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Interaction of BDNF and cytokines in executive dysfunction in patients with chronic schizophrenia

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ABSTRACT

Multiple lines of evidence indicate that patients with chronic schizophrenia (SCZ) display executive dysfunction across the illness course. However, the potential molecular pathophysiologic mechanisms remain poorly elucidated. Neurodevelopmental changes caused by alterations of inflammatory mediators and neurotrophins have been shown to occur in the earliest stages of SCZ, and be associated with executive dysfunction (ED) in SCZ. Therefore, the current study was to investigate whether the interplay between BDNF and inflammatory mediators was involved in the disruption of executive function of long-term hospitalized patients with chronic SCZ. Serum cytokines and BDNF levels were measured in 112 long-term hospitalized patients with chronic SCZ and 44 healthy normal controls. Executive functions were assessed by verbal fluency tests (VFT), the Stroop word-color test (Stroop), and the Wisconsin card sorting tests (WCST).The results showed that the patients had higher IL-2, IL-6, IL-8, but lower TNF-α and BDNF compared to control subjects. In the patient group, BDNF was positively associated with IL-2 and IL-8 levels, while lower BDNF levels were correlated with ED measured by VFT and WCST tests. Multiple stepwise regression analyses confirmed that BDNF × IL-8 and BDNF × TNF-α were factors influencing the total score of VFT, while BDNF × IL-8 and BDNF × TNF-α were recognized as influencing factors for WCST scores. Our results suggest complex interactions between BDNF and cytokines were involved in the pathophysiology of executive function impairments in patients with SCZ.

1. Introduction

Schizophrenia (SCZ) is conceptualized as a neurodevelopmental disorder and characterized by a wide range of deficits throughout multiple neurocognitive domains (Lieberman and First, 2018). Multiple robust findings suggest that executive dysfunction (ED) exists in patients with SCZ as one of the most common and significant neurocognitive dysfunctions in this disorder (Orellana and Slachevsky, 2013; Thai et al., 2018). Executive function involves the abilities to plan and build goal-oriented behaviors and problem-solving activities in a strategic and flexible manner (Diamond, 2013). Since ED is always associated with many aspects of daily functioning, such as occupational, social, professional, emotional and adaptive functions, it has been identified as a pivotal determinant of long-term quality of life (Kluwe-Schiavon et al., 2013; Xu et al., 2014). Therefore, understanding the factors related to ED is critical for developing approaches for enhancing cognitive rehabilitation and improving functional outcomes in patients suffering from SCZ.

More recent studies have supported a neurodevelopmental hypothesis in SCZ, which postulated that erroneous genetics interacted with environmental factors during critical periods may adversely impact the neurodevelopment process (Anderson and Maes, 2013). Cytokines can regulate the immune-inflammatory system reactions and neurodevelopment at all stages, emerging as part of a common pathway of genetic and environment factor (Garre et al., 2017; Reboucas et al., 2018). Then, cytokines have been hypothesized to transmit peripheral inflammatory signals to the brain through developing blood-brain barrier, perturbing structural and functional development of the brain (Hueston et al., 2018). Lately, several meta-analyses of cytokines alteration in the cerebrospinal fluid or serum and one meta-analysis

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about cytokine genetic variation in SCZ have been published (Tourjman et al., 2013; Upthegrove et al., 2014; Goldsmith et al., 2016; Capuzzi et al., 2017; Zhang et al., 2018). Of particular interest, serum levels of those cytokines have been shown to be significantly related to positive, negative, excitation, andaffective symptom dimensions of SCZ, which in turn tend to normalize with alleviation of psychotic symptoms after antipsychotic treatment, indicating a critical role in the pathophysiology of SCZ (Goldsmith et al., 2019; Romeo et al., 2018).

