Psychiatry Research 273 (2019) 528–536

Contents lists available at ScienceDirect

Psychiatry Research

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

Brain-derived neurotrophic factor is associated with cognitive impairments in first-episode and chronic schizophrenia

Ye Yang[a,b,c,d,e,1], Yi Liu[a,b,c,d,e,1], Guodong Wang[a,b,c,d,e], Gangrui Hei[a,b,c,d,e], Xiaoyi Wang[a,b,c,d,e], Ranran Li[a,b,c,d,e], Li Li[a,b,c,d,e], Renrong Wu[a,b,c,d,e], ing Zhao[a,b,c,d,e]

[a] Department of Psychiatry, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[b] Mental Health Institute, The Second Xiangya Hospital, Central South University, Changsha, China
[c] National Clinical Research Center on Mental Disorders, Changsha, China
[d] National Technology Institute on Mental Disorders, Changsha, China
[e] Hunan Key Laboratory of Psychiatry and Mental Health, Changsha, China

ARTICLE INFO

Keywords:
Schizophrenia
BDNF
Cognitive impairment
Correlation

ABSTRACT

Brain-derived neurotrophic factor (BDNF) may be related to the pathophysiology of schizophrenia. This study aims to examine the relation between plasma BDNF levels and the cognition of patients with schizophrenia. We recruited 31 patients with chronic schizophrenia, 34 first-episode patients, and 35 healthy control subjects. We examined the MATRICS Consensus Cognitive Battery (MCCB) and the plasma BDNF levels in all groups. The schizophrenic symptoms were assessed using the positive and negative syndrome scale. The BDNF levels of schizophrenic patients were remarkably lower than those of the controls. The cognitive MCCB global composite scores and part index scores of schizophrenic patients were remarkably lower than those of the controls. Moreover, remarkable correlations were observed between BDNF levels and partial cognitive dimensions, such as visual learning, memory, and processing speed. Therefore, BDNF may be involved in the pathophysiology and cognitive impairment of schizophrenia.

1. Introduction

Schizophrenia is a complex psychiatric disorder characterized by severe impairment in different cognitive aspects, including intellectual ability, processing speed, and attention (Bortolato et al., 2015). These deficits not only appear during acute episodes but also persist during the entire course of the illness, particularly in the chronic phase, thereby leading to serious cognitive impairments. The damage to certain cognitive domains, such as information processing and executive function, occurs at an accelerated rate (Cervellione et al., 2007; Bowie et al., 2008). Moreover, the motor function, which is an important aspect of cognitive function, becomes increasingly worse with increased follow-up time (Jaeger et al., 2003). Cognitive impairment is a core symptom of schizophrenia that persists during acute and chronic phases and is associated with reduced functional outcome. Researchers have drawn inconsistent findings regarding the cognitive deficits in first-episode and chronic patients. Several studies suggested that patients with first-episode schizophrenia display superior cognitive function to patients with chronic schizophrenia in various cognitive domains (Braw et al., 2007; González-Blanch et al., 2007). Other studies demonstrated that the severity of cognitive deficits of first-episode patients was similar to that experienced by chronic patients (Hoff et al., 1992; McCleery et al., 2014). Although cognitive damages and their adverse effects are widespread in individuals with schizophrenia, limited information on their underlying neurobiological mechanisms are available (Wong et al., 2003). Many possible hypotheses have been posited regarding the underlying mechanisms of cognitive deficits in schizophrenia, and recent ideas suggest that schizophrenia is a neuroplasticity disorder. This hypothesis offers a new perspective on the possible mediators of cognitive function (Anderson et al., 2013). Neuroplasticity in schizophrenia can be affected by neuropeptides, oxidative stress, and inflammatory responses (Ng et al., 2008; Maas et al., 2017). In particular, neurotrophins play an important role in neurodevelopment, synapse regulation, and synaptic plasticity. Thus, the low expression of brain-derived neurotrophic factor (BDNF) is associated with cognitive impairment (Zhang et al., 2012a,b; Asevedo et al., 2013).

* Corresponding author at: Department of Psychiatry, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, China.
E-mail address: wurenrong@csu.edu.cn (R. Wu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.psychres.2019.01.051
Received 22 August 2018; Received in revised form 11 December 2018; Accepted 13 January 2019
Available online 18 January 2019
0165-1781/

BDNF is a member of the neurotrophin family of growth factors and is widely distributed in the central nervous system (CNS); it passes freely through the blood–brain barrier (BBB) (Pan et al., 1998). The BDNF levels in serum and plasma are highly correlated with those in cerebrospinal fluid (CSF) (Pillai et al., 2010). Therefore, peripheral BDNF levels can possibly reflect the BDNF levels in the brain. BDNF is vital in adjusting memory-associated neuroplasticity given that it is responsible for maintaining cell stabilization and maturation, promoting synapse formation, and transmitting synapses (Hao et al., 2017). Moreover, BDNF plays a critical role in long-term potentiation (LTP) in the hippocampal, which is involved in learning and memory. BDNF signaling regulates the morphologies of neurons and synapses. For example, BDNF can increase the dendritic complexity in different regional neurons in the brain (Calfa et al., 2012). Furthermore, BDNF Val66Met polymorphism plays a key role in the correlation between cognitive function and serum BDNF levels, thereby confirming that the polymorphism of the BDNF gene is involved in the processing of hippocampal memory (Zhang et al., 2012a,b; Hao et al., 2017).

The effects of BNDF on memory and cognitive function have been reported in animal models or healthy adults (Gorski et al., 2003; Komulainen et al., 2008). Although researchers have separately explored the relationship between BDNF levels and cognitive function in chronic and first-episode schizophrenia (Xiao et al., 2017; Man, 2018), no study has considered and compared the correlation between BDNF levels and cognitive function in first-episode and chronic schizophrenia. Therefore, this study aims to investigate whether BDNF levels are correlated with cognitive function in the different courses of schizophrenia.

2. Participants and methods

2.1. Participants

This study was conducted in accordance with the recommended guidelines prescribed by the National Health and Medical Research Council of the Second Xiangya Hospital Ethics Committee. The protocol was approved by the Second Xiangya Hospital Ethics Committee. All subjects provided written informed consent in accordance with the Declaration of Helsinki. This study was performed between 2015 and 2016. Sixty-five patients were recruited from the inpatients and outpatients of Second Xiangya Hospital of Central South University. Among the 65 patients, 31 were first-episode patients and 34 were chronic patients. All patients satisfied the The Diagnostic and Statistical Manual of Mental Disorders IV(DSM-IV) diagnosis of schizophrenia. Among these patients, some were in the acute phase, whereas others were in the outpatient clinic for regular follow-up visits and in remission. No patient manifested a comorbidity with other psychiatric disorders. The course of chronic patients is approximately 7.6 ± 2.8 years. Patients with chronic schizophrenia mostly undergo monotherapy and combination therapy except for five untreated patients. Antipsychotic drugs include atypical antipsychotic drugs, including olanzapine, clozapine, and risperidone, and typical antipsychotic drugs, namely, haloperidol, aripiprazole, chlorpromazine, and quetiapine. The course of the first episode was basically within three months, where 20 patients take antipsychotics prior to joining the group and 14 patients join the group without any antipsychotic drugs. In addition, the main drug therapy is atypical antipsychotic drugs including olanzapine and risperidone; the duration of drug use was within three months. All antipsychotic drugs were converted to approximate chlorpromazine equivalents for each subject using standard guidelines. The 35 healthy controls were volunteers from the Changsha community and were matched for patients' sex. All subjects were Han Chinese, who were recruited from the Changsha area during the same period.

