 February 2009

Received in revised form 18 April 2009

Accepted 21 April 2009

Available online xxxxx

Keywords:

Bipolar disorder

Major depression disorder

BDNF

Diagnostic biomarker

Depression

ABSTRACT

Bipolar disorder (BD) and major depressive disorder (MDD) are major psychiatric disorders and a diagnostic challenge during depressive episodes. Noteworthy, the proper differentiation between BD depressive state and MDD has important treatment implications. BDNF levels may be valuable adjunctive tool for these differential diagnosis. Ten subjects with MDD, forty with BD type I and thirty healthy comparison subjects were recruited. All subjects had BDNF serum levels measured and, in patients, BDNF serum levels were assessed during acute depressive episode. Optimal sensitivity and specificity of serum BDNF for the differential diagnosis of unipolar and bipolar depression were determined by the receiver operating characteristic (ROC) curve analysis, using a nonparametric approach. Serum BDNF levels in depressive BD patients were lower compared to MDD patients and controls (0.15 ± 0.08 , 0.35 ± 0.08 , and 0.38 ± 0.12 , respectively, $p < 0.001$). The area under the curve (AUC) of the ROC analysis in BD depression vs. MDD was 0.95 (ranged from 0.89 to 1.00). Overall, the AUC of the ROC analysis (BD depression vs. MDD and controls) was 0.94 (95% CI 0.89 to 0.99, $p < 0.001$). A proposed "best" cutoff of 0.26 resulted in 88% sensitivity and 90% specificity. Serum BDNF levels appears as a promising tool to discriminate bipolar from unipolar depression. Our results suggest the role of BDNF as an adjunctive tool to promote prompt and accurate diagnosis of BD. However, further investigation and replication of these results are warranted.

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1. Introduction

Bipolar disorder (BD) and major depression disorder (MDD) are two highly prevalent and disabling disorders in psychiatry (Yatham et al., 2009). Despite clear phenomenological criteria, the differential diagnosis of unipolar and bipolar depression remains a clinical challenge. The differential diagnosis between BD depressive episodes and MDD is critical to prevent misdiagnosis, delay in appropriate treatment and poor prognosis. Several potential biological markers have been recognized lately. Mood disorders have been widely recognized as disorders that affect neurotrophins, particularly brain-derived neurotrophic factor (BDNF). BDNF is involved in promoting synaptic plasticity and neuronal connectivity (Berk et al., 2008; Kapczinski et al., 2008a,b,c). The idea that changes in BDNF levels may be involved in the path-

ophysiology of BD depressive episodes and of MDD have been extensively reported (Duman et al., 1997, 2000; Cunha et al., 2006; Gama et al., 2007; Machado-Vieira et al., 2007; Guimaraes et al., 2008; Kapczinski et al., 2008b,c; Kauer-Sant'Anna et al., 2008; Fernandes et al., 2009; Oliveira et al., 2009). However, as far as we are aware, BDNF has not been examined as a potential blood diagnostic test for depressive episodes. BDNF have not been examined as a potential blood diagnostic test.

The aim of this study was to investigate the properties of serum BDNF as a potential diagnostic biomarker. To this purpose, we assessed serum BDNF levels during depressive episode, and compared the levels between BD and MDD patients.

2. Methods and materials

BD type I and MDD inpatient and outpatient subjects, currently in acute depressive episode, were recruited from Bipolar Disorders Program and Psychiatry Inpatient Unit – Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. Diagnosis of depressive episodes and of BD and MDD were established according to Structured

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Clinical Interview for DSM-IV-Axis I Disorders (SCID-I) (APA, 2000) by trained psychiatrists. Severity of depressive episodes was evaluated using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Our sample was powered to analyze the difference between BD and MDD using a ROC curve with a power of 80% and an alpha one-sided of 0.05 for an accuracy of 0.8 with a ratio between MDD and BD of 2.0. For this purpose a minimum of eight per group would be necessary; and we have included 10 patients with MDD and 40 with BD.

We conducted an exploratory study with 10 MDD and 40 BD type I patients in acute depressive episode, and 30 healthy controls. All patients were taking psychiatric medication. Psychiatric assessment in controls was carried out using SCID-I, non-patient version. Control subjects were not on medication, and had no history of major psychiatric disorders, dementia or mental retardation in their first-degree relatives. Patients and controls with drug abuse or untreated or uncontrolled major medical illness were excluded. The Hospital de Clinicas de Porto Alegre Ethics Committee approved the study protocol and all subjects provided written informed consent before entering in the study.