Specifically, there is emerging evidence that the cytokines of the immune system play a pathogenic role underlying several domains of neurocognitive impairments (Wu et al., 2016a, 2016b; Wilson et al., 2018; Xiu et al., 2018). Several cytokines and related components of immune-inflammatory system in the dorsolateral prefrontal cortex (DLPFC) have been demonstrated to be associated with cognitive decline in SCZ (Misiak et al., 2018; Lopez-Gonzalez et al., 2019). Further evidence from a recent study showed that cognitive dysfunctions were in part caused by altered production or regulation of tryptophan catabolite with neurotoxicity, excitotoxicity, immune inflammation, oxidation and nitrification potential, which may lead to neurodegeneration (Kanchanatawan et al., 2018). The tryptophan catabolite pathway is well-known to be regulated by proinflammatory cytokines to produce the neurotoxic kynurenine pathway metabolites (Kim and Won, 2017). In addition, preclinical studies provide evidence that system inflammation causes cognition and behavior changes by inducing microglia in the brain to release proinflammatory cytokines (Khandaker et al., 2015). In all dimensions of neurocognitive function in patients with SCZ, executive dysfunction is suggested to be the most relevant to poor functional outcomes (Berberian et al., 2019). However, the studies linking ED and inflammation in SCZ are still scarce. To our best knowledge, there are only 3 studies focusing on the relationship between proinflammatory cytokines and the degree of executive dysfunctioning in the patients with SCZ (Asevedo et al., 2013, 2014; Sirivichayakul et al., 2019). Thus, the exact mechanisms of executive dysfunction induced through immune/inflammatory reactions remain little known and require further investigation.

Brain-derived neurotrophic factor (BDNF) is one of neurotrophins, which has been associated not only with neurodevelopment, but also with synaptic plasticity and cognitive functions, such as memory and learning (Kowianski et al., 2018; Toh et al., 2018a, 2018b). Clinical studies have found decreased levels of BDNF in peripheral blood and certain brain regions of SCZ patients compared to normal controls and close relationships between cognitive function and BDNF levels (Hori et al., 2017a, 2017b; Heitz et al., 2018; Man et al., 2018), supported by several meta-analyses although with inconsistent reports in different groups (Qin et al., 2017; Rodrigues-Amorim et al., 2018). Interestingly, among these studies, there were findings indicating a relationship between BDNF and executive function (Hori et al., 2017a, 2017b; Aas et al., 2018). For example, Hori et al. showed that the executive functions in patients with SCZ undergoing aripiprazole treatment were significantly associated with serum BDNF levels (Hori et al., 2017a, 2017b). Moreover, Aas et al. reported a positive association between the improvement of executive function and increased BDNF mRNA levels after physical activity in SCZ (Aas et al., 2018). Taken together, these studies show that BDNF may play a major pathological role in the ED, one of the core features in neurocognitive dysfunction of SCZ.

Previous studies have shown that the cytokines and BDNF interact closely to regulate the immune and nervous systems in the brain (Calabrese et al., 2014). For example, TNF-α could possibly regulate the extracellular secretion of BDNF, with findings of negative correlations with BDNF in the neurocognitive dysfunction of patients with SCZ (Zhang et al., 2017). IL- 1β suppresses the normal expression of BDNF (Patterson, 2015; Carlos et al., 2017) and BDNF levels are closely related to IL-6 levels in major depressive disorder (MDD) patients (Patas et al., 2014). A more recent literature in long-term heroin addicts found that decreased plasma transforming growth factor (TGF)-β1 and BDNF levels contributed to ED after long-term heroin use (Lu et al., 2017), suggesting a potential role of BDNF interaction with cytokines in the EDs of SCZ patients. The study from our group also found that serum BDNF levels positively correlated with serum IL-2 levels and IL-8 levels in chronic patients with SCZ, and an interaction between BDNF and TNF-α was correlated with decreased performance on the PANSS neurocognitive factor (Zhang et al., 2016). However, we did not systematically measure neurocognitive functions with specific neurocognitive assessments in this study.

Verbal fluency tests (VFT), the Stroop word-color tests (Stroop) and Wisconsin card sorting tests (WCST) are all useful probes of the executive functions in neuropsychological research. In the present study, the executive functions were assessed by VFT, WCST and Stroop tests in patients with chronic SCZ. This study aimed to investigate the association between BDNF, cytokine serum levels and ED and to evaluate if any of such association was mediated independently or interactively in relation to ED in this population. We hypothesized that decreased BDNF serum levels may be associated with altered cytokines in schizophrenia, and the interaction between BDNF and cytokines may contribute to the ED of schizophrenia. Thus, we would use moderation analysis for their interaction in this present study.