All subjects underwent a comprehensive assessment, which included medical history, physical examination, clinical evaluations of psychiatric symptoms, and related laboratory tests. None of the subjects had any physical disease or substance dependence. All subjects provided signed informed consent to participate in this study. The privacy rights of human subjects must always be observed, as approved by the Institutional Review Board, Second Xiangya Hospital of Central South University.

2.2. Clinical and neuropsychological assessment

We assessed the cognitive function by using the MATRICS Consensus Cognitive Battery, which was originally developed by the US National Institute of Mental Health (NIMH). The MATRICS Consensus Cognitive Battery (MCCB), which consists of 10 standardized cognitive measure dimensions, is used to calculate the scores and global composite scores of seven cognitive domains, including speed of processing (symbol coding, category fluency, and trail making test), attention/vigilance (continuous performance test), working memory (digital sequence and Wechsler memory scale spatial span), verbal learning (Hopkins verbal learning test), visual learning (brief visuospatial memory test), reasoning/problem solving (neuropsychological assessment battery), and social cognition (Mayer–Salovey–Caruso Emotional Intelligence Test) (Barch et al., 2009). In recent years, the MCCB has been translated to Chinese and has been widely used in clinical practice. Its clinical validity and test-retest reliability have been confirmed (Shi and Kang et al., 2015; Wu et al., 2016a,b). Several psychiatrists use positive and negative syndrome scale (PANSS) to evaluate the psychiatric symptoms of patients. These psychiatrists conduct training courses for PANSS assessment at the same time. After training, the consistency between the scores of the evaluators was 0.8. We collected blood samples in the morning of the day of assessment to ensure the consistency of the BDNF levels and cognitive function.

2.3. Plasma BDNF measurement

Plasma samples were collected from subjects between 7 a.m. and 9 a.m. after fasting overnight. The plasma was separated by centrifugation at 3000 rpm for 10 min and then stored at −80 °C until analysis. The BDNF levels were assessed by high-sensitivity sandwich enzyme-linked immunosorbent assay (ELISA) using a commercially available kit (R&D Systems, Quantikine). All samples were assayed by the same technician, who was blind to the clinical status of the subjects in the same assay batch. The BDNF levels of section samples were assayed in duplicates. Testing was performed by technicians, and all samples were coded prior to testing. Inter- and intra-assay variation coefficients were 9% and 5%, respectively.

2.4. Statistical analysis

Between-group differences in demographic and clinical variables were assessed using ANOVA for continuous variables and chi-squared test for categorical variables. For the BDNF levels and the MCCB global composite score and sub-scores, ANCOVAs were constructed, where the groups were the independent variables; the BDNF/ MCCB global composite score and sub-scores were the dependent variables; sex, age, and education were the covariates. The relationships between BDNF levels and MCCB scores were evaluated using Pearson's correlation analyses. All statistical analyses were performed using SPSS version 23.0. The statistical significance was set at $p < 0.05$.

3. Results

3.1. Sample characteristics

The demographic and clinical data are presented in Table 1. The patients and healthy controls had no significant differences in terms of gender but were different in age and education ($p < 0.001$). Educational level was remarkably higher in the control group than in both

Table 1
Sociodemographic, clinical and immunological characteristics of the sample.

Variable	Chronic $N = 31$	First-episode $N = 34$	Control $N = 35$	F or $X2$	DF	P-Value
Sociodemographics						
Age[a](years),mean (SD)	27.35(3.71)	22.29(5.21)	25.57(1.77)	14.819	2,97	<0.001
Sex(M/F)	16/15	19/15	16/19	21.083	2	0.698
Education(years),mean (SD)	10.41(2.73)	11.17(2.56)	16.33(2.20)	49.225	2,86	<0.001
illness duration(years),mean (SD)	7.6 (2.8)					
PANSS						
PANSS Positive, mean (SD)	18.03(6.21)	17.55(5.30)		0.101	1,56	0.751
PANSS General, mean (SD)	32.90(7.54)	31.93(5.13)		0.325	1,56	0.571
PANSS Negative,mean (SD)	19.76(7.94)	18.34(7.89)		0.463	1,56	0.499
PANSS Total, mean (SD)	70.69(18.64)	67.83(14.35)		0.429	1,56	0.515
Antipsychotic	26	20				
Blood makers						
BDNF (pg/ml) , mean (SD)	40,429.59(19,484.21)	44,437.08(18,476.05)	53,016.15(20,905.63)	3.241	2,91	0.044

[a] Data presented as mean (SD).

patient groups. These differences were controlled as covariates in the following analysis. No significant differences were observed between first-episode and chronic patients ($p > 0.05$).

3.2. BDNF levels in the control, first-episode, and chronic schizophrenia patients

The mean ± standard deviation (SD) of the BDNF levels of the patients with chronic schizophrenia was 40,429.59 ± 19,484.21 pg/mL, whereas that of the first-episode patients was 44,437.08 ± 18,476.05 pg/mL. Compared with chronic and first-episode patients, the controls had a significantly higher plasma BDNF level of 53,016.15 ± 20,905.63 pg/mL (Fig. 1). Six subjects (one chronic patient and five controls) failed to present detect BDNF levels. The BDNF levels were significantly lower in the patients than in the healthy controls ($F = 3.241$; $df = 2,91$; $p = 0.044$). Post-hoc analysis revealed that the controls had significantly higher levels than both patient groups ($p = 0.015$), and the controls only had a higher trend relative to the first-episode schizophrenia group ($p = 0.084$). On the contrary, these remarkable difference and trend were not observed between the patients with chronic schizophrenia and those with first-episode schizophrenia. Although chlorpromazine equivalent was included as a covariate in the analysis, no significant difference was observed ($p > 0.05$).

3.3. Cognitive performance of the control, first-episode, and chronic schizophrenia patients

The MCCB global composite score and index scores of 65 patients with schizophrenia and 35 healthy controls are shown in Table 2. The MATRICS program was used to compute the T-scores for each test. We used the Chinese norms for age, gender, and education to generate T-scores for the seven domains and overall composite score. Compared with the controls, the first-episode and chronic schizophrenia patients had lower cognitive assessment test scores in many domains (speed of processing, visual learning and memory, reasoning and problem solving, and comp MCCB total score) after their gender, age, and education were controlled ($p < 0.05$). Post-hoc tests revealed that comp MCCB total score ($p = 0.005$), speed of processing ($p < 0.001$), visual learning and memory ($p = 0.001$), and reasoning and problem solving ($p = 0.022$) were significantly lower in the first-episode and chronic patients than in the controls ($p < 0.05$). However, the difference

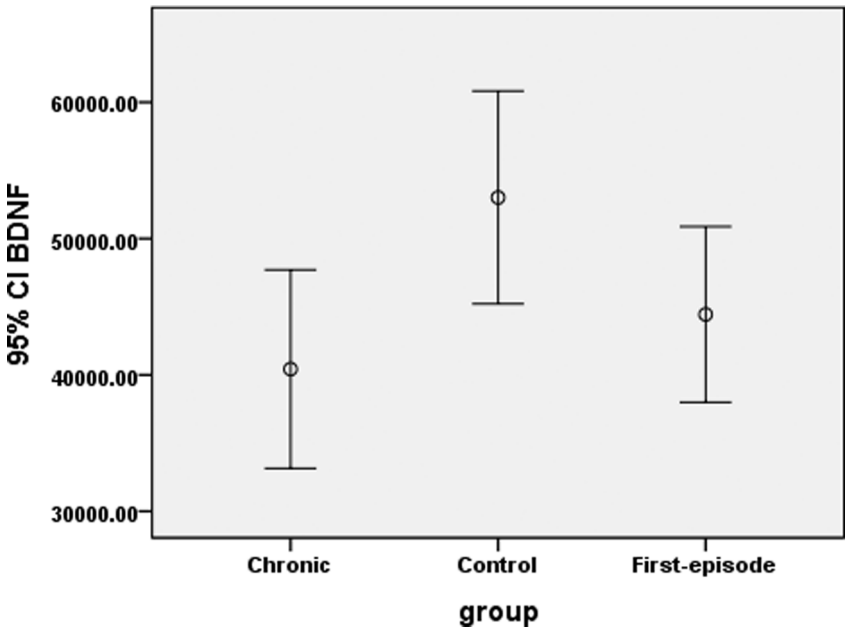

Fig. 1. BDNF levels were significantly lower in patients than healthy controls ($F = 3.241$, $p = 0.044$). There is no significant difference between the chronic schizophrenia and the first-episode schizophrenia ($p > 0.05$).