Five milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The blood samples were drawn in the afternoon (around 5 pm). The blood was immediately centrifuged at 4000g for 10 min, and serum was kept frozen at -80°C until assayed. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Chemicon, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:25 in sample diluents and standard curve ranged from 7.8 to 500 pg of BDNF. Plates were then washed four times with wash buffer, added monoclonal anti-BDNF rabbit antibody (diluted 1:1000 with sample diluents), and incubated for 3 h at room temperature. After washing, a second incubation with anti-rabbit antibody peroxidase conjugated (diluted 1:1000) for 1 h at room temperature was carried out. After addition of streptavidin-enzyme, substrate and stop solution, the amount of BDNF was determined (absorbance set in 450 nm). The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration. Total protein was measured by Lowry's method using bovine serum albumin (BSA) as a standard.

Statistical analysis was performed using Analyze-it for Excel Program and SPSS 16.0 for Windows. Most of the BDNF values were fitted in a standard distribution curve and were therefore subjected to parametric analyses. All values are presented as mean \pm standard deviation (SD), except when indicated. For the comparisons between the groups, one-way analysis of variance (ANOVA) test

with individual differences assessed using a Tukey post-test if the ANOVA was significant, and independent *t* test were employed. Pearson's correlation coefficient was also used. Optimal sensitivity and specificity of serum BDNF ratio for the diagnosis of depressive BD episode were determined by the receiver operating characteristic (ROC) curve analysis utilizing a nonparametric approach. The Youden index was calculated for each cutoff value as corresponding [(sensitivity + specificity) – 1] to find the cutoff values that maximize discriminating power of the test. *P* values <0.05 two-tailed were considered statistically significant for the ANOVA and χ^2 , and for the ROC curve analysis *p* <0.05 one-tailed were considered statistically significant.

3. Results

The characteristics of BD and MDD patients and controls are summarized in Table 1. BD and MDD patients were similar regarding gender, age, presence of psychosis, and HDRS score. BD and MDD patients and controls were similar regarding gender, and age. BDNF was not correlated to age or severity of depressive symptoms assessed by the HDRS (all *p* >0.05). Use of medication was similar in both groups regarding antidepressants and antipsychotics; 60% of BD patients were using mood stabilizers (lithium or

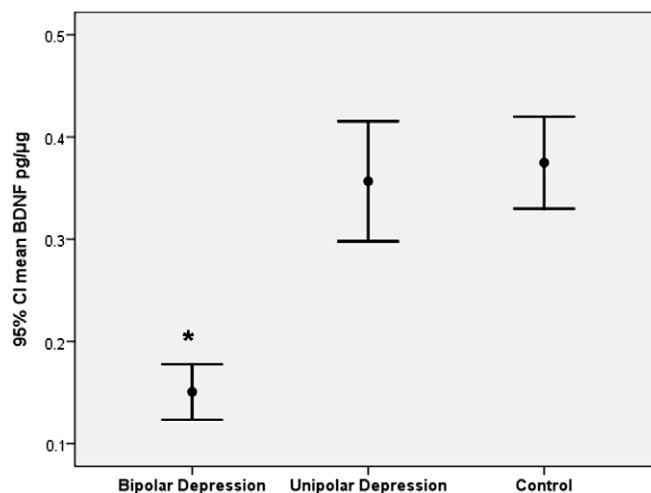


Fig. 1. Serum brain-derived neurotrophic factor (BDNF) levels in pg/ μg ratio (mean \pm 95% CI) in bipolar and unipolar depression, and in healthy controls. *p* <0.001 for bipolar depression vs. unipolar depression/control (One-way ANOVA with Tukey post-test).

Table 1
Characteristics of the bipolar and unipolar depression patients, and controls.