2. Materials and methods

2.1. Subjects

232 patients with the DSM-IV diagnosis of SCZ were recruited from the inpatient units of Beijing Huilongguan Hospital and confirmed by a independent experienced psychiatrist based on the Structured Clinical Interview for DSM-IV (SCID). The current study was conducted from December 2006 to May 2008. The patients also satisfied the following criteria: age 20–75 years, with minimum duration of illness at least 5 years and at least 5 years of education. The exclusion criteria were: (a) ongoing infections; (b) using immunosuppressive agents; (c) past history of autoimmune disorders, allergies; (d) taking drugs for physical diseases; (e) substance dependence/abuse except for tobacco; (f) the use of alcohol or more casual use of recreational drugs; (g) breast-feeding or pregnant females; and (h) medical abnormalities, including central nervous system diseases, acute, unstable or significant medical illnesses (e. g. cancer, hypertension, lung disease, diabetes, or cerebrovascular disease). The average age of the patients was 51.1 ± 8.8years (range 24–73 years).

Sixty unrelated healthy normal control subjects were recruited by advertisement from the local community near the hospital in the same period as the patients. A research psychiatrist excluded those potential controls with Axis I disorders after a clinical interview. Those control subjects with common mood disorders and anxiety disorders were excluded by this psychiatrist using the SCID diagnostic criteria. We also excluded those subjects who were taking psychotropic medications (e.g. antipsychotic, anti-anxiety, antidepressant, or mood stabilizing drugs), hormonal agents, anti-inflammatory agents, anti-hypertensives, and anti-hyperlipidemics. With the exception of antipsychotic medications, these same treatment exclusion criteria also applied to the patients. The average age of the control subjects was 47.7 ± 4.5 years (range 22–70 years). For the current study, we selectively enrolled the participants with fewer years of education to match with the individuals with schizophrenia who were less educated than general population. The socioeconomic background of the patients and normal controls was comparable.

All participants provided written informed consent to participate in this study, which received the approval from the Institutional Review Board, Beijing Hui-Long-Guan Hospital.

2.2. Assessment

Participants were examined with executive function assessment batteries by four expert psychologists on the same day of blood

Table 1
Demographic characteristics, clinical data, and cytokines in schizophrenia and healthy controls.

Variable	Schizophrenia (n = 232)	Healthy controls (n = 60)	F orχ^2 (p-Value)
Gender(male/female)	155/77	44/16	0.93 (0.33)
Age (years)	51.1 ± 8.8	47.7 ± 4.5	
Education (years)	9.8 ± 2.7	10.2 ± 3.1	
Smokers/nonsmokers	98/92	33/27	0.21(0.64)
Body mass index (kg/m^2)	24.5 ± 3.9	24.7 ± 3.7	0.06 (0.84)
BDNF (ng/ml)	6.9 ± 2.4	9.7 ± 4.5	22.1(< 0.001)
IL-2 (ng/ml)	7.0 ± 2.9	4.2 ± 2.6	24.4(< 0.001)
IL-6 (ng/ml)	0.35 ± 0.11	0.29 ± 0.19	5.9(0.008)
IL-8 (ng/ml)	0.97 ± 0.30	0.88 ± 0.57	4.74(0.014)
TNF-a (ng/ml)	10.0 ± 2.0	37.2 ± 5.1	1963(< 0.001)
Age of onset (years)	24.2 ± 3.6		
Duration of illness (years)	23.9 ± 8.1		
Antipsychotic types (atypical, n / typical, n)	174/58		
Daily antipsychotic dose (mg/day, CPZ equivalents)	403.4 ± 181.5		
PANSS score, mean ± SD			
Positive symptoms	15.9 ± 6.2		
Negative symptoms	24.5 ± 6.2		
General psychopathology	33.4 ± 8.4		
Total score	73.8 ± 16.5		

sampling. To assess the executive functions associated with prefrontal cortex, the following tests were administered: the Stroop test, VFT and the WCST. The VFT is a verbal measure of semantic fluency and the skill of updating in the executive function (Whiteside et al., 2016). In the VFT test, each patient was requested to say as many words of the same category as possible in one minute, which could be semantic, such as animals and fruits or regular phrases. The Stroop (color word conflict test) assesses the selective attention capacity and processing speed ability (Slimani et al., 2018). In the Stroop test, 30 colored words incongruent with the color were used and the participants were asked to read the word (C) and the secondary color itself (D). The difference between reaction times (D-C) was calculated. The WCST measures a person's ability to shift cognitive set through abstract reasoning in working memory (Lange et al., 2016). The WCST was administered using the standard protocol described by Heaton (RK, 1980). Briefly, all participants were presented with a number of stimulus cards and matched cards, but without instructing as to the matching rule; feedback was only given regarding whether the match was correct or incorrect.

