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The *BDNF* Val66Met polymorphism and plasma brain-derived neurotrophic factor levels in Han Chinese patients with bipolar disorder and schizophrenia

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Abstract

Objective—Brain-derived neurotrophic factor (BDNF) is widely distributed in the peripheral and central nervous systems. BDNF and its gene polymorphism may be important in synaptic plasticity and neuron survival, and may become a key target in the pathophysiology of several mental illnesses. To elucidate the role of BDNF, we compared the plasma BDNF levels and the BDNF Val66Met gene variants effect in several mental disorders.

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Author Contributions

SLC and RBL wrote the first draft. SYL, YHC, SHC and CHC managed the lab work and statistics. TYW, PSC, IHL, TLY and YKY managed the participant recruitment. JSH supervised this work and edited the manuscript.

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Conflict of interest

All of the authors declared no conflicts of interest.

Method—We enrolled 644 participants: 177 patients with bipolar I disorder (BP-I), 190 with bipolar II disorder (BP-II), 151 with schizophrenia, and 126 healthy controls. Their plasma BDNF levels and *BDNF* Val66Met single nucleotide polymorphisms (SNP) were checked before pharmacological treatment.

Results—Plasma levels of BDNF were significantly lower in patients with schizophrenia than in healthy controls and patients with bipolar disorder ($F = 37.667$, $p < 0.001$); the distribution of the *BDNF* Val66Met SNP was not different between groups ($\chi^2 = 5.289$, $p = 0.507$). Nor were plasma BDNF levels significantly different between Met/Met, Met/Val, and Val/Val carriers in each group, which indicated that the *BDNF* Val66Met SNP did not influence plasma BDNF levels in our participants. Plasma BDNF levels were, however, significantly negatively correlated with depression scores in patients with bipolar disorder and with negative symptoms in patients with schizophrenia.

Conclusion—We conclude that plasma BDNF profiles in different mental disorders are not affected by *BDNF* Val66Met gene variants, but by the process and progression of the illness itself.

Keywords

BDNF Val66Met gene; bipolar disorders; plasma BDNF; schizophrenia

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the nerve growth factor family, which is involved in neuron survival and differentiation (Mizuno et al., 1994), synaptogenesis, and maintenance (Ohira and Hayashi, 2009). BDNF is a basic dimeric protein that has to be maintained throughout life to preserve essential functions such as learning and memory. In humans, BDNF is expressed in the postnatal brain, with the highest mRNA levels in the hippocampus and cortex (Webster et al., 2002). BDNF promotes the survival of a wide range of neurons, which suggests that BDNF might be a biomarker for the pathophysiology of mental illness. For instance, the effects of BDNF on dopaminergic neurons might be associated with the pathogenesis of schizophrenia, which is apparently related to dopaminergic dysfunction (Hyman et al., 1991). Moreover, because BDNF acts on the primary sensory and cholinergic neurons of the basal forebrain (Alderson et al., 1990), its dysfunction might also be related to mood disorders and schizophrenia (Dilsaver, 1986, Berman et al., 2007). Thus, the plasma brain BDNF levels in these mental illnesses have been studied. In manic and depressed patients with bipolar disorder, serum BDNF levels are significantly lower than normal (Cunha et al., 2006, Monteleone et al., 2008). Low serum BDNF levels during acute manic and depressive episodes recover to levels similar to those of controls after patients have been treated and return to a euthymic state. BDNF levels in euthymic also decrease with age and the length of the illness (Fernandes et al., 2011). In patients with schizophrenia, BDNF data are inconsistent. Some studies show BDNF levels significantly lower than normal in serum (Toyooka et al., 2002) and related brain areas (Iritani et al., 2003, Weickert et al., 2003), but others show unaltered (Shimizu et al., 2003) or higher than normal serum BDNF levels in patients with schizophrenia (Gama et al., 2007). Furthermore, postmortem patients with schizophrenia also have elevated BDNF levels in the cortex and hippocampus (Takahashi et al., 2000). However, because of a dearth

of published reports, small sample sizes, and inconsistent results, the role of BDNF in mental illness requires additional study.