| Characteristics | Group* | | | <i>p</i> value |
|------------------------------------------|-------------------------------------|--------------------------------------|---------------------------|----------------|
| | Bipolar depression (<i>n</i> = 40) | Unipolar depression (<i>n</i> = 10) | Controls (<i>n</i> = 30) | |
| Male sex ^a | 13/40 | 4/10 | 12/30 | 0.903 |
| Age – years ^b | 41.32 \pm 8.45 | 44.80 \pm 17.97 | 41.00 \pm 11.99 | 0.562 |
| Presence of psychosis ^a | 25/40 | 4/10 | – | 0.170 |
| Inpatient patients ^a | 18/40 | 10/10 | – | 0.189 |
| HDRS score ^c | 23.40 \pm 7.53 | 26.30 \pm 5.50 | – | 0.284 |
| Mood stabilizers ^a | 24/40 | 0/10 | – | 0.001 |
| Antidepressants ^a | 17/40 | 7/10 | – | 0.360 |
| Antipsychotics ^a | 18/40 | 9/10 | – | 0.082 |
| BDNF (pg/ μg) ^{b,d} | 0.15 \pm 0.08 | 0.35 \pm 0.08 | 0.38 \pm 0.12 | 0.001 |

Abbreviations: HDRS (Hamilton Depression Rating Scale); BDNF (brain-derived neurotrophic factor).

* Columns show mean \pm standard deviation (SD) for all categories except male sex, presence of psychosis, inpatient patient, and medications.

^a Chi-square test.

^b One-way ANOVA test with Tukey post-test.

^c Unpaired *t* test.

^d BDNF in bipolar disorder depression $<$ major depressive disorder (*p* = 0.006).

Table 2

Comparison between patients with bipolar disorder depression and other groups: receiver operating characteristics (ROC) curve analysis.

| ROC analysis | BD vs. MDD | BD vs. control | BD vs. MDD/control |
|------------------------------|-------------------|------------------|--------------------|
| AUC* | 0.950 (0.89–1.00) | 0.94 (0.89–1.00) | 0.94 (0.89–0.99) |
| SE | 0.028 | 0.026 | 0.025 |
| P | <0.001 | <0.001 | <0.001 |
| Cutoff | <0.260 | <0.270 | <0.230 |
| Sensitivity (%) [†] | 88 (73–96) | 90.00 (77–96) | 85 (70–95) |
| Specificity (%) [†] | 90 (56–97) | 87 (70–96) | 95 (83–99) |
| Accuracy (%) [†] | 88 | 84 | 84 |

SE = standard error.

[†] 95% Confidence interval shown in parenthesis.

divalproate), compared to none of the MDD patients. Serum BDNF levels in depressive BD patients were lower when compared to MDD patients and controls. BDNF did not differ between the MDD patients and controls (Table 1, Fig. 1).

ROC curve analysis was used to explore discriminatory value of serum BDNF levels. As reported in Table 2, the area under the curve (AUC) of the ROC analysis in BD depression vs. MDD was 0.95 (ranged from 0.89 to 1.00) (Figs. 2 and 3). Overall, the AUC of the ROC analysis (BD depression vs. MDD and controls) was 0.94 (standard error 0.025, $p < 0.001$, 95% CI 0.89 to 0.99). A proposed “best” cutoff of 0.26 resulted in 88% sensitivity and 90% specificity. As shown in Table 2, sensitivity, specificity, and accuracy values were still high when the BD depression group was contrasted to MDD group of patients and controls.

4. Discussion

As far as we are aware, this is the first study to examine diagnostic properties of serum BDNF as a potential tool to support clinical differentiation between those with BD and those with MDD.

Our results suggest that serum BDNF levels in bipolar depression are lower compared to unipolar depression, and that BDNF may be a diagnostic biomarker in depressive states. One of the key issues in psychiatry management is the necessity of reliable biomarkers for increasing diagnostic accuracy. Diagnostic exams have been considered a longstanding ‘Holy Grail’ in psychiatry (Le-Niculescu et al., 2009). MDD and BD during depressive episodes remain a diagnostic challenge, because of overlap of core clinical features, and the difficulty in ascertain past manic and hypomanic episodes. This frequently leads to misdiagnosis of MDD in patients with bipolar depression. Our results raise the possibility of an useful adjunctive biological marker for differential diagnosis of depressive episodes. Serum BDNF. Serum BDNF levels in BD was more than 50% lower than in controls and in patients with MDD. Serum BDNF levels was not influenced by age and gender, and showed an overall accuracy of 95% in diagnosing bipolar depression.