Table 2
Comparison of MCCB scores among controls, first-episode, and chronic schizophrenia patients.

The cognitive test scores	Chronic	First-episode	Control	ANOVA	*DF*	Test post hoc Chornic vs First-episode	Chornic vs control	First-episoe vs control
Speed of processing	37.13 ± 10.23	36.25 ± 6.74	48.80 ± 6.67	$F = 18.653$ $P < 0.001$	2,85	$P = 0.688$	$P < 0.001$	$P < 0.001$
Attention/vigilance	38.44 ± 14.01	43.79 ± 13.58	43.89 ± 8.93	$F = 1.718$ $P = 0.186$	2,80	$P = 0.514$	$P = 0.175$	$P = 0.416$
Working memory	46.41 ± 14.57	37.00 ± 10.72	43.82 ± 10.85	$F = 3.274$ $P = 0.043$	2,85	$P = 0.360$	$P = 0.078$	$P = 0.306$
Verbal learning and memory	30.48 ± 12.40	30.74 ± 11.22	37.29 ± 10.34	$F = 3.293$ $P = 0.042$	2,85	$P = 0.862$	$P = 0.083$	$P = 0.060$
Visual learning and memory	37.97 ± 11.44	39.52 ± 8.93	50.36 ± 13.66	$F = 9.966$ $P < 0.001$	2,85	$P = 0.539$	$P < 0.001$	$P = 0.001$
Reasoning and problem solving	35.38 ± 14.69	38.16 ± 11.80	51.61 ± 9.04	$F = 14.686$ $P < 0.001$	2,85	$P = 0.139$	$P = 0.001$	$P = 0.022$
Social cognition	45.14 ± 18.03	47.68 ± 14.79	49.96 ± 16.61	$F = 0.600$ $P = 0.551$	2,84	$P = 0.885$	$P = 0.710$	$P = 0.800$
Comp MCCB total score	43.78 ± 9.62	44.85 ± 7.65	52.97 ± 6.25	$F = 10.707$ $P < 0.001$	2,76	$P = 0.678$	$P = 0.001$	$P = 0.005$

Data presented as mean ± SD.

between chronic and first-episode patients was insignificant ($p > 0.05$). Considering the effects of drugs on cognitive function, we included chlorpromazine equivalent as a covariate in the analysis, and still no significant difference in cognitive function was found between the two groups ($p > 0.05$).

3.4. Correlation between BDNF levels and cognitive performance

Neuropsychological assessment was performed on the first-episode and chronic patients and the healthy controls, and the results revealed a remarkable positive correlation between BDNF levels and partial cognitive dimensions. The BDNF levels were significantly correlated with the speed of processing score ($r = 0.221$, $p = 0.046$; Fig. 2), the visual learning and memory score ($r = 0.305$, $p = 0.005$; Fig. 3), and the MCCB global composite score ($r = 0.261$, $p = 0.026$; Fig. 4). On the contrary, no significant associations were detected between BDNF levels and working memory, verbal learning and memory, attention/vigilance, and social cognition ($p > 0.05$). Subsequent stratified analyses were conducted between controls and patients. For the healthy controls, no significant association was observed between the BDNF levels and the MCCB global composite score or any subgroup scores ($p > 0.05$). For the patient groups, the BDNF levels were positively related to visual learning and memory ($r = 0.276$, $p = 0.034$). In addition, the BDNF levels were positively correlated with the PANSS ($r = 0.277$, $p = 0.037$). However, for the patient subgroup, we did not detect a correlation between BDNF levels and any dimension of cognitive function in either first-episode or chronic schizophrenic patients ($p > 0.05$).

In addition, correlation analysis was conducted to detect the relationships between the PANSS total and its subscale scores and cognitive performance on the MCCB total and its subscale scores in patients, thereby showing negative associations between the PANSS negative subscale score and multiple dimensions of cognitive performance on MCCB. Verbal learning and memory were not only correlated with the negative symptoms of PANSS, but also with the positive symptoms of PANSS and the total score of PANSS (all $P < 0.05$) (Table 3).

4. Discussion

The inter-group analysis revealed the following. 1) The BDNF levels were remarkably reduced in patients with chronic schizophrenia and had lower tendency in first-episode patients. 2) Compared with the healthy controls, the chronic and first-episode patients exhibited poor cognitive function in several areas. 3) Low BDNF levels were associated with cognitive impairments in schizophrenia, particularly in speed of processing, visual learning, and working memory domains. The BDNF levels were remarkably lower in chronic patients than in the healthy controls. This finding is consistent with previous studies (Zhang et al., 2012a,b; Wu et al., 2015). However, some studies reported increased levels (Gama et al., 2007; Reis et al., 2008) or indistinguishable differences (Huang et al., 2006; Niitsu et al., 2011). These contradictory findings may be attributed to differences in techniques, samples, and stages of the disease. A lower trend was observed only in first-episode patients. This finding is also consistent with the results of most previous studies, which found reduced BDNF levels in first-episode schizophrenia (Rizos et al., 2008; Song et al., 2015; Chiou et al., 2017). In addition, we did not observe remarkable differences in BDNF levels between chronic schizophrenia and first-episode schizophrenia, consistent with a recent study (Heitz et al., 2018). The result may be related to smaller sample size and drug use, given that first-episode schizophrenia and chronic schizophrenia patients both use antipsychotic drugs. Recently, a prospective longitudinal study has shown that olanzapine treatment can improve psychiatric symptoms and cognitive dysfunction, parallel with increased plasma BDNF levels. Thus, the effects of drugs cannot be completely ruled out (Zhang et al.,