In contrast, a number of genetic association studies have shown that a single nucleotide polymorphism (SNP) in the promoter of the *BDNF* gene at codon 66 (G196A, rs6265) is associated with mental illness. The SNP in the *BDNF* gene leads to a valine (Val) to methionine (Met) substitution at codon 66 in the pro domain (BDNFMet). This BDNF polymorphism (Val66Met) dramatically alters the intracellular trafficking and packaging of pro-BDNF, and reduces the trafficking and secretion of BDNF protein (Egan et al., 2003). In Caucasian patients with bipolar disorder, *BDNFMet66* allele carriers are likely to have smaller regional brain volumes and more total cerebrospinal fluid (CSF) in the lateral ventricles than do Val66 homozygote carriers (Teh et al., 2012). A Val66Met polymorphism in the *BDNF* gene and one in bipolar disorder have been tentatively associated (Fan and Sklar, 2008). In patients with schizophrenia, this Val66Met SNP in the *BDNF* gene has also been associated with aggressive behavior (Spalletta et al., 2010), the executive function (Lu et al., 2012), obsessive-compulsive symptoms (Hashim et al., 2012), and prefrontal brain function (Whalley et al., 2010). One meta-analysis of case-control studies (Gratacos et al., 2007) found a relationship between the SNP and substance-related disorders, eating disorders, and schizophrenia. Another meta-analysis, however, found no association between the SNP and schizophrenia or bipolar disorder (Kanazawa et al., 2007). Thus, the role of the *BDNF* Val66Met SNP in mental illness requires additional study. The inconsistent BDNF expression profiles might be attributable to the very small sample sizes of the studies on these mental disorders. In addition, correlations between different mental disorders and the *BDNF* Val/Met SNP and plasma BDNF levels have not been reported. To clarify the plasma BDNF profile in human mental disorders, we included a large number of healthy controls and patients with bipolar I disorder, bipolar II disorder, and schizophrenia in the present study. Their plasma BDNF levels were analyzed and compared. The *BDNF* Val66Met SNP variant distribution in these participants was also studied to determine its association with these groups. Because the *BDNF* Val66Met variant inhibits the trafficking and secretion of BDNF protein, we also studied its effect on the plasma BDNF protein levels in all participants.

2. Experimental procedure

2.1. Participants

From the Department of Psychiatry at National Cheng Kung University Hospital and the National Defense Medical Center, we enrolled 644 Taiwanese participants: 126 healthy controls, 177 with bipolar I disorder (BP-I), 190 with bipolar II disorder (BP-II), and 151 with schizophrenia. The Chinese version of the Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L), which has good reliability and validity, was used to screen all participants' psychiatric conditions, to confirm that they fit DSM-IV diagnostic criteria, and to verify that the participants had no physical and mental comorbidities (Endicott and Spitzer, 1978, Huang et al., 2004).

The healthy control group included 126 volunteers recruited from the hospital staff and community. At first, we put up a notice in the hospitals and communities to recruit healthy

volunteers. The volunteers were first screened by telephone. Subjects whom had sleep disorder, substance abuse, mood swing or possible psychiatric traits in life were first excluded. The remained volunteers were then carefully screened. The Chinese version of the SADS-L was used to screen the psychiatric conditions of the controls. All of them were free of present and past major and minor mental illnesses (affective disorder, schizophrenia, anxiety disorder, personality disorder, alcohol abuse/dependence, and illegal substance use disorders). Additionally, none of the first-degree relatives of the healthy controls had a history of psychiatric disorder.

Mood disorder diagnoses were made according to DSM-IV criteria, except that, for bipolar II disorder, the 4 day duration criterion for hypomania was replaced with a 2-day cutoff duration because the 4-day minimum might not be evidence-based (Dunner, P. Goodnick, Editor. 1998) and because the 2-day cutoff has been supported by several previous reports (Benazzi and Akiskal, 2006). The inclusion criteria for patients with BP were as follows: 1) being a psychiatric inpatient and or outpatient who sought psychiatric care or had been referred for psychiatric evaluation because they were clinically suspected of having a mood disorder; 2) a diagnosis of bipolar I or II disorder based on DSM-IV criteria and confirmed by the Chinese version of the modified SADS-L; 3) a man or woman between 18 and 65 years old; 4) a Hamilton Depression Rating Scale (HDRS) score of at least 18 or a Young Mania Rating Scale (YMRS) score of at least 14 at the screening stage; 5) drug naïve or at least for the medications normally prescribed for bipolar disorder; 6) could communicate in Mandarin Chinese or Taiwanese; and 7) an informed consent form signed by the patient or a legal representative.