2.3. Blood sampling

Serum samples were obtained to analyze serum BDNF and cytokines levels at the same day of the executive function ratings. Peripheral venous blood was drawn at 8 am in a climate-controlled room after overnight fasting from the participants. All samples were measured by the same technician, blinded to subject status.

2.4. Measurement of BDNF levels and cytokines levels in the serum

Fasting serum BDNF levels were measured by sandwich ELISA as described in a previous report from our group (Wu et al., 2016a, 2016b). Intra- and inter-assay variation coefficients were*7%and 10%*, respectively. Serum TNF-α, and IL*s* were measured in duplicate following a standard protocol previously detailed in a report from our group (Zhang et al., 2016). The sensitivities for TNF-α, IL-8, IL-6 and IL-2 were 0.1 ng/ml, 0.4 ng/ml, 0.2 ng/ml, and 0.1 ng/ml, respectively, intra-assay coefficients from 5% to 9%, and with inter-assay coefficients from 7% to 10%, respectively.

2.5. Statistical analysis

Clinical and demographic data were analyzed by analysis of variance (ANOVA) for the continuous variables and the chi-squared test for categorical variables. Firstly, we used ANOVA to analyze the differences of those biomarkers among the healthy controls and SCZ patients. If the results of ANOVA were significant, we then performed ANCOVA analysis to control for the confounding effects of age, education, smoking, gender and body mass index (BMI). Secondly, we correlated the serum levels of BDNF and cytokines in healthy controls and the patients separately. Finally, we used regression analyses to explore the links between serum levels of BDNF, cytokines and executive function and their interaction effects in the patients with SCZ. Executive function scores were selected as dependent variables, while cytokines, BDNF, as well as their interaction terms were assessed as independent variables. The regression models were corrected for the possible effects of age, education, smoking, gender, BMI, illness duration, duration of antipsychotic treatment, dosage and medication type (typical vs atypical antipsychotics).

3. Results

3.1. Executive functions in the patients and healthy normal controls

We found no significant differences in the gender, age, education years, BMI, and smoking status between healthy controls and the patients (Table 1).In the current study, the Stroop tests, VFT and WCST tests were available for 107 patients with SCZ and 42 healthy normal controls. The results of executive functions are shown in Table 2. There

Table 2
Neurocognitive batteries in schizophrenic patients and healthy control subjects.

	Schizophrenia N = 107	Control n = 42	F	p
VFT total score	39.6 ± 18.5	65.8 ± 11.4	108.2	< 0.001
VFT-animal	16.1 ± 7.2	19.7 ± 3.7	10.3	0.002
VFT-fruit	10.6 ± 4.6	13.2 ± 2.9	11.0	0.001
VFT-phrase	13.6 ± 9.8	32.3 ± 8.0	114.1	< 0.001
Stroop score				
Stroop-word	26.5 ± 20.8	14.5 ± 3.4	12.9	< 0.001
Stroop-color	36.1 ± 23.1	21.4 ± 5.7	15.4	< 0.001
Stroop-word/color	39.5 ± 24.8	21.1 ± 5.7	21.1	< 0.001
Stroop D-C	16.4 ± 3.7	7.0 ± 4.8	15.7	< 0.001
WCST errors				
Nonperseverative errors	44.2 ± 27.2	23.2 ± 17.8	19.8	< 0.001
Perseverative errors	34.0 ± 22.3	20.4 ± 11.5	13.4	< 0.001
Total errors	78.2 ± 22.8	43.8 ± 24.1	61.4	< 0.001
Categories completed	0.9 ± 1.5	4.2 ± 1.9	108.6	< 0.001

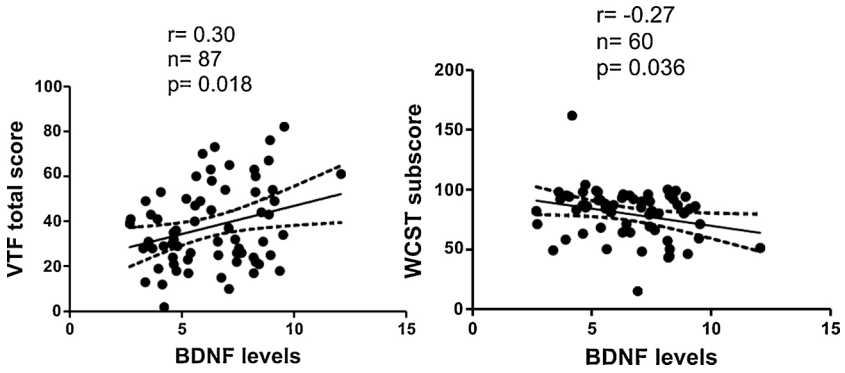

Fig. 1. Correlation analysis revealed significant associations of BDNF levels with the executive functions.