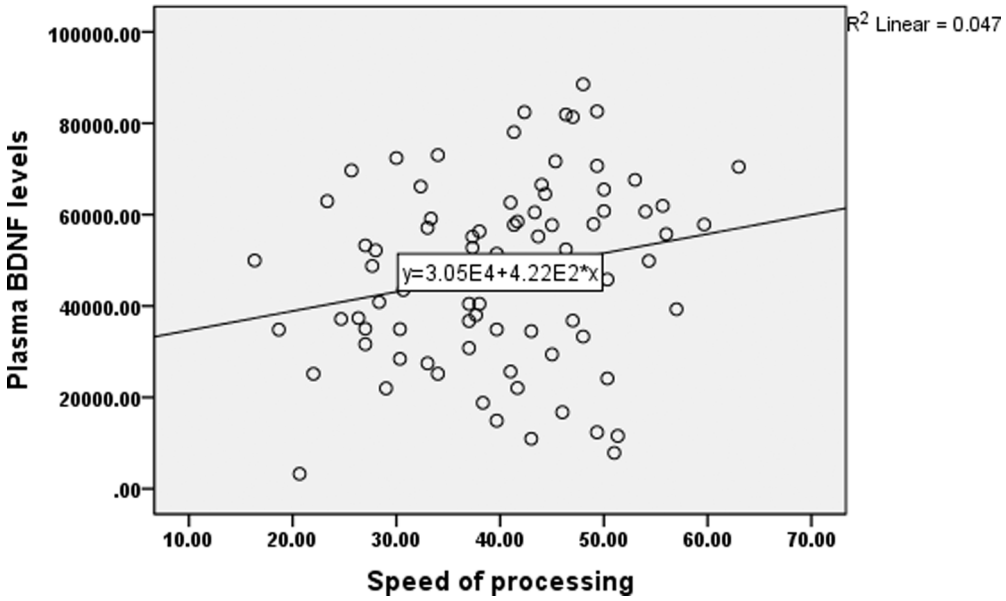

Fig. 2. Plasma BDNF was positively associated with the speed of processing index in total study population. ($p < 0.05$).

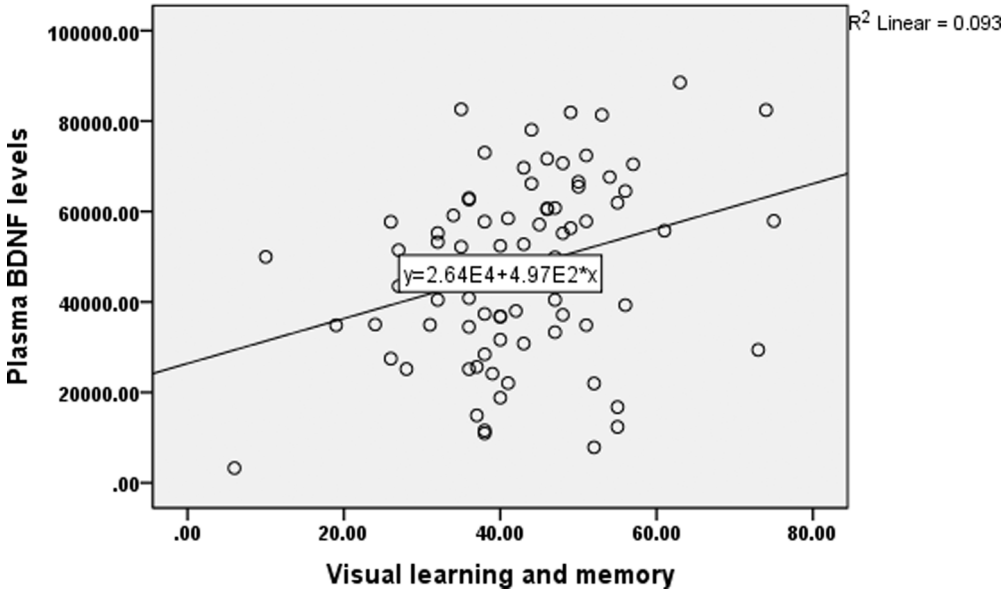

Fig. 3. Plasma BDNF was positively associated with the Visual learning and memory index in total study population ($p < 0.05$).

2018).

BDNF plays an important role in different courses of schizophrenia and may, therefore, play a role in the pathogenesis of schizophrenia (Buckley et al., 2011; Favalli et al., 2012). To our knowledge, BDNF is widely distributed in the CNS and is involved in the development and survival of neurons (Hariri et al., 2003), specifically in the prefrontal and hypothalamus brain regions, where it promotes various neuromodulatory processes, such as neuronal survival, differentiation, and synapse formation (Nawa et al., 2000; Pang 2004). The BDNF levels were decreased in the hypothalamus and prefrontal cortex in patients with schizophrenia in postmortem studies and animal models (Lipska et al., 2001; Banerjee et al., 2013). BDNF can freely cross the BBB (Pan et al., 1998). A research has demonstrated that parallel changes occurred in the BDNF levels in plasma and CSF of patients with schizophrenia (Pillai et al., 2010), thereby confirming that the BDNF levels in peripheral serum or plasma are strongly correlated with the CNS concentrations. Abnormal BDNF expression levels in brain tissues may influence brain function (Schmidt et al., 2010), and such influence may be a potential mechanism of schizophrenia, thereby supporting the hypothesis of neurodegenerative process in schizophrenia (Shoval et al., 2005; Favalli et al., 2012). However, BDNF is not a specific biomarker for schizophrenia. Changes in BDNF levels can be described in other mental illnesses, such as depression and bipolar disorder (Lee et al., 2016; Caldieraro et al., 2018), as well as other neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson disease (PD) (Zuccato et al., 2009; Borba et al., 2017).

Abnormal levels of oxidative stress and inflammatory activation have been reported in schizophrenic patients (Norbert Müller, 2010; Maas et al., 2017), and interaction may exist between oxidative stress, inflammatory factors, and BDNF levels (Zhang et al., 2015; Zhang et al.,

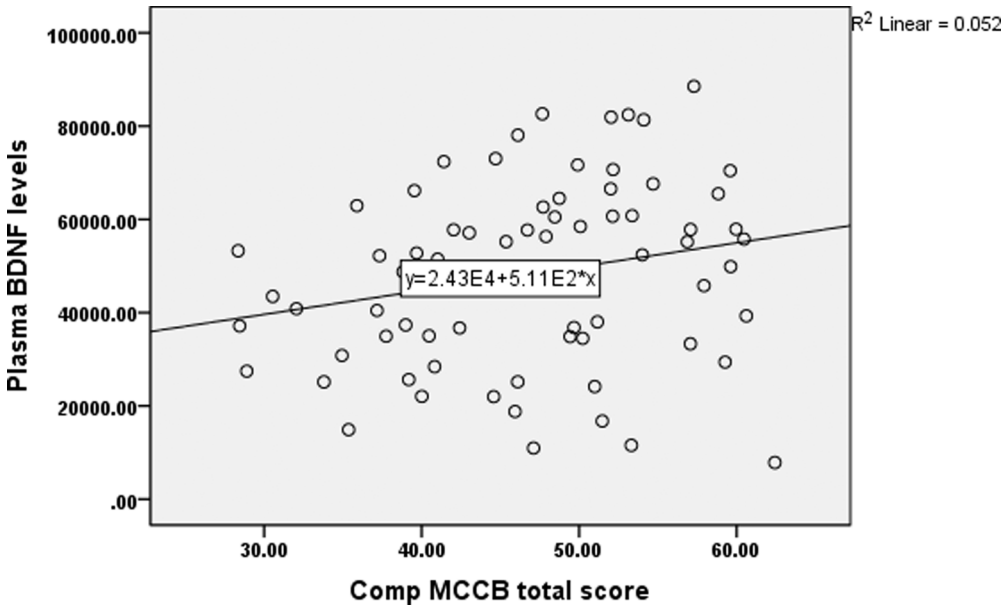

Fig. 4. Plasma BDNF was positively associated with the MCCB global composite score in total study population ($p < 0.05$).

Table 3
Associations between neurocognitive function and PANSS score.

