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Brain-derived neurotrophic factor (BDNF) and bipolar disorder

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is deemed to be associated with the psychopathology of bipolar I disorder (BD). However, studies focusing on accuracy of BDNF levels to differentiate these patients from healthy controls (HCs) are scarce. Over a discrete twelve-year period, we investigated serum BDNF levels in patients with BD and compared them to age-, sex- and body mass index (BMI)-matched HCs. There were lower serum BDNF levels in 83 samples with BD than in 222 HCs samples (5.7 ± 4.2 ng/ml vs. 12.2 ± 7.5 ng/ml, $F = 46.784$). Pearson's correlation test showed significant positive correlations between Young Mania Rating Scale scores and the BDNF levels among 61 manic patients ($\gamma = 0.339$). The receiver operating characteristic curve analysis showed BDNF levels demonstrated a moderate accuracy of being able to differentiate BD patients from HCs (AUC = 0.801). The most adequate cut-off points of the BDNF level were 6.74 ng/ml (sensitivity = 82.0%, specificity = 63.9%). Our results support that BDNF demonstrated moderate accuracy to distinguish BD patients from HCs. In the future, greater samples would be required to prove these results.

1. Introduction

Brain-derived neurotrophic factor (BDNF), which was first purified (Barde et al., 1982) after the unexpected discovery of the nerve growth factor (Levi-Montalcini and Hamburger, 1951), plays a pivotal role in neurogenesis and neuroplasticity. The mature form of BDNF is a 13 kDa polypeptide, which is originated from the precursor protein, pre-proBDNF, in the endoplasmic reticulum. ProBDNF (~32 kDa) is transformed to mature BDNF and BDNF pro-peptide (~17 kDa), the N-terminal fragment of proBDNF, after splits of the signal peptide. BDNF is detected throughout the brain and is especially rich in the cerebral cortex and hippocampus, brain areas crucial for the control of cognition, mood, and emotion (Post, 2007). Other tissues than the brain, including vascular endothelial cells, smooth muscle, and liver, also serve as origins of BDNF (Cassiman et al., 2001).

Duman, Heninger, and Nestler initially proposed the neurotrophic hypothesis in 1997 (Duman et al., 1997), and they assumed that stress would reduce the expression of BDNF and result in atrophy of stress-vulnerable hippocampal neurons. The assumption that the flawed function and diminished volume of these neurons may be associated with depression is supported by clinical imaging researches, which exhibited a dwindling size of specific brain areas. These discoveries establish the cornerstone for an avant-garde molecular and cellular hypothesis of depression. Therefore, major depressive disorder was depicted as being secondary to deviant neurogenesis in brain areas that govern emotion and memory, with deviant neurogenesis in relation to decreased expression of BDNF. After that Karege et al. carried out the pioneer study of BDNF levels in peripheral blood in 2002 (Karege et al., 2002). Kuhn, a physicist and science historian, had observed that, at any given time, researchers in a specific field are inclined to hold resembling basic hypotheses about their topic of study (Kuhn, 1962); this rapidly took place in the case for neurotrophic hypothesis, which, since its initial proposal, was promptly extended to cover BD by Laske in 2005 (Christoph Laske et al., 2005).

The study on peripheral BDNF was initially impelled to figure out the pathophysiology of mood disorders; however, in recent decades, BDNF has been applied to serve as a potential biomarker focusing on promotion of individualized medicine in psychiatry (Fernandes et al., 2009). BDNF was an manifest option, as its concentration in peripheral blood can be facilely measured compared to cerebrospinal fluid (CSF) study, and its concentration in plasma and serum is eminently associated with BDNF levels in CSF, since BDNF freely passes the blood – brain barrier (Pillai et al., 2010). On these grounds, peripheral BDNF levels have been investigated as a potential biomarker of diagnosis in BD. Manifold reports have capitalized on this “window to the brain”, with the great majority indicating reduced BDNF concentrations in these subjects (Lin et al., 2016; Nuernberg et al., 2016; Wu et al., 2017). BDNF was thought to be engaged in the pathophysiology of BD (Mansur

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et al., 2017; Pfaffenseller et al., 2018), and the alteration of BDNF in the blood of patients with BD have been supported by lots of meta-analyses (Fernandes et al., 2014; 2015; Munkholm et al., 2016). Nevertheless, meta-analyses could be impeded by heterogeneous patient populations, heterogeneity of BDNF assays and the lack of BDNF standard values. Furthermore, the capacity, efficacy, and relationship of peripheral BDNF concentrations to disease activity are not entirely established. To clarify these arguments, our study was designed to examine, in a "true-to-life" setting, the hypothesis that the BDNF serum level declines in BD patients during acute stages, and serum BDNF could serve as a biomarker to differentiate these patients from healthy controls (HCs).