Patients with schizophrenia were screened using the modified Chinese version of the SADS-L. They were checked for comorbid psychiatric conditions and to verify that their diagnosis fit DSM-IV diagnostic criteria. The inclusion criteria for patients with schizophrenia were: 1) being a psychiatric inpatient and or outpatient who sought psychiatric care or had been referred for psychiatric evaluation because they were clinically suspected of having a psychosis symptom; 2) a diagnosis of schizophrenia based on DSM-IV criteria and confirmed by the Chinese version of the modified SADS-L; 3) a man or woman between 18 and 65 years old; 4) drug naïve or at least for the medications normally prescribed for schizophrenia; 5) could communicate in Mandarin Chinese or Taiwanese; and 6) an informed consent form signed by the patient or a legal representative.

The following were the exclusion criteria for patients with bipolar disorder and schizophrenia: 1) women who were pregnant or had childbearing potential under the specific physiological condition; 2) any major mental illness other than BP or schizophrenia, including alcoholism and illegal substance use disorder; 3) any clinically significant comorbid medical condition, e.g., cardiac, hepatic, or renal disease, with current evidence of poor control of that disease.

Study design—The research protocol was approved by the institutional review board for the Protection of Human Subjects at National Cheng Kung University Hospital and the National Defense Medical Center. To minimize the effect of ethnic differences on gene frequencies, only participants who were unrelated and came from the Han Chinese

population in Taiwan were recruited. Before the participants signed a written informed consent form, all procedures were fully explained to them.

2.2. Collecting and assessing blood samples

Ten milliliters of whole blood was drawn from the antecubital vein of each study participant. Blood were collected in tubes with EDTA (ethylenediaminetetraacetic acid) for plasma preparation. Plasma was isolated from the whole blood after it had been centrifuged at 3000 *g* for 15 min at 4°C and then immediately stored at –80°C. Plasma BDNF levels were quantified using enzyme-linked immunosorbent assays (ELISA). A kit (Quantikine Human Cytokine Kit; R&D Systems) and an ELISA reader (SpectraMax-M2; Molecular Devices) were used to analyze plasma BDNF levels.

2.3. Genotyping

DNA was extracted from the venous blood using a salting method. The *G196A (Val66Met)* *BDNF* gene polymorphism was examined using a polymerase chain reaction (PCR) plus restriction fragment length polymorphism analysis. The following primers were used:

Forward: 5'-AGA GGC TTG ACA TCA TTG GCT-3';

Reverse: 5'-CGT GTA CAA GTC TGC GTC CT-3'.

DNA fragments were amplified in an Eppendorf thermal cycler and then digested overnight by PmlI restriction endonuclease (MBI Fermentas, Inc., Thermo Fisher Scientific). The digestion products were separated on a 4% agarose gel and visualized using ethidium bromide staining. Band size was determined using a DNA Ladder (O'Range Ruler 50 bp; MBI Fermentas). The undigested PCR product was 113 bp (allele A). Allele G was comprised of digested bands of 78 and 35 bp.

2.4. Data analysis and statistics

One-way analysis of variance (ANOVA), and then the Tukey-Kramer Post-hoc test was used for statistical evaluations. A χ^2 test was used for categorical variables. Data are means $\pm$ standard deviation (SD). To determine whether the plasma BDNF levels were significantly correlated with the genotype and disease symptoms, linear regression models were used. SPSS 17.0 for Windows was used for statistical computations. Significance was set at $p < 0.05$.

3. Results

There were no differences in demographic data (gender, age, and body weight) between the healthy controls and patients (Table 1). Patients with schizophrenia had significantly lower plasma BDNF levels than did healthy controls [$F(3,644) = 37.667$, $p < 0.0001$] (Table 1). Patients with schizophrenia had the lowest plasma BDNF levels (6.7 ± 7.0 ng/mL) and healthy controls had the highest (17.3 ± 9.1 ng/mL); patients in both bipolar disorder groups had levels almost as high as did the controls: BP-I = 15.3 ± 10.0 and BP-II = 14.6 ± 10.0 .