The cognitive test scores	PANSS P		PANSS N		PANSS sum	
	r	*P*	*r*	*p*	*r*	*P*
Speed of processing	−0.018	0.546	−0.291	0.027*	−0.209	0.116
Attention/vigilance	−0.045	0.744	−0.219	0.108	−0.163	0.233
Working memory	−0.132	0.322	−0.131	0.328	−0.140	0.295
Verbal learning and memory	−0.297	0.024*	−0.291	0.027*	−0.290	0.027*
Visual learning and memory	−0.210	0.113	−0.377	0.004	−0.302	0.021*
Reasoning and problem solving	−0.066	0.621	−0.313	0.017*	−0.213	0.109
Social cognition	−0.204	0.128	−0.166	0.216	−0.184	0.171
Comp MCCB total score	−0.192	0.176	−0.234	0.099	−0.206	0.148

Correlations are Pearson correction coefficient.
PANSS P: Positive and negative symptom positive score;
PANSS N: Positive and negative symptom negative score;
PANSS Sum: Positive and negative symptom total score.
* $p < 0.05$.

2016). Therefore, abnormal levels of BDNF may be related to chronic stress state induced by schizophrenia, and this change is, in turn, involved in the pathological mechanism of schizophrenia, thereby affecting its clinical symptoms. In addition, our subjects are not drug-naive first-episode schizophrenia patients. Although previous studies have shown remarkable decreases in BDNF levels in first-episode drug-naive patients and patients with chronic schizophrenia, the effect of drug therapy on BDNF could not be excluded even when controversy about the effect of antipsychotics on BDNF levels exists. For example, a recent study has shown no change in serum BDNF levels in first-episode schizophrenic patients after four weeks of antipsychotic treatment (Chiou et al., 2017). However, this finding contradicts the results of another research, which has reported an evident elevation of BDNF levels in peripheral blood after 16 weeks of olanzapine treatment. Therefore, a further research is required in the future for verification.

The current study has assessed the neuropsychological performance at two phases of schizophrenia. Our work indicated that, compared with the healthy controls, patients with schizophrenia experienced cognitive deficits in different domains regardless of whether it was a case of first-episode or chronic schizophrenia. This finding is consistent with that of previous studies (Sharma et al., 2003; Condray et al., 2011; Wu et al., 2016a,b). Several meta-analysis studies and reviews indicated that patients with schizophrenia had poorer cognitive functions in many fields than healthy controls (Bortolato et al., 2015; Healey et al., 2016; Moustafa et al., 2016). Animal models of schizophrenia also validated this hypothesis. The performance of these schizophrenia-like rodent models displayed altered social interaction as well as learning and memory impairment (Jones et al., 2011). Post-hoc tests showed that the comparative results of chronic and first-episode schizophrenia patients presented no difference in cognitive function, thereby suggesting that cognitive impairments in first-episode and chronic schizophrenia are similar. This conclusion is consistent with existing evidence (Sponheim et al., 2010) . Nonetheless, other studies have reported cognitive deterioration with the progression of the disease (Braw et al., 2007; González-Blanch et al., 2007). This contradiction may be related to the different courses of disease and the drugs used by the subjects in different studies, and may also be related to the different methods of cognitive assessment. The deficiency of cognitive function in schizophrenia may be related to an abnormal brain structure. For example, neuroimaging techniques revealed abnormal functional and structural changes in the brain, particularly in the hippocampus (Asami et al., 2012; Shepherd et al., 2012; Singh et al., 2018), and those abnormalities in the structure of the hippocampus are related to the neurocognitive function in schizophrenia (Tamminga et al., 2010; Wible 2013). These results suggested that the cognitive performance of patients with schizophrenia may be influenced by brain abnormalities.

Correlation analysis indicated a remarkable positive relationship between plasma BDNF levels and cognitive function. This correlation was detected not only in the total subjects but also in the patient group. Thus, we speculated that poor cognitive function in schizophrenia may be related to lower plasma BDNF levels. This hypothesis is similar to that in previous studies (Zhang et al., 2012a,b; Wu et al., 2015; Xiao et al., 2017). A recent study similar to our work also reported a correlation between BDNF levels and cognitive function, but reported higher levels of BDNF in the first-episode patients and chronic patients than with high-risk groups. However, the study did not include a control group; thus, determining whether the BDNF levels were higher or lower than that of the control group is impossible (Heitz et al., 2018). No correlation was found in first-episode and chronic schizophrenia. This finding contradicted a number of previous reports but was

consistent with studies that reported no correlation between BDNF levels and cognitive performance in patients with schizophrenia (Niitsu et al., 2011; Man, 2018). The discrepancy may be due to the differences in cognitive assessment methods and disease duration. Our research suggests that the small sample size might have prevented further subgroup analyses and impeded the detection of correlation. However, this correlation still existed when we considered first-episode schizophrenia and chronic schizophrenia as different stages in the continuous course of schizophrenia and included them in the correlation analysis as a whole. Many reviews have suggested that BDNF plays an important role in the regulation of neurogenesis and synaptic plasticity in the brain of schizophrenia (Nieto et al., 2013; Calabrese et al., 2016). In addition, a recent meta-analysis reported a positive association of peripheral BDNF levels with reasoning/problem solving (Ahmed et al., 2015). Therefore, BDNF may be an important regulator of cognitive processes. A recent clinical observation further confirms this hypothesis. After 12 weeks of olanzapine treatment, a parallel relationship was found between the improvement of cognitive function and the increase in serum BDNF level (Zhang et al., 2018). In addition, a remarkable negative correlation was observed between the negative score of PANSS and the cognitive function of different dimensions of MCCB. Therefore, a parallel relationship exists between the severity of the patient's condition and cognitive impairment, thereby further supporting our findings. All correlations were weak (r 0.1–0.3), except for the correlation between BDNF levels and visual learning and memory score (($r = 0.305$, $p = 0.005$), although they passed the Pearson correlation.

Accumulating evidence suggests that lower levels of BDNF are associated with cognitive impairment in different disorders, including depression, AD, bipolar disorder, and even diabetes. This finding provides a new perspective for understanding the cognitive impairment of schizophrenia (Diniz et al., 2014; Lee et al., 2016; Murillo et al., 2016; Borba et al., 2017). Considerable evidence posits that BDNF is associated not only with neurodevelopment and neuroprotection but also with synaptic plasticity (Vicario-Abejon et al., 2002; Favalli et al., 2012; Gómez-Palacio-Schjetnan A 2013). The BDNF gene knockout animal model experienced impaired spatial learning and memory retention associated to hippocampal-related memory (Gorski et al., 2003). These findings suggested that BDNF plays an important role in hippocampal-dependent learning and memory (Lu and Christian et al., 2008; Calfa et al., 2012; Jindal and Pillai et al., 2010).