We examine whether there is discrepancy in serum brain-derived neurotrophic factor levels between patients with BD during acute manic stage or acute depressive stage and HCs. We also examined whether the serum brain-derived neurotrophic factor levels could be applied to discriminate these acute patients from HCs.

2. Methods

2.1. Study design and participants

We aimed to investigate the serum BDNF levels in patients with BD compared to age-, sex- and body mass index (BMI)- matched HCs by clinical observation within a twelve-year period (Dec. 2003 ~ Nov. 2004, Aug. 2005 ~ Nov. 2006, Aug. 2007 ~ Jul. 2012, Nov. 2012 ~ Oct. 2013, Aug. 2014 ~ Nov. 2017). Patients and HCs were enrolled at Chang Gung Memorial Hospital in Kaohsiung (CGMHK), Taiwan. Patients with BD in acute phases were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 1997) by the psychiatrists at CGMHK. Since medication status and effect of this on BDNF levels were reported (Molendijk et al., 2011; Molendijk et al., 2014), the patients were off medication for at least one week. According to the diagnosis, the severity of symptoms was assessed using the Young Mania Rating Scale score (YMRS) (Young et al., 1978) or 17-item Hamilton Depression Rating Scale (17-item HDRS) (Hamilton, 1960).

The medical students and staff, recruited as the HCs at CGMHK, were evaluated by Tiao-Lai Huang, via the SCID (First et al., 1997) or the Chinese Health Questionnaire-12 (Chong and Wilkinson, 1989) based on DSM-III-R, DSM-IV, DSM-IV-TR and DSM-5 to exclude present and past major and minor mental illnesses (illegal substance use disorder, alcohol abuse/dependence, personality disorder, schizophrenia, affective disorder and anxiety disorder). Some data had been published (Chen and Huang, 2011; Chiou and Huang, 2017a, b; Huang and Lee, 2006; Huang et al., 2008), and we progressively added the samples into this study. All HCs and patients were screened to exclude the persons with any systemic disease including lung, liver, kidney, thyroid and heart diseases. They had neither acute infections nor allergic reactions.

Approval was obtained from the Chang Gung Memorial Hospital Institutional Review Board. All subjects enlisted in the study provided written informed consent for their participation in the study.

2.2. Laboratory analysis

The participants' venous blood samples (5 ml) were collected and serum BDNF levels were assessed by an ELISA Kit (BDNF Emax Immunoassay System, Promega Co, USA). The storage temperature is 4 °C. All venous blood samples were taken after the patient had fasted for at least 8 h. Absorbencies were identified utilizing a microtiter plate reader (absorbency at 450 nm). The intra-assay and inter-assay variations were both less than 10%.

2.3. Statistical analysis

The subjects were divided into different diagnostic groups (i.e., patients with BD or HCs). Student's *t*-tests were applied to test parameters, containing age, sex, and BMI, of the patients and control groups. Relationship of BDNF levels and the severity scores was examined by means of Pearson's correlation test. Previous studies showed that parameters, including ages and sex, affect circulating BDNF levels in peripheral blood (Elfving et al., 2012). Therefore, BDNF levels of the patient and control groups were compared using an analysis of covariance (ANCOVA) with sex, age and BMI adjustments for group mean differences in different groups and sex.

The estimation validity of BDNF to discriminate patients from HCs was investigated using receiver operating characteristic (ROC) analyses with calculations of the area under the ROC curve (AUC), sensitivity and specificity. The suitable BDNF cutoff level was defined as the level that showed the greatest sensitivity among the greatest values on the Youden index [(sensitivity + specificity) - 1]. The Youden index is thought to be an efficient index for determining the suitable cutoff score (Perkins and Schisterman, 2006).

All results are showed as means ± standard deviation. Data analysis was calculated using IBM SPSS Statistics 12. Two-tailed significance values were adopted and significance levels were determined at 0.05.