In the *BDNF* Val66Met variant distribution analysis, there was no significant difference between these four groups ($\chi^2 = 5.289$, $p = 0.507$), nor was there a significant difference in

BDNF Met and Val allele distribution frequency between groups ($\chi^2 = 1.649$, $p = 0.648$) (Table 2). We did a multivariate linear regression analysis of the correlation of plasma BDNF level with the *BDNF* gene variants (Met/Met, Met/Val, Val/Val) and different diagnosis (healthy control, BPI, BPII and schizophrenia). Plasma BDNF level were significantly correlated to different diagnosis ($\beta = -0.328$, $p < 0.0001$) but not significantly correlated to *BDNF* Val66Met carriers ($\beta = 0.016$, $p = 0.665$), which indicated the *BDNF* Val66Met variant does not affect peripheral BDNF levels but the different diagnosis of mental illnesses does. In patients with schizophrenia, all types of *BDNF* Val66Met carriers had the lowest plasma BDNF levels (Table 3), which indicated that the progression of schizophrenia might affect plasma BDNF levels, but the *BDNF* Val66Met variant did not.

We further did a multivariate linear regression analysis of the correlation of plasma BDNF level with the clinical symptoms. In patients with bipolar disorder, plasma BDNF levels were significantly negative correlated with the HDRS scores ($\beta = -0.174$, $p = 0.014$), but not the YMRS scores ($\beta = -0.117$, $p = 0.096$) or with comorbidities (anxiety disorder, nicotine dependency, phobias, and impulsivity: $\beta = 0.078$, $p = 0.178$). In patients with schizophrenia, plasma BDNF levels were significantly negatively correlated with negative symptoms ($\beta = -0.336$, $p = 0.047$) but not with positive symptoms ($\beta = 0.008$, $p = 0.948$), aggressive symptoms ($\beta = -0.083$, $p = 0.412$), or the sum of symptoms ($\beta = 0.2$, $p = 0.365$).

4. Discussion

We found different plasma BDNF expression profiles in patients with bipolar disorder and those with schizophrenia. Patients with BP-I and BP-II had non significantly lower plasma BDNF levels than did healthy controls, but patients with schizophrenia had significantly lower levels than did the other three groups of patients. BDNF can cross the blood-brain barrier (Pan et al., 1998), and BDNF levels in the brain and plasma undergo similar changes during maturation and aging in rats (Karege et al., 2002) and rhesus macaques (Cirulli et al., 2009). Moreover, lower plasma BDNF protein levels in humans might reflect the degree of neuronal degeneration in Alzheimer's disease (Laske et al., 2006) and age-related white matter atrophy in adult humans (Driscoll et al., 2012). These findings suggest that plasma BDNF levels might reflect BDNF levels in the brain, and that they might indicate the severity of mental disorders and the degree of a patient's neuronal degeneration.

4.1. BDNF levels and bipolar disorder

Although plasma BDNF levels in BP patients were not significantly lower than controls. However, they tended to be lowered than the healthy control and were significantly negatively correlated with the HDRS score, which indicated that they might influence the depressive behavior of patients with bipolar disorder. Previous study reported that serum BDNF levels were associated with depression-related personality trait in the general population of Caucasian people (Terracciano et al., 2011). Moreover, studies have reported that serum BDNF is lower in patients with BP during their manic and depressive episodes (Cunha et al., 2006, Monteleone et al., 2008). Peripheral levels (serum and plasma) of BDNF were lower in patients with depression and significantly increased after antidepressant treatment (Brunoni et al., 2008). These findings support the hypothesis of

peripheral BDNF as a possible biological marker for depressive symptom in bipolar disorder. Agents which could potentiate the systemic BDNF might benefit the treatment of depressive symptom in bipolar disorder. In addition, peripheral administration of BDNF could increase hippocampal neurogenesis in adult mice and produces anti-depression effects (Schmidt and Duman, 2010). Hippocampal neuronal degeneration had been highly correlated to depression-like behavior. Thus, the down regulation of peripheral BDNF might represent the decreased neuronal protective ability in bipolar disorder. However, the mechanism of peripheral BDNF level in depression or related neuronal protective effects should be further studied.

4.2. BDNF levels and schizophrenia

We found that, in patients with schizophrenia, plasma BDNF levels were significantly lower than in healthy controls and patients with bipolar disorder, and that they were significantly negatively correlated with the negative symptoms. Schizophrenia is a complex and severe brain disorder that causes diverse disturbances in cognition, reality testing, mood, interpersonal relations, and work functions. Some quantitative abnormalities in the brain structures of patients with schizophrenia have been reported, e.g., enlarged ventricles, decreased cerebral and temporal lobe volume, and thalamic anomalies (Galderisi et al., 2008). Moreover, accumulating evidence has indicated an association between BDNF and schizophrenia. Reduced BDNF concentrations in the serum (Toyooka et al., 2002, Chen da et al., 2009), plasma (Buckley et al., 2007b), cerebral spinal fluid (Pillai et al., 2010), dorsolateral frontal cortex (Weickert et al., 2003), anterior cingulate cortex (Iritani et al., 2003), and hippocampus (Durany et al., 2001) were found in patients with schizophrenia. BDNF is known to modulate dopaminergic, GABAergic, and serotonergic receptors and regulate the synaptic transmission and plasticity in adult neuronal synapses (Alderson et al., 1990, Hyman et al., 1991, Daftary et al., 2012). Thus, BDNF dysregulation might be involved in the alteration of neuronal functions and lead to increase susceptibility to schizophrenia-like symptoms (Buckley et al., 2007a).