The possible mechanism underlying hippocampus dependent learning and memory is widely hypothesized to be LTP, which can be inducted by BDNF. A study has reported that BDNF and its high-affinity receptor, TrkB, play important roles in organizing persistent neural activity at the single-neuron and network levels, thereby regulating the working memory (Galloway and Woo et al., 2008). Meanwhile, another research has explored the relationship between serum BDNF levels and hippocampal volume in patients with first-episode schizophrenia and healthy control subjects, and they found a parallel decreasing relationship between serum BDNF and hippocampal volume (Rizos and Papathanasiou et al., 2011). Another study on elderly adults drew a similar conclusion that poor memory in the elderly was associated with decreased hypothalamus volume and reduced serum BDNF levels (Erickson and Prakash et al., 2010). This indication can also be observed in patients with AD (Borba et al., 2017). From these observations, we speculate that peripheral BDNF levels may be associated with abnormal brain structures, which may be a factor contributing to abnormal brain function. Moreover, the BDNF gene expression, transcription, and protein expression in the brain tissues of schizophrenia patients differed from those of the normal controls. A previous study showed an association between the BDNF Met variant and poor visuospatial/constructional performance, thereby suggesting that the connection between cognitive defects and decreased BDNF levels in schizophrenia depended on the BDNF Val66Met polymorphism (Zhang et al., 2012a,b). BDNF serum levels were remarkably increased in patients with chronic schizophrenia after cognitive training, thereby indicating that a parallel change occurred in BDNF levels and cognitive performance (Katsumi et al., 2017), consistent with another study (Skilleter and Weickert et al., 2015). Therefore, peripheral BDNF is a candidate biomarker of impaired learning ability in schizophrenia

However, the exact mechanism responsible for the association between BDNF levels and cognitive impairments in schizophrenia remains unclear. The hypothesis of neuroprotective effect of BDNF has been well-established. Binding and activating to TrkB can induce various intracellular signaling pathways, including mitogen activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK), phosphoinositide 3-kinase (PI3K), and phospholipase Cg (PLCg) pathways (Schlessinger, 2000; Rössler et al., 2004; Numakawa et al., 2010). Animal studies have shown that BDNF can mediate neuroprotective effects of glutamate and norepinephrine (NE) on hippocampal neurons via PI3K and MAPK signaling pathways (Almeida et al., 2005; Chen et al., 2007). These observations from preclinical studies are supported by clinical research. A recent study has shown that in the prefrontal cortex of schizophrenic patients, the protein expression of ERK signaling pathway, such as MEK1, ERK1/2, and B-Raf, was remarkably reduced, limiting the neuroprotective effect of BDNF in schizophrenic patients (Yuan et al., 2009). Further research using a longitudinal and prospective approach is necessary to explore the precise mechanism of the relationship between BDNF and cognitive performance in schizophrenia.

This study has several limitations. The primary limitation of our study is the small sample size due to the difficulty in completing the assessment of cognitive function in patients with the first-episode acute phase, limiting the acquisition of sample size. We only carried out relevant research without causality studies. Therefore, the underlying accurate causality is unclear. Furthermore, BDNF level was assessed in plasma, which reflected an indirect measurement of the brain BDNF levels. However, whether the peripheral BDNF level can reflect the level of CNS remains to be explored. Another limitation is that BDNF levels may be affected by stress and inflammatory responses. Long-term studies may be required to assess the effects of stress and inflammation on the BDNF levels. In addition, in our study, all subjects, including those with first-episode and chronic schizophrenia, were recruited from cross-sectional study populations. Thus, given that longitudinal follow-up studies have not been conducted, this work cannot be considered a continuous course of schizophrenia. Large-scale longitudinal follow-up studies must be conducted for further exploration.

The present results suggest that BDNF was decreased in patients with schizophrenia, including first-episode and chronic schizophrenia, thereby confirming that BDNF may be a biomarker of cognitive deficits in schizophrenia, particularly in the speed of processing, visual learning and memory, reasoning, and problem solving. However, the specific mechanism of the connection between BDNF and cognitive deficits has yet to be clarified. BDNF levels are expected to be markers for further investigating cognitive deficits in schizophrenia. Large-sample studies must be conducted to verify and examine the role of BDNF in the cognitive deficits in schizophrenia.

Acknowledgements

The research was supported by grant 2016YFC1306900 from the National Key Research and Development Program of China and grants 81622018 and 81630033 from the National Natural Science Foundation of China.

Declaration of interest

None.

References

Ahmed, A.O., Mantini, A.M., Fridberg, D.J., Buckley, P.F., 2015. Brain-derived neurotrophic factor (BDNF) and neurocognitive deficits in people with schizophrenia: a meta-analysis. Psychiatry Res. 226, 1–13.

Almeida, R.D., Manadas, B.J., Melo, C.V., Gomes, J.R., Mendes, C.S., Grãos, M.M., et al., 2005. Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. Cell Death Differ. 12, 1329–1343.

Anderson, G., Berk, M., Dodd, S., Bechter, K., Altamura, A.C., Dell'Osso, B., et al., 2013. Immuno-inflammatory, oxidative and nitrosative stress, and neuroprogressive pathways in the etiology, course and treatment of schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 42, 1–4.

Asami, T., Bouix, S., Whitford, T.J., Shenton, M.E., Salisbury, D.F., McCarley, R.W., 2012. Longitudinal loss of gray matter volume in patients with first-episode schizophrenia: DARTEL automated analysis and ROI validation. Neuroimage 59, 986–996.

Asevedo, E., Gadelha, A., Noto, C., Mansur, R.B., Zugman, A., Belangero, S.I., et al., 2013. Impact of peripheral levels of chemokines, BDNF and oxidative markers on cognition in individuals with schizophrenia. J. Psychiatr. Res. 47, 1376–1382.

Banerjee, R., Ghosh, A.K., Ghosh, B., Bhattacharyya, S., Mondal, A.C., 2013. Decreased mRNA and protein expression of BDNF, NGF, and their receptors in the hippocampus from suicide: an analysis in human postmortem brain. Clin. Med. Insights Pathol. 6, 1–11.

Barch, D.M., Carter, C.S., Arnsten, A., Buchanan, R.W., Cohen, J.D., Geyer, M., et al., 2009. Selecting paradigms from cognitive neuroscience for translation into use in clinical trials: proceedings of the third CNTRICS meeting. Schizophr. Bull. 35, 109–114.

Borba, E.M., Duarte, J.A., Bristot, G., Scotton, E., Camozzato, A.L., Chaves, M.L.F., 2017. Brain-derived neurotrophic factor serum levels and hippocampal volume in mild cognitive impairment and dementia due to alzheimer disease. Dement. Geriatr. Cognit. Disord. Extra 6, 559–567.

Bortolato, B., Miskowiak, K.W., Kohler, C.A., Vieta, E., Carvalho, A.F., 2015. Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. Neuropsychiatr. Dis. Treat. 11, 3111–3125.

Bowie, C.R., Reichenberg, A., McClure, M.M., Leung, W.L., Harvey, P.D., 2008. Age-associated differences in cognitive performance in older community dwelling schizophrenia patients: differential sensitivity of clinical neuropsychological and experimental information processing tests. Schizophr. Res. 106, 50–58.

Braw, Y., Bloch, Y., Mendelovich, S., Ratzoni, G., Gal, G., Harari, H., et al., 2007. Cognition in young schizophrenia outpatients: comparison of first-episode with multiepisode patients. Schizophr. Bull. 34, 544–554.

Buckley, P.F., Pillai, A., Howell, K.R., 2011. Brain-derived neurotrophic factor: findings in schizophrenia. Curr. Opin. Psychiatry 24, 122–127.

Calabrese, F., Riva, M.A., Molteni, R., 2016. Synaptic alterations associated with depression and schizophrenia: potential as a therapeutic target. Expert Opin. Ther. Targets 20, 1195–1207.

Caldieraro, M.A., McKee, M., Leistner-Segal, S., Vares, E.A., Kubaski, F., Spanemberg, L., et al., 2018. Val66Met polymorphism association with serum BDNF and inflammatory biomarkers in major depression. World J. Biol. Psychiatry 19, 402–409.

Calfa, G., Chapleau, C.A., Campbell, S., Inoue, T., Morse, S.J., Lubin, F.D., et al., 2012. HDAC activity is required for BDNF to increase quantal neurotransmitter release and dendritic spine density in CA1 pyramidal neurons. Hippocampus 22, 1493–1500.