3. Results

3.1. Demographic data

Overall, we recruited 83 patient samples during acute episodes and 222 HC samples. The patient samples consisted of 61 bipolar mania and 22 bipolar depression diagnoses.

Table 1 exhibits that the patients with bipolar I disorder were not significantly different with the HCs in terms of age, sex and BMI. (36.8 ± 11.4 years vs. 34.3 ± 7.0 years, df = 106.3, p = 0.064; 0.46 ± 0.50 vs. 0.36 ± 0.48, df = 142.0, p = 0.129; 23.9 ± 4.7 kg/m^2 vs. 22.8 ± 3.5 kg/m^2, df = 118.9, p = 0.059). In subgroups, the male

Table 1
Serum BDNF levels and demographic data of subjects with bipolar I disorder and healthy controls.

Diagnostic groups		Age (years)	Sex♠	BMI (kg/m^2)	Serum BDNF levels (ng/ml)	Manic group/ Depressive group	YMRS	17-item HDRS
T	**SUBJECTS** *(n = 83)*	36.8 ± 11.4	0.46 ± 0.50	23.9 ± 4.7	5.7 ± 4.2	**SUBJECTS** *(n = 61)(n = 22)*	35.6 ± 8.1	42.0 ± 7.6
	Healthy controls *(n = 222)*	34.3 ± 7.0	0.36 ± 0.48	22.8 ± 3.5	12.2 ± 7.5	N.A.		
P value		0.064	0.129	0.059	< 0.001*			
M	**SUBJECTS** *(n = 38)*	39.7 ± 11.3	N.A.	24.0 ± 4.4	5.7 ± 4.1	**SUBJECTS** *(n = 31)(n = 7)*	35.7 ± 8.2	46.4 ± 8.6
	Healthy controls *(n = 80)*	33.7 ± 6.3		24.7 ± 3.3	11.6 ± 5.9	N.A.		
P value		0.004*		0.333	< 0.001*			
F	**SUBJECTS** *(n = 45)*	34.3 ± 10.9		23.8 ± 4.9	5.7 ± 4.3	**SUBJECTS** *(n = 30)(n = 15)*	35.5 ± 8.2	39.9 ± 6.4
	Healthy controls *(n = 142)*	34.6 ± 7.4		21.8 ± 3.2	12.5 ± 8.3	N.A.		
P value		0.859		0.011*	< 0.001*			

T = Total. M = Male. F = Female. SUBJECTS = Subjects with bipolar I disorder. BMI = body mass index. BDNF = brain-derived neurotrophic factor. YMRS, Young Mania Rating Scale. 17-item HDRS, 17-item Hamilton Depression Rating Scale.

♠ Female = 0. Male = 1.

* $p < 0.05$.

HCs were significantly younger than male patients (33.7 ± 6.3 years vs. 39.7 ± 11.3 years, df = 48.1, p = 0.004), and female patients had greater BMI than female HCs (23.8 ± 4.9 kg/m^2 vs. 21.8 ± 3.2 kg/m^2, df = 56.6, p = 0.011).

3.2. BDNF levels in patients and HCs

The ANCOVAs were established with diagnostic groups as the independent variables and BDNF levels as the dependent variables; age, sex and BMI were the covariates.

Table 1 depicts that the serum BDNF levels in patients with bipolar I disorder were significantly lower than those in HCs (5.7 ± 4.2 ng/ml vs. 12.2 ± 7.5 ng/ml, $F = 46.784$, $p < 0.001$). There were also significantly differences in BDNF levels between male and female subgroups (5.7 ± 4.1 ng/ml vs. 11.6 ± 5.9 ng/ml, $F = 19.688$, $p < 0.001$; 5.7 ± 4.3 ng/ml vs. 12.5 ± 8.3 ng/ml, $F = 29.546$, $p < 0.001$). Pearson's correlation test revealed that significant positive correlations between YMRS scores and the BDNF levels among 61 manic patients ($\gamma = 0.339$, P = 0.007). But 17-item HDRS scores had no correlation with BDNF levels among 22 depressed patients ($\gamma = -0.090$, $P = 0.690$).