The functional consequence of decreased BDNF in mood disorders is still under investigation. Current evidences suggest that BDNF is a physiopathologic biomarker in psychiatry (Duman et al., 1997, 2000; Hashimoto et al., 2004; Post, 2007; Kapczinski et al., 2008a,b; Andreazza et al., 2008; Gama et al., 2008; Sen et al., 2008). Our findings of lower BDNF serum levels in BD during depressive episodes are in line with previous reports (Cunha et al., 2006; Machado-Vieira et al., 2007; Oliveira et al., 2009). According a recent meta-analysis (Sen et al., 2008), serum BDNF is decreased in MDD; our results may not be discordant with this report, if we take into account that mean BDNF serum levels in MDD group were lower than in the control group, however statistical significance was not reached, which probably would occur if sample was larger. However, the primary objective of this study was to discriminate BD from MDD and healthy subjects rather than to examine differences in BDNF levels between MDD and controls, which is already consistently reported in previous studies.

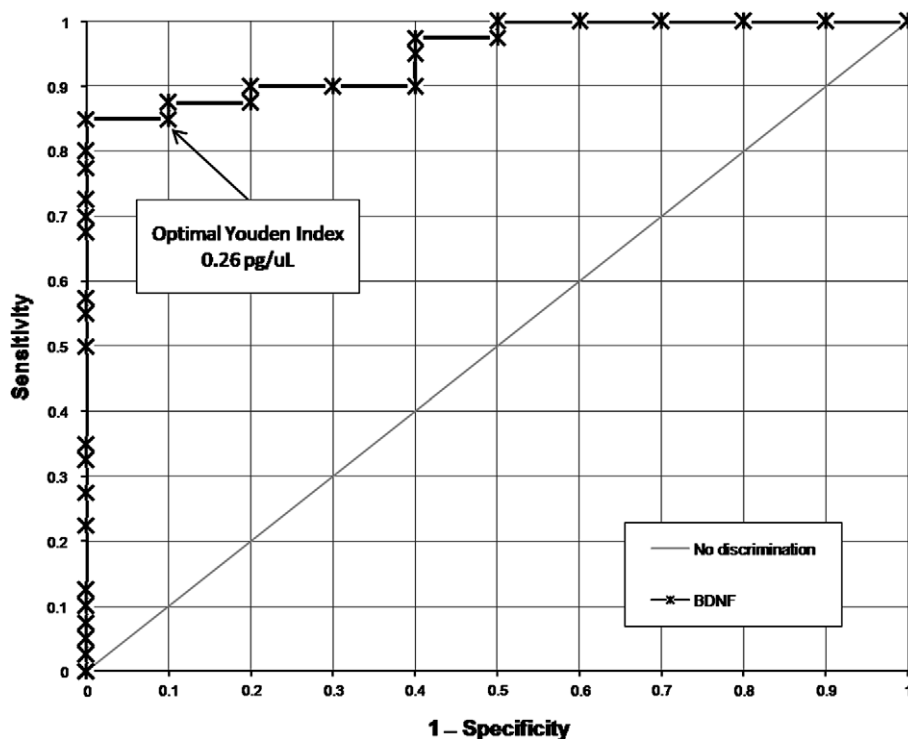


Fig. 2. Receiver operating characteristic (ROC) curve for BDNF during depressive episodes. The Youden index is calculated as [(sensitivity + specificity) – 1]. Sensitivity indicates the probability that a case is correctly identified (true positive), and 1 – specificity is the probability that a nonsymptomatic subject is falsely identified as a case (false positive). Area under the ROC curve = 0.95.