Cervellione, K.L., Burdick, K.E., Cottone, J.G., Rhinewine, J.P., Kumra, S., 2007. Neurocognitive deficits in adolescents with schizophrenia: longitudinal stability and predictive utility for short-term functional outcome. J. Am. Acad. Child Adolesc. Psychiatry 46, 867–878.

Chen, J., Kitanishi, T., Ikeda, T., Matsuki, N., Yamada, M.K., 2007. Contextual learning induces an increase in the number of hippocampal CA1 neurons expressing high levels of BDNF. Neurobiol. Learn. Mem. 88, 409–415.

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

Condray, R., Yao, J.K., 2011. Cognition, dopamine and bioactive lipids in schizophrenia. Front. Biosci. 3, 298–330.

Diniz, B.S., Teixeira, A.L., Machado-Vieira, R., Talib, L.L., Radanovic, M., Gattaz, W.F., et al., 2014. Reduced cerebrospinal fluid levels of brain-derived neurotrophic factor is associated with cognitive impairment in late-life major depression. J. Gerontol. B Psychol. Sci. Soc. Sci. 69, 845–851.

Favalli, G., Li, J., Belmonte-de-Abreu, P., Wong, A.H.C., Daskalakis, Z.J., 2012. The role of BDNF in the pathophysiology and treatment of schizophrenia. J. Psychiatr. Res. 46, 1–11.

Galloway, E.M., Woo, N.H., Lu, B., 2008. Persistent neural activity in the prefrontal cortex: a mechanism by which BDNF regulates working memory? Prog. Brain Res. 169, 251–266.

Gama, C.S., Andreazza, A.C., Kunz, M., Berk, M., Silva Belmonte-de-Abreu, P., Kapczinski, F., 2007. Serum levels of brain-derived neurotrophic factor in patients with schizophrenia and bipolar disorder. Neurosci. Lett. 420, 45–48.

Gómez-Palacio-Schjetnan A, E.M., 2013. Neurotrophins and synaptic plasticity. Curr. Top. Behav. Neurosci. 15, 117–136.

González-Blanch, C., Crespo-Facorro, B., Álvarez-Jiménez, M., Rodríguez-Sánchez, J.M., Pelayo-Terán, J.M., Pérez-Iglesias, R., et al., 2007. Cognitive dimensions in first-episode schizophrenia spectrum disorders. J. Psychiatr. Res. 41, 968–977.

Gorski, J.A., Balogh, S.A., Wehner, J.M., Jones, K.R., 2003. Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. Neuroscience 121, 341–354.

Hao, R., Qi, Y., Hou, D.N., Ji, Y.Y., Zheng, C.Y., Li, C.Y., et al., 2017. Corrigendum: BDNF val66met polymorphism impairs hippocampal long-term depression by down-regulation of 5-HT3 receptors. Front. Cell. Neurosci. 11, 351.

Hariri, A.R., Goldberg, T.E., Mattay, V.S., Kolachana, B.S., Callicott, J.H., Egan, M.F., et al., 2003. Brain-derived neurotrophic factor val66met polymorphism affects human memory-related hippocampal activity and predicts memory performance. J. Neurosci. 23, 6690–6694.

Healey, K.M., B., C., P., D., 2016. Deficits in social cognition in first episode psychosis: a review of the literature. Clin. Psychol. 50, 108–137.

Heitz, U., Papmeyer, M., Studerus, E., Egloff, L., Ittig, S., Andreou, C., et al., 2018. Plasma and serum brain-derived neurotrophic factor (BDNF) levels and their association with neurocognition in at-risk mental state, first episode psychosis and chronic schizophrenia patients. World J. Biol. Psychiatry 1–10.

Hoff, A.L., R., H., O., D., 1992. Neuropsychological functioning of first-episode schizophreniform patients. Am. J. Psychiatry.

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

Jaeger, J., Czobor, P., Berns, S.M., 2003. Basic neuropsychological dimensions in schizophrenia. Schizophr. Res. 65, 105–116.

Jones, C.A., Watson, D.J.G., Fone, K.C.F., 2011. Animal models of schizophrenia. Br. J. Pharmacol. 164, 1162–1194.

Katsumi, A., Hoshino, H., Fujimoto, S., Yabe, H., Ikebuchi, E., Nakagome, K., et al., 2017. Effects of cognitive remediation on cognitive and social functions in individuals with schizophrenia. Neuropsychol. Rehabil. 1–13.

Komulainen, P., Pedersen, M., Hänninen, T., Bruunsgaard, H., Lakka, T.A., Kivipelto, M., et al., 2008. BDNF is a novel marker of cognitive function in ageing women: the DR's EXTRA study. Neurobiol. Learn. Mem. 90, 596–603.

Lee, S.Y., Wang, T.Y., Chen, S.L., Chang, Y.H., Chen, P.S., Huang, S.Y., et al., 2016. The correlation between plasma brain-derived neurotrophic factor and cognitive function in bipolar disorder is modulated by the BDNF Val66Met polymorphism. Sci. Rep. 6, 37950.

Lipska, B.K., Khaing, Z.Z., Weickert, C.S., Weinberger, D.R., 2001. BDNF mRNA expression in rat hippocampus and prefrontal cortex: effects of neonatal ventral hippocampal damage and antipsychotic drugs. Eur. J. Neurosci. 14, 135–144.

Lu, Y., Christian, K., Lu, B., 2008. BDNF: A key regulator for protein synthesis-dependent LTP and long-term memory? Neurobiol. Learn. Memory 89, 312–323.

Maas, D.A., Valles, A., Martens, G., 2017. Oxidative stress, prefrontal cortex hypomyelination and cognitive symptoms in schizophrenia. Transl. Psychiatry 7, e1171.

Man, L., Lv, X., Du, X.D., Yin, G., Zhu, X., Zhang, Y., et al., 2018. Cognitive impairments and low BDNF serum levels in first-episode drug-naive patients with schizophrenia. Psychiatry Res. 263, 1–6.

McCleery, A., Ventura, J., Kern, R.S., Subotnik, K.L., Gretchen-Doorly, D., Green, M.F., et al., 2014. Cognitive functioning in first-episode schizophrenia: MATRICS Consensus Cognitive Battery (MCCB) profile of impairment. Schizophr. Res. 157, 33–39.

Moustafa, A.A., Garami, J.K., Mahlberg, J., Golembieski, J., Keri, S., Misiak, B., et al., 2016. Cognitive function in schizophrenia: conflicting findings and future directions. Rev. Neurosci. 27, 435–448.

Murillo, O.B., Ramirez, E.J., Ramos-Rodriguez, E., Martinez-Garza, S., Macias-Cervantes, H., Solorio-Meza, S., et al., 2016. Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes. World J. Diabetes 7, 615–620.

Nawa, H., Takahashi, M., Patterson, P.H., 2000. Cytokine and growth factor involvement in schizophrenia–support for the developmental model. Mol. Psychiatry 5, 594–603.

Ng, F., Berk, M., Dean, O., Bush, A.I., 2008. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int. J. Neuropsychopharmacol. 11, 851–876.

Nieto, R., Kukuljan, M., Silva, H., 2013. BDNF and schizophrenia: from neurodevelopment to neuronal plasticity, learning, and memory. Front. Psychiatry 4.

Niitsu, T., Shirayama, Y., Matsuzawa, D., Hasegawa, T., Kanahara, N., Hashimoto, T., et al., 2011. Associations of serum brain-derived neurotrophic factor with cognitive impairments and negative symptoms in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 1836–1840.

Müller, N., 2010. Immune system and schizophrenia. Curr. Immunol. Rev. 3 213-210.