3.3. BDNF levels in differentiation between patients and HCs

The ROC curve analysis (Fig. 1A) shows that BDNF levels demonstrated a moderate validity of being able to distinguish between patients with bipolar disorder and HCs (AUC = 0.801, standard error = 0.028, asymptotic 95% confidential interval = 0.746 to 0.855). The optimal cut-off point for the BDNF level was 6.74 ng/ml (sensitivity = 82.0%, specificity = 63.9%). BDNF levels demonstrated similar diagnostic power in male (Fig. 1 A1) and female subgroups (Fig. 1 A2) (AUC = 0.803, sensitivity = 80.0% and specificity = 68.4% at the BDNF level of 6.75 ng/ml; AUC = 0.800, sensitivity = 84.5% and specificity = 60.0% at the BDNF level of 6.60 ng/ml, respectively).

4. Discussion

The major findings in this study, which concentrated on patients in acute states, are as follows: (1) There were lower serum BDNF levels in BD patients than HCs. (2) The receiver operating characteristic curve analysis showed that BDNF levels demonstrated a moderate accuracy of being able to distinguish BD patients from HCs.

4.1. BDNF levels in BD patients and HCs

We demonstrated that the serum BDNF levels in patients with BD were significantly lower than in HCs, which was in line with the outcome of recent meta-analyses (Fernandes et al., 2015). Our results, as well as those previously reported (Piccinni et al., 2015; Wu et al., 2017), reinforce the hypothesis that the down-regulated BDNF expression, not only plays a pivotal role in neuroplasticity, developmental processes and reconstruction, but also relates to the pathophysiology of BD.

We found that YMRS scores were related to the BDNF levels among manic patients, which was in line with previous studies (Cunha et al., 2006; de Oliveira et al., 2009; Machado-Vieira et al., 2007), but differed with others (Barbosa et al., 2010; Munkholm et al., 2014; Tramontina et al., 2009). Although the above results required replication in further studies with larger samples, we assumed that BDNF plays a pivotal role in eliciting the dynamic clinical and neurobiological changes observed in diverse illness stages.

Although the above results required replication in further studies with larger samples, we assumed that BDNF plays a pivotal role in eliciting the dynamic clinical and neurobiological changes observed in diverse illness stages.

4.2. The accuracy of BDNF to distinguish BD patients from HCs

Exact diagnosis of mental illness is critical for the treatment. However, no appropriate biomarker has yet been found to be applied in the diagnosis of any psychiatric disorder, and the diagnostic criteria still mainly rely on clinical interviews. And there is restriction on the present diagnostic criteria. It is not unbiased for psychiatrists to diagnose mental illness solely on the basis of interviews. Furthermore, treatment may be improper because of inaccurate diagnosis. In recent years, previous scholars proposed that BDNF is a physiopathological biomarker in psychiatry (Fernandes et al., 2014), but research performed to examine the role of BDNF in differentiating BD patients from HCs was scarce. We demonstrated that BDNF levels demonstrated a moderate accuracy of being able to discriminate BD patients from HCs. Rabie et al. (2014) also showed that serum BDNF possessed good accuracy to discriminate BD patients from HCs with AUC higher than 0.89. But Chen et al. (2017) failed to excellently distinguish these patients from HCs solely by BDNF. Multiple-assay methods may play a role as biomarker better, as recently has been investigated (Chen et al., 2017; Li et al., 2018).

Some limitations should be kept in mind when explaining the data in this study. The primary limitation of this study is that there were some epidemiological differences between patients and HCs. However, these variables were ameliorated by means of ANCOVA. Furthermore, limitation is that the impacts of sleep problems (Giese et al., 2014), smoking (Bus et al., 2011) or seasonality (Molendijk et al., 2012) were