Although other studies had reported contradictory findings on BDNF expression in patients with schizophrenia. Takahashi et al. (Takahashi et al., 2000) reported elevated BDNF levels in the anterior cingulate cortex and hippocampus in 10 postmortem brains of patients with schizophrenia. Our findings agreed with those of Toyooka et al. (Toyooka et al., 2002), Pillai et al. (Pillai et al., 2010), and Buckley et al. (Buckley et al., 2007b), who reported significantly lower peripheral BDNF levels in patients with schizophrenia. Reduced peripheral BDNF levels were assumed to reflect the decrease of brain BDNF activity and may be used as an index of neuroplasticity status that underlies the pathophysiology of psychosis (Pillai et al., 2010). Our results resembled the previous study that peripheral BDNF levels were negative correlated to the negative symptoms of schizophrenia (Sotiropoulou et al., 2013). However, we did not find significant correlation between plasma BDNF and positive symptoms of schizophrenia, which is in accordance with previous studies (Chen da et al., 2009, Pillai et al., 2010). Inferred from previous findings, we propose that lower plasma BDNF level, an index of poorer neuroplasticity, might play an important role in the progression of negative symptoms. We hypothesize that BDNF dysregulation in the peripheral might lead contribute to central nervous systems BDNF expression and cause

permanent alterations in brain function and leads to an increased risk of developing negative symptoms in schizophrenia. If organic mental illness and neurological disorder are ruled out, the plasma BDNF level might be one biological marker of negative symptom in schizophrenia.

4.3. The relationship of plasma BDNF levels to BDNF Val66Met gene variants in mental illness

To our knowledge, this is the first investigation that compares plasma BDNF levels with the *BDNF* Val66Met SNP within different mental disorders. In this study, the distribution of *BDNF* Val66Met SNP genotypes was not different in healthy control and patients with mental illness, which is in accordance with previous studies (Zhang et al., 2012, Sotiropoulou et al., 2013). In addition, we found no significant differences in plasma BDNF levels in different *BDNF* Val66Met SNP genotypes in all of groups, which indicated that the *BDNF* Val66Met gene polymorphism did not influence the plasma BDNF level in healthy humans and patients with bipolar disorder and schizophrenia. Our data resembled the previous study that revealed no significant difference in circulating BDNF levels between genotype subgroups of the *BDNF* Val66Met polymorphism in healthy control or patients with schizophrenia (Zhang et al., 2012). When stratified by the *BDNF* Val66Met genotypes, significant lower plasma BDNF level was found in the group of patients with schizophrenia compared to healthy control, which is consistent with the findings of Zhang et al. (2012). The plasma BDNF level seems to depend more on diagnostic effect than genetic effect. However, our data were different from Sotiropoulou et al. (Sotiropoulou et al., 2013) who studied a total of 50 patients with schizophrenia and found that the Met allele carriers had lower circulating BDNF level and higher scores in the PANSS-Negative scale. In the current study, we include more patients (n=151) with schizophrenia than the study by Sotiropoulou et al. (2013); we found the plasma BDNF levels and PANSS scores were not significantly different between the Met and Val carriers. Thus, we hypothesized that the down regulation of plasma BDNF in patients with schizophrenia does not depend on the *BDNF* Val66Met *SNP* genotype, but on the degree of progression and pathology of illness in Han Chinese people.

Our study has some limitations. Although plasma BDNF might pass through the blood brain barrier and might be correlated with brain BDNF expression, the exact level of brain BDNF expression and its effect on different mental illnesses needs further study to draw stronger conclusions. Spinal cerebral fluid BDNF levels might be required to confirm our hypotheses and findings. However, for ethical reasons, we could not collect spinal cerebral fluid from most of our patients. Noninvasive methods of measuring brain BDNF and brain function need to be developed for more in-depth studies.