Numakawa, T., Suzuki, S., Kumamaru, E., Adachi, N., Richards, M., Kunugi, H., 2010. BDNF function and intracellular signaling in neurons. Histol. Histopathol. 25, 237.

Pan, W., Banks, W.A., Fasold, M.B., Bluth, J., Kastin, A.J., 1998. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37, 1553–1561.

Pang, P.T., 2004. Cleavage of proBDNF by tPA/Plasmin is essential for long-term hippocampal plasticity. Science 306, 487–491.

Pillai, A., Kale, A., Joshi, S., Naphade, N., Raju, M.S.V.K., Nasrallah, H., et al., 2010. Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. Int. J. Neuropsychopharmacol. 13, 535.

Reis, H.J., Nicolato, R., Barbosa, I.G., Prado, P.H.T.D., Romano-Silva, M.A., Teixeira, A.L., 2008. Increased serum levels of brain-derived neurotrophic factor in chronic institutionalized patients with schizophrenia. Neurosci. Lett. 439, 157–159.

Rizos, E.N., Rontos, I., Laskos, E., Arsenis, G., Michalopoulou, P.G., Vasilopoulos, D., et al., 2008. Investigation of serum BDNF levels in drug-naive patients with schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1308–1311.

Rizos, E.N., Papathanasiou, M., Michalopoulou, P.G., Mazioti, A., Douzenis, A., Kastania, A., et al., 2011. Association of serum BDNF levels with hippocampal volumes in first psychotic episode drug-naive schizophrenic patients. Schizophr. Res. 129, 201–204.

Rössler, O.G., Giehl, K.M., Thiel, G., 2004. Neuroprotection of immortalized hippocampal neurones by brain-derived neurotrophic factor and Raf-1 protein kinase: role of

extracellular signal-regulated protein kinase and phosphatidylinositol 3-kinase. J. Neurochem. 88, 1240–1252.
Schlessinger, J., 2000. Cell signaling by receptor tyrosine kinases. Cell 103, 211–225.
Schmidt, H.D., Duman, R.S., 2010. Peripheral BDNF produces antidepressant-like effects in cellular and behavioral models. Neuropsychopharmacology 35, 2378–2391.
Sharma, T., Antonova, L., 2003. Cognitive function in schizophrenia. Deficits, functional consequences, and future treatment. Psychiatr. Clin. N. Am. 26, 25–40.
Shepherd, A.M., Laurens, K.R., Matheson, S.L., Carr, V.J., Green, M.J., 2012. Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. Neurosci. Biobehav. Rev. 36, 1342–1356.
Shi, C., Kang, L., Yao, S., Ma, Y., Li, T., Liang, Y., et al., 2015. The MATRICS Consensus Cognitive Battery (MCCB): Co-norming and standardization in China. Schizophr. Res. 169, 109–115.
Shoval, G., Weizman, A., 2005. The possible role of neurotrophins in the pathogenesis and therapy of schizophrenia. Eur. Neuropsychopharmacol. 15, 319–329.
Singh, S., Khushu, S., Kumar, P., Goyal, S., Bhatia, T., Deshpande, S.N., 2018. Evidence for regional hippocampal damage in patients with schizophrenia. Neuroradiology 60, 199–205.
Skilleter, A.J., Weickert, C.S., Vercammen, A., Lenroot, R., Weickert, T.W., 2015. Peripheral BDNF: a candidate biomarker of healthy neural activity during learning is disrupted in schizophrenia. Psychol. Med. 45, 841–854.
Song, X., Quan, M., Lv, L., Li, X., Pang, L., Kennedy, D., et al., 2015. Decreased cortical thickness in drug naïve first episode schizophrenia: in relation to serum levels of BDNF. J. Psychiatr. Res. 60, 22–28.
Sponheim, S.R., Jung, R.E., Seidman, L.J., Mesholam-Gately, R.I., Manoach, D.S., O'Leary, D.S., et al., 2010. Cognitive deficits in recent-onset and chronic schizophrenia. J. Psychiatr. Res. 44, 421–428.
Tamminga, C.A., Stan, A.D., Wagner, A.D., 2010. The hippocampal formation in schizophrenia. 167, 1178–1193.
Vicario-Abejon, C., Owens, D., McKay, R., Segal, M., 2002. Role of neurotrophins in central synapse formation and stabilization. Nat. Rev. Neurosci. 3, 965–974.
Wible, C.G., 2013. Hippocampal physiology, structure and function and the neuroscience of schizophrenia: a unified account of declarative memory deficits, working memory deficits and schizophrenic symptoms. Behav. Sci.3 298–315.
Wong, A.H.C., Van Tol, H.H.M., 2003. Schizophrenia: from phenomenology to neurobiology. Neurosci. Biobehav. Rev. 27, 269–306.
Wu, J.Q., C., D.C., T., 2016a. Cognitive impairments in first-episode drug-naive and chronic medicated schizophrenia: MATRICS consensus cognitive battery in a Chinese Han population. Psychiatry Res. 76, 163–168.
Wu, J.Q., Chen, D.C., Tan, Y.L., Tan, S.P., Hui, L., Lv, M.H., et al., 2015. Altered BDNF is correlated to cognition impairment in schizophrenia patients with tardive dyskinesia. Psychopharmacology 232, 223–232.
Wu, J.Q., Chen, D.C., Tan, Y.L., Xiu, M.H., De Yang, F., Soares, J.C., et al., 2016b. Cognitive impairments in first-episode drug-naive and chronic medicated schizophrenia: MATRICS consensus cognitive battery in a Chinese Han population. Psychiatry Res. 238, 196–202.
Xiao, W., Ye, F., Liu, C., Tang, X., Li, J., Dong, H., et al., 2017. Cognitive impairment in first-episode drug-naïve patients with schizophrenia: Relationships with serum concentrations of brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor. Prog. Neuropsychopharmacol. Biol. Psychiatry 76, 163–168.
Yuan, P., Zhou, R., Wang, Y., Li, X., Li, J., Chen, G., et al., 2009. Altered levels of extracellular signal-regulated kinase signaling proteins in postmortem frontal cortex of individuals with mood disorders and schizophrenia. J. Affect. Disord. 124, 164–169.
Zhang, X.Y., Chen, D., Tan, Y., Tan, S., Wang, Z., Yang, F., et al., 2015. The interplay between BDNF and oxidative stress in chronic schizophrenia. Psychoneuroendocrinology 51, 201–208.
Zhang, X.Y., Chen, D.C., Xiu, M.H., Haile, C.N., Luo, X., Xu, K., et al., 2012a. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. Hum. Genet. 131, 1187–1195.
Zhang, X.Y., Liang, J., Chen, D.C., Xiu, M.H., Yang, F.D., Kosten, T.A., et al., 2012b. Low BDNF is associated with cognitive impairment in chronic patients with schizophrenia. Psychopharmacology 222, 277–284.
Zhang, X.Y., Tan, Y., Chen, D., Tan, S., Yang, F., Wu, H.E., et al., 2016. Interaction of BDNF with cytokines in chronic schizophrenia. Brain Behav. Immun. 51, 169–175.
Zhang, Y., Fang, X., Fan, W., Tang, W., Cai, J., Song, L., et al., 2018. Brain-derived neurotrophic factor as a biomarker for cognitive recovery in acute schizophrenia: 12-week results from a prospective longitudinal study. Psychopharmacology 235, 1191–1198.
Zuccato, C., Cattaneo, E., 2009. Brain-derived neurotrophic factor in neurodegenerative diseases. Nat. Rev. Neurol. 5, 311–322.