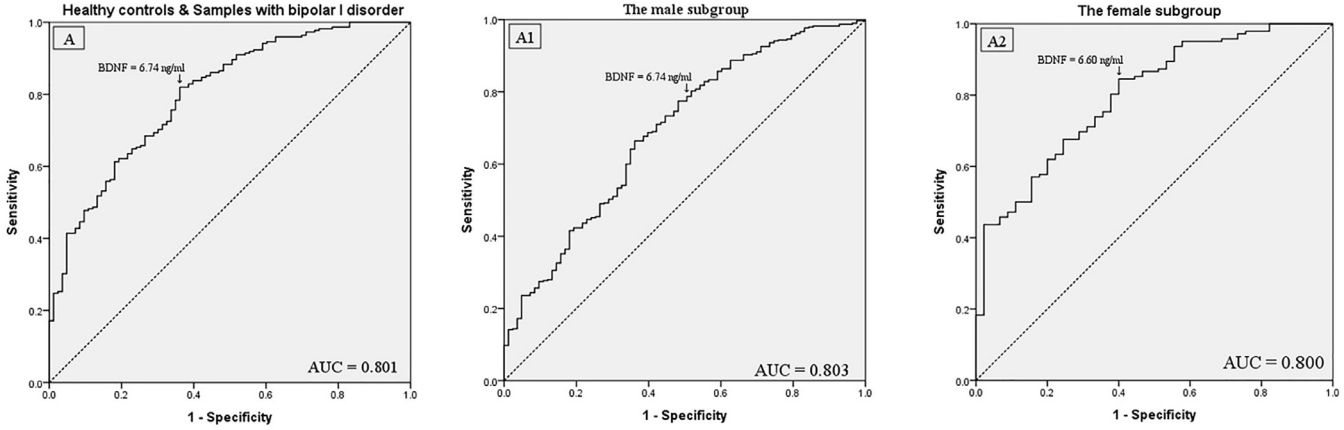

Fig. 1. Receiver operating characteristic (ROC) curve using brain derived neurotrophic factor (BDNF) to discriminate healthy controls (N = 222) from: (A) samples with bipolar I disorder (N = 83). The subgroup A1 means male subgroup, and the subgroup A2 means the female subgroup.

not studied, since these factors have been reported to affect BDNF expression. Lastly, one week is insufficient to preclude the effects of medication on BDNF level.

Our results demonstrated BD patients had lower serum BDNF levels than HCs. The serum BDNF levels showed moderate accuracy to distinguish BD patients from HCs. In the future, studies with greater samples will be needed to study the ability of BDNF to discriminate BD patients with HCs.

Disclosure of interest

The authors declare no financial or other conflicts of interest.

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Declarations of interest

None

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References

Barbosa, I.G., Huguet, R.B., Mendonca, V.A., Neves, F.S., Reis, H.J., Bauer, M.E., Janka, Z., Palotas, A., Teixeira, A.L., 2010. Increased plasma levels of brain-derived neurotrophic factor in patients with long-term bipolar disorder. Neurosci. Lett. 475 (2), 95–98.

Barde, Y.A., Edgar, D., Thoenen, H., 1982. Purification of a new neurotrophic factor from mammalian brain. EMBO J. 1 (5), 549–553.

Bus, B.A., Molendijk, M.L., Penninx, B.J., Buitelaar, J.K., Kenis, G., Prickaerts, J., Elzinga, B.M., Voshaar, R.C., 2011. Determinants of serum brain-derived neurotrophic factor. Psychoneuroendocrinology 36 (2), 228–239.

Cassiman, D., Denef, C., Desmet, V.J., Roskams, T., 2001. Human and rat hepatic stellate cells express neurotrophins and neurotrophin receptors. Hepatology 33 (1), 148–158.

Chen, C.C., Huang, T.L., 2011. Effects of antipsychotics on the serum BDNF levels in schizophrenia. Psychiatry Res. 189 (3), 327–330.

Chen, S., Jiang, H., Liu, Y., Hou, Z., Yue, Y., Zhang, Y., Zhao, F., Xu, Z., Li, Y., Mou, X., Li, L., Wang, T., Zhao, J., Han, C., Sui, Y., Wang, M., Yang, Z., Lu, Y., Zhu, Y., Li, J., Shen, X., Sun, F., Chen, Q., Chen, H., Yuan, Y., 2017. Combined serum levels of multiple proteins in tPA-BDNF pathway may aid the diagnosis of five mental disorders. Sci. Rep. 7 (1), 6871.

Chiou, Y.J., Huang, T.L., 2017a. Serum Brain-Derived Neurotrophic Factors in Taiwanese Patients with Drug-Naive First-Episode Major Depressive Disorder: effects of Antidepressants. Int. J. Neuropsychopharmacol. 20 (3), 213–218.

Chiou, Y.J., Huang, T.L., 2017b. Serum brain-derived neurotrophic factors in Taiwanese patients with drug-naive first-episode schizophrenia: effects of antipsychotics. World J. Biol. Psychiatry 18 (5), 382–391.