4.4. Conclusion

In conclusion, we found different plasma BDNF expression profiles in patients with BP-I, BP-II, and schizophrenia. The level of plasma BDNF was not affected by the *BDNF* Val66Met variants, but by the process of the mental illness itself. The down regulation of plasma BDNF might indicate less neuronal protection and a certain degree of neuronal degeneration in mental illness.

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Abbreviations

BDNF	brain-derived neurotrophic factor
BP	bipolar disorder
BP-I	bipolar I disorder
BP-II	bipolar II disorder
SNP	single nucleotide polymorphism

Reference

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Highlights

- The *BDNF* Val66Met polymorphism in Han Chinese patients with different mental illness
- The plasma BDNF levels in Han Chinese patients varied with different mental illness.
- Plasma BDNF in mental disorders is affected by the process and progression of illness

Table 1.

Demographic data and plasma BDNF baseline levels

	Healthy Controls		Patients with		χ^2/F	p-value
			BP-I	BP-II	Schizophrenia	
Number of Patients	126		177	190	151	
Gender (M/F)	77/49		92/85	96/94	84/67	0.269 ^a
Age (years)	32.4 ± 7.5		32.8 ± 11.4	30.7 ± 10.9	30.8 ± 8.3	0.114 ^b
Body Weight (kg)	65.0 ± 13.1		64.9 ± 11.9	63.1 ± 13.7	66.6 ± 14.0	0.361 ^b
Plasma BDNF (ng/mL)	17.3 ± 9.1		15.3 ± 10.0	14.6 ± 10.0	6.7 ± 7.0***	< 0.0001 ^b
Hamilton Depression Rating Scale	-		14.8 ± 7.4	18.9 ± 4.3	-	
Young Mania Rating Scale	-		12.6 ± 6.2	8.8 ± 4.3	-	
PANSS Sum Score	-		-	-	87.5 ± 13.9	
CGI score	-		-	-	5.0 ± 0.1	

Data are means ± standard deviation (SD).

BP-I: bipolar I disorder; BP-II: bipolar II disorder; M: male; F: female; BDNF: brain-derived neurotrophic factor; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; PANSS: Positive and Negative Syndrome Scale; CGI: Clinical Global Impressions Scale For Bipolar Illness.

^aCompared with χ^2 test.^bCompared with healthy controls (ANOVA with LSD post-hoc tests).

Table 2.

BDNF Val66Met gene distribution in patients and healthy controls.

Participant	<i>n</i>	Genotype		χ^2	<i>P</i>	Allele frequency		χ^2	<i>P</i> -value
		Met/Met (%)	Met/Val (%)			Met (%)	Val (%)		
Healthy Controls	126	31 (24.6)	57 (45.2)	38 (30.2)		119 (47.2)	133 (52.8)		
BP-I	177	44 (24.9)	96 (54.2)	37 (20.9)	3.725 0.155 ^a	184 (52.0)	170 (48.0)	1.331	0.249 ^a
BP-II	190	46 (24.2)	105 (55.3)	39 (20.5)	4.375 0.112 ^a	197 (51.8)	183 (48.2)	1.294	0.255 ^a
Schizophrenia	151	37 (24.5)	79 (52.3)	35 (23.2)	1.971 0.373 ^a	153 (50.7)	149 (49.3)	0.650	0.420 ^a

BP-I: bipolar I disorder; BP-II: bipolar II disorder. ^acomparisons among all groups. ^acompared with healthy controls.

Table 3.Plasma BDNF level based on *BDNF* Val66Met gene

Groups/ Plasma BDNF (ng/mL)	<i>BDNF</i> Val66Met gene				F	P-value
	Met/Met	Met/Val	Val/Val			
Healthy Controls	18.1 ± 9.1	16.6 ± 9.1	17.6 ± 9.4	0.285		0.752 ^a
Patients with BP-I	12.6 ± 8.4	16.7 ± 10.3	15.2 ± 10.4	2.495		0.086 ^a
Patients with BP-II	13.9 ± 10.0	15.1 ± 8.8	15.0 ± 13.4	0.176		0.839 ^a
Patients with Schizophrenia	7.7 ± 8.5	5.7 ± 5.0	8.0 ± 8.8	1.689		0.188 ^a

Data are means ± S.D. Abbreviation: BP-I, bipolar I disorder; BP-II, bipolar II disorder.

^aMet/Met vs. Met/Val vs. Val/Val within same group.