were significantly decreased scores of VFT, WCST and Stroop in patients with SCZ compared with healthy controls when controlling for gender, smoking, education, BMI and age (all $p < 0.01$). After further Bonferroni correction for multiple comparisons, the significant reductions in all tests still remain (all $p < 0.05$).

3.2. BDNF and cytokines levels in healthy normal controls and schizophrenia patients

In the study, BDNF and cytokines were available for 112 patients and 44 healthy normal controls. There were significantly lower levels of TNF-α, BDNF and elevated IL-2, IL-6, IL-8 serum levels in patients with SCZ than healthy normal controls (all $p < 0.05$), after controlling for age, smoking, education, BMI and gender.

Partial correlation analyses were performed to detect the relationships between BDNF and cytokines, controlling for education, BMI, age, smoking and gender. The results demonstrated significantly positive correlations between BDNF and IL-2 ($r = 0.40$, $df = 90$, $p = 0.001$) and IL-8 ($r = 0.41$, $df = 90$, $p = 0.001$) only in the patient group. There was no any statistically significant association between BDNF and cytokines in healthy control subjects (all $p > 0.05$).

Further, there was no statistical difference in BDNF or cytokine levels based on antipsychotic type, dose, or duration of antipsychotic drug (all $p > 0.05$) in the SCZ patients. In particular, *107 patients (46.1%)*were taking clozapine; however, we did not find any significant differences in serum levels of BDNF, IL-2, IL-6, IL-8, or TNF-a between patients with and without clozapine or with clozapine versus typical antipsychotics (all $p > 0.05$).

3.3. Association between executive function and clinical characteristics

Firstly, we tested the influences of clinical symptoms on executive functions in the patients. Partial correlation analysis revealed no statistically significant association between VTF total score and subscores of psychological symptoms, treatment duration, onset age, or antipsychotic dose/day. There were significant associations between the Stroop (D-C) scores and positive symptoms ($r = 0.34$, $p = 0.036$), general psychological symptoms ($r = 0.33$, $p = 0.041$) and onset age ($r = 0.35$, $p = 0.03$) in the patients. In addition, partial correlation analysis showed a significant association between positive symptoms and WCST scores in the patient group ($r = 0.33$, $p = 0.04$). However, after Bonferroni correction, there was no significant association in all results (all $p > 0.05$).

3.4. Association between psychopathological symptoms and serum levels of BDNF and cytokines

We performed Bonferroni corrected partial correlation analyses between BDNF, cytokines and psychopathological symptoms in the patients with SCZ. The results showed that IL-2 negatively associated with positive subscore ($p < 0.05$), but not between other cytokines or BDNF with clinical symptoms (all $p > 0.05$).

3.5. Association between executive functions and serum levels of BDNF and cytokines

For all subjects including the patients and controls, the partial correlation analysis showed there were significantly negative relationships between TNF-α and the Stroop (D-C) score ($r = -0.44$, $df = 141$, $p = 0.0001$; Bonferroni correction: $p < 0.05$).

For the controls, BDNF and cytokine levels were not associated with any sub-domain of executive functions. In the patients, there was a significantly positive relationship between BDNF and VFT scores (*$r = 0.30$, $df = 87$, $p = 0.018$*), as well as a significantly negative relationship between BDNF and WCST score ($r = -0.27$, *$df = 60$,* $p = 0.036$) after controlling for age, education, gender, onset age, duration of the illness and antipsychotic type, but not between BDNF and the Stroop score ($p > 0.05$). (Fig. 1). There was no significant association between any other sub-domains of executive function with ILs and BDNF. After adjusting by Bonferroni corrections, however, all results showed no significance.

The stepwise multiple regression analyses identified the BDNF × IL-8 (beta = 2.81, t = 2.6, p = 0.013) and BDNF × TNF-α (beta = 0.25, t = 2.3, p = 0.023) as the influencing factors for the VFT total score. Moreover, BDNF × IL-8 (beta=-1.82, $t = -2.15$, $p = 0.038$) and BDNF × TNF-α (beta = -0.264,*$t = -2.6$*, $p = 0.013$) were recognized as the influencing factors for the WCST subscore. (Fig. 2).