Chong, M.Y., Wilkinson, G., 1989. Validation of 30- and 12-item versions of the Chinese Health Questionnaire (CHQ) in patients admitted for general health screening. Psychol. Med. 19 (2), 495–505.

Christoph Laske, E.S., Gerhard, W Eschweiler, Andreas Wittorf, E., Richartz-Salzburger, M., Bartels, G., Buchkremer, K.Schott, 2005. Brain-derived neurotrophic factor (BDNF) in serum of patients with mania, major depression and healthy controls. Neurol. Psychiatry Brain Res. 12 (1), 25–28.

Cunha, A.B., Frey, B.N., Andreazza, A.C., Goi, J.D., Rosa, A.R., Goncalves, C.A., Santin, A., Kapczinski, F., 2006. Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci .Lett. 398 (3), 215–219.

de Oliveira, G.S., Cereser, K.M., Fernandes, B.S., Kauer-Sant'Anna, M., Fries, G.R., Stertz, L., Aguiar, B., Pfaffenseller, B., Kapczinski, F., 2009. Decreased brain-derived neurotrophic factor in medicated and drug-free bipolar patients. J. Psychiatr. Res. 43 (14), 1171–1174.

Duman, R.S., Heninger, G.R., Nestler, E.J., 1997. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 54 (7), 597–606.

Elfving, B., Buttenschon, H.N., Foldager, L., Poulsen, P.H., Andersen, J.H., Grynderup, M.B., Hansen, A.M., Kolstad, H.A., Kaerlev, L., Mikkelsen, S., Thomsen, J.F., Borglum, A.D., Wegener, G., Mors, O., 2012. Depression, the Val66Met polymorphism, age, and gender influence the serum BDNF level. J. Psychiatry Res. 46 (9), 1118–1125.

Fernandes, B.S., Berk, M., Turck, C.W., Steiner, J., Goncalves, C.A., 2014. Decreased peripheral brain-derived neurotrophic factor levels are a biomarker of disease activity in major psychiatric disorders: a comparative meta-analysis. Mol. Psychiatry 19 (7), 750–751.

Fernandes, B.S., Gama, C.S., Kauer-Sant'Anna, M., Lobato, M.I., Belmonte-de-Abreu, P., Kapczinski, F., 2009. Serum brain-derived neurotrophic factor in bipolar and unipolar depression: a potential adjunctive tool for differential diagnosis. J. Psychiatry Res. 43 (15), 1200–1204.

Fernandes, B.S., Molendijk, M.L., Kohler, C.A., Soares, J.C., Leite, C.M., Machado-Vieira, R., Ribeiro, T.L., Silva, J.C., Sales, P.M., Quevedo, J., Oertel-Knochel, V., Vieta, E., Gonzalez-Pinto, A., Berk, M., Carvalho, A.F., 2015. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med. 13, 289.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1997. User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV). American Psychiatric Press, Washington, DC.

Giese, M., Unternahrer, E., Huttig, H., Beck, J., Brand, S., Calabrese, P., Holsboer-Trachsler, E., Eckert, A., 2014. BDNF: an indicator of insomnia? Mol. Psychiatry 19 (2), 151–152.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Huang, T.L., Lee, C.T., 2006. Associations between serum brain-derived neurotrophic factor levels and clinical phenotypes in schizophrenia patients. J. Psychiatry Res. 40 (7), 664–668.

Huang, T.L., Lee, C.T., Liu, Y.L., 2008. Serum brain-derived neurotrophic factor levels in patients with major depression: effects of antidepressants. J. Psychiatry Res. 42 (7), 521–525.

Karege, F., Perret, G., Bondolfi, G., Schwald, M., Bertschy, G., Aubry, J.M., 2002. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res. 109 (2), 143–148.

Kuhn, T.S., 1962. Historical structure of scientific discovery. Science 136 (3518), 760–764.

Levi-Montalcini, R., Hamburger, V., 1951. Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. J. Exp. Zool. 116 (2), 321–361.

Li, C., Tao, H., Yang, X., Zhang, X., Liu, Y., Tang, Y., Tang, A., 2018. Assessment of a combination of Serum Proteins as potential biomarkers to clinically predict Schizophrenia. Int. J. Med. Sci. 15 (9), 900–906.