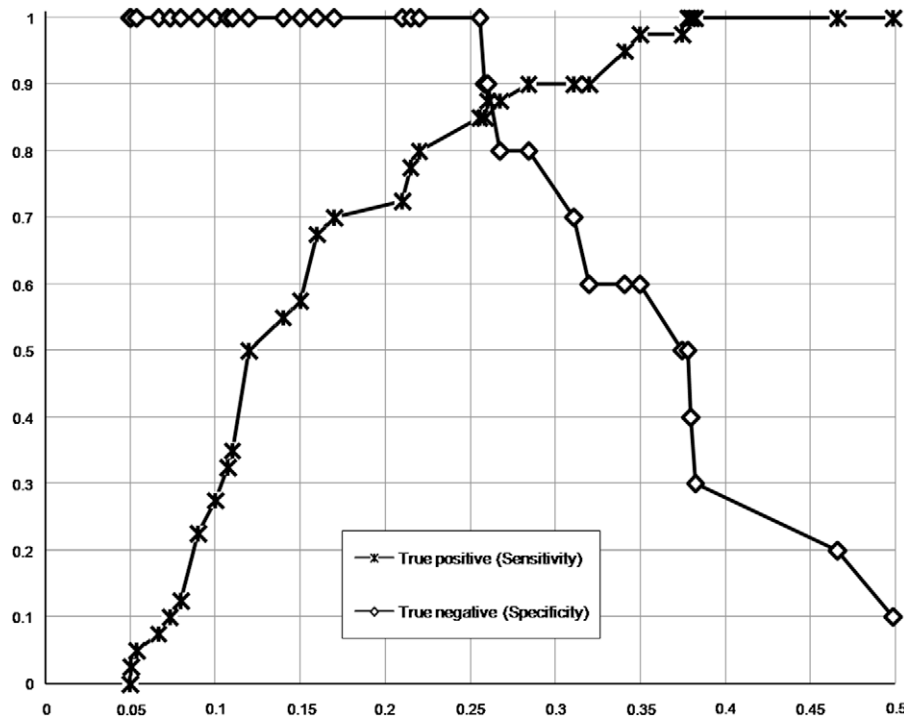


Fig. 3. Sensitivity and specificity at each possible cutoff point for BDNF during depressive episodes. The Youden index is calculated as [(sensitivity + specificity) – 1]. Sensitivity indicates the probability that a case is correctly identified (true positive), and 1 – specificity is the probability that a nonsymptomatic subject is falsely identified as a case (false positive).

These results should be interpreted with caution given a number of limitations. Firstly, a naturalistic follow-up study with patients with current depressive episode is warranted to confirm prospectively the diagnosis. In the absence of a follow-up, we cannot rule out future hypomanic or manic episodes. However, our clinical diagnoses were based on stringent criteria, and were confirmed by an interviewer with expert in mood disorders field. Secondly, we indeed carried out an exploratory study, which is the first step in studies addressing diagnostic tests, matching *a posteriori* BD and MDD patients. Finally, a question that frequently emerges in studies about BDNF serum levels in mood disorders is the effects of medication. This is considered to be an important limitation in most of the studies (Cunha et al., 2006), since BDNF can be increased by mood stabilizers, antidepressants, and antipsychotics (Frey et al., 2006; Hashimoto et al., 2003; Jacobsen and Mork, 2004; Rantamaki et al., 2006; Omata et al., 2008; Tseng et al., 2008). However, all patients in the study were on medication, and rates of antidepressants and antipsychotics use were similar between groups. BD patients were on mood stabilizers, which is a conservative bias, as they increase BDNF levels (Hashimoto et al., 2003; Jacobsen and Mork, 2004; Frey et al., 2006; Rantamaki et al., 2006; Omata et al., 2008; Tseng et al., 2008). Moreover, in a recent study, serum BDNF levels were similar in medicated and drug-free patients with BD, suggesting that mood state is associated with BDNF levels independent of medication use (Oliveira et al., 2009). In order to approach clinical settings, a valuable diagnostic test in psychiatry should discriminate patients with and without use of psychiatry medication.

Serum BDNF holds the promises to help in differential diagnosis of unipolar and bipolar depression if added to clinical features. Use of combined serum BDNF levels and other neurotrophins would also be of interest in order to further improve the diagnostic accuracy in these conditions. Further prospective studies and replication of these findings are warranted.

Author contributions

BF designed the study, wrote the protocol, participated in data acquisition and interpretation, and was responsible for the analysis and interpretation of data, drafting the article and final approval of this version. CSG participated in study design, data acquisition and interpretation, drafting the article and final approval of this version. MK was responsible for drafting the article and final approval of this version. FK, MIL, and PBA were responsible for study design and interpretation of data, drafting the article and final approval of this version.

Role of funding sources

This study was supported by Stanley Medical Research Institute, NARSAD, INCT for Translational Medicine, CNPq, CAPES and FINE-HCPA. These agencies had no role in study design, acquisition and interpretation of data or writing the report.

Conflicts of interest

Flavio Kapczinski has received research grants from CNPq, CAPES, SMRI, NARSAD, Lilly, Astra-Zeneca, and Janssen. Clarissa S. Gama has received Grant/Research Support from CNPq, FINE-HCPA, Endeavour. She has been a paid speaker for Lundbeck and Astra Zeneca. Marcia Kauer-Sant'Anna has received research grants from Astra-Zeneca, FINE-HCPA, CNPq, CAPES, SMRI, NARSAD, and Lilly. Brisa Fernandes has declared no conflict of interest.

Acknowledgement

This study was supported by Stanley Medical Research Institute, NARSAD, INCT for Translational Medicine, CNPq, CAPES and FINE-HCPA.

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