4. Discussion

The present study is the first to explore the interrelationships between BDNF, cytokines and EDs in patients with SCZ in the Han Chinese population. There are three main findings of the study. (1) As we have reported previously, we observed a significant decrease in BDNF levels as well as significant alterations in cytokines in patients with schizophrenia compared to healthy normal controls. (2) Reduced BDNF levels were independently associated with executive function deficits measured by VFT and WCST tests in patients. (3) The interactions between lower BDNF levels and decreased TNF-α or increased IL-8 were the influencing factors for some sub-domains of executive function deficits in the patients with SCZ.

Our findings of poor executive functioning in chronic patients with SCZ vs control subjects were consistent with many other published studies, which have reported a decline in certain aspects of executive function in all stages of the illness, even before the onset of the first psychotic episode in the patients with SCZ (Fatouros-Bergman et al., 2014; Puetz et al., 2014). These results were also in accordance with our previous studies, in which the global deficits of neurocognitive function were measured by the MATRICS Consensus Cognitive Battery (MCCB) and the Repeatable Battery for the Assessment of

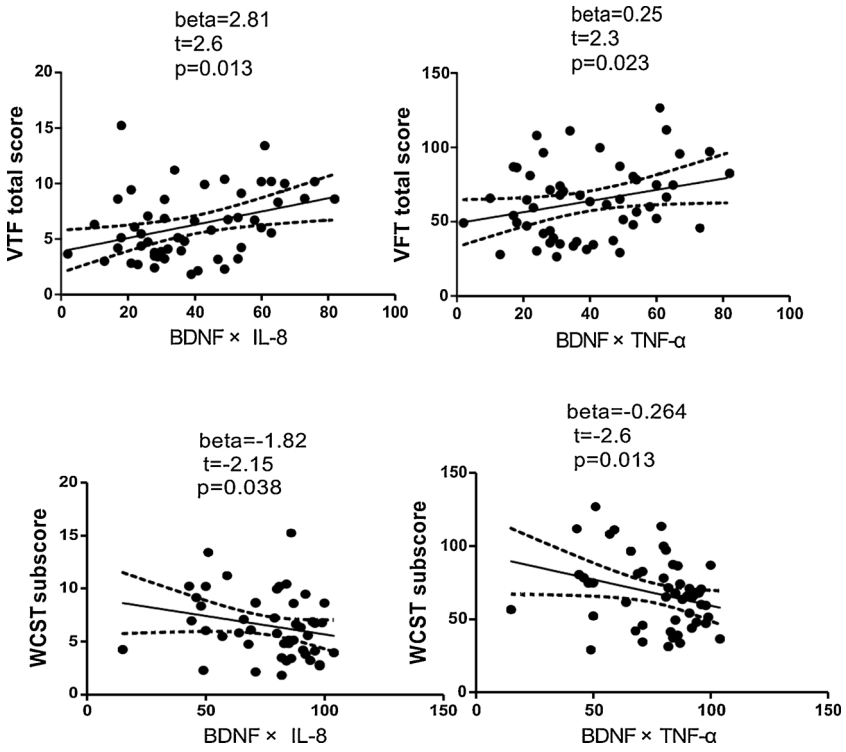

Fig. 2. Correlation analysis revealed significant associations of BDNF × IL-8 and BDNF × TNF-α levels with the executive functions.

Neuropsychological Status (RBANS) (Wu et al., 2016a, 2016b; Chen et al., 2019). The decrease in each score of three executive functional tests compared with healthy normal controls showed that the patients in the present study displayed extensively impaired executive function, providing additional evidence for the neurocognitive dysfunctions in the patients with SCZ. Our results were consistent with other case-control and longitudinal studies in chronic patients with SCZ (Hori et al., 2017a, 2017b; Aas et al., 2018). Clinical studies showed that ED has been more consistently found to be associated with amotivation and negative symptoms in previous studies, which are the major determinant of functional outcome in SCZ (Green et al., 2000). Indeed, the patients in our study were all chronic, long-hospitalized, and social function was severely impaired. In sum, all these studies demonstrated impaired executive function in SCZ patients.