Lin, C.C., Lee, C.T., Lo, Y.T., Huang, T.L., 2016. Brain-derived neurotrophic factor protein and mRNA levels in patients with bipolar mania - A preliminary study. Biomed. J. 39 (4), 272–276.

Machado-Vieira, R., Dietrich, M.O., Leke, R., Cereser, V.H., Zanatto, V., Kapczinski, F., Souza, D.O., Portela, L.V., Gentil, V., 2007. Decreased plasma brain derived neurotrophic factor levels in unmedicated bipolar patients during manic episode. Biol. Psychiatry 61 (2), 142–144.

Mansur, R.B., Brietzke, E., McIntyre, R.S., Cao, B., Lee, Y., Japiassu, L., Chen, K., Lu, R., Lu, W., Li, T., Xu, G., Lin, K., 2017. BDNF and BMI effects on brain structures of bipolar offspring: results from the global mood and brain science initiative. Acta Psychiatry Scand. 136 (6), 607–614.

Molendijk, M.L., Bus, B.A., Spinhoven, P., Penninx, B.W., Kenis, G., Prickaerts, J., Voshaar, R.C., Elzinga, B.M., 2011. Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment. Mol. Psychiatry 16 (11), 1088–1095.

Molendijk, M.L., Haffmans, J.P., Bus, B.A., Spinhoven, P., Penninx, B.W., Prickaerts, J., Oude Voshaar, R.C., Elzinga, B.M., 2012. Serum BDNF concentrations show strong seasonal variation and correlations with the amount of ambient sunlight. PLoS One 7 (11), e48046.

Molendijk, M.L., Spinhoven, P., Polak, M., Bus, B.A., Penninx, B.W., Elzinga, B.M., 2014. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N = 9484). Mol. Psychiatry 19 (7), 791–800.

Munkholm, K., Pedersen, B.K., Kessing, L.V., Vinberg, M., 2014. Elevated levels of plasma brain derived neurotrophic factor in rapid cycling bipolar disorder patients. Psychoneuroendocrinology 47, 199–211.

Munkholm, K., Vinberg, M., Kessing, L.V., 2016. Peripheral blood brain-derived neurotrophic factor in bipolar disorder: a comprehensive systematic review and meta-analysis. Mol. Psychiatry 21 (2), 216–228.

Nuernberg, G.L., Aguiar, B., Bristot, G., Fleck, M.P., Rocha, N.S., 2016. Brain-derived neurotrophic factor increase during treatment in severe mental illness inpatients. Transl. Psychiatry 6 (12), e985.

Perkins, N.J., Schisterman, E.F., 2006. The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am. J. Epidemiol. 163 (7), 670–675.

Pfaffenseller, B., Kapczinski, F., Gallitano, A.L., Klamt, F., 2018. EGR3 Immediate Early Gene and the Brain-Derived Neurotrophic Factor in Bipolar Disorder. Front Behav. Neurosci. 12, 15.

Piccinni, A., Veltri, A., Costanzo, D., Vanelli, F., Franceschini, C., Moroni, I., Domenici, L., Origlia, N., Marazziti, D., Akiskal, H.S., Dell'Osso, L., 2015. Decreased plasma levels of brain-derived neurotrophic factor (BDNF) during mixed episodes of bipolar disorder. J. Affect. Disord. 171, 167–170.

Pillai, A., Kale, A., Joshi, S., Naphade, N., Raju, M.S., Nasrallah, H., Mahadik, S.P., 2010.

Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. Int. J. Neuropsychopharmacol. 13 (4), 535–539.
Post, R.M., 2007. Role of BDNF in bipolar and unipolar disorder: clinical and theoretical implications. J. Psychiatry Res. 41 (12), 979–990.
Rabie, M.A., Mohsen, M., Ibrahim, M., El-Sawy Mahmoud, R., 2014. Serum level of brain derived neurotrophic factor (BDNF) among patients with bipolar disorder. J. Affect Disord. 162, 67–72.
Tramontina, J.F., Andreazza, A.C., Kauer-Sant'anna, M., Stertz, L., Goi, J., Chiarani, F., Kapczinski, F., 2009. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci. Lett. 452 (2), 111–113.
Wu, Y.-S., Chiou, Y.-J., Huang, T.-L., 2017. Associations between Serum Brain-Derived Neurotrophic Factors and Bipolar Disorder. Neuropsychiatry (London) 7 (6), 968–973.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.