The role of the brain-derived neurotrophic factors in the progression of bipolar disorders

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Introduction
Bipolar disorder (BPD) is considered to be the most prevalent psychiatric conditions, and is also among the most severe and debilitating. It was suggested that the brain-derived neurotrophic factor (BDNF) plays an important role in the pathophysiology of mood disorders. BDNF appears to be an unspecific biomarker of neuropsychiatric disorders characterized by neurodegenerative changes.

Aim
The aim of the study was to investigate the association between BDNFs and progression of BPDs.

Participants and methods
After receiving approval from the ethical committee in kasr El Eini hospital, 80 participants were randomly selected in a comparative cross sectional study. The sample consisted of two groups: a group of patients with BPDs ($n=40$), including patients with manic, depressive, mixed episode, or in remission, and a control group ($n=40$). The patients were recruited from the psychiatric outpatient clinic. Patients were diagnosed by a lecturer of psychiatry according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition criteria. Psychometric procedure: the Hamilton rating scale of depression and the Young Mania Rating Scale were used: laboratory: Radio-immune assay of BDNFs was carried out.

Results
Fifty-five percent of the patients in the bipolar group had three or more episodes. There was a statistically significant difference between the cases and the controls in the level of BDNF. There was a negative correlation between the BDNF and the number of episodes ($P=0.000$) and there was also a negative correlation between BDNF and disease duration ($P=0.000$). There were no correlations between BDNF and the diagnosis of BPD ($P=0.3$).

Conclusion
BDNF was lower than normal in bipolar patients and this was correlated with the number of episodes and duration of disease.

Keywords:
brain-derived neurotrophic factor, bipolar disorder, number of episodes

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Introduction

Mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BPD), are the most prevalent psychiatric conditions, and are also among the most severe and debilitating. However, the precise neurobiology underlying these disorders is currently unknown. One way to combat these disorders is to discover novel biomarkers for them. The development of such biomarkers will aid both in the diagnosis of mood disorders and in the development of effective psychiatric medications to treat them. A number of preclinical studies have suggested that the brain-derived neurotrophic factor (BDNF) plays an important role in the pathophysiology of mood disorders (Hashimoto, 2010).

BD has a poorer longer-term outcome than previously thought, with persistent cognitive impairment and functional decline. The neurobiological underpinnings that might underlie these changes remain unknown. Changes in the levels of BDNF and cytokines may be potentially responsible and BDNF was decreased only in those patients in the late stage of BPD. Moreover, when the levels were compared between patients at early and late stages of illness, there was a significant decrease in BDNF and IL-6 in the later stage of BD compared with the early stage and hence BDNF and continued elevations in cytokines; thus, these may have the potential to serve as markers of illness progression in BD (Kauer-Sant'Anna *et al.*, 2009).

BPD follows a staged trajectory in which persistence of illness is associated with a number of clinical features

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such as progressive shortening of the interepisode interval and decreased probability of treatment response. The biochemical foundation of this process appears to incorporate changes in inflammatory cytokines, cortisone, neurotrophins, and oxidative stress. There is a growing body of evidence to suggest that these markers may differ between the early and late stages of the disorder. The presence of a series of tangible targets raises the spectra of development of rational neuroprotective strategies, involving judicious use of current therapies and novel agents. Most of the currently used mood stabilizers exert effects on oxidative stress and neurotrophins, while novel potentially neuroprotective agents are being developed. These developments need to be combined with service initiatives to maximize the opportunities for early diagnosis and intervention (Berker *et al.*, 2010).

Aim

This study was conducted to examine the associations between BDNFs and progression of BPDs.

Participants and methods

After receiving consent from the ethical committee in Kasr El Eini hospital, and written informed consent, 80 participants were randomly selected in a comparative cross sectional study. The sample consisted of two groups: a group of patients with BPDs ($n = 40$), including patients with manic, depressive, mixed episode, or in remission, and a control group ($n = 40$). The patients were recruited from Kasr Al Aini psychiatric hospital (outpatient's clinic, inpatient department). The control group was recruited from among relatives of patients attending Kasr Al Aini outpatient's clinic. This was done over 6 months. Patients were diagnosed by a lecturer of psychiatry according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (APA, 1994) criteria. Both sexes were included and the age limit was 20–50 years. We excluded patients with other psychiatric disorders, mental retardation, organic mental disorders, and substance-induced psychiatric disorders. We compared patients with few episodes with patients with several episodes and compared both with the control group. The diagnosis of BPD in remission was established according to three factors: syndromal (DSM-IV criteria for disorder no longer met), symptomatic (Young Mania Rating Scale score ≤ 5 and Hamilton Depression Rating Scale score ≤ 8), and functional (regaining of premorbid occupational and residential status). These ratings were carried out according to Tohen *et al.* (2003).