The decreased serum BDNF levels in patients compared with healthy normal controls is consistent with most recent studies including our studies and a recent meta-analysis (Fernandes et al., 2015). Overall, these results suggested that dysregulated BDNF signaling pathway were involved in SCZ. The increased IL-8, IL-6, IL-2 and diminished TNF-α in patients in the current study was not consistent with some prior studies (Singh et al., 2011), some of which showed no difference or decreased levels of these three cytokines in the patients (Singh et al., 2009; Pedrini et al., 2012; Di Nicola et al., 2013). The discrepancy in the immune components related to immune responses among different literatures may be due to complex confounding factors, such duration of illness, medication, diet, stage of the disorder, storage temperature and time, serum or plasma samples used and cytokine assays. Further, we found a positive association between BDNF and IL-2 as well as IL-8, though this is not in the same direction as the original finding of elevated IL-2 and IL-8 with a decrease in BDNF levels in patients with schizophrenia compared to controls. The exact mechanism of this correlation remains unknown. These results are in agreement with the activation of immune systems caused by bacterial/viral infections or autoimmune diseases, which may produce more inflammatory cytokines and lead to the secondary brain injuries (Fineberg and Ellman, 2013). Due to its important role in the maintenance of neuronal function, BDNF may be increased relatively and act as a compensatory mechanism as the activation of immune systems and increased cytokine levels. However, no sufficient BDNF may be produced in the SCZ patients to fight against the inflammatory damage caused by increased cytokines, such as IL-2 and IL-8. In this way, our statistical analysis displayed lower BDNF levels but higher IL-2 and IL-8 levels in the same patients; however, there was a positive association between BDNF and IL-2 as well as IL-8.

In the current study, we found that reduced serum BDNF levels negatively correlated with executive function in chronic patients with SCZ, but we did not find any association between the three cytokines and executive functions measured by WCST, the Stroop or VFT tests in the same samples. This significant relationship of BDNF and ED were consistent with other studies (Hori et al., 2017a, 2017b; Aas et al., 2018). It is well known that BDNF has an important role in neurogenesis and neuroplasticity of the brain, as well as a neuroprotective effect during CNS inflammation. Once the BDNF production pathway was altered, it could lead to less efficient neuroprotection and, consequently, more noticeable brain damage leading to subcortical brain atrophy (Kalinowska-Lyszczarz et al., 2017). Reduced BDNF in the present study may suggest abnormal neurogenesis in some functional regions involved in the executive function in the brain of the patients with SCZ, consistent with previous literature. For example, early studies showed that reduced BDNF levels influence executive functions (an acute impact) and anatomical development (a long-term structural impact) of the dorsolateral region of the prefrontal cortex (DLPFC) (Rybakowski et al., 2003). In addition to SCZ, numerous psychiatric disorders (depression, bipolar disorder, obsessive-compulsive disorder, autism spectrum disorders), characterized by ED, have a deficient BDNF signaling as a common pathophysiological feature (da Rocha et al., 2011; Newton et al., 2017; Wagner et al., 2018). Interestingly, treatments regulating the BDNF signaling pathways in the brain, may achieve an improvement in executive functions (Hori et al., 2017a, 2017b; Aas et al., 2018). In sum, all these evidences showed a tight relationship between BDNF with executive functions in SCZ, and the reduced BDNF levels found in this study may suggest an abnormality in the frontal lobe structures and brain connectivity present as executive

functions in patients with SCZ.

In contrast to our findings, several studies have reported that disrupted TNF-α signaling and other inflammatory-associated components could result in impaired executive function. For example, a study in SCZ to investigate possible relationship between peripheral levels of IL-8, BDNF and oxidative markers and neurocognitive function, showed that IL-8 was positively correlated with verbal fluency test scores (Asevedo et al., 2013). Another study in recurrent depressive disorder demonstrated that elevated expression of TNF-α negatively correlated with cognitive efficiency: executive functions and verbal fluency (Bobinska et al., 2017). Inflammation-related signaling pathways appeared to play multiple different roles and triggers different signaling pathways in different diseases. Therefore, many researchers have reported the lack of consistent results regarding cytokines in EDs in other diseases. For example, the study in children born extremely preterm demonstrated that increased risks of the ED composite were associated with high concentrations of inflammatory proteins (IL-8 and TNF-α) and neurotrophic proteins. A study in chronic kidney disease with declined neurocognitive function showed that higher levels of TNF-α were associated with a lower risk of impaired executive function (Kurella Tamura et al., 2017). In HIV related neurocognitive disorders, IL-6 and IL-8 were significantly linked to executive function, but not BDNF, or TNF-α (Falasca et al., 2017). In the sample of working adults, low grade inflammatory processes in terms of higher systemic levels of pro-inflammatory biomarkers (MCP-1, IL-6 & CRP) were shown to be associated with poorer executive functioning (Stenfors et al., 2017). In sum, there are significant differences in immune responses across various studies of disorder states that impact brain and cognitive function.