Tools

Semistructural interview

A specially designed semistructural interview derived from the Kasr El Aini psychiatric sheet was used to cover demographic data, personal data, past history, and family history.

The structured clinical interview for the DSM Axis of disorders

The structured clinical interview for DSM-IV Axis I disorders provides broad coverage of Axis I psychiatric diagnosis according to DSM-IV (First *et al.*, 1997).

Hamilton Depression Rating Scale

This scale was formulated by Hamilton (1960, 1967). The original version consisted of 17 items and was later increased to 24 items by Klerman *et al.* (1985). The scale is not meant to be a diagnostic instrument (Preskorn and Fast, 1993). Hamilton Depression Rating Scale was found to distinguish between different groups of patients drawn from general practice, day-patient care, and inpatients (Carrol *et al.*, 1973). The concurrent validity is high (Kearns *et al.*, 1982). The interrater reliability of Hamilton Depression Rating Scale is also consistently high (Hamilton, 1960).

Young Mania Rating Scale

The Young Mania Rating Scale was developed in 1978, and the interrater reliability for the scale is high (Young *et al.*, 1978). The choice of items was made on the basis of published descriptions of the core symptoms of the manic phase of BPD and includes abnormalities that exist over the entire range of illness, from mild to severe. Depressive symptoms are not assessed. The severity rating for each of 11 items is based on the patient's subjective report of his or her condition over the previous 48 h and on the clinician's behavioral interview, with an emphasis on the clinician's observations. There are four items that are graded on a 0–8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), whereas the remaining seven items are graded on a 0–4 scale. These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients.

Laboratory

The radioimmune assay technique using the Quantikine human BDNF Immunoassay, which is a 3.5 h solid phase enzyme-linked immunosorbent assay designed to measure human BDNF in cell culture supernates, serum, and plasma, was used. It contains recombinant human BDNF expressed in Sf 21 cells and antibodies raised against the recombinant factor. This immunoassay has been shown to quantify the recombinant BDNF accurately. These results indicate that the Quantikine kit can be used to determine the relative mass values for natural human BDNF (R&D Systems Inc., Minneapolis, MN, USA).

The statistical methods

Data were statistically described in terms of mean ± SD, frequencies (number of cases), and percentages when appropriate. Comparison of age between the study groups was carried out using the Student *t*-test for independent samples. For comparing categorical data, the χ^2-test was performed. An exact test was used when the expected frequency was less than 5. Correlation between various variables was assessed using the Spearman rank correlation equation for nonnormal variables. *P*-values less than 0.05 were considered statistically significant. All statistical calculations were performed using computer programs Microsoft Excel 2007 (Microsoft Corporation, New York, USA) and Statistical Package for the Social Science (SPSS; SPSS Inc., Chicago, Illinois, USA) version 15 for Microsoft Windows.

Results

52.5% of the sample comprised men and 47.5% were women. Both groups were matched for age. Sixty five percent of the patients showed bipolar manic (Table 1). Fifty five percent of patients had more than three episodes (Table 2). There was a negative correlation between the BDNF and number of episodes ($P = 0.000$) (correlation coefficient = −0.636) and there was also a negative correlation between BDNF and disease duration ($P = 0.000$) (correlation coefficient = −0.666). There was no correlation between BDNF and the diagnosis of BPD ($P = 0.3$).

Discussion

BDNF is the most widely distributed neurotrophin in the central nervous system, where it plays several pivotal roles in synaptic plasticity and neuronal survival. As a consequence, BDNF has become a key target in the pathophysiology of several neurological and psychiatric diseases. Recent studies have consistently reported altered levels of BDNF in the circulation (i.e. serum or plasma) of patients with major depression, BPD, Alzheimer's disease, Huntington's disease, and Parkinson's disease. Correlations between serum BDNF levels and affective, cognitive, and motor symptoms have also been described. BDNF appears to be an unspecific biomarker of neuropsychiatric disorders characterized by neurodegenerative changes (Teixeira *et al.*, 2010). The aim of this study is to detect the differences in the levels of BDNF in bipolar patients and healthy controls and to detect the relation between the number of the episodes (disease progression) and the serum level of BDNF in patients with BPD.

We found significant differences between patients with BPD and healthy controls as regards the level of serum BDNF as 40% of the patients had a low serum level of BDNF versus 15% only of the healthy controls (Table 3). Also, we found that there was a negative correlation between the level of the BDNF and the number of episodes of BPD. There was also a negative correlation between the serum level of BDNF and the duration of illness.

The above result is supported by recent data, which suggest that changes in neuroplasticity, cell resilience, and connectivity are the main neuropathological findings in BD. Data from differential lines of research converge to BDNF as an important contributor to the neuroplasticity changes described among BD patients. BDNF has also been shown to decrease as the disorder progresses. These findings suggest that BDNF plays a central role in the progression of BD (Grande *et al.*, 2010).

Grande *et al.* (2010) also found that BDNF serum levels have been shown to be decreased in depressive and manic episodes, returning to normal levels in euthymia. But in our study we did not obtain this finding, perhaps due to the small sample in our study.

In addition, our study is in concordance with the study carried out by Kauer-Sant′Anna *et al.* (2009) to examine BDNF levels and their relationship in BD patients in the early and late stages of the disorder. BDNF was decreased only in those patients in the late stage of BPD. Moreover, BDNF levels were negatively correlated with the length of illness. When the levels were compared between patients at early and late stages of illness, there was a significant decrease in BDNF in the later stage of BD compared with the early stage.

Also, Machado-Vieira *et al.* (2007) investigated whether BDNF levels are altered during mania. Sixty participants (14 men and 46 women) were selected and included in the study. Thirty patients meeting the structured clinical interview for DSM-IV Axis I criteria for manic episodes were age and sex matched with 30 healthy controls. They found that the mean BDNF levels were significantly decreased in drug-free/naive patients compared with healthy controls. Severity of the manic episode presented a significantly negative correlation to plasma BDNF levels.

In contrast to our results (Table 4) are those obtained by Dias *et al.* (2009), who measured serum BDNF levels using an enzyme-linked immunosorbent assay method in 65 euthymic type I BD patients and 50 healthy controls and found no significant differences in serum BDNF levels in BD patients and healthy controls. They found significant positive associations between serum BDNF levels and illness duration, and manic and depressive episodes only in female BD patients. This difference can be explained by the fact that the patients were in the euthymic stage, but in our study, there were patients with different diagnosis (manic, depressive, euthymic).

As regards the relation between the BDNF and sex differences, 52.5% of the sample comprised men and 47.5% comprised women, both matched for age. The

Table 1 Different diagnoses of the bipolar group

	Number	Percentage
Bipolar depression	1	2.5
Bipolar manic	26	65
Bipolar mixed	2	5
Bipolar in remission	11	27.5

Table 2 Number of episodes

	Number	Percentage
<3	18	45
≥3	22	55

Table 3 Level of brain-derived neurotrophic factor

	Cases	Control	
	Number (%)	Number (%)	*P*
Within range	24 (60)	34 (85)	0.01
Low	16 (40)	6 (15)	

Table 4 Sex differences in the level of brain-derived neurotrophic factor

	Males	Females	
	Number (%)	Number (%)	*P*
Within range	13 (61.9)	11 (57.9)	0.7
Low	8 (38.1)	8 (42.1)	

results show no significant differences between male and female patients. This is also in contrast to the study carried out by Dias *et al.* (2009).

One of the limitations of this study will be the effect of drug taking by the patients. As all patients in our study were taking drugs, the possible question is that whether the drugs affect the level of BDNF. A study was carried out by De Oliveira *et al.* (2009), who examined the effect of the medication on the level of BDNF in BPD. BDNF serum levels were assessed using enzyme-linked immunosorbent assay. Serum BDNF levels in drug-free and medicated BD patients were decreased when compared with controls. The BDNF levels did not differ between medicated and drug-free BD patients. When analyzing patients according to mood states, serum BDNF levels were lower in BD patients during both manic and depressive episodes as compared with healthy controls. Results suggest that the association of lower serum BDNF and BD mood episodes is maintained even in medicated patients, which strengthens the notion that BDNF serum levels may be considered a biomarker of mood episodes.

The change in the level of neurotrophic factors in patients with BPD may be a new challenge in the treatment of mood disorders. Most of the currently used mood stabilizers exert effects on oxidative stress and neurotrophins, while novel potentially neuroprotective agents are being developed. These developments need to be combined with service initiatives to maximize the opportunities for early diagnosis and intervention (Berk *et al.*, 2010).

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Conflicts of interest

There are no conflicts of interest.

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