Furthermore, another important finding of the present study was that the interaction of low BDNF concentrations and low TNF-α concentrations and the interaction of low BDNF concentrations and elevated IL-8 concentrations were positively correlated with ED measured by VFT and WCST tests in the patients with SCZ. These interactions were consistent with our prior study, which found an interaction between reduced BDNF and TNF-α was negatively associated with PANSS cognitive factor (Zhang et al., 2016). This correlation also was consistent with a study in healthy subjects, which showed a statistically significant interaction effect on spatial memory retention by a polymorphism of TNF-α (rs113325588), which lowers TNF-α levels, and BDNF Val66Met variant, which decreases BDNF levels (Yogeetha et al., 2013). It is the first study to find a significant interactive effect of IL-8 and BDNF on EDs in SCZ patients. However, we could not provide a causal pathophysiological explanation for these significant associations between BDNF and cytokines. It is well known that there are complex interrelationships between BDNF and cytokines after activation of immune system by infection or trauma (Felger and Lotrich, 2013). BDNF and its receptor TrkB have been found to express in peripheral blood, which once stimulated, release significant amount of neuroprotective BDNF related to neurocognitive functions (Martinez-Cengotitabengoa et al., 2016). Lower serum levels of BDNF in this study suggested that neuroprotective function was deficient in the patients with SCZ. As we described above, patients with SCZ have been associated with autoimmune disease or bacterial or viral infections (Bergdolt and Dunaevsky, 2019). Activated monocytes and T cells migrated into the central nervous system, where they not only infected brain resident cells, but also produced proinflammatory cytokines such as TNF-α, IL-2 and IL-1ß. In turn, these cytokines and other components of immune system further activate microglia and astrocytes to release neurotoxic factors such as excitatory amino acids and inflammatory mediators, resulting in neuronal dysfunction and death (Suzumura, 2013; Minogue, 2017). Our results are also complemented by those more recent studies showing that complex of network of low BDNF expression and alterations of cytokines in serum have been implicated in the executive function deficits (Aas et al., 2018; Toh et al., 2018a, 2018b). Therefore, an interactive effect between the immune response and BDNF may play a role in the pathological mechanism of executive function deficits in SCZ, which include a pathogenesis of inflammatory harm from elevated IL-2 and IL-8 levels and deficiency of neurotrophin and TNF-α compensation.

The results of the present study must be cautiously interpreted because of several study limitations. First, the sample size is relatively small and reduces the power of a study. In particular, the sample became smaller when the comparisons between two groups were among five cytokines controlling for several confounding factors. Second, it is still uncertain whether BDNF as well as these cytokines in serum reflect similar levels within the central nervous system. Since a major source of peripheral BDNF derives from platelet, future studies should isolate peripheral blood mononuclear cells to analyze the interrelationships between BDNF and cytokines. Third, there is a slight difference in the number of samples between two groups, which may result in a statistical bias in the analysis because of the imbalance in the sample size. Fourth, cytokines in blood have very complex interactions due to the known complexity of the immune system, which play pathological effects on neurocognition. But, the current study did not measure other anti- and pro-inflammatory cytokines. Thus, measuring the current subset of cytokines here does not seem to be reliable approach to a more exhaustive account of the associations between cognitive performance and immune cytokines in patients. Fifth, it is only a cross-sectional study, but not a longitudinal study. Thus, we cannot rule out the effect of duration of illness and antipsychotic treatment on ED in the present study.

In summary, our study demonstrated that diminished serum BDNF levels and altered cytokines levels may be involved in the pathophysiology of executive function deficits of the patients with SCZ. Inflammatory cytokines appear to interact with BNDF to play a fundamental role in ED, providing more evidence for the neurodevelopmental hypothesis of schizophrenia. However, given the cross-sectional design of the present study, a definitive account that defines the causal relationships between the BDNF system, immune dysfunction and cognitive impairments in schizophrenia is yet to be elucidated.

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